10th Annual
Science Symposium
Volume II
May 13, 2004
Paradise Valley College
Estrella Mountain College
South Mountain College
Foreword

The 10th Annual Science Symposium was held on May 13, 2004. Students enrolled in General Organic Chemistry II, CHM 236 from Paradise Valley College (PVC), Estrella Mountain College (EMC) and South Mountain College (SMC), participated in the event. I want to thank Dr. Michael Bishop for his leadership and the participation of his students.

Each contributor was responsible for selecting and researching their topic, preparing a paper and orally presenting their project to their peers. This booklet contains each of those papers.

As an instructor and faculty advisor for this symposium, I want to thank and congratulate each participant for their effort, courage and dedication. By participating these individuals perpetuate this event annually. I am both proud and honored to present the work of these individuals.

I would like to dedicate this symposium to Dr. Gina Kranitz, past president of Paradise Valley College. She was an advocate for education and supported this symposium. Her battle was cancer was long and valiant. She left an indelible mark on PVC and we will miss her. As educators and students we acknowledge the freedoms we have to meet, learn, discuss and debate any topics we so choose.

William L. "Hank" Mancini, PhD
Table of Contents

Methanol: Fuel from the Past, Fuel of the Future
   by John Lawrence Knight

Creatine
   by Naomi Anne Lahti

Latest Treatment for IBS Patients
   by Heather Madden

Halitosis
   by W. Craig Milton

Meth Labs
   by La Shelle Meyers

The Countenance of Janus: A Historical Account of Chemistry’s Infinite Realm of Possibility
   by Andrew Murphy

Depletion of Ozone Layer
   by John Hai-Khoi Ngo

Sweeteners: Health Implications of Sucrose, Aspartame, Saccharine and Sucralose
   by Danielle Heather Nobles

Alprazolam (Xanax)
   by Nancy C. Croot Ogana

Vaccine Preservatives, Specially Thimerosal as a Possible Cause of Autism
   by Emily Elizabeth Oliver

Concerta (Methylphenidate)
   by Kyle Autin Ong

Gleevec: The Revolutionary Therapy For Chronic Mylogenous Leukemia
   by Shelley Ostlund

Chemical and Biological Aspects of Anthrax Vaccine Absorbed
   by Crystal Lee Palermo

Targeted Therapy For Non-small Cell Lung Cancer
   by Tuan Ky Quan

Vitamin E - Is it a Powerful Antioxidant or a Waste of Money?
   by Todd S. Reese
Carcinomas and Other Health Concerns and Their Possible Links to MTBE
by Irene Gaye Robinson

The Carcinogenic Effects of Benzene
by Kelly Lynn Schmidt

Caffeine - Just Another Happy Drug
by Krissie Sesi

Antidepressants and Wellbutrin
by Sneha Nikhil Shah

Chinese Restaurant Syndrome: Monosodium Glutamate
by Matthew Eugene Sloan

Anthrax: A Way To Find A Vaccine
by Charles Nelson Sovetsky

Evolution of Modern Inhalation Anesthetics
by Joel Stoker

Mitoquinone in the Mitochondria
by Brian James Szumnarski

Antabuse (Disulfiram)
by Forid Torabi

Silicone and Saline Breast Implants
by My Kha Truong

Anti-Anxiety Medication Prozac and Ativan
by Stephanie Jane Velasquez

High Cholesterol and the Class of Statin Drugs
by Christy Lee Wilmoth

Fructose: Sweet or Sour
by Jeremy Roger Witt

Rohypnol: The Date Rape Drug
by Bertina B. Yellowhair

Namenda
by Timothy Joseph Youkhana

Hermansky-Pudlak Syndrome: A Triad of Defects
by Rosanna Diana Zvonek
Methanol:
Fuel from the Past
Fuel of the Future

John Knight
16 April 2004
Abstract
A short introduction is given discussing two major problems concerning our nation’s dependence on fossil fuels and offers an alternative source in methanol. A brief background on the nature, chemical structure, physical and chemical characteristics of methanol is presented, then a few basic facts about the molecule itself. A look at the chemistry behind the formation of methanol is given and a short history on the discovery of methanol and the methods of production is discussed along with some uses of methanol. Benefits and drawbacks of methanol use compared to that of gasoline and other fossil fuels are discussed. The question of moving the nation to methanol use for the transportation industry is then explored. Points considered are cost effectiveness, the environment, and diminishing our dependence on foreign fuels. The question of feasibility is asked, but not answered definitively to allow for an open discussion.

Introduction
In the early 1970’s, the Organization of Petroleum Exporting Countries (OPEC) cut their production of crude oil and tightened the reigns on the oil flowing to our part of the world. This caused the price of crude oil to triple from $4.00 to $12.00 per barrel. This led to record high levels in the price of gasoline. It also created long lines at the nation’s gas stations. The long lines and high prices were a warning sign and should have been a wake up call to the leaders of our country on the reality of our dependence on these countries to provide us with one of our most precious resources, oil. But after the initial shock and a couple of years of relatively steady prices, the long lines were forgotten and it was back to business as usual. Unfortunately, business as usual meant that the rate at which this country’s consumption of foreign oil, hence the nation’s dependence on it, would continue to escalate. By 1985, forty three percent of our total energy consumption as a nation was from petroleum.

About the same time frame, scientists monitoring air quality around the country were beginning to see smog levels rising in major metropolitan areas at an increasing rate. They were also studying a phenomenon that seemed to be cropping up around urban centers in the Northeast. They called it “acid rain.” Acid rain is formed when emissions from burning coal and other fossil fuels mix with moisture in the air to form sulfuric and nitric acids. These acids are combined with water vapor, condense and fall to earth as acid rain. It was found that industrial plants burning coal for fuel were the major culprits of acid rain but vehicle emissions played a part in the problem too.

A rise in the level of greenhouse gasses such as carbon dioxide (CO₂) was also being monitored and it was argued that these gasses were a major contributor to a rise in the temperature of the Earth’s atmosphere. This phenomenon is known now as the “greenhouse effect.”

These incidents have a common thread in that the source of the problem is the combustion of fossil fuels. This presentation offers what seems to be a logical alternative to fossil fuels. It’s not a new space-age miracle fuel, nor can the statement be made that it will be our nation’s definitive fuel of the future. But with time, research and development it could very well lead to great improvements in the quality of the air we breathe as well secure the nation’s energy future. What is this alternative? Methanol.
Background

What is methanol? Methanol, also known as methyl alcohol, is the simplest, aliphatic alcohol. As shown below in Figure 1, its structure consists of one carbon atom bonded with three hydrogen atoms and a hydroxyl group. At ambient temperature and atmospheric pressure methanol is a colorless, tasteless liquid and has a faint, sweet, pungent odor similar to ethyl alcohol. It is commonly known as wood alcohol because it is the main alcohol made from the destructive distillation of wood.

![Methanol (CH₃OH)](image)

Physical Properties

Methanol has a molecular weight of 32.04 g/mol and a density of 0.792 g/ml. Methanol is highly flammable. Its boiling point is 64.7°C at atmospheric pressure and it has a flash point of 11.1°C. Methanol vapors are slightly heavier than air and have been known to travel fairly long distances along the ground until they meet an ignition source, ignite, and flash back to the point of origin. If methanol vapors are allowed to accumulate in confined spaces there is a potential for an explosion if they are ignited. Given its flammability, methanol is listed as "a stable material."(4) Methanol dissolves well with other alcohols, esters, ketones and aromatics. It is 100% soluble in water and is so flammable that "methanol-water mixtures containing as little as 21% methanol are flammable liquids."(4)

Chemical Properties and Reactions

Methanol reactions mainly involve the hydroxyl group of the molecule, as in the reaction with HCl. The un-bonded electron pairs on the oxygen atom give it a partial negative charge and the inductive effect the oxygen atom has on both the carbon atom and the hydroxyl hydrogen give them a partial positive charge. The oxygen atom acts as a Bronsted-Lowry base and can accept a proton. Methanol reacts with HCl through an S_N2 type mechanism where the acid produces a protonated alcohol, and then the chloride ion, a good nucleophile, attacks the carbon atom in a backside attack, pushes the water molecule, a good leaving group, off. This causes an inversion of configuration, and produces methyl chloride as shown in Figure 2.
Dehydration of methanol will produce methyl ethe as in Figure 3.

Direct oxidation will yield formaldehyde when using Pyridinium chlorochromate (PCC) as in Figure 4.
When reacted in acid with Benzoic acid, methanol can be used to yield Methyl benzoate shown in Figure 5.

There are other reactions that methanol can undergo such as with phosphorous tribromide (PBr₃) and thionyl chloride (SOCl₂), but the point is, methanol can be used to produce various other molecules and compounds.

Toxicity
Methanol is also highly toxic. Inhalation of a small amount of methanol can cause headache, drowsiness, nausea, vomiting, and blindness. If the concentration is high enough, it could cause death. Ingestion of a few teaspoons of methanol can cause blindness and a few tablespoons can be fatal if not treated.

Formation
The basic methanol synthesis is carried out by reacting carbon monoxide and carbon dioxide with hydrogen in the presence of a suitable catalyst. The synthesis is shown below.

\[
\text{CO} + 2\text{H}_2 \rightleftharpoons \text{CH}_3\text{OH} \\
\text{and} \\
\text{CO}_2 + 3\text{H}_2 \rightleftharpoons \text{CH}_3\text{OH} + \text{H}_2\text{O}
\]

The product formed is a mixture of methanol and water and must be distilled to remove the water and any other impurities in the mix.
History

P. Boyle first recovered methanol from the components of wood vinegar in the year 1661, but as there was no use for it at that time, methanol was all but forgotten. In 1835 Justus von Liebig identified its chemical properties and introduced it as methyl alcohol. He also gave it its correct chemical formula. Methanol was recovered by the distillation of wood at an increasing rate for the next hundred years.

Prior to 1923 the only source of methanol for the chemical industry was "wood alcohol" which was produced by heating wood in the absence of air. This produced charcoal, wood tar and a watery distillate that contained methanol. Fractional distillation of the watery distillate produced a higher quality methanol, but it was difficult to get pure methanol from this process. This lower quality methanol could be used for cooking fuel and lighting and was used as fuel in early automobiles, but it wasn't pure. Also, the yield from this process was very low. According to information from the Clean Fuels Development Coalition (CFDC), before modern technologies were developed, "one ton of hardwood would yield only one or two percent or about six gallons of methanol, softwoods only half as much." M. Appl, a consultant from J.E Sinor Consultants of Dannstadt-Schauemheim, Germany corroborates this at the World Methanol Conference, Frankfurt, Germany in December 1998 saying, "In 1924 about 3 million tons of wood were processed worldwide, which would have corresponded to about 30,000 tons of methanol."

So, as demand for methanol increased, new methods of production were sought to increase the yield and improve the purity to meet this new demand. With the advent of the industrial revolution, coal was being mined and eventually it started to replace wood as fuel. Coal was used for the production of coke for the steel manufacturing process. One byproduct of this process was coal tar and it provided a great raw material for the chemical industry. Also, when coal is reacted with steam and oxygen it produces a gas called synthesis gas. The synthesis gas is a mixture of hydrogen gas, carbon monoxide, and carbon dioxide. Soon after synthesis gasses started being produced from coal, methanol production from wood distillation dropped off drastically. But as the demand for methanol rose and the gasses from the coke plants failed to keep up with demand, gasification processes were developed to collect hydrogen and carbon monoxide gasses using steam and heat. A breakthrough came, not in the field of coke production or even methanol production, but in the hydrogenation of nitrogen to ammonia.

Around 1908 German chemists Fritz Haber and Carl Bosch developed a process for the synthesis of ammonia by hydrogenation of nitrogen under high pressure. In 1918 Fritz Haber was awarded the Nobel Prize for this process. Organic chemists then began looking for ways to hydrogenate other molecules. This discovery led to many other chemical processes including the synthesis of methanol.

In 1913 Alwin Mittasch and C. Schneider discovered a process in which methanol could be synthetically produced. They also noticed that depending on the catalyst used, products with various amounts of methanol were recovered. The first catalyst they used was an iron, but the iron catalyst not only produced methanol but also methane. Chemists tried different catalysts to improve the yield of methanol and decrease the production of by-products. In 1923 a chemist named M. Pier, working for the German company Badische Anilin-und SodaFabrik (BASF) had produced methanol with a good yield using
zinc chromate as a catalyst. BASF built the first commercial methanol plant in Leunawerke, Germany and in September 1926 the first tank car filled with crude methanol rolled out the door. From that point, German synthetic methanol production overtook production of methanol from wood.(10)

Methanol production in the United States started in 1926. The Commercial Solvents Corporation first began using hydrogen, and carbon dioxide formed during the fermentation of corn but soon converted to coal as its main source of fuel. (1) Although coal as a fuel for synthesis gasses was a step forward, the process has been improved by producing them from the reaction of carbon monoxide and water. This allows methanol to be produced at lower pressures and therefore a lower energy cost.

\[ \text{CO} + \text{H}_2\text{O} \rightarrow \text{H}_2 + \text{CO} \]

Today most of the synthesis gasses for methanol production come from natural gas, or methane (CH₄). Methane has an advantage over coal in that it is hydrogen rich and the excess hydrogen can be used to make ammonia. Transportation costs for methane is also lower per unit than coal. This helps lower the overall cost and operating expenses for the production plant.

\[ 2 \text{CH}_4 + 3 \text{H}_2\text{O} \rightarrow \text{CO} + \text{CO}_2 + 7\text{H}_2 \]

Once the synthesis gasses are produced, from whatever fuel source, they are catalyzed and reacted to produce a methanol and water mixture. The mixture is collected and purified by distillation.

Modern Applications

Methanol is used today for a number of purposes. The production of other chemicals such as formaldehyde, acetic acid, acetic anhydride and various other solvents is a large part of the methanol industry today. Ninety percent of methanol production in 1990 was used for this purpose.(1). The production of various other chemicals is still the largest use of methanol today. Methanol is used in the automotive industry today largely as a compound to react with isobutane to make the fuel additive MTBE. It is also used to some extent, as in earlier years, as a neat fuel for methanol burning automobiles and busses. Another use for methanol being researched today relating to the automobile industry is the possibility of using it as a source of hydrogen for the fuel cell.

Methanol as an Alternative

Methanol use as an alternative fuel for the transportation industry isn’t a wholly new concept. As mentioned previously methanol was used as a fuel source for automobiles as early as 1913. But with the coming of the petroleum industry and the process for the refinement of gasoline, methanol was largely relegated to the chemical industry.

It was in the early seventies that people once again started to seek an alternative to fossil fuels. The Arab oil embargo meant skyrocketing gasoline prices and the realization that the burning of fossil fuels was contributing to the formation of acid rain had
industries searching for an alternative. Methanol was one of the alternatives being studied.

Why methanol? Methanol offers several distinct advantages over gasoline and coal in the areas of air quality, variability and availability of resources, and national energy security.

In regards to the environment methanol presents several distinct advantages, especially in the automotive industry. Methanol has a polar molecular structure, therefore it's bonds very strong. The strong bonds make methanol a more stable, less volatile molecule. This lowers the potential for evaporation and equates to fewer fumes escaping when refueling, so there is a reduction in the addition of volatile organic compounds to the atmosphere at the pump. That may not sound like such a large amount, but the EPA estimates that for every thousand gallons of gasoline pumped, almost ten pounds of gasoline fumes are released into the surrounding environment. (11) Methanol and methanol-gasoline mixes are also known to emit lower nitrogen oxide levels than straight gasoline and there are no sulfur dioxide emissions from the combustion of methanol. This lowers the emissions of compounds that tend to contribute to the formation of acid rain. Also, although the unburned fuel emissions are about the same as gasoline, they are not as reactive. Krupnick states that the main organic emission from a methanol burning vehicle is methanol. (12) As stated previously, methanol is a relatively stable, less volatile compound so the tendency to form ozone is also reduced.

Methanol is also relatively inexpensive to make, and the synthesis gasses can be derived from a number of different sources. Methanol is now being produced worldwide from sources such as biomass, coal, naphtha, and natural gas. (13) There is even a patented process called the Seafuel Synthesis Process that derives hydrogen and carbon dioxide from seawater to use as synthesis gasses. (1) In an analysis in 1989 the U.S. Department of Energy estimated the gasoline-equivalent price of a gallon of methanol produced from a natural gas feedstock using the current technology would be $1.30 and a gallon produced using advanced technology would be $1.11. (13)

Another advantage to moving the transportation industry to methanol would be to decrease our nation's dependence on foreign oil. It can be argued that a methanol-mobile nation would no longer be susceptible to the fluctuations in the price of fuel due to cuts in production or hikes in the price of crude oil. Proponents point out that even though we would still have to import methanol, methanol production would come from a wider variety of sources therefore reducing dependence on any one particular source. (13) Methanol can also be used to make hydrogen for the fuel cell.

Methanol is by no means a perfect alternative. It does have some drawbacks. One by-product from the combustion of methanol is the formation of formaldehyde. Formaldehyde irritates the eyes, nose and throat and can cause upper respiratory problems, but even though emissions of formaldehyde from methanol vehicles are greater than from gasoline vehicles and can pose health risks, it is an unstable compound in the air and decomposes quickly. Also, formaldehyde emissions were found to be one-tenth the volume of overall hydrocarbon emissions. (1)

Another argument posed by some detractors is that methanol production would come mainly from natural gas because it can be produced at a lower cost than from coal or biomass. They point out that natural gas supplies are relatively concentrated in the
former USSR and the OPEC countries, we would still be dependent on those countries for a large supply of methanol or the synthesis fuels for it.

There are also questions and problems with vehicle performance. There are three types of methanol burning vehicles being produced and studied today. They are vehicles that operate on neat, or 100% methanol (M100 vehicles), vehicles which operate on a mix of 85% methanol and 15% gasoline (M85 vehicles) and flexible fuel vehicles (FFV) that can operate on any percent mixture of methanol and gasoline.

Krupnick sites mixed results in the performance of methanol vehicles. Methanol has a higher octane rating than gasoline, but lower energy content. This suggests greater power for methanol vehicles, but lower fuel efficiency. This being the case, there are sacrifices the consumer would have to make in the operation of a methanol-burning vehicle. To compensate for the reduced driving range, the consumer would have to face a choice of either a smaller passenger compartment to make room for a larger gas tank, or be willing to refuel at more frequent intervals. Another problem found in both M85 and M100 vehicles is trouble with cold starting. Since methanol does not evaporate easily, there is a tendency to have problems cold starting a methanol vehicle, especially in cold weather. Also, there are problems with abnormal wear on methanol engines. This is a result of liquid methanol collecting inside the cylinders of the engine and diluting the engine oil that lubricates the cylinder walls and reduces engine wear.

These problems with methanol burning vehicles, whether M85, M100, or FFV’s have been studied and some ways to overcome these shortfalls have been designed. There are several solutions to overcome cold starting problems. Adding a more volatile hydrocarbon such as propane to the fuel has been found to eliminate this problem. Another solution is to atomize the fuel prior to injection into the engine. The atomized droplets have a greater ability to absorb energy to enable the fuel to change from liquid to vapor. Another solution was achieved by having a minimum cranking speed of 110 rpm.

Conclusions

There has been a lot of debate in the government and in the private sector about whether it would be feasible to push industry in this country toward the use of methanol and methanol blends instead of fossil fuels, especially in the realm of the automotive industry. Many studies have been performed on a variety of issues such as cost effectiveness, environmental impact, and energy security for the nation, a few of which has been discussed here. After researching the pros and cons of methanol use versus fossil fuels, one conclusion that can be drawn is that it would be possible to have the transportation industry turn to methanol as an alternate fuel source. The larger and more critical question as to the feasibility has yet to be answered unequivocally. In Moving America to Methanol, Gray makes a strong case for the switch and even sets out a blueprint for the transition. He cites positive impacts on the environment and an overall increase in the energy security for the country. Krupnick takes a more cautious, pessimistic stance, citing smaller savings in costs. He also says that the question of energy security is not so clear cut due to the fact that methanol would still have to be imported from some of the same countries that we now are dependent on for the importation of oil. About the only perspective on which most all research agrees is the
fact that methanol and methanol-gasoline blends are cleaner burning fuels than straight gasoline and would improve the overall air quality.

If it is feasible to make such a move, there are still questions concerning public acceptance and questions such as how and over what time frame could the nation fully implement the transition. I have found that many agree that something should be done to clean the air and reduce the nation's dependence on receiving oil from other countries, but most don't think anything will can or will be done until the government gets serious about making the transition.

My own conclusions are that without a large commitment from both the government and the private sector, methanol will play a secondary role to fossil fuels, especially in the automotive and transportation industry. But, without a doubt, I believe that the transition from fossil fuels to methanol and methanol blends should be made. After all, we know there is a limited supply of crude oil to be pumped and, as the supply dwindles, the price for it will increase. Also, how much longer can we continue to pour tons of pollutants into the atmosphere until we no longer have an atmosphere that will sustain life as we know it? The ultimate question we should be asking ourselves as a nation is not "Can we afford to do it", but "Can we afford not to?"

Whether or not we make the full transition to a methanol-mobile nation has yet to be determined. But I believe one thing is certain, methanol use will play an important role in our economy and become increasingly important in the automotive industry whether it is as a neat fuel, fuel mixtures, or a producer of hydrogen for fuel cells.
Bibliography


2. DOE Energy Information Administration, Monthly Energy Review. DOE/EIA-0035 85/01


CREATINE

By Naomi Lahti
CHEM 236, Dr. Mansini
4/16/2004
ABSTRACT

To provide an overview of the data on the discovery, common usage, efficacy and safety of the nutritional supplement creatine.

INTRODUCTION

Creatine use is common among professional athletes, for whom even minute differences in performance can mean the difference between winning and losing. They turn to this amino acid compound with hopes of improving muscle mass, strength, and recovery time. Mark McGwire, Sammy Sosa, and others have openly acknowledged their use of creatine supplements. The Los Angeles Lakers are reported to keep tubs of creatine in their locker room. It has been estimated that 50% of National Football players, and at least 25% of professional hockey, baseball, and basketball players take creatine.

Many college coaches and trainers have been quick to follow the lead of the professionals, and there is concern that high school students and children may use creatine in attempt to emulate their sport’s heroes. Because creatine is considered a nutritional supplement, as defined by the Dietary Supplement and Health Education Act (DSHEA) of 1994, it is available over-the-counter in pharmacies, health food stores, and supermarkets. Some coaches forbid or advise against creatine use because its long-term safety profile is unknown. The athletics director for the University of South Carolina has prohibited creatine use without a prescription.

Although the International Olympic Committee regulations state that consuming a substance in abnormal quantities for the purpose of artificially and unfairly enhancing performance is “doping,” Olympic athletes are permitted to use creatine because of its classification as a nutritional supplement. While it could be argued that creatine should be banned from professional sports, no reliable method currently exists to test for creatine if such a rule is made.

In 1996 creatine sales were estimated at $50 million. Sales exceeded $100 million in 1997, and for 1998 total sales were expected to exceed $200 million. In 1996 the American public purchased 1.2 million kilograms of creatine. By 1998 consumption had risen to nearly 4 million kilograms. With popular magazines running articles with titles such as “The Rise of Creatine, Nature’s Steroid,” “Packaged Pep,” and “Eat Powder: Build Muscle: Burn Calories,” and personal endorsements from stars like the Baltimore Orioles’ Brady Anderson and Denver Bronco’s John Elway, interest in creatine is unlikely to wane. Everyday, more people are considering creatine for its purported benefits, and many will turn to their community pharmacist for advice.

The key player who discovered creatine was the French scientist Chevreul, who, in 1832 stumbled upon a new ingredient of animal meat to which he gave the name creatine. Chevreul’s findings were confirmed by the German scientist Justus von Liebig who reiterated that creatine is a regular constituent of flesh. Creatine levels in wild animals were 10 times greater than that of captive animals suggesting that physical activity might have an influence on the amount of creatine present in flesh. The general conclusion was that creatine levels were influenced by muscle exercise. “A meat extract (Liebig’s Fleischextrait) was the only source for creatine supplementation over the next
century. Anecdotal reports in the early 1990’s suggested that creatine supplementation might improve sport performance.¹

“Today, creatine is one of the best-studied supplements in the field of sports nutrition and its proven efficacy as an ergogenic substance was reviewed and accepted by numerous authorities.”² 20-30 g of creatine per day for several days is a common modus operandi that can indeed induce an increase in human skeletal muscle total creatine and phosphorylcreatine. Nowadays, creatine supplements are used worldwide by healthy individuals as well as athletes to increase their maximal performance and to gain better adaptations during intense training sessions.

Creatine is a naturally occurring nitrogen compound synthesized from the amino acids arginine, glycine and methionine which are mainly located in skeletal muscle followed by cardiac and smooth muscle, brain, kidney and spermatozoa. “Creatine Monohydrate is a white, odourless crystalline powder, clear and colourless in solution.”² Creatine is synthesized in the liver by methylation of guanidinoacetate using SAM as the methyl donor. Guanidinoacetate itself is formed in the kidney from the amino acids arginine and glycine.¹

Figure 1

---

¹ From: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2077460/>
² From: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4677938/>
Creatine is used as a storage form of high energy phosphate. The phosphate of ATP is transferred to creatine, generating creatine phosphate, through the action of creatine kinase. The reaction is reversible such that when energy demand is high (e.g. during muscle exertion) creatine phosphate donates its phosphate to ADP to yield ATP. Both creatine and creatine phosphate are found in muscle, brain and blood. “Creatinine is formed in muscle from creatine phosphate by a nonenzymatic dehydration and loss of phosphate.” The amount of creatinine produced is related to muscle mass and remains remarkably constant from day to day. Creatinine is excreted by the kidneys and the level of excretion (creatinine clearance rate) is a measure of renal function.

Creatine is an essential player in one of the three primary energy systems used for muscle contraction. When your muscles contract, the initial fuel for this movement is a compound called ATP (adenosine triphosphate). The body uses creatine in its process of naturally replenishing ATP. When you exercise or tense a muscle, force is produced. That force is translated into a muscle contraction. In order for the muscle to function properly, it requires energy. The energy it uses comes from several different sources, but the primary source comes from the nutrients that you obtain from your diet. These nutrients are then broken down & absorbed; they will then continue on in the system for usage.

ATP provides its energy by releasing one of its phosphate molecules. “Its phosphorylated form plays a pivotal role in energy metabolism by supplying phosphate group ADP to regenerate ATP.” It then becomes a different compound called ADP (adenosine diphosphate). When this process of ATP being broken down into ADP, energy is released and used by the contracting muscles. Without this in sufficient amounts, your muscle would not be able to work or perform properly. The body naturally produces creatine (about 2 grams per day).

Muscle can only store so much ATP, typically only giving about 5-10 seconds of muscle exertion before those storage receptors are depleted. This results in muscle failure along with bio energetic depletion or ATP depletion. When this happens, your body tries to restore its immediate source of ATP by borrowing a high energy phosphate from a chemical called creatine phosphate (CP). Muscle cells store the chemical CP in the same way it stores ATP. If high intensity exercise goes beyond 10 seconds, your body will continue to try and restore its ATP levels by a process called glycolysis. This process is complicated and is a slow method of restoring ATP levels, especially for the anaerobic athletes who require instant energy to maintain and sustain high-powered muscle contractions.

By orally supplementing with creatine, you can enhance your body’s storage levels of CP. As the muscle runs out of ATP it can recharge itself by borrowing this CP phosphate molecule. Research has shown that “by supplementing with 5 grams of creatine, 4-6 times a day, for 2 or more days, the human body showed a significant increase in total creatine concentration.”

The phosphate group in creatine phosphate is attached by a "high-energy" bond like that in ATP. “Creatine phosphate derives its high-energy phosphate from ATP and can donate it back to ADP to form ATP.”

\[
\text{creatinine phosphate + ADP } \leftrightarrow \text{ creatine + ATP}
\]
"The pool of creatine phosphate in the fiber is about 10 times larger than that of ATP and thus serves as a modest reservoir of ATP."\(^4\)

Six subjects performing 5 sets of 30 maximal contractions with one-minute recovery periods had greater peak muscle torque production in the final 10 contractions of set 1, throughout sets 2 to 4, and during the middle ten contractions of set 5 after creatine monohydrate supplementation for 5 days, compared to baseline performance and to six subjects taking placebos. "They also had lower plasma ammonia accumulation, supporting the hypothesis of improved ATP replacement."\(^5\) No difference was seen in blood lactate levels. The body shows an adaptive response, building creatine stores in the muscles more rapidly when subjected to at least an hour a day of intense exercise along with frequent creatine-loading. "One hour of hard exercise per day using one leg augmented the increase in total creatine content of the exercised leg, but had no effect on the collateral."\(^5\)

There are three basic types of creatine supplements - creatine monohydrate, creatine phosphate and creatine citrate. Creatine Monohydrate is basically creatine bound with water. "Each molecule of creatine monohydrate is made up of 88% creatine and 12% water."\(^6\) This means that if one takes 5 grams of creatine monohydrate one will really be putting 4.40 grams (5 * .88) of creatine in the body. "Creatine Monohydrate is by far the most common form for a creatine supplement."\(^6\) The majority of studies and research have been conducted using creatine monohydrate.

In order for creatine to be effective it needs to bond with a phosphate group and become creatine phosphate. For this reason, one may think that directly taking creatine phosphate would be better than just taking creatine Monohydrate. The fact is - taking a creatine phosphate supplement has never been shown to be more effective than just taking creatine monohydrate. "Creatine phosphate has only 62.3% creatine and 37.7%
phosphate.” In addition, creatine phosphate is more expensive than creatine monohydrate.

Creatine citrate became popular because it is more water soluble than other forms of creatine. The problem is that creatine citrate has only 400 milligrams of creatine per gram of creatine citrate. In addition, it is more expensive than creatine monohydrate.

Here is the yield of “free” creatine if one takes 5 grams of each creatine supplement:
- creatine monohydrate yields 4.40 grams of creatine
- creatine phosphate yields 3.12 grams of creatine
- creatine citrate yields 2 grams of creatine

Getting the most creatine into one’s body is not necessarily the end of the story. How the creatine is absorbed plays a key rule. “People who defend creatine citrate claim that it has a 90% absorption rate while creatine monohydrate has only a 40% rate.” This means that while creatine citrate delivers less creatine per gram - a much higher percentage is absorbed by the muscles.

When one takes creatine in powder form - it stays in the blood stream for about 1 - 1.5 hours. For muscle growth the creatine must be absorbed into the muscles. So, if working out and the creatine supply in the muscles is depleted AND there is creatine available in the blood stream, the muscles can replenish their creatine supply from the creatine in the blood.

The important point is if the muscles are fully saturated with creatine and one is not working out (so the creatine stores are not depleted) then after 1.5 hours the creatine in the blood will be converted into creatinine and excreted.

Usually, the use of creatine is split into a loading and maintenance phase. During the loading phase, large quantities of creatine monohydrate are taken. Because the creatine only slowly disappears from the body, a maintenance phase in which less creatine is taken will still provide the body with adequate levels of creatine.

It is discouraged to use caffeine while on creatine; while creatine makes your muscles hold water, caffeine will do the opposite, thereby reducing the effects of the creatine intake.

It is not recommended to mix creatine with citrus juice. Orange, grapefruit, cranberry, in fact, most fruit juices have been most recently found to neutralize the activity of creatine monohydrate. The reason is the waste product creatinine develops. Some put creatine on their tongue and drink it down with grapefruit juice. One is not getting creatine, but waste product.

It is suggested to mix creatine monohydrate with warm water—in a glass. This is the only way to ensure one is getting the full benefits of creatine in its dry form. Creatine does not have to dissolve to be effective.

Do be sure to drink a full eight ounce glass of good water 8 times a day. “Creatine pulls water from other parts of the body to perform its work in cell volumization of the muscle.” This is what makes the muscle larger and firmer.
Creatine (creatine monohydrate) dosage derived from works by Pierre Dahl (nutritionist at NSTC in Stockholm, Sweden) and professor Hultman (at Huddling Hospital in Stockholm, Sweden). (8)

Table 1

Recommendations:

<table>
<thead>
<tr>
<th>Bodyweight</th>
<th>Phase 1 (loading)</th>
<th>Phase 2 (maintenance)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>days 1-4</td>
<td>days 5 and on</td>
</tr>
<tr>
<td>65-74kg</td>
<td>10g per day</td>
<td>3g per day</td>
</tr>
<tr>
<td>143-163lbs</td>
<td>(2x5g per day)</td>
<td></td>
</tr>
<tr>
<td>75-84kg</td>
<td>15g per day</td>
<td>4g per day</td>
</tr>
<tr>
<td>165-185lbs</td>
<td>(2x7.5g per day)</td>
<td></td>
</tr>
<tr>
<td>85-95kg</td>
<td>20g per day</td>
<td>5g per day</td>
</tr>
<tr>
<td>187-209lbs</td>
<td>(2x10 per day)</td>
<td></td>
</tr>
</tbody>
</table>

In the 1990's chemical synthesis became more efficient and two methods starting from different starting materials have been established in the large-scale industrial production. “Degussa developed and patented the so-called 'cyanamide' route (cf. US 5,719,319) guaranteeing highest quality, purity and safety.” (8)

\[
\text{H}_2\text{N}^-\text{CN} + \text{H}_2\text{C}^-\text{N}^-\text{CO} \rightarrow \text{HN}^-\text{N}^-\text{CH}_{3}^+ \text{O}^-\text{H}_2\text{O}
\]

Glycine

Sarcosine

Creatine Monohydrate

“The reaction conditions as well as the treatment of the crude creatine monohydrate are crucial for the quality of the product. Cheaper production costs can be achieved by increasing the amount of potential impurities such as Dicyandiamide (dimerization of Cyanamide), Creatinine (Cyclization of creatine) and Dihydrotriazines therefore potentially reducing the safety of the product.” (8)

\[
\text{H}_2\text{N}^-\text{NH} \quad \text{NC}^-\text{NH}_2
\]

Dicyandiamide

\[
\text{O}^-\text{N}^-\text{NH} \quad \text{N}^-\text{CH}_3
\]

Dihydrotiazine

\[
\text{H}_2\text{N}^-\text{NH} \quad \text{O}^-\text{N}^-\text{NH} \quad \text{N}^-\text{CH}_3
\]

Creatinine

Modern analytical methods can detect impurities in creatine products in the parts per million (ppm) range. "HPLC analytics can quantify impurities at 13 ppm for Dicyandiamide (DCD), 67 ppm for Creatinine and 15 ppm for Dihydrotiazine. Amounts
as low as 4 ppm DCD, 20 ppm Creatinine and 4.5 ppm Dihydrotriazine are detectable.⁸

Publications on available products on the market showed huge differences in the
quality of creatine products of different manufactures and of end-consumer products. No
impurities could be detected in products from the German manufacturer (Degussa,
formally SKW, is the only German producer). In certain products, single impurities of
more than 5% could be detected, raising questions on the short and especially long-term
safety of such products.

Figure 3

[Diagram showing Creapure and selected competitor products with data on creatine,
DCD, and Dihydrotriazine concentrations]

Alternative production methods using thiourea as starting material is adding
additional health concerns. Worldwide authorities warn about potential health risks
resulting from the presence impurities in Dietary Supplements and in creatine
monohydrate products (e.g. Report of the Scientific Committee on Food (SCF), Opinion
on safety aspects of creatine supplementation (adopted by the SCF on 7 September 2000).

Degussa’s Creapure has the strictest specification on potential impurities in
creatine monohydrate. Dihydrotriazine, potentially the most harmful impurity, is not
detectable in Creapure at all.

All raw materials used in the production of Creapure are subject to in-house
specification procedures. Each produced batch is tested for potential impurities such as
cyanamide, diacerylamide and dihydrotriazine. A quality control procedure independent
of production and certified under GLP (Good Laboratory Practice) regulations is used to
test the lots produced and monitor release of the product for dispatch.

“There have been hundreds of studies done on creatine that all show that it is a
safe supplement.”⁸ There are really very few side effects reported with creatine use but
they include: upset stomach, muscle cramping, diarrhea and dehydration. Most of these
side effects can be minimized by drinking plenty of water when taking creatine. In
addition, people tend to have more side effects when taking the powder as opposed to a
more direct delivery method like serum or effervescent powder.

It is important to understand that creatine does not affect ones hormone levels.
This means that one does not get side effects like bad skin and mood swings. It is also
important to note that everyone is different. While 95% of the people may have no
problems with creatine - it may just really bother ones stomach. In the end if one finds
that creatine causes problems then it makes sense not to take it.
Many scientists agree that when taken within normal dosage, creatine in theory should pose no long term health risks. On the other hand, other people like to have data saying that it has been tested over a long period before they will say it is safe. They will point to the fact that no study has studied creatine use for over 3 months.

On November 12, 1999 at the 19th Annual Southwest American College of Sports Medicine Meeting, two long term creatine studies were presented from the Exercise & Sport Nutrition Lab at the University of Memphis. Both studies showed that "9 months of creatine supplementation (taking an average of 5 grams per day) in athletes had no negative effects on markers of renal function or muscle and liver enzymes in comparison to athletes not taking creatine."9

It has been suggested that "a long-term, nitrogen-rich diet might itself induce renal hyper filtration and thereby contribute to the functional and structural deterioration of the kidney."10 Theoretically, the high nitrogen content (32%) of creatine could add some strain on the kidney if taken in large excess for a long period of time.

Nine highly trained athletes consumed regularly creatine monohydrate of different origins (organic synthesis). The powder was diluted in hot water. Individual doses from 1 to 20 g creatine were taken up to 1 to 4 doses per day. Side effects were almost absent but muscle cramps (one subject) and headache (one subject) were occasionally reported. "However, we do not have evidence that these slight side effects were really related to creatine supplementation."9

"Very recently, Pritchard and Kalra have proposed that oral creatine supplementation will lead to renal dysfunction."10 Indeed, these authors reported that their one subject, who had glomerulonephritis with tubular damage for 8 years, being treated with the nephrotoxic cyclosporin drug for the past 5 years, had substantial renal dysfunction after consuming creatine for 7 weeks. This report and the widespread use of this ergogenic product among athletes meant that the safety of creatine use could be questioned.

Some studies have shown that creatine can help reduce your chances of heart disease and adult on-set diabetes. "It was found that after 51 days of taking creatine the study group had a 22% decrease in VLDL-cholesterol levels and a 23% decrease in blood triglyceride levels. VLDL-cholesterol and triglycerides are risk factors for heart disease and adult on-set diabetes."11

This point is made to show that as more studies are done it may be that more benefits of creatine are discovered. Studies don’t always just show negative long term effects. A classic example of this has been the recent discoveries with alcohol. New studies show that 2 drinks a day can have very beneficial effects in reducing your chance of heart disease. Of course, like creatine - if you abuse alcohol it can have negative effects.

Creatine also helps with resistance training by bloating the muscle with creatine rich fluid. This allows for greater leverage and requires the muscle to move less and lift more weight. While this may seem kind of trivial, some researchers today think that one of the stimulating factors of steroid use is water retention. Anabolic steroids may actually work in part because of cellular fluid retention in the muscles. The swelling action and the related stretching of the cells may in and of itself cause a reaction which stimulates the muscle cells to grow. So in some respects creatine might be as good as steroids.
Creatine has been used in clinical trials for several classes of neuromuscular disorder. Although not a cure per se, creatine supplementation may improve the quality of life of those afflicted with these disorders. In fact, preliminary studies have demonstrated that creatine supplementation improves strength in patients with several classes of neuromuscular disorder. Creatine has also been used postoperatively on patients recovering from orthopaedic surgery.

Creatine may be helpful for certain muscular dystrophies (facioscapulohumeral dystrophy, Becker dystrophy, Duchenne dystrophy, sarcoglycan-deficient limb girdle muscular dystrophy). “Creatine has been found to increase strength by about 10 percent in older men who took the supplement for one week.” 

Creatine has also been used postoperatively on patients recovering from orthopaedic surgery.

Creatine may be helpful for certain muscular dystrophies (facioscapulohumeral dystrophy, Becker dystrophy, Duchenne dystrophy, sarcoglycan-deficient limb girdle muscular dystrophy). “Creatine has been found to increase strength by about 10 percent in older men who took the supplement for one week.” 

Creatine helped these older men in their daily activities such as getting out of a chair.

Liver and kidney damage can be a problem if creatine is abused. Any creatine your body does not use is excreted as a waste product called creatinine. If you take 20 grams a day of creatine - your body will not be able to use most of it and will have to excrete the excess. Over time this constant excretion of creatinine can put a lot of work on your kidneys and liver. If you force them to work to hard that can lead to serious problems.

Some common side effects and cautions of creatine would include: Nausea, stomach upset, dizziness or weakness, loose stools, diarrhea, and weight gain are the most common, and generally occur with dosages greater than 5 grams a day. Muscle cramping is also reported. Strains and sprains can occur (perhaps even muscle tears) when individuals over enthusiastically and rapidly increase their workout regimen before their tendons and ligaments have adapted to the increase in muscle size and power. “Long term consequences of daily creatine ingestion, especially in high dosages, are currently not known.” There is a possibility that excess creatine can put stress on the kidneys and liver.

Creatine converts into creatinine which, in high dosages, could act as a toxin. “Whether there is a potential for increasing the risk of cancer with regular high dose use is currently not known.” Individuals with kidney disease should not use creatine. A few anecdotes stated that high doses of creatine may cause anxiety or depression. There are no reports to date that creatine influences the size of genital organs or has a significant effect, positive or negative, on sex drive. Creatine does not seem to have a direct effect on libido, although feeling good about one’s toned body could influence self-image and how others react to us and make us feel more attractive and sexual. The influence of creatine on sperm count or motility, if any, is not known at this time. Short term creatine supplementation does not seem to affect blood pressure, heart rate, or kidney function. A small to modest amount of alcohol intake should not interfere with low dose creatine use. It wouldn’t be wise taking creatine while pregnant. There are no reports of creatine having an influence on hair loss.
Although many trials have studied the effects of creatine, high-quality research is lacking. Studies have employed very small sample sizes and produced variable results. Furthermore, the results observed in highly trained athletes cannot necessarily be extrapolated to the general public. It is also not clear whether individual variations in baseline creatine levels affect the efficacy of supplementation. Drug interactions with most supplements, including creatine, have not been studied.

Commercially marketed creatine supplements do not meet the same rigid quality control standards as pharmaceuticals, because they follow looser DSHEA rules. Therefore, it is difficult to apply efficacy and safety results from published trials to general practice. The dose delivered by a commercially available product may be more or less than that suggested by the labelling. This could influence the effectiveness of creatine. The lack of adequate quality control could result in impurities in creatine supplements, which could lead to unexpected adverse effects.

Although creatine is becoming increasingly popular, the evidence of its benefits is limited at best. Based on its mechanism of action, creatine may possibly enhance the performance of high-intensity, short-duration exercise such as sprinting or power-lifting, but that benefits have not been proven in the clinical trials to date. Patients engaged in endurance sports should know that there are few data supporting creatine use for lower-intensity, longer-duration exercises, and that the weight gain associated with creatine supplementation may be detrimental to their performance. Because of the potential risks and the questionable benefits, pharmacists should warn patients with renal dysfunction to avoid creatine supplements. If consumers choose to use creatine supplements, they should be counselled on the variable efficacy data and the unknown risks of toxicity.
Bibliography

   Creighton University. 19 Mar. 2004
   <http://altmed.creighton.edu/creatine/background.htm>

   University of Brescia IU School of Medicine. 20 Mar. 2004
   <http://www.med.unibs.it/-marchesi/aminoacidderivatives.html>

   Leiden University. 19 Mar. 2004
   <http://www.bla.net/opul/crfac.htm>

   George Washington University. 19 Mar. 2004

   Official Journal of the American College of Sports Medicine. 30 (05/98): S126

   Absolute Creatine LLC.
   <http://www.absolute-creatine.com/2.htm>

7. Nissen, Steven. “Effect of dietary supplements on lean mass and strength gains with
   resistance exercise: a meta-analysis.” Journal of Applied Physiology. 1 (02/03): 651-659

   Washington University. 19 Mar. 2004
   <http://www.creatapure.de/bioactives/html/e/products/brands/creatapure/history.htm>

   function in healthy athletes.” Official Journals of the American College of Sports
   Medicine. 31 (08/99): 1108-1110


    supplementation protect against neurological and atherosclerotic disease.” International
    Journal of Sports Medicine. 22 (01/01): 76-80
Latest Treatment for IBS Patients

Heather Madden

April 16, 2004
Latest Treatment for IBS Patients

Are you experiencing abdominal pain or discomfort? Are you bloated, have recurring constipation? Then you may be one of the many, (as much as 6 million) women that suffer from *Irritable Bowel Syndrome with Constipation (IBS)*. About 5% of women in the United States suffer from IBS. It is characterized by these recurring symptoms over time – the “ABCs”:

- Abdominal discomfort/pain
- Bloating
- Constipation

It is not clear why some people develop IBS and have been told their symptoms were merely a result of stress or something they ate. When, undoubtedly, it may be that your gastrointestinal tract (GI) might be more sensitive and happens to work at a slower rate than it should. IBS is a chronic condition and without proper treatment, it could cause great deal of discomfort and distress.\(^1\)

Patients suffering from IBS, now have somewhere to turn to for temporary relief from many of their life altering symptoms. IBS patients tend to endure symptoms that consist of constipation, bloating, abdominal pain, hard bowel movements, etc. A new treatment for IBS is available today, Tegaserod maleate, prescribed under the brand name Zelnorm\(^6\), is the first, and only, to be approved to relieve all three symptoms of IBS by the Food and Drug Administration (FDA). It was released as of July 2002 to the public by Novartis Pharmaceuticals, for those patients suffering from abdominal discomfort caused by constipation as their main symptom. Zelnorm\(^6\) is only able to provide short term treatment. It does not cure IBS and does not treat diarrhea-predominant IBS \(^2\). In brief, Zelnorm\(^6\) assists in the movement of stools through the bowels by selectively activating 5HT4 receptors present throughout the GI tract, to help coordinate the nerves, muscles, and fluid, so that it can begin to function properly.\(^1\)\(^1\)\(^0\).

Tegaserod as the maleate salt is a white to off-white crystalline powder, which has a molecular weight of 417.47, an empirical formula of C\(_{16}\)H\(_{23}\)N\(_3\)O\(_5\)C\(_4\)F\(_4\)O\(_4\), and is chemically designed as 3-(5-methoxy-1H-indol-3-ylmethylene)-N-pentylcarbazimidamide hydrogen maleate. The structural formula is

![Structural formula of Tegaserod](image-url)
Tegaserod maleate weighs 1.385 mg and is equivalent to 1 mg of tegaserod. It is only slightly soluble in ethanol and even less soluble in water.

Patients who have IBS tend to have altered motor and sensory functions of the gut. The enteric nervous system, which works to assimilate and process information in the intestines, and the 5-hydroxytryptamine (5-HT, serotonin) are thought to be key elements in the origin of IBS. Serotonin, an amine that is formed from amino acid 5-hydroxytryptophan, in the EC and in other similar cells called enterochromaffin-like cells (ECL). These cells also secrete histamine and kinins, which likewise have important messenger functions in glandular secretions and on blood vessels. Serotonin acts in paracrine fashion. Both EC and ECL cells are widely distributed in the GI tract. Serotonin receptors activate calcium and potassium channels through linking proteins and the cAMP second-messenger systems. After acting on the postsynaptic receptors, the neurotransmitters are taken up by the presynaptic terminal and enzymatically degraded. Almost all of the body’s serotonin (95%) is stored in the enterochromaffin cells (EC) of the gastrointestinal tract and also in the enteric nerves acting as neurotransmitters. In particular, the serotonin 5HT4 receptors serve an important role in the maintenance of gastrointestinal function. Tegaserod is a 5-HT4 receptor partial agonist that binds with high affinity at human 5-HT4 receptors, whereas it has no appreciable affinity for 5-HT3 or dopamine receptors. It does have a moderate affinity for 5-HT1 receptors though. Tegaserod, by acting as an agonist at neuronal 5-HT4 receptors triggers the release of further neurotransmitters such as calcitonin gene-related peptide from sensory neurons. The activation of 5-HT4 receptors in the GI tract stimulates the peristaltic reflex and intestinal secretion, as well as inhibits visceral sensitivity.

Tegaserod is more or less 98% bound to plasma proteins, mainly alpha-1-acid glycoprotein. Highest plasma concentration is reached approximately 1 hour after oral dosing. When administered to fasting subjects, the absolute bioavailability of tegaserod is approximately 10%. When dispensed with food, the bioavailability is reduced by 40%-65% with a concentration max (Cmax) of about 20%-40%. Subjects who administered tegaserod either 30 minutes prior to or 2.5 hours after a meal have similar reductions in their plasma concentration. When administered after a meal the time max (Tmax) is prolonged to approximately 1 to 2 hours, but decreases T_max when taken 30 minutes prior to a meal. Following intravenous dosing, tegaserod displays evident distribution into tissues at a volume of 368, plus or minus, 223 L.

There are two pathways in which the metabolism of tegaserod takes place. The first way is done in the stomach by a presystemic acid catalyzed hydrolysis followed by oxidation and conjugation which produces the main metabolite of tegaserod, 5-methoxyindole-3-carboxylic acid glucuronide. The main metabolite has insignificant affinity for 5HT4 receptors in vitro. In humans, systemic exposure to tegaserod was not altered at neutral gastric pH values. The second way the body metabolizes tegaserod is by direct glucuronidation which leads to generation of three isomeric N-glucuronides. The amount of tegaserod being excreted out of plasma is 77, give or take, 15 L/h with an estimated half life (T1/2) of 11, plus or minus, 5 hours following that of intravenous dosing. Surprisingly, about two-thirds of the oral dosage of tegaserod is excreted.
unchanged in the feces, while only one-third is excreted in the urine, primarily as the main metabolite (4).

Clinical studies were performed on 2,470 women with IBS and were other wide healthy patients for 16 weeks in three multicenters. These women ranged in ages between 17-89, with the average age being 43 years old. Of this sampling, 86% of the women were of Caucasian decent, 10% were of African American decent and the remaining 4% were of mixed nationalities. In order to have been accepted as test patients, they had to have been experiencing IBS symptoms consecutively for at least three month prior to the treatment period of tegaserod, and were experiencing at least two of the three constipation symptoms, each occurring at least 25% of the time over a 3 month period: 1) less than 3 bowl movements per week, 2) hard or lumpy stools, or 3) straining with a bowel movement (4).

The study began with a four week baseline, or “wash-out”, placebo-free period. During which, patients are drug free from all drugs whether it be prescription or over the counter. The four week study was then followed by a twelve week double blind study. Two studies were fixed dose and the third used a dose-titration study. Those in the fixed dosed studies received 6mg of Zelnorm® twice daily. The drugs effectiveness was based on patients’ ratings on their intensity and relief of symptoms. Those treated with Zelnorm® had positive outcomes, reporting a greater relief from symptoms and a higher frequency of bowel movements. Their greatest difference was experienced within the first four weeks of treatment.

Once per week during the 4 week baseline period and during the 12 week double-blind treatment period, patient’s were asked, “Please consider how you felt the past week in regard to your IBS, in particular your overall well-being, and symptoms of abdominal discomfort, pain and altered bowel habit. Compared to the way you usually felt before entering the study, how would you rate your relief of symptoms during the past week?” The response variable consisted of the following 5 categories: completely relieved, considerably relieved, somewhat relieved, unchanged, or worse (5). Those who were considerably or completely relieved within a month, for two of the four weeks or relieved to some extent for each of the four weeks were categorized as “responders”.

These responses are calculated below for the first and third month. As one can see, there was a greater difference in response to the Zelnorm® from the placebo in the first month than in the third month (4).
<table>
<thead>
<tr>
<th>Study</th>
<th>Zelnorm™ 6 mg bid</th>
<th>Placebo</th>
<th>Difference</th>
<th>Zelnorm™ 6 mg bid</th>
<th>Placebo</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Proportion of</td>
<td></td>
<td>(95%</td>
<td>Proportion of</td>
<td></td>
<td>(95%</td>
</tr>
<tr>
<td></td>
<td>responders</td>
<td></td>
<td>Confidence</td>
<td>responders</td>
<td></td>
<td>Confidence</td>
</tr>
<tr>
<td>1</td>
<td>76/244 (31%)</td>
<td>42/240</td>
<td>(6% to 21%)</td>
<td>95/244 (39%)</td>
<td>66/240</td>
<td>(3% to 20%)</td>
</tr>
<tr>
<td>2</td>
<td>265/767 (35%)</td>
<td>164/752</td>
<td>(8% to 17%)</td>
<td>334/767 (44%)</td>
<td>202/752</td>
<td>(9% to 16%)</td>
</tr>
<tr>
<td>3</td>
<td>80/233 (34%)</td>
<td>47/234</td>
<td>(6% to 22%)</td>
<td>100/233 (43%)</td>
<td>88/234</td>
<td>(14% to 14%)</td>
</tr>
</tbody>
</table>

The analyses from the responders based on the weekly questionnaire are graphed below over studies 1, 2, and 3.

Besides the weekly observations, they also constructed daily assessments concerning individual's daily symptoms dealing with abdominal pain and/or discomfort and bloating based on a 6 or 7 point scale of intensity. Each positive response was defined as a point reduction in the scale.

Their studies also showed that patients taking Zelnorm™ in the first four weeks of the fixed dose treatment had 8%-11% more responders than that of the placebo patients for abdominal pain and discomfort, while, 9%-12% more patients on Zelnorm™ found relief from bloating. Whereas, in month three, only 1%-10% showed relief from abdominal pain and discomfort and only 4%-11% for bloating. Other research determined that patients were also having an increase of bowel movements. The initial average number of stools per week during the baseline period was about 3.8. In the first month of testing, the average number of stools per person was about 6.3 per week, and then by month three, the average decreased to about 6 per week. Those patients taking the placebo were initially passing bowel movements about 4 times per week, then increased to 5.1 stools per week in the first month and then 5.5 per week by the third month. For those
patients in the titration study, they were given anywhere from 2mg to as much as 12 mg of Zelnorm® twice daily. In this study, they found that Zelnorm® has no significant effect on IBS beyond the recommended dose of 6mg given twice daily. In greater dosages, patients merely had added headaches and increased diarrhea. Zelnorm® has not been tested for effectiveness past a twelve week time period (4).

Patients suffering from mild to moderate renal (kidney) impairment are able to take recommended dosages of Zelnorm®, but for those with severe renal impairment, Zelnorm® is not suggested. The same is understood for patients with mild hepatic (liver) impairment, but should be taken with caution. Patients with moderate to severe hepatic impairment have not yet been passably studied, therefore taking Zelnorm® is not recommended.

The studies have also found that there has been no effect on the pharmacokinetics of tegaserod due to gender. Their understandings of the effects due to race are still inconclusive at this time. Age, on the other hand, does seem to play a minor role in the absorption of tegaserod into the plasma. Test results have shown that healthy, elderly (65-85 years) individuals seem to endure 22% and 40% greater peak plasma concentrations and exposure than subjects that range from 18-40 years of age, but still within the variability. Therefore, dosage standards are based by weight rather than age to accommodate each individual’s needs. A study was also performed on the male population, but due to the insignificant size of the sampling, the FDA ruled out the results until a larger population has been adequately tested. For that reason, Zelnorm® has not be determined as to the how safe or effective it is in men. It has also not been tested effectively in pediatric patients either, thus, Zelnorm® is not prescribed to those below the age of 18. They also urge patients that plan to become or are already pregnant not to take Zelnorm®, even though the pregnancy risk category is only B. Do not breast feed while taking Zelnorm®, for it is likely to be excreted.

Zelnorm® is also not for patients suffering from severe renal impairment, moderate to severe hepatic impairment, have a history of bowel obstruction, systematic gall bladder disease, suspected sphincter of Oddi dysfunction, abdominal adhesions, and/ or known hypersensitivity to the tegaserod or any of its excipients (3). Zelnorm® is also not intended for those who are already experiencing recurrent diarrhea. Patient’s should also discontinue the use of Zelnorm® immediately if they experience new or worsening abdominal pain and should communicate with their physician if frequent diarrhea persists after the first week of taking Zelnorm®, especially if accompanied by cramping or dizziness (4).

For best results, patients should ingest Zelnorm® 30 minutes prior to a meal, and be aware that possible episodes of diarrhea may occur during therapy. The majority of patients only endured one episode of diarrhea during therapy and in most cases it happened during the first week and was resolved with the continuation of therapy (4). In vivo studies, when dextromethorphan and theophylline were given in collaboration with tegaserod, the two did not affect the pharmacokinetics of either compound, therefore had no clinically relevant drug-drug interactions with those drugs metabolized by CYP2D6.
(fluoxetine, omeprazole, captopril) or CYP1A2 (estradiol, omeprazole). When digoxin is co-administered with tegaserod, there is a reduction in the peak plasma concentration and exposure of digoxin by approximately 15%, but the bioavailability is not enough to make dose adjustments. The pharmacokinetic and pharmacodynamic interaction study with warfarin demonstrated no effect when simultaneously administered with tegaserod. Oral contraceptives, when administered along with tegaserod, only reduced the peak concentrations and exposure of levonorgestrel by 8% and are not expected to alter the risk of ovulation. Therefore it is also safe to take with tegaserod. The main metabolite of tegaserod hydrogen maleate in humans is, 5-methoxyindole-3-carboxylic acid glucuronide, which at this time, does not seem to inhibit any of the following P450 isoenzymes; CYP2C8, CYP2C9, CYP2C19, CYP2E1 and CYP3A4 in vitro tests.

The most common side effects that occurred in the test patients taking Zelnorm® consist of, but are not limited to; abdominal pain, diarrhea, nausea, flatulence, headache, dizziness, back pain, and influenza-like symptoms.

Further statistics were calculated from a third phase of clinical trials that consisted of 2,632 patients in which adverse reactions were being studied. These adverse events occurred in at least 1% of IBS patients and occurred more frequently for those on Zelnorm® than those on the placebo.

<table>
<thead>
<tr>
<th>System/Adverse Experience</th>
<th>Zelnorm® 6 mg b.i.d. (n=1,327)</th>
<th>Placebo (n=1,305)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gastrointestinal system disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>12%</td>
<td>11%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>9%</td>
<td>4%</td>
</tr>
<tr>
<td>Nausea</td>
<td>8%</td>
<td>7%</td>
</tr>
<tr>
<td>Flatulence</td>
<td>6%</td>
<td>8%</td>
</tr>
<tr>
<td><strong>Central and peripheral nervous system</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>15%</td>
<td>12%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>4%</td>
<td>3%</td>
</tr>
<tr>
<td>Migraine</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td><strong>Body as a whole —General disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Accidental trauma</td>
<td>3%</td>
<td>2%</td>
</tr>
<tr>
<td>Leg pain</td>
<td>1%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td><strong>Musculoskeletal system disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Back pain</td>
<td>9%</td>
<td>4%</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>2%</td>
<td>1%</td>
</tr>
</tbody>
</table>

A minute number of patients were reported as having abdominal surgeries while being on the treatment of Zelnorm®, but that study is still inconclusive, since some were reported as having the same surgery while taking the placebo. Most of the surgeries were found to have been mainly correlated to the gallbladder. Gallbladder surgery is more pronounced in patients with IBS than that of the general population. Hence, it has not been determined whether or not the treatment of Zelnorm® will increase the chance of having abdominal surgery.
A list of adverse reactions was prepared relating to the possibility that the symptoms below could be related to Zelnorm®. These symptoms were present in at least two patients in the phase three clinical trials and happened to occur more often in Zelnorm® patients than those on the placebo (4).

**Adverse Reactions/ Symptoms**

**Body as a Whole:** pain, flushing, facial edema  
**Cardiovascular:** hypotension, angina pectoris, syncope, arrhythmia, bundle branch block, supraventricular tachycardia (“Zelnorm® did not adversely affect cardiac function in more than 2500 patients”) (7).  
**Central Nervous System:** vertigo  
**Female Reproductive:** ovarian cyst, miscarriage, menorrhagia  
**Gastrointestinal:** irritable colon, fecal incontinence, tenesmus, increased appetite, eructation, increased SGOT, increased SGPT, bilirubinemia, cholecystitis, appendicitis, subileus  
**Metabolic:** increased creatine phosphokinase  
**Musculoskeletal:** back pain, cramps, arthopathy, accidental injury  
**Neoplasms:** breast carcinoma  
**Psychiatric:** attempted suicide, impaired concentration, emotional lability, increased appetite, sleep disorder, depression  
**Respiratory:** asthma  
**Skin:** pruritus, increased sweating  
**Urinary:** albuminuria, frequent micturition, polyuria, renal pain  
**Other:** leg pain, suspected sphincter of Oddi spasm, bile duct stone, and cholecystitis with elevated transaminases  

*Reactions may be common, uncommon, life-threatening, or COMMON and LIFE-THREATENING*

At this point in time there have yet to be any reports of someone overdosing on Zelnorm®. During studies, three volunteers received a single dose of 120 mg, 10 times the approved dosage, and were found to be experiencing diarrhea and headaches. Two of the three volunteers admitted to having intermittent abdominal pain and only one of the three volunteers stated that they had obtained orthostatic hypotension. Another study group of 28 individuals were exposed to 90-180 mg per day for several days and found that 100% of them encountered diarrhea, 57% headache, 18% abdominal pain, 18% flatulence, 7% nausea, and 7% vomiting (4).

Zelnorm® is supplied in two strengths of blister packs (unit dose), both containing a quantity of 60 tablets. The lowest strength comes in 2 mg with engravings that read “NVR” and “DL”. The greater dose is 6 mg with the engravings as follows, “NVR” and “EH”. The tablets are a slight whitish marbled color, circular, with beveled sides.

As a result from all the clinical studies performed to this date, they have found that the optimum dosing should be 3 mg taken twice daily on an empty stomach preceding meals for 4-6 weeks, and for those who seem to be responding to the medication by increasing the movement of stools and decreasing abdominal pain and discomfort may continue
therapy for an additional 4-6 weeks. If you miss a dose of Zelnorm®, just skip that day's dose and continue as normal the following day. Do not take two pills at one time. When Zelnorm® was tested at higher strengths, it was found to only increase the adverse effects, rather than a higher plasma concentration. It has also been stated by those at Novartis that “based on the large distribution volume and high protein binding of tegaserod it is unlikely that tegaserod could be removed by dialysis.”

Zelnorm® has not been proven to work in all women and still needs necessary studies as to how it will work in men. Further testing is also necessary to determine the effects of Zelnorm® on the GI tract and plasma concentration when taken longer than the recommended 12 week period. From the manufacturer’s standpoint, “once the twelve week period has ended, the body’s tract should be able to continue working properly since it has been “trained” for the past 12 weeks.” But no tests have been done to prove this notion, so symptoms may return within 1-2 weeks after discontinuing therapy. The final conclusion from these studies shows that in certain cases the treatment is worse than the initial symptoms, but overall, the majority of women who have IBS will be able to successfully receive some form of relief from this new drug, but there is still plenty to be understood through further testing and research. As reported, “In a consensus opinion, tegaserod received the only “Grade A” recommendation for the treatment of IBS with constipation, supported by the strongest level of clinical evidence.”


Halitosis

W. Craig Milton  
Chem 236  
Organic Chemistry  
Dr. Michael Bishop
Abstract

Halitosis is a chronic disease caused by the breaking down of amino acids by certain bacteria in the oral cavity. This process releases certain toxic, and odiferous compounds. These compounds, specifically methyl mercaptan and hydrogen sulfide, are known as volatile sulfur compounds (VSCs). The current and effective treatment for halitosis is the breaking apart of these sulfur compounds with a compound known as chlorine dioxide.

Introduction

In today’s society a great emphasis is placed on a person’s image and “look.” We pride ourselves on the ability that we have to intercommunicate with other people as well as be part of the “popular” group. Bad breath is a condition that can and does change our very outlook on these relationships. If a person realizes that their breath has a “foul odor” on it, in an instant they turn bright red and turn away from any other associates with whom they may be conversing. If at all handy they immediately pop a mint, or break out the Winterfresh gum. When a piece of gum or a mint is not readily accessible many simply cover their mouths with their hands hoping to spare the innocent victim of the inevitable torture that would otherwise be inevitable. Others feel so embarrassed they immediately take flight in search of a tooth brush and mouthwash. We’re not even going to mention the thought of kissing.

Bad breath’s importance has far more impact than most people realize. Knowledge and written reference to this condition dates back to ancient cultures. A clear example comes from the Hebraic liturgics (the Talmud), dating back more than two thousand years ago, which clearly states the terms of a marriage license (the Ketuba) may be legally broken in case of malodour of one of the partners. Similar references can be found in writings from Greek, Roman, early Christian, and Islamic cultures (Sanz 2001). Though bad breath has been a common social taboo for centuries, very little about it was actually known. Approximately, thirty years ago an instrument called the osmoscope was invented. The osmoscope was developed to measure the sources of malodor. Within the last thirty years our knowledge and understanding about a problematic social taboo known as bad breath, or halitosis, have grown and expanded giving us the knowledge we have today.

Halitosis (from the Latin halitus meaning breath, and osis, meaning condition), refers to a foul, odorous smell originating in the oral cavity of the mouth. “Although several non-oral sites have been related to oral malodor, including the upper and lower respiratory tracts, the gastrointestinal tract, and some diseases involving the kidneys and liver, it is thought that around 90% of all bad breath odors emanate from the mouth itself (Sanz 2001).”

In clinical settings there are two types of halitosis. There is “genuine halitosis” and “pseudo-halitosis.” Pseudo-halitosis is where the bad breath does not actually exist. The subject merely believes that they have the bad breath. Genuine halitosis is the real thing and can be diagnosed using either organoleptic or physic-chemical means. Genuine halitosis itself is broken down into two parts, physiologic halitosis and pathologic halitosis, with pathologic halitosis being further broken down into oral and extraoral.
Physiological halitosis will be “of a temporary nature and exists when volatile odoriferous hematologically borne substances are released into the lungs from food, notably herbs, spices, curries, and selected vegetables such as onions, garlic, radishes, turnips, and leeks, or from [flavored] drinks, such as tea and coffee, and particularly those containing unique derivatives of water and alcohol soluble esters and polyphenols. These include wine, whisky, liquors, and beer. Physiological halitosis will also occur with dehydration, starvation, constipation, loose stools, or other conditions that may affect the gut, most of which are reversible (Touyz 1993).” The malodor arises through putrefactive process within the oral cavity. “Physiologic halitosis, also termed transient halitosis, has its origin in the dorsum of the tongue, is self-limited, does not prevent the patient from carrying on a normal life, and usually does not need any therapy. This situation, more commonly known as “morning breath,” is more a cosmetic problem than a health-related condition (Sanz 2001).”

Pathologic halitosis, however, is a much more severe and serious problem. It is permanent, and cannot be fixed by simple oral hygiene. It can, and often does, cause the victim to be unable to have a “normal life.” Pathological halitosis occurs by essentially the same mechanism as physiological halitosis. It comes from regional or systemic pathology, such as diabetic ketosis, (from producing acetoacetic acid, hydroxybutyric acid, acetone and other ketones), uremia, gastritis, gastric ulcer, oesophagitis, pyloric stenosis, or hepatitis (Touyz 1993).

The two subsets of pathologic halitosis simply refer to the location of the origination of the bad breath. Oral pathologic halitosis has its origin in the oral cavity and/or in the posterior dorsum of the tongue. Oral halitosis is caused by disease, pathologic condition, or a malfunction of oral tissues. Also included in this subdivision would be halitosis coming from the coating of the tongue. Extraoral halitosis constitutes any malodor that originates from the pulmonary tract or upper digestive tract, as well as any odor that comes from the nasal, perinasal, and/or laryngeal regions (Yaegaki 2006).

On the surface of the tongue live several microorganisms known as bacteria. These bacteria break down any oral debris left in the mouth, as well as blood and some oral tissues. Many of the bacteria contained in the oral cavity are meant to be there and help in the digestive process. However, thorough poor oral hygiene and such habits as smoking or the drinking of alcohol these bacteria can cause serious oral diseases. These diseases include, but are not limited to: plaque, gingivitis, periodontitis and necrosis (Touyz 1993).

When the bacteria break down the certain substances in the mouth they release certain odorous compounds known as VSCs (Volatile Sulfur Compounds). The major VSCs that contribute to halitosis are hydrogen sulfide (H₂S), methyl mercaptan (CH₃SH), and dimethyl sulfide (CH₃SCH₃) (Richter 1996). Of these hydrogen sulfide and methyl mercaptan are the predominant factors in the air of the oral cavity. “Both of these compounds are highly toxic, especially methyl mercaptan (Yoshinuma 2000). The focus of this paper will be to discuss these two compounds as well as their synthesis and treatment.

However, before we discuss the compounds themselves it is vitally important that the chemical environment be set. “Apart from the presence of gram-negative anaerobic bacteria, certain physical-chemical conditions are needed for the production of odoriferous gases. These conditions such as pH, pO₂ (oxygen level), and Eh (oxidation-
reduction potential are usually determined by the bacterial metabolism. If the main nutrient sources are carbohydrates, their fermentation shifts the environment towards an acidic pH and the VSC formation is inhibited. If, on the contrary, the main nutrient source is protein, its metabolic end products such as nitrogenous compounds (including urea, free amino acids, and amino acids) increase the pH. This neutral or Alkaline environment will favor anaerobic bacterial growth and VSC production, thereby, increasing oral malodor (Sanz 2001).

**Hydrogen Sulfide (H₂S)**

Hydrogen sulfide is also known as hydrosulfuric acid, hydrogen sulfuric acid, sulfured hydrogen, heptic gas, stink damp, sulfur hydride, sulfured hydrogen, dihydrogen monosulfide, dihydrogen sulfide, and sewer gas. Structurally it would be represented thus:

\[ H - S - H \]

Hydrogen sulfide is a colorless, flammable gas with a characteristic odor of rotten eggs. It has a molecular mass of 34.08 and its vapor pressure at 21.9°C is 1929 Pa. It is soluble in water with a water solubility of 1g per 242 ml at 20°C. Hydrogen sulfide is also soluble in alcohol, ether, gasoline, crude oil, kerosene, glycerol, and carbon disulfide.

The most common methods used to measure hydrogen sulfide are gas chromatography with flame photometric detection, gas chromatography with electrochemical detection, iodometric methods, the methylene blue colorimetric method, ion chromatography with conductivity, and potentiometric titration with a sulfide ion-selective electrode (Chou 2003).

Hydrogen sulfide is a natural compound. Natural sources account for approximately 90% of the total amount of hydrogen sulfide in the atmosphere. Hydrogen sulfide is produced through the breakdown of sulfates and sulfur containing organic compounds by non-specific and anaerobic bacteria. It is found primarily as a gas and is found naturally in volcanic gases, natural gas, crude petroleum, groundwater and hot springs. Hydrogen sulfide is emitted from stagnant or polluted waters and manure or coal pits with low oxygen content (Chou 2003).

In oral halitosis it has been noted that hydrogen sulfide is produced from the breakdown of the amino acid L-cysteine by the enzyme L-cysteine desulfhydrase, which catalyses the α, β-elimination of L-cysteine to hydrogen sulfide, pyruvate and ammonia.

\[
\text{L-cysteine} \xrightarrow{\text{L-cysteine desulfhydrase}} \text{pyruvate} + \text{H}_2\text{S} + \text{NH}_3
\]
Very little is known about the enzyme L-cysteine desulphydrase, except that it is produced by the bacteria in the oral cavity.

**Methyl Mercaptan**

Methyl mercaptan is a colorless gas with a smell like rotten cabbage. It is a natural substance found in blood, the brain, and in other tissues of human and animal bodies. It is released from animal feces. It occurs naturally in certain foods, such as cheese and nuts. It is released from the decaying organic matter in marshes and is present in the natural gas of certain regions in the United States. It can be found in coal tar and in some crude oils. It is released as a decay product of wood. Commercially, it is manufactured for use in the plastics industry and in pesticides. Methyl mercaptan has been used in organic synthesis and is an intermediate for jet fuel additives, fungicides, and methionine.

Methyl mercaptan is easily ignited. When heated to decomposition, it emits highly toxic fumes, and flammable vapors. Vapors from liquefied methyl mercaptan gas are heavier than air and may collect in low lying areas. Methyl mercaptan is a highly irritant substance when it comes in contact with moist tissues such as the skin, the upper respiratory tract and the eyes. If exposure is significant methyl mercaptan can cause headache, dizziness, nausea, vomiting, corona, and even death. It is possible that the presence of methyl mercaptan in the oral cavity can cause the induction or progression of periodontal disease (Yoshimura 2000).

Methyl mercaptan is produced by the breakdown of the amino acid L-methionine by the enzyme L-methionine-α-deamino-γ-mercaptomethane-lyase (METase). METase catalyzes the α, γ elimination of L-methionine to produce α-ketobutyrate, methyl mercaptan and ammonia (Yoshimura 2000).

\[
\text{METase} \quad \text{L-methionine} \quad \rightarrow \quad \text{C}_4\text{H}_7\text{O}_2 + \text{CH}_3\text{SH} + \text{NH}_3
\]
The treatment for VSCs is a variety of physical and chemical means. The physical treatment usually consists of scraping the tongue with a tongue scraper. This process will remove most of the plaque buildup on the tongue. The chemical portion of the treatment has to do with the actual breakdown of the VSC causing agents. Perfumes, mints, and alcohol will not affect any sulfur odor. In fact, it is widely known that alcohol will actually make the odor worse by dehydrating the mouth. The most effective compound for odor control today is chlorine dioxide (ClO₂). The chlorine dioxide actually breaks the sulfur bond in VSCs, leaving innocuous, odorless end products (Babad). Other companies today are using zinc compounds in addition to the chlorine dioxide, the zinc is effective against other organic odors which are unaffected by the chlorine dioxide.

It is interesting to note the actual end products that occur when the hydrogen sulfide reacts with the chlorine dioxide. According to the following equation, when hydrogen sulfide and chlorine dioxide react they form hydrochloric acid, sulfur dioxide, and water.

$$6\text{ClO}_2 + 5\text{H}_2\text{S} \rightarrow 6\text{HCl} + 5\text{SO}_2 + 2\text{H}_2\text{O}$$

Sulfur dioxide is a minor pollutant and is released into the atmosphere as a gas. The product is produced in such miniscule quantities, it is not likely going to cause any harm. Hydrochloric acid is a natural substance in the body. It serves as the primary chemical in the process of breaking down food particles in the stomach. Since our procedure is taking place in the mouth, the beginning point for digestion, the hydrochloric acid will simply move on through the digestive tract, and possibly remain in the stomach.

According to the most recent studies, this process of breaking the sulfur-hydrogen bonds in the VSCs with chlorine dioxide seems to be an effective and non-toxic method of treating halitosis. The products are not harmful, and the outcome is exactly as desired.

Overall, it is plain to say that nobody wants to live with bad breath. When we break it down though, chronic halitosis is merely a chemical equation. It is the chemical breakdown of various amino acids that occur naturally in our systems. The treatment is simple: good oral hygiene and a regular visit to your dentist will put a stop to the mouth covering and worrying about that chronic disease known as halitosis.
Bibliography

Babad, Melvin S. Breath Treatment Made Simple(r); www.hallimeter.com


Richter, Jon L. Diagnosis and Treatment of Halitosis. 1996. Compendium


www.niddk.nih.gov/tfacts139.html

www.breathsolution.com

www.fios.com/halitosis_data.htm

www.freshbreathonline.com
METH LABS

La Shelle Myers
Spring 2004
CHM 236
Dr. Bishop
EMCC
Abstract:

Methamphetamine is a dangerous highly addictive illegal drug. There are many meth/clandestine labs across the country produced illegally. These labs are extremely bad for everyone, not just for the lab operators. The lab seizures have decreased within the past couple years.
Methamphetamine was first synthesized in Japan in 1919. It was developed from its parent drug amphetamine and was originally used in bronchial inhalers, in the treatment of narcolepsy and obesity, and in nasal decongestants. In the early 1970s meth became a Schedule II drug with little medical use and a high potential for dependence and abuse. It is a long-acting, powerful, psychological, and physical drug stimulant that is highly addictive. Meth can be used to treat ADHD, which is attention-deficit hyperactivity disorder. The term clandestine, meaning secret or concealed, is used or is a common term used in place of or to describe meth labs as a collection of ingredients and materials used to manufacture illegal drugs. The key component of methamphetamine is ephedrine, which is a controlled substance. The finished form of meth usually appears as a powdery substance in a wide range of colors and is solid in pill form, capsules, crystals, and powder. It may be odorless or give off a chemical smell. Meth can be injected, smoked, snorted, swallowed, or inhaled by smoking in its crystal form. The common street names for methamphetamine are meth, chalk, go-fast, vitamin C, crank, speed, ice, fire, cryptic, glass, snot, croak, zip, and crissy.

The recrystallized form of methamphetamine hydrochloride is called ice. It will dissolve in water and breaks down to smaller particles. (5) Ice generally takes the form of clear crystallized chunks. (5) It induces a profound sense of euphoria in the user by blocking the reuptake and stimulating the release of dopamine and noradrenaline in the central nervous system. (5) Ice is considered to be a “power drug” whose typical use is followed by prolonged depression and fatigue. Smoking meth will extend its effects for up to 24 hours per ingestion, which is opposite from base cocaine. The smoked form of meth is known on the streets as snot, which can only be smoked and is very addictive.

Meth is made in drug laboratories that vary from those that look like chemistry labs to small home-based labs set up in kitchens, bathrooms, bedrooms, garages, and outbuildings. (2) Drug labs have also been discovered in backpacks, car trunks, businesses, mini storage units, hotel/motel rooms, houseboats, and car trunks. (2) The main purpose of these drug labs is to produce illegal drugs cheaply, quickly, and secretly. Meth is made through a cooking process that involves heating materials that are explosive, toxic, flammable, and corrosive. Generally the large “super” highly organized labs can manufacture 10 or more pounds of meth per production cycle. The smaller labs, sometimes referred to as “mom and pop” labs can manufacture only 1 to 4 ounces of meth per production cycle. Approximately 34 different chemicals can be used to produce methamphetamine. The most common are pseudoephedrine, ephedrine, red phosphorous, ether, phenylpropanolamine, anhydrous ammonia, iodine, hydroiodic acid, and hydrochloric acid. Ephedrine, pseudoephedrine, and phenylpropanolamine are manufactured outside of the United States. The largest producer of ephedrine is Germany. The major exporters of ephedrine and pseudoephedrine are China and India. Taiwan and Japan are major exporters for phenylpropanolamine. Most ephedrine is smuggled through Mexico into the United States. Since the 1980s, ice has been smuggled from Taiwan and South Korea into Hawaii, where use became widespread by 1988. (4) By 1990, distribution of ice had spread to the U.S. mainland. (4)
Over-the-counter cold and allergy tablets containing ephedrine or pseudoephedrine can be placed in a solution of alcohol, water, or other solvent for several hours until the pseudoephedrine or ephedrine separates from the tablet, which is part of the ephedrine or pseudoephedrine reduction method. The IUPAC name for ephedrine is erythro-2-(methylamino)-1-phenylpropan-1-ol and the IUPAC name for pseudoephedrine is threo-2-(methylamino)-1-phenylpropan-1-ol. Both are commonly used as racemic mixtures. Ephedrine is available as the pure levorotatory (-) isomer Biophedrine and pseudoephedrine is available as the more active (+) isomer Sudafed. (8) The common household products and equipment used to make meth are aluminum foil, strainer, hotplate, clamps, tape, plastic jugs, plastic tote box, gasoline can, rubber gloves, paper towels, rubber tubing, blender, coffee filters, funnels, glass jars, turkey baster, measuring cup, bottles, glass jugs, glass pie dishes, dishes, tempered glass baking, propane cylinder, and books for meth lab instruction. Some chemicals or sources needed to manufacture meth are acetone, paint thinner, campfire fuel, muriatic acid, gasoline, kerosene, table salt/rock salt, MSM which is animal product, sodium metal, iodine, red phosphorus, sodium hydroxide, anhydrous ammonia, trichloroethane, lithium, methanol, sulfuric acid, ether, toluene, alcohol, pseudoephedrine, ephedrine.

The difference between methamphetamine and pseudoephedrine is the alpha-hydroxy group. By reacting ephedrine with thionyl chloride, it replaces the hydroxide with chlorine and produces N-methyl-alpha-chloroamphetamine as an intermediate. To hydrogenate the product, lithium aluminum hydride, sodium borohydride, or hydrogen gas with nickel or platinum metal as a catalyst can be used. The product resulting is N-methylamphetamine and hydrochloride in which water can be evaporated off, yielding methamphetamine hydrochloride.

Synthesis for making methamphetamine hydrochloride:

Ephedrine $+\text{ thionyl chloride} \rightarrow \text{N-methyl-alpha-chloroamphetamine}$

\[
\begin{align*}
\text{H}_2\text{N} & \text{O} \\
\text{H} & \\
\text{N} & \\
\text{H} & \text{C}_1 - \text{S}-\text{Cl}
\end{align*}
\]

\[
\begin{align*}
\text{LiAlH}_4 & \rightarrow \text{HCl} + \text{N-methylamphetamine} \xrightarrow{\Delta} \text{methamphetamine hydrochloride}
\end{align*}
\]

\[
\begin{align*}
\text{H}_2\text{O}^+ & \\
\text{H} & -\text{Cl}
\end{align*}
\]
Other methods of synthesizing methamphetamine are by reducing the condensation product of methylamine and phenylacetone, reduction of ephedrine or pseudoephedrine with hydroiodic acid and red phosphorus, and synthesis from amphetamine.

Chemical Information:

Methamphetamine, C_{10}H_{15}N
Molecular Weight 149.2352g

Methamphetamine hydrochloride, C_{10}H_{16}ClN
Molecular Weight 185.6961g

Amphetamine, C_{9}H_{13}N
Molecular Weight 135.2084g
Ephedrine, $\text{C}_{10}\text{H}_{15}\text{NO}$
Molecular Weight $165.2346\text{g}$
Melting Point $37^{\circ} - 39^{\circ}\text{C}$

Pseudoephedrine, $\text{C}_{10}\text{H}_{15}\text{NO}$
Molecular Weight $165.2346\text{g}$
Melting Point $117^{\circ} - 118^{\circ}\text{C}$

Methamphetamine Free Base, $\text{C}_{9}\text{H}_{6}\text{CH}_{2}\text{CH(NHCH}_{3}\text{)}\text{CH}_{3}$
Molecular Weight $149.24\text{g}$
Melting Point $170^{\circ} - 175^{\circ}\text{C}$
Hill Convention: $\text{C}_{10}\text{H}_{15}\text{N}$
Percent Composition $\text{C 80.48\% H 10.13\% N 9.39\%}$
Methamphetamine strongly activates certain systems in the brain. It is closely related chemically to amphetamine, but the central nervous system effects of meth are greater. (7) Immediately after smoking meth or intravenous injection, the user experiences an intense “rush” or “flash” that lasts only a few minutes and is described as extremely pleasurable. (7) Snorting or ingesting meth orally produces euphoria which is a high but not an intense rush. Some of the short-term effects of using methamphetamine include loss of appetite, increased blood pressure, insomnia, convulsions, hallucinations, anxiety, nervousness, irritability, and aggression. Stroke, heart and blood vessel toxicity, addiction, Alzheimer’s disease, extreme paranoia, toxic psychosis, repetitive behavior patterns, hallucinations, convulsions, long-term damage to brain cells similar to that caused by strokes, and delusions of parasites of insects under the skin are some long-term effects of using methamphetamine. Depending on the amount of meth taken, how it’s taken, the person’s mood, and other factors may cause death, numbness in hands and feet, malnutrition, uncontrolled movements, headache, blurred vision, problems sleeping, exhaustion, nausea, vomiting, organ damage, increased body temperature, faster heartbeat, dry itchy skin, nasal damage and bleeding, acne, and sores. Meth exposes it’s user to dangers like legal problems, social problems, financial problems, lowered resistance, and HIV infection and other STDs.

Contamination is one of the greatest dangers of a meth lab occurring by ingestion, second hand smoke, soiled clothing, household items used in the lab, and through skin. An estimated 3 to 6 people working in clandestine U.S. drug labs die each year from explosions, fires, or toxic fumes. (1) One out of every 5 or 6 labs discovered is found because of a fire or an explosion. (1) Meth is also a danger to society being linked to car crashes, environmental hazards, physical injury from toxic fumes, chemical burns, fires, explosions, crimes, hazardous wastes, child abuse and neglect, and harm to newborns. Children poses a higher risk of ingesting meth lab chemicals into their bodies because of their size and higher rate of respiration and metabolism. Most chemicals used to produce meth are often stored in unlabeled drink and food containers on countertops and floors, which place infants and toddlers at an increased risk due to childhood behaviors like crawling and playing on the floor and putting their hands and other objects into their mouth.

Many lab cooks do not take basic lab safety precautions. (1) Most of the people running or working in these dangerous labs are under the influence of drugs and alcohol, contributing to some of the explosions. Poor lab ventilation also increases the risks of both toxic fume inhalation and explosions. (1) Good ventilation spreads toxic fumes outside, where they put other people at risk. (1) Heating the chemical red phosphorous can create phosphine, a deadly gas. (1) The average cost of cleaning up the immediate and apparent hazardous materials in an average-sized clandestine drug lab ranges from $2,500 to $10,000. (1) It can cost up to $150.00 to clean up hazardous materials in the larger super labs. (1) An estimated cost of $50,000 for thorough decontamination of an average-sized site has been reported. For every pound of meth produced, 5 to 6 pounds of hazardous waste is generated. (2) Meth labs are all around bad and dangerous for everyone, not just the lab cooks.
Profitability of Clandestine Drug Labs
$40 to $150 for 1 gram
$60 to $150 for 1/8 of an ounce
$500 to $2,700 for 1oz
$4,500 to $20,000 for 1lb
$18,000 for 1kg
Experts estimate that one ounce of meth equals about 110 meth ‘hits.’ (4)

A 2000 survey of 544 respondents indicated that majority of 18 to 23 year olds compared to the other age groups were using meth. (4)

The following statistics were provided by Sergeant Don Sherrard from the City of Phoenix Police Department Drug Enforcement Bureau, who is a Clandestine Lab Supervisor.

Phoenix Police Department Clan Lab Seizure Statistics 1996 - April 2004

<table>
<thead>
<tr>
<th>Clan Lab Seizures</th>
<th>Children in Clan Labs (beginning March of 1999)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1996</td>
<td>1999</td>
</tr>
<tr>
<td>1997</td>
<td>2000</td>
</tr>
<tr>
<td>1998</td>
<td>2001</td>
</tr>
<tr>
<td>1999</td>
<td>2002</td>
</tr>
<tr>
<td>2000</td>
<td>2003</td>
</tr>
<tr>
<td>2001</td>
<td>2004 (To Date)</td>
</tr>
<tr>
<td>2002</td>
<td></td>
</tr>
<tr>
<td>2003</td>
<td></td>
</tr>
<tr>
<td>2004</td>
<td></td>
</tr>
<tr>
<td>Month</td>
<td>Count</td>
</tr>
<tr>
<td>------------</td>
<td>-------</td>
</tr>
<tr>
<td>April</td>
<td>54</td>
</tr>
<tr>
<td>August</td>
<td>42</td>
</tr>
<tr>
<td>December</td>
<td>51</td>
</tr>
<tr>
<td>February</td>
<td>43</td>
</tr>
<tr>
<td>January</td>
<td>56</td>
</tr>
<tr>
<td>July</td>
<td>47</td>
</tr>
<tr>
<td>June</td>
<td>39</td>
</tr>
<tr>
<td>March</td>
<td>49</td>
</tr>
<tr>
<td>May</td>
<td>57</td>
</tr>
<tr>
<td>November</td>
<td>56</td>
</tr>
<tr>
<td>October</td>
<td>56</td>
</tr>
<tr>
<td>September</td>
<td>52</td>
</tr>
<tr>
<td>Total</td>
<td>602</td>
</tr>
</tbody>
</table>
The following 2003 Nationwide Methamphetamine Laboratory Incidents map indicates that California had an estimated 1,239 incidents, Iowa had an estimated 1,240 incidents, and Missouri had the most with an estimated 2,860 incidents.
Bibliography:

1. Clandestine Drug Labs, Michael S. Scott, 2002

2. http://www.ag.state.az.us/DEC


The Countenance of Janus
A Historical Account of Chemistry’s Infinite Realm of Possibility

Andrew Murphy
Chemistry 236
Dr. Michael Bishop
April 19, 2004
Abstract

History has provided for us a view of the many discoveries that man has ever made. Each and every discovery is detailed precisely whether for good or evil. This paper will demonstrate the many events that occurred in chemistry from the early Greeks and their questions about nature through both the First and Second World Wars. In addition, it will hopefully portray the beauty of chemistry and its discoveries along with its ugly side of meaningless destruction all in the name of hubris.
The ancient philosophers for centuries have posed many questions regarding the existence of things, the presence of an omnipotent thinker, the intellect of man, and ultimately the search for truth. Although the ancients disagreed at times both on the questions of the chief good and the fundamental problems associated with physis or nature, they did maintain that the chief motive for investigating nature and its mysteries is to obtain peace of mind.

Epicurus a philosopher and scientist states in his “Principal Doctrines,” “that if we are not troubled at all by apprehensions about phenomena in the sky and concerning death, lest it somehow concern us, and again by our failure to perceive the limits of pains and desires, we should have no need of the study of nature.” Later in a letter to Pythocles he maintains, “bear in mind that there is no other end to the knowledge of things in the sky than peace of mind and firm conviction.” Furthermore, in a letter to the Greek historian Herodotus, Epicurus proclaims, “The solstices, eclipses, risings and settings of the celestial bodies and so on take place without the ministration or ordering of gods, and the regularity of phenomena in the sky is due to the arrangement of atoms.”

Many philosophers denied owing any debt to the many earlier thinkers that came before them. This “cerebral hygiene” creates an injustice to the conscientious scientist whom strongly relies on the great wisdom pasted down from century to century. At any rate, we must put the human condition in perspective and truly understand that the majority of the meditations on the physical world were inspired from the fifth century atomists, Leucippus and Democritus. Like them many maintained that atoms and the realm of nothingness co-exist alone. There are an infinite number of atoms and they are all in constant movement in the realm of nothingness. They collide with, and deflect from, one another, and in doing so form very complex bodies of molecules. All the characteristics such as heat, color, taste, and aroma are derived from the differences in the primary properties of atoms—shape and position.

So far it appears that the later philosophical developments are following the Democritian way of thought. Yet at certain intervals in the development of their thinking, these later philosophies tend to veer from Democritian thought and respond to what appears to be a criticism that Aristotle had brought against atomism. Another issue that the atomists left unanswered concerned the nature of the atoms. The earlier philosophers held that the atoms are physically indivisible; it does not appear, however, that the ancients considered the notion that the atoms may be mathematically divisible, that is, divisible in thought. Aristotle objected to the earlier atomists with support that shows he held the belief that the atomis did not distinguish between the physical and mathematical indivisibility. A contemporary scientist of Aristotle responds by stating that atoms are the indivisible units by which all physical phenomena are composed of; yet the atom itself has a definite size and is made of mathematically indivisible parts.

One of the more important introductions to atomistic thought concerns weight. Many of the earlier intellectuals held that the primary properties of atoms are shape, arrangement, and position. Later, the property of weight was added—earlier atomists regarded weight as a secondary property that was acquired when atoms have had time to come together to form a universe. Earlier chemists maintained that all atoms are in a perpetual state of movement in
every direction and their interactions in the form of collisions cause a disruption in the universe’s entropy that in turn causes an attraction for other atoms.

The notion of atoms encountering chance collisions was modified slightly after the idea was promulgated. By contrast, the idea of world formation was described as all atoms traveling in the same direction and speed. This purposed idea caused immediate strife within the scientific climate of the time. One of the first intellectuals to respond to this description of the universe was Aristotle. For instance, he held that the heavier the body the faster it should fall in space. Contrastingly, contemporaries argued that if all atoms are moving in the void of nothingness than the mass of the object does not have any bearing on the atoms velocity. These different points of interpretation and explanation for the existence of the cosmos led to further confusion about the idea that if all atoms fall at the same rate no atoms shall ever meet or collide therefore no universe would be created. Further meditation on the cosmological question led later chemists to put forward the idea that occasionally an atom may deviate from its normal vertical descent by a quantum amount. At the same time, there appeared to be no logical explanation for the deviation it was simply a cause without an effect.

As this deviation, quantum disarrangement, and/or the cosmological swerve became widely accepted it also became less controversial. As soon as the scientific climate began to agree that the atoms of the universe move at the same speed and in the same direction, there must be exceptions if there is to be any explanation about the cosmological process. We have come to know that this world we live in, at least, exists: somehow then a series of infinitesimal collisions of atoms had to have taken place. Moreover, this suggestion of atoms deviating from a determined path of motion is less shocking to us than it may have been for the ancients. At this time recall to mind the Heisenberg Uncertainty Principle, the behavior of a particle cannot be completely described—that is, we are unable to determine at the same time both its location and momentum. Hopefully we have adequately seen that the early philosophers/scientists and their philosophical musings influenced the nature of all scientific inquiry. Their influence albeit is two-edged, they set the groundwork for scientific inquisition and strongly encouraged abstract investigation into the fundamental questions of the physical realm. The great advances made in chemistry were the work of men, not only as philosophers, but men of science and mathematics and it is to their discoveries that we now turn.

After the First World War Germany appeared to be in a state of political turmoil, yet still maintained an impetus for scientific discovery. German science of the second decade of the twentieth century focused the majority of its efforts on the discipline of chemistry. In 1828 a very unique and dubious organic discovery was unleashed. Friedrich Wöhler, an organic chemist, converted ammonium cyanate into urea an organic substance. This discovery sent shock waves through the chemical world. With this new technique the notion of synthesizing materials that do not occur in nature became routine. August Wilhelm von Hofmann is credited with doing work on coal tar (waste product of coal burning). Hofmann discovered that coal tar would yield aniline. This then led to speculation that dyes could be produced from coal tar. Dye production was then making its way into the biological sciences. For example, staining of plants and animal cells with aniline dye. A further use of dye was used in the staining method of plant cell walls green and the cytoplasm red. This dye used in the process was methyl green. Methyl violet another dye was found to be effective in highlighting certain bacteria that helped in the
research of bovine anthrax bacillus and tuberculosis. Further discoveries in biochemistry were becoming known, for example, the founding of the ophthalmoscope and the first look at the human optic nerve. At this time in research, the mechanistic, mathematical, and empirical asceticism of scientific inquiry was separating itself from any philosophical ties. As time went on there appeared to be no end in sight for the colossal German scientific machine as biomedical discoveries began to enter into the scene. In 1890 the discoveries of aspirin, novocaine, and salvarsan put the Bayer pharmaceutical laboratory on the map as a powerhouse of discovery. As the scientific research continued, the products of German discovery would be found in all the markets of the world: soaps, paints, inks, dyes, drugs, steel and iron production, explosives, and the infamous production of fertilizers.

As the dawn of the First World War was approaching some of the research conducted was now turning to the war effort. In the eighteenth century it had been discovered that ammonia, a molecule essential to fertilizers and explosives was composed of a nitrogen atom and three hydrogen atoms. For years scientists had been trying to synthesize ammonia from nitrogen and hydrogen atoms failing at each attempt. Eventually, a chemist named Fritz Haber produced a minute amount of ammonia under pressure two hundred times the atmosphere at sea level and at temperatures of two hundred degrees Celsius or three hundred degrees Fahrenheit. Haber then began to seek an alternative method to produce ammonia that was less vigorous. He finally concluded that the production of ammonia would require a catalyst to speed the reaction. Haber discovered that the metal osmium yielded the product ammonia in excess. As a result of the Haber nitrogen-fixing formula, upwards of five tons of ammonia was being produced by day. On the eve of war the ammonia factories were capable of manufacturing forty tons of synthetic ammonia a day, mostly used for fertilizer. As the war continued all imports to Germany were blockaded; it took the war council of Berlin several months to understand the significance of the Haber process in the production of explosives. Germany's arsenal of weapons was rapidly decreasing as a result of ally blockades. In turn, Berlin sought to exploit the existing ammonia plants for the conversion of ammonia, with the aid of nitric acid, to explosives. Subsequently, the existence of nitric acid plants equaled that of the ammonia factories. As a result of the Haber process to fix nitrogen and the mass production of nitrates the production chemicals suitable for fertilizer and explosives had reached two thousand four hundred tons a month, this allowed for continued success in the war.

As the war and its efforts to ensure its success continued, Fritz Haber turned his genius in another direction. Haber surrounded himself with the many great scientist of the time; among them was Otto Hahn the discoverer of fission. These new soldiers were men who calculated suffering and death with a series of scientific journals and equations, and had no real traditional weapons yet they were armed with chemical formulae. In 1915, Haber and his scientists conducted an experiment that put even them in grave danger. These new soldiers armed themselves with large canisters weighing two hundred pounds of chlorine gas in its liquid form. When under attack, they released the contents of the canisters. Chlorine attacks the mucous membranes of its victims causing suffocation and blindness. Later in the same year, the Germans used a similar method against the Russians, this time using a mixture of phosgene and chlorine. As the progression of the war continued, Haber had continued to research the many potential methods of gas warfare. He did eventually arrive at a suitable method that was favored above all. This new and accepted weapon became known as Buntkreutz; it was a mixture of a
gas that was similar in chemical structure to that of phosgene. Its sole purpose was to penetrate enemy gas masks forcing victims to remove their masks only then leaving themselves exposed to pure phosgene. After the First World War, the allies attempted to bring Fritz Haber to trial as a war criminal. This attempt was unsuccessful as Haber was unable to be located. He had fled to Switzerland until the political climate of the time had quenched the notion of war criminals. Haber returned to Germany to aid in the rebuilding of his homeland and to receive his Nobel Prize for ammonia fixation. After his return to Germany, Haber continued his work on chemical weapons. He was persuasive enough to be given national support for his new efforts in research. Many countries for his genius in chemical weaponry sought Haber. Fritz Haber strongly urged the politicians of the time to consider the mass development of hydrocyanic acid: it would serve two functions—as a pesticide, and later as an atrocious lethal gas used against humans. It subsequently became known as Zyklon B.

As the state of German existence, after World War One, lingered without any real direction slow and gradual development of the Nazi regime began to emerge. By 1936 Adolf Hitler was in full control of German politics and psychology. One of Hitler’s initial goals was to re-energize the life of German science in hope that it will aid in the supremacy of German society. Also, in the same year, Dr. Gerhard Schrader, a research chemist was working on insecticides (following the Haber model), discovered a lethal chemical that came to be known as tabun, which later becomes classified in the category of organic phosphorous compounds. Tabun’s mode of action attacks the enzyme cholinesterase—a neurotransmitter—which in turn further reacts with the neurotransmitter acetylcholine. When acetylcholine collects unhindered, it induces contractions especially in the respiratory system causing the victim to choke. This discovery pleased Schrader’s superiors and he was urged to continue his research with organic phosphorous compounds. Later in Schrader’s research he discovered isopropyl methylphosphoro-fluoridate, which demonstrated itself to be even deadlier than tabun. It has now been referred to as sarin. In addition to the work being done by Schrader, other chemical factories were mass-producing chemical weapons similar to those used in World War One. As the research in chemistry continued many great synthesizes were discovered. We now turn our attention to these discoveries.

As Germany expanded as an industrial powerhouse and war machine it revealed in the unlimited energy supply it received from coal. Coal was used as energy for steam power, heating, and provided the starting material for many synthetic products. The existence of gasoline and the diesel engine added to the might of the German nation, but it also created dependence, for Germany, on oil. As once before, the expertise of the chemists came to Germany’s aid. Chemists retired to the laboratory in hope of developing synthetic petroleum from coal and its derivatives. Success again is granted to the German scientists, as the method of hydrogenation comes into being. This method requires that different varieties of coal be reacted with hydrogen gas at extremely high temperatures and pressure. This form of hydrogenation became known as the “Bergius” method. It involved splitting a coal molecule and inserting hydrogen with high temperature and pressure to produce oil molecules. At the same time, two chemists in another part of the country were doing coal research. Their process was later known as the F-T synthesis, this was the initial brainchild of the chemical powerhouse BASF. The F-T process required passing water gas (mixture of carbon monoxide and hydrogen produced by
treating coke with steam) over an extremely hot catalyst that will yield a mixture of hydrocarbons. These products were used solely as fuels.

The success of the German synthetic fuel factories is owed to the discovery of an efficient catalyst. The process of splitting the coal molecule and the invention of different catalysts that are able to hydrogenate the smaller molecules allowed the fuel product to then be distilled to many different octanes. It later was discovered that the F-T process of hydrogenation was better geared to diesel engines. Whereas, the Bergius hydrogenation process was better produced for aviation fuel. Meanwhile as the synthetic fuel factories continued to flourish under the Nazi regime, a new discovery was being unraveled in the laboratory. The production of synthetic rubber had been created. This procedure involved the molecule butadiene and the element sodium.

As the Second World War continued its intensity so did the need for faster and more advanced discoveries in chemistry. Many ideas were presented to Nazi superiors about the possibility of producing an atomic weapon that would not only destroy an enemy with one swipe yet reduce all regime costs. The creation of an atomic weapon required that isotope separation techniques be formulated. One of the key characters in the notion of atomic weaponry was Werner Heisenberg. Heisenberg stated that there was really no visible obstacle present in constructing such a weapon. The only resistance that he considered was on the part of the regime and their lack of initial support. Heisenberg was asked a series of questions regarding the efficacy, equipment, and success of an atomic weapon. He responded, that the success of the weapon is inevitable. The lack of a cyclotron is essentially the sole reason that atomic energy in Germany has not begun. In actuality, it appears that the production of atomic energy during the Second World War never took flight because Nazi superiors did not truly desire its production. In the case of Heisenberg, he had many roles to fulfill in Germany at the time; he was a professor that truly enjoyed his work and students. We could speculate that if the regime’s superiors would have considered the possibility of defeat then the discussion of atomic power would have ended and the mass effort to ensure its success would have become a reality.

As the war ran its course and finally came to an end with the fall of a dictatorial regime, the research continued for many years to follow. Many discoveries were made post-war, if fact, to many to be mentioned here with any type of satisfactory attention they demand. Yet, there is a particular discovery that brought the world’s chemists together in admiration. In 1954 a chemist named Georg Wittig formulated what is now referred to as the Wittig synthesis. We have seen carbonyl compounds undergo addition by a multiplicity of carbanion reagents, for example, Grignard reagents, organolithium reagents, and the acetylide ion. Professor Wittig essentially unveiled a method of adding a phosphorus-stabilized carbanion to either a ketone or aldehyde. Many scientists would conjecture that the resulting product is a mere alcohol; such speculation would be erroneous. An explanation at this time is needed to fully grasp the Wittig product. The intermediate that is formed in the reaction undergoes elimination to produce the alkene. As a very learned professor has told us all, as we will never forget, that carbon/carbon bonds are very difficult to produce. Let us now turn our attention to the speciality of the Wittig product. The phosphorous carbanion is known as an ylide; it is a molecule that apparently does not have an all-encompassing charge yet has a negatively charged carbon atom that is bonded to a positively charged heteroatom. The phosphorous ylide is typically produced by the reaction of
triphenylphosphine with an alkyl halide (preferably primary) in a two-step mechanism. Initially we have a nucleophilic attack by the triphenylphosphine on the unhindered primary alkyl halide. The resultant product is an alkyltriphosphophonium salt. Secondly, the salt is then treated with a very strong base, in order, to remove a proton bonded to the carbon with the phosphorous. This abstraction of the proton yields the phosphorous ylide with its resonance forms. This ylide appears to have carbanion character and is nucleophilic. Due to this characteristic trait, the ylide is able then to attack the carbonyl carbon of either a ketone or aldehyde. After the attack is complete, there is now the formation of a betaine compound. The betaine has unusual significance in that it contains both a negatively charged oxygen atom adjacent to the positively charged phosphorous atom. This close proximity of the two atoms and the opposite charges allows the formation of a four-membered oxaphosphetane ring.

This ring and its rapid formation may indicate that it possesses a significant amount of stability; it has never been isolated so it would then lead us to conclude the contrary. As the reaction proceeds the oxaphosphetane ring spontaneously collapses to yield the, prior thought exceptionally difficult, alkene and triphenylphosphine oxide.

Finally, man has sought the knowledge of life and may have truly come to understand its mechanism. Yet, it is difficult to maintain the notion that we are the omnipotent intellects that the ancient Greeks sought to explain. As time moves forward the growth of man’s infinite realm of possibility may one day answer a significant amount of questions that he has posed to himself and civilization. For example, eschatologists study and philosophize about the end and its arrival; it is an important discussion but unfortunately not a question to be answered by the chemists or scientist—contrary to popular opinion. What has been discovered and learned in chemistry through history has been phenomenal. What is the good that the ancients sought? It may be the understanding of nature or the proof of one’s existence. Through history we have seen the beginning of chemistry, its development for the good, and unfortunately its beautiful discoveries used for destruction and annihilation. Recall to mind the work of Dr. Gerhard Schrader and his discoveries with organic phosphorous compounds. Will history repeat itself or will time move forward and not look back. Has history brought us the Wittig reaction to display a work of genius, or just another chemical explanation to be used in the unfortunate demise of many unsuspected innocents? We may speculate until the end of time about the role of chemistry in civilization but we must always harken back to the questions brought to us by the Greeks: What is the good that we seek?
The Haber Process and Summary

\[ \text{H}_2(g) + 3\text{H}_2(g) \rightleftharpoons 2\text{NH}_3(g) \quad \Delta H = -92 \text{kJ/mol} \]

Nitrogen from the air

Hydrogen from natural gas

400 - 450°C
200 atm
Fe catalyst

Nitrogen + Hydrogen → gases are cooled and NH₃ turns to liquid

The Synthesis of Aspirin

C₇H₆O₃
Salicylic Acid

C₄H₆O₃
Acetic Acid

C₂H₅CO
Acetyl

C₈H₈O₄
Acetyl Salicylic Acid

C₂H₄O₂
Acetic Acid

The Synthesis of Rubber

1,4-polymerization of 1,3-butadiene

\[ \text{cis-1,4-polybutadiene} \]

The Wittig Reaction

\[ pH - P \rightarrow pH \rightarrow pH \]

triphenylphosphine
Alkyl Halide

Phosphonium salt

\[ ph \rightarrow p \rightarrow c \rightarrow H \]

Triphenylphosphine Oxide

Phosphorous ylide

\[ R', C=O \rightarrow R', C=C - R \rightarrow H, C=C - R \rightarrow Ph_3 \rightarrow O \quad \text{Triphenylphosphine oxide} \]

R, C=O
Ketone

R, C=O
Aldehyde

R, C=O
Aldol

R, C=O
Phosphonate

R, C=O
Phosphine

R, C=O
Phosphine Oxide

R, C=O
Alkene
Bibliography

4. The Haber Process. [www.chemguide.co.uk/physical/equilibria/haber.html](http://www.chemguide.co.uk/physical/equilibria/haber.html)
Depletion of Ozone Layer

Prepared for
Dr. Hank Mancini
Chemistry 236 Sp'04
Paradise Valley Community College

Exosphere → 400 km altitude
Thermosphere → 300 km
Mesosphere → 50 km
Stratosphere → 40 km
Troposphere → 10 km

Prepared by
John Ngo
April 16, 2004
Depletion of Ozone Layer

Table of Contents

Abstract
What is ozone?
How can ozone be destroyed?
The effects of ozone on Earth
What can we do to save the tropospheric ozone layer?
Conclusion
Abstract

We often hear news about ozone depletion and the names of chemicals that cause it. We hear little about the negative effects on Earth and what we can do to prevent the depletion. This article will hopefully help one to have a better understanding of ozone, how ozone can be destroyed, the negative effects on earth, and what we can do to help.

What is ozone?

Ozone is a form of oxygen molecule that contains three oxygen atoms, \((O_3 : 3 \text{ oxygen atoms})\).\(^1\) Ozone occurs naturally in the atmosphere.\(^2\) It is blue in color and has a strong odor. Normal oxygen, which we breathe, has two oxygen atoms and is colorless and odorless. Ozone is much less common in the air than normal oxygen. Out of each 10 million air molecules, about 2 million are normal oxygen, but only 3 million are ozone.\(^1\)

The earth’s atmosphere is composed of several layers. The lowest region, the troposphere, extends from the Earth’s surface up to about 10 kilometers (km) in altitude. Virtually all human activities occur in the troposphere where most of the weather occurs; such as rain, snow and clouds. Mt. Everest, the tallest mountain on the planet, is only about 9 km high. Above the troposphere is the stratosphere, from 10 km to about 50 km; an important region in which effects such as the Ozone Hole and Global Warming originate. Supersonic jet airliners such as the Concorde fly in the lower stratosphere whereas subsonic commercial airliners are usually in the troposphere. The narrow region between these two parts of the atmosphere is called the “Tropopause.”\(^2\)

As shown in the graph, most atmospheric ozone is concentrated in the stratosphere, about 15-30 kilometers above the Earth’s surface.\(^3\)
It is believed that at any given time, ozone molecules are constantly formed and destroyed in the stratosphere,\(^1\) for example: NO\(_x\) emissions from subsonic aircraft flying in the troposphere and the lowermost stratosphere lead to a significant increase in ozone in the upper troposphere. Emissions of NO\(_x\) and H\(_2\)O from supersonic aircraft cruising in the stratosphere are calculated to decrease the column abundance of ozone.\(^4\) The total amount, however, remains relatively stable. The concentration of the ozone layer can be thought of as a stream's depth at a particular location. Although water is constantly flowing in and out, the depth remains constant.\(^1\)

Ozone forms a layer in the stratosphere, thinnest in the tropics (around the equator) and denser towards the poles. The amount of ozone above a point on the earth's surface is measured in Dobson units (DU)- typically ~260 DU near the tropics and higher elsewhere, though there are large seasonal fluctuations. It is created when ultraviolet radiation (sunlight) strikes the stratosphere, dissociating (or "splitting") oxygen molecules (O\(_2\)) to atomic oxygen (O). The atomic oxygen quickly combines with further oxygen molecules to form ozone:

\[
O_2 + h\nu \rightarrow O + O \quad (1)
\]

\[
O + O_2 \rightarrow O_3 \quad (2)
\]

\((1/\nu = \text{wavelength} < \sim 240 \text{ nm})\)

It's ironic that at ground level, ozone is a health hazard - it is a major constituent of photochemical smog. However, in the stratosphere we could not survive without it. Up in the stratosphere it absorbs some of the potentially harmful ultra-violet (UV) radiation from the sun (at wavelengths between 240 and 320 nm) which can cause skin cancer and damage vegetation, among other things.

Although the UV radiation splits the ozone molecule, ozone can reform through the following reactions resulting in no net loss of ozone:

\[
O_3 + h\nu \rightarrow O_2 + O \quad (3)
\]

\[
O + O_2 \rightarrow O_3 \quad (2)
\]

Ozone is also destroyed by the following reaction:

\[
O + O_3 \rightarrow O_2 + O_2 \quad (4)
\]

The reactions above, labeled (1)-(4) are known as the "Chapman reactions". Reaction (2) becomes slower with increasing altitude while reaction (3) becomes faster. The concentration of ozone is a balance between these competing reactions. In the upper atmosphere, atomic oxygen dominates where UV levels are high. Moving down through the stratosphere, the air gets denser, UV absorption increases, and ozone levels peak at roughly 20km. As we move closer to the ground, UV levels decrease and ozone levels
decrease. The layer of ozone formed in the stratosphere by these reactions is sometimes called the 'Chapman layer'.

How can ozone be destroyed?

In the 1960s, it was realized that the loss of ozone given by reaction (4) was too slow. It could not remove enough ozone to give the values seen in the real atmosphere. There had to be other, faster reactions that were controlling the ozone concentration in the stratosphere.

Back in 1974, F. Sherwood Rowland and Mario Molina wrote: "Chlorofluoromethanes are being added to the environment in steadily increasing amounts. These compounds are chemically inert and may remain in the atmosphere for 40-150 years, and concentrations can be expected to reach 10-30 times their present levels. Photo-dissociation of the Chlorofluoromethanes in the stratosphere produces significant amounts of chlorine atoms, and leads to the destruction of stratospheric ozone."

Not everybody shared the same concern of F. Sherwood Rowland and Mario Molina's. In 1975, S. Robert Orfco of Allied Chemical wrote: "The validity of Rowland-Molina hypothesis has not been established. There is no concrete evidence to show that the ozone-depleting reaction with chlorine in fact takes place in the stratosphere."

However, recent convincing scientific evidence has shown that the ozone shield is being depleted well beyond changes due to natural processes.

It is general consensus that chlorine in chlorofluorocarbon (CFC) is a major player in depletion of the ozone layer.

CFCs were invented about 65 years ago during a search for a new, nontoxic substance that could serve as a safe refrigerant. One of these new substances, often known by the DuPont trademark Freon, soon replaced ammonia as the standard cooling fluid in home refrigerators. It later became the main coolant in automobile air conditioners.

Chlorofluorocarbons (CFCs) are a class of man-made chemicals known by such trade names as "Freon", "Genetron", and "Isotron". CFCs have been used in a wide variety of manufacturing steps and products including as a solvent in the electronics industry, foaming or blowing agent, aerosol propellant, fire extinguisher agent, dry cleaning solvent, degreasing agent, a key component in making rigid foam insulation for houses and household appliances, and foam packaging insulation material (known by the trade name of "Styrofoam"). Use of CFCs has declined as concern over their interaction with the environment has grown.
The above graph shows where sources of man-made CFCs are from.\(^1\)

Scientists have shown that CFCs have remained undisturbed in the lower atmosphere for decades. Invulnerable to visible sunlight, nearly insoluble in water, and resistant to oxidation, CFCs display an impressive durability in the atmosphere's lower depths. But at altitudes above 18 miles, with 99 percent of all air molecules lying beneath them, CFCs are vulnerable. At this height, the high-energy ultraviolet radiation from the sun impinges directly on the CFC molecules, breaking them apart into chlorine atoms and residual fragments (22). Here, at the stratosphere, CFCs can reside for more than 100 years. If global CFC production was stopped today, we would still experience the effects for over one hundred years.\(^1\)

When chlorine and ozone react, they form the free radical chlorine oxide, which in turn becomes part of a chain reaction. Chlorine atoms induce the decomposition of two ozone molecules into three oxygen molecules in a net chain reaction in which the chlorine atoms are regenerated so that ozone decomposes. As a result of a chain reaction, a single chlorine atom can remove as many as 100,000 molecules of ozone.\(^7\)

The above chart is an illustration of how Chlorine destroys Ozone.\(^1\)
Chemically speaking, molecular chlorine is easily photo-dissociated (split by sunlight):

\[ \text{Cl}_2 + h\nu \rightarrow \text{Cl} + \text{Cl} \]

Measurements, which are taken of chemical species above the pole, show high levels of active forms of chlorine. However, there are still many more atoms of ozone than active chlorine, so how is it possible to destroy nearly all of the ozone?

The answer to this question lies in what are known as 'catalytic cycles'. A catalytic cycle is one in which a molecule significantly changes or enables a reaction cycle without being altered by the cycle itself.

The production of active chlorine requires sunlight, and sunlight drives the following catalytic cycles thought to be the main cycles involving chlorine and bromine, responsible for destroying the ozone:

(I) \[
\begin{align*}
\text{ClO} + \text{ClO} + M & \rightarrow \text{Cl}_2\text{O}_2 + M \\
\text{Cl}_2\text{O}_2 + h\nu & \rightarrow \text{Cl} + \text{ClO}_2 \\
\text{ClO}_2 + M & \rightarrow \text{Cl} + \text{O}_2 + M \\
\text{then:} & \quad 2 \times (\text{Cl} + \text{O}_3) \rightarrow 2 \times (\text{ClO} + \text{O}_2)
\end{align*}
\]

**net:** \[ 2 \text{O}_3 \rightarrow 3 \text{O}_2 \]

and

(II) \[
\begin{align*}
\text{ClO} + \text{BrO} & \rightarrow \text{Br} + \text{Cl} + \text{O}_2 \\
\text{Cl} + \text{O}_3 & \rightarrow \text{ClO} + \text{O}_2 \\
\text{Br} + \text{O}_3 & \rightarrow \text{BrO} + \text{O}_2
\end{align*}
\]

**net:** \[ 2 \text{O}_3 \rightarrow 3 \text{O}_2 \]

\(M\) is any air molecule.²

To make matters worse, other scientists have demonstrated that an entirely different group of compounds could further reduce ozone levels. Paul Crutzen first showed in 1970 that nitrogen oxides react catalytically with ozone, playing an important role in the natural ozone balance. Soil-borne microorganisms produce nitrogen oxides as a decay product, and Crutzen's work spotlighted how microbe-rich agricultural fertilizers might lead to reduced ozone levels. His research and that of Harold Johnson also focused attention on the effect of nitrogen oxides spewed by high-altitude aircraft. These emissions may also reduce ozone levels in the stratosphere.³
The effects of ozone depletion on earth

Ozone has dramatically different effects depending upon its location. Near the Earth's surface, where ozone comes into direct contact with life forms, it primarily displays a destructive side. Because it reacts strongly with other molecules, large concentrations of ozone near the ground prove toxic to living things. Long term exposure to ozone can cause premature aging of leaves and needles, which lead to early discoloring and abscission of leaves and needles. It is "bad ozone", which is also recognized as "smog". The "bad ozone" makes up about 10 percent of our planet's ozone. At higher altitudes, where 90 percent of the planet's ozone resides, it is "good ozone". It does a remarkable job of absorbing ultraviolet radiation. In the absence of this gaseous shield in the stratosphere, the harmful radiation has a perfect portal through which to strike Earth. Most importantly, it absorbs the portion of ultraviolet light called UVB, which is believed that changes in UVB-radiation can have a profound impact on photochemistry. UVB has been linked to many harmful effects, including cataracts, various types of skin cancers, and depressing the human immune system. It can kill one-celled organism such as bacteria and algae. Increased ultraviolet radiation reduces crop yields, depletes marine fisheries, damages construction materials, and increases smog.

What can we do to save the tropospheric ozone layer?

World-wide recognition of the global threat from CFCs has begun. In 1977, the EPA and FDA banned the use of CFCs in the production of most aerosol cans in the United States. However, these chemicals need to be reduced on a global scale. In 1987, thirty-five countries signed the Montreal Protocol on Substances that Deplete the Ozone Layer. Provisions of the agreement include a freeze on CFC production at 1986 levels by 1989, a 20% reduction by 1993, and a 50% reduction of 1986 levels by 1998. However, Governments which signed the Protocol need to enforce compliance, and nations that did not sign it must agree to reduce CFC production for these measures to be effective.

This is a global problem which we all can help solve at home. As consumers, we can influence industrial and government decision-makers with our dollars and votes. We can stop using aerosol products. We can avoid purchasing products wrapped in foam packaging material. (In 1989, McDonald's has been involved in a campaign to recycle styrofoam containers of all kinds. We can check with our local McDonalds to see if they are willing to accept styrofoam containers). When having the air conditioning system of our cars recharged, we can go to service stations which clean and recycle used coolant, rather than vaporizing it into the atmosphere. We can use materials other than rigid foam insulation (blown in with CFC-11 or CFC-12) to insulate our home. We can support legislation for reducing the amount of CFCs produced, and for compliance with the Montreal Protocol.
Worldwide production and use of ozone-depleting chemicals has fallen 95 percent from its peak in the late 1980s and continues to decline. This reduction has been achieved at modest cost.\textsuperscript{11}

Below are some additional tips we can do to protect the ozone layer:

**Car Air Conditioner Tips**

1. Go only to service facilities with EPA-certified technicians

2. Make sure refrigerants from your vehicle will be recovered and recycled during servicing

3. Repair all leaks in the a/c system (not required by federal law, but helpful in protecting the ozone layer)

   Although not required by federal law, this is one of the single best ways to do your part to protect the ozone layer. There are about 20-30 million cars on the road today that use CFC refrigerants in their air-conditioning (AC) systems. If leaky systems were repaired, it would prevent the release of millions of pounds of CFCs into the atmosphere each year.

4. If your air conditioner needs major repairs, talk to your certified service professional about having it converted to use an alternative refrigerant.

**Home Appliance Tips**

1. Repair air conditioners

   Although not required by federal law, this step prevents ozone-depleting refrigerants from escaping. Make certain the refrigerant is recovered before servicing.

2. If you purchase a new A/C system or heat pump, purchase one that uses non-ozone-depleting refrigerant.

3. Remove the refrigerant from refrigerators, air conditioners, and dehumidifiers before disposing of them

   Removing the refrigerant before disposal of old refrigerators alone would prevent the release of about 4 million pounds of CFCs each year. The used refrigerant can be recycled and reused. Ask your local government or waste hauler if the refrigerant will be removed before the appliance is discarded.

4. Make sure your service technician is EPA certified.

5. Work with local officials
Help start a refrigerant recovery and recycling program in your area if none exists. Not only will a responsible appliance disposal help to protect the ozone layer, but the recovered CFC-12 from appliances can be resold, helping to recoup a portion of the costs of the program.

Report Violations

If you suspect or witness unlawful releases of refrigerant or other improper service practices, you can file a report easily and anonymously by calling the Stratospheric Ozone Information Hotline at 1-800-296-1996.12

Conclusion

Ozone depletion is a serious matter. But, it can be controlled. If countries band together, we can tackle the depletion of ozone problems. Industrialized countries should make an effort to help third world countries to substitute CFCs with alternatives. We should provide more incentives to stop using CFCs. World leaders should get together to enforce the Montreal Protocol. I believe we can live in a world of clean air like we used to.
Sources:


SWEETENERS:
HEALTH IMPLICATIONS OF SUCROSE,
ASPARTAME, SACCHARINE,
AND SUCRALOSE

DANIELLE NOBLES
Organic Chemistry, Paradise Valley Community College,
Paradise Valley, Arizona
SWEETENERS:
HEALTH IMPLICATIONS OF SUCROSE, ASPARTAME,
SACCHARIN, AND SUCRALOSE

DANIELLE NOBLES
Organic Chemistry, Paradise Valley Community College,
Paradise Valley, Arizona

ABSTRACT: The taste of sweetness has been a source of craving for centuries. In the American culture today, sweets have become a daily staple in one form or another. Some prefer table sugar, some Sweet N Low®, some Equal®, and yet others maintain organic alternatives for sweetness. The history, chemical structures, studies, and biological breakdowns of the sweet substances sucrose, aspartame, saccharin, and sucralose are reviewed. Although studies of safety and non-safety have been reviewed, and reviewed again on some of these substances, it appears that, to date, good old-fashioned sucrose has the least amount of biologically negative consequences over time.

The different types of sweeteners today attempt to mimic the sweet taste first originated from sugar cane. Sucrose, the derivative of sugar cane, is the most consumed and well-known sweetener today. The world production of sucrose from 1993 to 1994 was 110 million metric tons, 64 percent from sugar cane, and the majority of the remaining 36 percent from sugar beets.¹ Production, along with consumption, continues to rise. The consumption of sucrose has increased 158 pounds per capita from 1995 to 1999.² The increase in sucrose consumption has been positively correlated with the increase in caloric intake of Americans. The result of caloric intake increases is the obvious increase in the average body weight of the American public. Due to the scare of weight gain and obesity, Americans have turned to non-caloric alternatives to sucrose. The question is of the biological safety and effectiveness of these non-caloric sweeteners as they compare to sucrose.

Sucrose, the compound to the left, has been dated back to the derivation place of sugarcane, New Guinea, as early as 12,000 B.C. It is said that Columbus brought sugar to what is now North America when he arrived in 1492-1493. The inaugurate year for sugar mills in this hemisphere was 1508. The first mill was established in Santo Domingo.¹

Since 1508, the production of sugar has skyrocketed, eliciting further experimentation in the realm of sweeteners. In 1953, two chemists by the names of Lemiux and Huber created a method for synthetic sucrose. A reaction was prepared by introducing a syrup-textured 1,3,4,6-tetra-O-acetyl-D-fructose to Brigl's anhydride, 1,2-anhydro-α-D-
glucopyranose triacetate. When this reaction was heated at 100°C for 104 hours, the product, sucrose octa-acetate, was collected with a yield of 5.5 percent. A yield of 8.8 percent occurred when the reaction was heated at 80°C for 168 hours. Remieux and Huber's synthetic method, though successful, was far more complicated and less economically beneficial than utilizing the original source. 

From its natural source, sucrose is a composite structure of one molecule of glucose and one molecule of fructose. This can be seen in the comparison of the molecules below. When sucrose enters the body, it is exposed to a water solution, and begins the metabolic process, it breaks down into its glucose and fructose components. Glucose and fructose are two of the three monosaccharides that are naturally digested in the body to provide it energy.

The metabolic process for sucrose, like other carbohydrates, begins with the break-down of the molecule, hydrolysis, and continues with glycolysis, the Krebs Cycle, and electron transport. Glycolysis is the conversion of glucose to pyruvate and energy. The glucose molecules are converted to glucose 6-phosphate by phosphorylation, or the addition of a phosphate molecule. The phosphate molecule comes from the presence of two ATP molecules, which become ADP after releasing the phosphate group. The second ATP molecule also bonds with the glucose molecule, changing glucose 6-phosphate to fructose 1,6-diphosphate. The fructose molecule of sucrose is converted to fructose 1,6-diphosphate as well. The fructose 1,6-diphosphate molecule is reduced to two, three carbon strands. These intermediates are oxidized, resulting in pyruvic acid and energy, in to form of 4 ATP molecules. The pyruvic acid then enters the mitochondrion.
Once the pyruvate, or pyruvic acid, enters the mitochondrion, it is exposed to oxygen, and is subsequently converted to acetyl CoA, the Krebs Cycle begins. The Krebs Cycle is a series of redox reactions, the first of which is a condensation reaction between acetyl CoA, oxaloacetate, and water to produce citric acid (step 1). Citric acid is converted to its isomer, isocitrate, by means of dehydration and subsequent hydration (steps 2A and 2B). Two oxidative decarboxylation reactions then occur, producing, as byproducts, carbon dioxide and NADH (steps 3 and 4). This is the point at which the ΔG is at a minimum.

The product from step 4, succinyl-CoA, then forms a high-energy phosphate bond with GDP, which creates GTP. The GTP continues reacting to produce the ATP shown in step 5. The process proceeds with the dehydration of succinate (step 6), the hydration of fumarate (step 7), and the dehydration of malate (step 8). The dehydration reactions produce FADH and NADH, respectively. All FADH and NADH molecules created in the Krebs Cycle go on to the electron transport chain, where they are converted to ATP. Once all NADH, FADH, and GTP molecules have been synthesized, 36 moles of ATP are created from each molecule of glucose. Furthermore, each molecule of sucrose shares this potential to create a tremendous amount of energy for the body.

Sucrose has been used and enjoyed as a sweetener for centuries. Sucrose is metabolized in the body naturally, just as other carbohydrates are. The result of sucrose metabolism is ATP, which is the energy used by the muscles and the brain to conduct
proper organ and neurological function. The only cited negative consequences of sucrose consumption are linked to overindulgence. The Food and Drug Administration suggests that additional sucrose should be limited to 48-72 grams, depending on a person’s daily caloric intake. Each gram elicits 4 kcal of energy. Extreme over consumption can lead to hyperactivity followed by fatigue. This is due to the differences in energy created over time. Persons with diabetes are obviously advised differently with regard to their sucrose intake.

Sucrose is also superior due to its chemical properties. Sucrose is produced in crystal, block, or powder form, and is stable in air. Sucrose absorbs moisture up to one percent, and releases this moisture at 90°C. One half ml of room temperature, or .2 ml of 100°C plus, water will dissolve one gram of sucrose. Sucrose is also soluble in alcohol and methanol, and partially soluble in glycerol and pyridine. Sucrose elicits a sweetness that is void of lingering after-taste, and possesses the properties which make it useful in cool, hot, or baked foods. It is also used as an additive to provide bulk, texture, preservation, color, and, of course flavor to foods and pharmaceuticals.

![Aspartame](https://example.com/aspartame.png)

Aspartame

Non-nutritive, or non-caloric, sweeteners are defined as high-potency sweeteners that provide no substantial amount of nutrients. Aspartame is one of the oldest synthesized and most widely used non-nutritive sweeteners. In 1965, a pharmaceutical chemist, James Schlatter, founded Aspartame while researching ulcer treatment medication. Schlatter started with a tetrapeptide found in the stomach. This molecule was to be synthesized, bypassing the intermediate now known as aspartane, aspartyl-phenylalanine methyl ester. It is said that the chemist got a bit of the substance on his hands, only to notice when he licked his fingers to separate paper. He had supposedly washed his hands since eating his donut breakfast, and attributed the sweet taste to the stable intermediate he had created. The synthesis of aspartane is explained by the chemist Hartmut Pietsch, and is summarized in the mechanism on the following page.

Aspartame was patented, and was originally approved by the Food and Drug Administration in 1974. This approval was relinquished after five months, due to negative biological concerns regarding the substance. Seven years later, with scientific review, aspartane was approved for use in cereals, powdered drinks, fillings, whip cream, and gum. It took another two years for aspartane to gain approval for use in carbonated beverages. In 1985, The American Medical Association deemed aspartane safe. In 1996, and after 26 evaluations by the Food and Drug Administration, aspartane was approved as a general-purpose sweetener. Regardless of the controversy, the demand for the sweetener increased from 8.4 million pounds to 17.5 million pounds from 1986 to 1992. Americans consume over 80 percent of the world’s usage of aspartane.
Aspartame enters the body in its molecular state, which is composed of a methanol, an aspartate, and a phenylanaline group. As the body processes the sweetener, it breaks down into these components, leaving the body to handle methanol, which metabolizes to formaldehyde, aspartate, an excitotoxin, and phenylalanine. When these components are evaluated independent of aspartame, they are known to have potentially detrimental or fatal effects in the human body.

Methanol enters the body, and is readily absorbed in the small intestine. After it is absorbed, methanol is slowly oxidized to formaldehyde. The rate of oxidation in human subjects has shown a half-life of about three hours. This slow rate increases the toxic effects of methanol in the body. Methanol is ingested naturally in an amount of less than 10 mg daily. The average amount of methanol ingested from aspartame-sweetened beverages is 55 mg per liter. This means that if a person drinks even one can of aspartame-sweetened soda, he or she has already exceeded the normal daily intake. By the addition of aspartame as a sweetener, the body is not only being exposed to excessive amounts of toxic methanol, but it is also being exposed to a comparable amount of its formaldehyde derivative.

Formaldehyde is known to be highly reactive, bonds with nucleic acids and proteins in the body, and, in both its gas and liquid forms, is listed by the Environmental Protection Agency as toxic and carcinogenic. If ingested, formaldehyde is known to cause inflammation, coagulation necrosis, or ulcers in the gastrointestinal tract. The liver, kidneys, heart, and brain can also have degenerative affects due to the presence of formaldehyde in the body. Other possible, severe consequences include proteinuria, acidosis, hematemesis, hematuria, anuria, and vertigo. More than 28 studies have proven
the carcinogenicity of formaldehyde in the human body. Although the majority of these studies report data from exposure to formaldehyde gas, others are linked to ingestion of the liquid form. Animal studies report ingestion to cause gene mutations, single strand breaks in DNA, and in vitro transformation in mouse cells. Hamster cells have shown inhibition with regard to DNA repair. Aspartame, being a parent to formaldehyde, shall be, and has been, correlated to many of these effects.

Aspartate, or aspartic acid, is classified as an excitotoxict neurotransmitter. Excitotoxins are amino acids or amino acid derivatives that have been reported to cause neuronal injury or death by reacting with specific neuron receptors. Aspartic acid, along with glutamate, has been scientifically linked to the cause of diseases such as Alzheimer’s, Huntington’s, Parkinson’s, and some dementias. Aspartate is one chemical that, due to its known effects, is being questioned as a cause for minor, age-related conditions, such as memory loss.

Phenylanaline is the aspartame by-product that has been the subject of study most often. The extensiveness of study is due to the scientifically identified correlation between this substance and the type of central nervous system damage characteristic of the disease phenylketonuria. Phenylketonuria is a congenital metabolic dysfunction. Persons with Phenylketonuria cannot properly metabolize phenylalanine, and therefore, are advised to abstain from consuming foods with aspartame. The question arose regarding whether a mother’s exposure to aspartame, and subsequently to phenylanaline, increased the exposure to the fetus as well. It was found that the phennaline easily permeates the placenta. When the concentrations of exposure were measured, the concentration to the fetus was one and one half times higher than that to the mother.

The Food and Drug Administration has stood to overlook the dangers of methanol, aspartate, and phenylanaline, when exposure is due to the use of aspartame. Their position is that the potency of the sweetener yields a decreased quantity of exposure. They base their position on studies that suggest either exposure does not produce a detectable biological change, or the change produced is not indicative of toxic level exposure.

Aspartame, though it remains an approved sweetener, does have limitations as such. Each gram of aspartame elicits 4 kcal of energy, an amount equal to that of sucrose. The reason aspartame can be considered a non-nutritive sweetener is due to its sweetness index. Aspartame is 180 to 200 times sweeter than sucrose. This is also the reason that the FDA is able to consider reduction in exposure as a factor in overlooking the harmful effects of its components. The FDA indicates that consumption under 50 mg of aspartame per kg of body weight is acceptable. This can be viewed as 18 cans of diet soda, or the equivalent, for a person whom weighs 132 pounds. This amount has been scrutinized for its lack of specificities with regard to aspartame’s metabolic derivatives.

The limitations for the use of aspartame as an additive are attributed to its properties. Aspartame is heat sensitive. The compound remains stable and is water soluble at room temperature; however, as temperature increases, the rate of
decomposition also increases. When aspartame is exposed to high temperatures, the methyl ester group undergoes bond cleavage, and the sweetener, consequently, loses its sweet taste. Aspartame also has a low dissolution rate. Low dissolution rates have been problematic when the sweetener is used in diet beverages. Many companies have patented different solutions to this particular problem.\textsuperscript{15}

Another readily used, non-nutritive sweetener is saccharin, the molecule pictured to the left. Saccharin, 3-oxo-2,3-dihydro-1,2-benzisothiazole 1,1-dioxide, \( \sigma \)-sulfobenzenimide, or \( \sigma \)-benzosulfimide, was accidentally discovered in 1878, making it the oldest of the non-nutritive sweeteners. On the day of saccharin's discovery, Chemist Constantine Fahlberg was working in a John Hopkins University laboratory, overseen by Ira Remsen. Later that evening, and while eating dinner, Fahlberg reported noticing a sweet taste on his hands. Saccharin was born; and, its synthesis was published attributing both Fahlberg and Remsen for its creation. As time passed, Fahlberg alone was awarded the patent. Remsen, a then future president of John Hopkins College, reportedly stated disgust for his former, and rich, laboratory partner.\textsuperscript{7}

Since the original synthesis of saccharin, the process has been enhanced. Fahlberg and Remsen synthesized the sweetener by means of separating ortho- and para-isometric intermediates. The Maumee Chemical Company discovered a more current method in 1950, and an even simpler method, as detailed below, since that date.\textsuperscript{15} The newer synthesis involves the intermediate diazonium ion.

\[
\begin{align*}
\text{C}_{6}\text{H}_{4}\text{NH}_{2} \xrightarrow{\text{HNO}_2} \xrightarrow{\text{HCl}} \xrightarrow{\text{N}_2} \xrightarrow{\text{H}^+} \text{C}_{6}\text{H}_{4}\text{COOCH}_{3} \xrightarrow{\text{HCl}} \text{C}_{6}\text{H}_{4}\text{COOCH}_{3}
\end{align*}
\]

Saccharin is one non-nutritive sweetener that is not metabolized in the body. The chemical does not show a build-up in body tissues; in fact, it is reportedly released in urine.\textsuperscript{16} The problem with a synthetic and foreign chemical that passes through the body is its strain on the liver. The liver is the organ vital to the cleansing of the body. The liver works to rid the body of toxins, impurities, and other debris from the bloodstream. It also metabolizes hormones, chemically processes vitamins, enzymes, and food, and produces glucose from carbohydrates and proteins. Additives, such as saccharin, can eventually affect the liver. When the liver has more toxins and debris to purify from the body than it is designed to handle, it can become strained. When the liver is strained, it can decrease in effectiveness to a point that is lower than normal. This phenomenon has been compared to a treadmill that is moving too quickly. There is a threshold for strain that will cause an amount of failure.
This failure of the liver to function properly means that toxins fail to be cleansed, chemical processes do not occur to par, glucose production for brain functioning is decreased, hormones are not properly metabolized, and all of the liver’s other functions are impaired. This result may be linked to the controversy of saccharin as a carcinogenic substance. In 1977, saccharin was reviewed for relinquishment of its FDA approval. A study indicated a carcinogenic effect when male rats were given large doses of saccharin. The American public was strongly against the relinquishment; therefore, Congress passed the Saccharin Study and Labeling Act. This Act allowed the continued use of saccharin, so long as all products containing the substance were labeled with a warning of its possible carcinogenic effects. The suspension of approval for the use of saccharin continued until 1997. In this year, the Food and Drug Administration indicated that saccharin and its derivatives may be used with or without the presence of a warning label. This revelation was attributed to new FDA standards that were designed to account for differences between humans and research subject exposure, not new research.

Saccharin, like other sweeteners, has properties that determine its use. Saccharin is 300 times sweeter than sucrose in powder form, and 500 times sweeter in an aqueous solution. Saccharin is not heat sensitive, but requires 290 ml of room temperature water to dissolve one gram. This means that it is less likely to fully dissolve in foods than other sweeteners. Another downfall is its bitter and metallic after taste, making it a less desirable alternative to some people.

The Food and Drug Administration indicates that saccharin can be ingested in an amount of 500 mg per day for children and 1000 mg per day for adults. This amount, though seemingly high, is comparable to the daily recommended allowance of sucrose. The difference is that saccharin is limited due to its toxicity and possible carcinogenic effects at higher dosages, whereas sucrose is not. The UK government contradicts the FDA by first stating an acceptable, daily dosage of 2.5 mg per kg of body weight. This is 150 mg for a person weighing 132 pounds. A study suggested that almost three percent of the studied group ingested more than the recommended amount, and 2.5 percent of diabetic people studied consumed more than 455 mg per day. The UK now indicates an acceptable amount of five mg per kg of body weight, still much lower than that of the FDA.

The potential and proven problems caused by the currently approved non-nutritive sweeteners have caused a desire for other alternatives. One study evaluated the intensity of sweetness as it related to molecular structure. Hough and Khan indicate that the design of new sweeteners must be based on the human taste buds, and therefore the receptor sites on the tongue. There are theories with regard to molecular structure and their abilities to bond with these receptor sites. The first, presented in 1967 by Shallenberger and Acree, stated that there must be one hydroxyl group that is a hydrogen bond donor, AH, and another hydroxyl group that acts as a hydrogen bond acceptor. The theories have continued. In 1978, Hough and Khan state that an important configuration is a 1'-chloro substituent on the fructofuranose unit of sugar is important for increasing the intensity of sweetness.
Ironically, the synthesis of sucralose follows the pattern of thinking Hough and Khan developed years ago. Sucrose, the molecule to the left, is a trichlorodisaccharide that is synthesized by substituting the three hydroxyl groups for three chloro groups via blocking and unblocking specific alcohol groups.\textsuperscript{13}

Despite the fact that the synthesis of sucralose follows a predetermined pattern for the creation of intense sweeteners, it is said that the discovery was accidental.\textsuperscript{7} The British sugar company Tate and Lyle were funding a mechanism for using sucrose as a chemical intermediate. The funded chemists, from King’s College, were synthesizing halogenated sucrose molecules. Misunderstanding the request of Professor Leslie Hough (ironically named), a student, Shashikant Phadris, tasted the chlorinated sugar instead of testing it. The discovery was sucralose.

Sucralose breaks down into its respective chlorinated morosaccharides in the body. These components are 4-chloro-4-deoxy-galactose and 1,6-dichloro-1,6-dideoxyfructose. This breakdown is displayed below. There is much uncertainty as to the biological effects of sucralose’s components, as there has not yet been a sufficient amount of long-term, scientific studies to make any conclusions. This is the reason for its only recent approval by the FDA. The petition to approve sucralose had been pending in the United States since 1987. The sweetener was first approved in Canada in 1991, followed by other countries, prior to the US.\textsuperscript{15}

Some scrutiny has been placed on the molecular base of sucralose as it compares to the base of products such as pesticides. Studies have not, however, implied that sucralose is either carcinogenic, or that it causes genetic alterations, birth defects, or neurological damage. These results held true up to 500 mg per day in human subjects.\textsuperscript{16} One topic for scrutiny may be its release of HCl, in small quantities, upon being stored at high temperatures. This reaction is said to be reversible with the presence of diluting agents such as maltodextrin. The problem is that the general public is likely not aware of this problem. To date, sucralose remains safe, as stated by the Food and Drug Administration.

The majority of the properties of sucralose appear to make it a viable alternative to sucrose. Sucralose is 400 to 800 times sweeter than sucrose, and it does not harbor a poor after taste. Sucralose is not heat sensitive, and is more soluble than saccharin in water.\textsuperscript{4} This makes it versatile for use in both hot and cold beverages and foods. Sucralose is not metabolized as a carbohydrate, but may pass through the liver as a toxin.
Overall, and given current research, sucralose appears to be a more reasonable alternative to its calorific counterpart, sucrose, than other approved, non-nutritive sweeteners.

Additional alternatives to non-nutritive sweeteners have derived from the synthesis of plant extracts. Organic sources appear to be heading the innovative movement for safer sweetener alternatives. At least since 1998, studies have reported the use of non-sacchariferous plant species as a source for low-calorie sweeteners. These possible sweeteners are recorded to have a sweetness potential of 100-10,000 times greater than sucrose. The oldest of these non-sacchariferous plants is Licorice. Licorice has been used since 500 B.C., and has a potential sweetness that is 100 times larger than sucrose. Thaumatin, an extract of the Marantaceae species, was discovered in 1855, and is recorded as being 10,000 times sweeter than sucrose. These are only two of the many plant hosts for sweetness.

Many Americans are turning to plant derived sweeteners. One of these plant hosts is Stevia Rebudiana. Steviolude, the derivative sweetener, is 250 to 300 times sweeter than sucrose. Steviolide is not heat sensitive, and can be used in both hot and cold substances. About one-fourth to one-third teaspoon of steviolide can be used in place of one entire cup of sugar. Steviolide is manufactured in both powder and liquid forms.

Stevioide has not been approved by the FDA, but it can be purchased, as a dietary supplement, in local health food stores. Variations of steviolide increase the consumer choice with regard to the sweetener. Steviolide can also be combined with other sweeteners to achieve a desired taste.

Stevioide has not been sufficiently researched in the United States, but has been an approved sweetener in Japan since 1970. It is either not, or scarcely reported as to its biological break-down in the body. Steviolide, however, does appear to be a possible alternative to more synthetic sweeteners, and may be the beginning of a movement toward the use of plant derivatives to sweeten foods.

The American public has a conflicting desire to increase sugar consumption, while decreasing body weight. This conflict has lead to the increased supply and demand of non-nutritive sweeteners. Unfortunately, an inverse correlation between non-nutritive sweetener usage and body weight has not occurred. This may lead to the belief that the reduction in calories from sucrose, at 4 kcal per gram, to its alternatives, from 0 to 4 kcal per gram, has not been significant enough to facilitate body weight reduction. Instead,
Americans are merely exposing themselves to toxic substances, possible carcinogens, and other biologically undesirable and unnecessary conditions.

Alternative sweeteners do, however, have a place in society. When an alternative sweetener is necessary, this review suggests that the least synthetic substances are likely to have the least amount of negative side effects. In other words, plant derivatives or sucralose may be the best alternative choice, but no substance has proven to be healthier than good, old-fashioned sucrose.
BIBLIOGRAPHY


CHEMISTRY 236
ORGANIC CHEMISTRY

FINAL PROJECT

Alprazolam
(Xanax)

16 April, 2004

Nancy C. Groat Ogana

Dr. Hank Mancini
Paradise Valley Community College
ABSTRACT

Alprazolam, the generic name for xanax, is an oral medication indicated for symptoms of anxiety with depressive symptoms, panic disorder with or without agoraphobia and could also be used as a sedative. Alprazolam is a benzodiazepine, a class of medications that work on the Central Nervous System, which falls under a general category of psychotropic agents that include Anxiolytics, Sedatives and Hypnotics. Alprazolam is commercially manufactured in the United States by Upjohn and Pharmacia Companies, and the concentrate version is manufactured by Roxane.

CLINICAL PHARMACOLOGY

Mechanism of Action

Benzodiazepines work by enhancing the gamma-aminobutyric acid (GABA)-Benzodiazepine receptors. Benzodiazepines do not produce a true “anesthetic result” and consciousness is still experienced and complete motor relaxation is not achieved even after administration of large doses. “Retrograde amnesia may take place and this creates the illusion that anesthesia has occurred” (1). However, surgical anesthesia effect can be achieved by combining Alprazolam with other Central Nervous System depressants.

Alprazolam is believed to work by partial aid of GABA, a major inhibitory neurotransmitter of the Central Nervous System with receptor sub-units GABA-A and GABA-B. According to the Walgreens’ Pharmacy website, the GABA-A receptors couple with the Alprazolam receptors. The Central Nervous System has three receptors namely Benzodiazepine, found in the cerebral cortex and cerebellum, the BNZ₂ receptors found in the cerebral cortex and in the spinal cord and the BNZ₃ receptors found in the peripheral tissues. Alprazolam and other Benzodiazepines bind to BNZ₁ and BNZ₂,
stimulating effects of GABA. Unlike barbiturates like alcohol that augment GABA response by keeping the chloride channels open for longer periods of time, Alprazolam and other Benzodiazepines increase GABA’s affinity for the GABA receptors, and it is the “binding of GABA to the site that opens the chloride channel resulting in a hyperpolarized cell membrane that prevents further excitation of the cell”(2). Activation of BNZ₂ is thought to affect muscle relaxation, anticonvulsant activity, motor movement and memory. Alprazolam is also thought to negatively impact cerebral concentrations.

CHEMISTRY

Chemical Structure:

![Chemical Structure of Alprazolam]

Chemical name: 8- chloro-1-methyl-6-phenyl-4H-S-triazolo [4,3-α] [1,4] benzodiazepine.

Molecular Weight (MW): 308.77

Molecular Formula (MF):

Melting Point: 228.0°C

Alprazolam is a white to off-white powder. It is readily soluble in methanol and
Ethanol but has no appreciable solubility in water at physiological pH. (5). Alprazolam would have a UV-Vis absorption, indicating presence of a chromophore in the substance. An IR of this drug would show absorption peaks between 2300-2100 cm\(^{-1}\) because of the C≡C bonding, 3100-3000 cm\(^{-1}\) absorption peak because it is an =ene, 1250-1020 cm\(^{-1}\) because of the C-N bonding and a peak between 840-690 cm\(^{-1}\) that would confirm its aromaticity. Commercial Alprazolam tablets come in different concentrations ranging from 0.25mg, 0.5mg, 1.0mg, and 2.0mg immediate release tablets, all of which have an extended release version (XR) as well, and the 3.0mg tablets that come in extended release formula only. The 2.0mg tablets are multi-scored and are readily breakable into segments of one milligram or one half milligrams.

Alprazolam contains inactive ingredients that include cellulose, corn starch, docusate, silicon dioxide and sodium benzoate. In addition, the one half milligram tablet also contains FD&C Yellow Number six, and the one milligram tablet contains FD&C Blue Number two. Alprazolam is also commercially available as a concentrate solution of 1mg/ml. The drug should be stored in tight containers and away from light, at temperatures ranging from 15\(^0\) -30\(^0\)C.

This drug is a controlled substance under the Controlled Substance Act of 1970 by the Drug Enforcement Administration as a schedule IV (3). Under this act, drugs and substances are categorized according to their medical use, abuse and potential harmfulness. However, in some countries, Alprazolam is available without a prescription and is not a controlled substance.
PHARMACOKINETICS

Dosage and Administration

Alprazolam is administered orally. Before administration, oral concentrate doses should be diluted with thirty milliliters of water or of other diluents used like juice or semi-solid foods.

The smallest effective dose of Alprazolam should be ministered to avoid ataxia. In case of rebound of symptoms in previously stabilized patients, dose adjustment or change in administration time of the same dose should be considered. Alprazolam may be taken on an empty stomach or with food or milk. The tablet may be crushed.

INDICATIONS AND USAGE

Alprazolam is indicated for treatment of anxiety disorder like APA Diagnostic and Statistical Manual (DSM –III-R) or short term relief of anxiety disorder. Some characteristics of Generalized Anxiety Disorder include exaggerated worry over two or more life situations for a period of six months or longer, during which the person has had worries on more days than not about these situations. This drug is also used to treat acute stress disorder, a condition resulting from recent extreme stress, and which resolves after a short period of time. Symptoms associated with anxiety include motor tension, restlessness, palpitations, fatigue, dry mouth, sweating mood swings, nausea, diarrhea and insomnia (4).

This medication is also indicated for treatment of Panic Disorder, a condition whereby panic attacks are experienced on and off. The panic attacks are unexpected at first but become regular with time. Four such attacks within a month or constant fear of having another attack would be considered a Panic Disorder. The patient would also experience
paranoia, abdominal distress, dyspnea, sweating and tachycardia. Effectiveness of Alprazolam has been achieved in four months period in Clinical Studies of Anxiety Disorder patients, and four to ten weeks in Panic Disorder patients. Alprazolam use in children under eighteen is still not proven (5).

DISTRIBUTION AND ELIMINATION

Alprazolam is rapidly absorbed following oral administration of the immediate release tablets, with a usual onset action time of fifteen to thirty minutes and peak plasma concentrations achieved within one to two hours.

According to the Walgreens’ Pharmacy website, the drug is ninety percent plasma protein-bound, mainly to serum albumin (2). “Generally, Benzodiazepines and their metabolites cross the placenta; and the concentration in the fetal circulation has been reported to be equal to or greater than the maternal plasma drug concentrations” (3). Alprazolam can also distribute in breast milk.

Alprazolam has a half-life of approximately eleven and a half hours. According to the Walgreens’ website, Alprazolam undergoes oxidative metabolism in the liver through CYP3A4, producing metabolites with little or no activity. The alpha-hydroxy-alprazolam metabolite is approximately one half as potent as the parent compound while the benzophenone derivative is inactive. Both metabolites are primarily secreted in the urine. The Extended Release Tablets have a comparably slower absorption rate with a constant concentration maintained between five and eleven hours following administration. The Extended Release tablets have a half-life of between eleven to sixteen hours (2).

CONTRAINdications
Alprazolam is contraindicated in patients sensitive to the drug and other benzodiazepines. Alprazolam may be used in patients with open angle glaucoma but may not be used in those with acute angle glaucoma. Alprazolam is contraindicated with medications that significantly disable the oxidative metabolism aided by cytochrome P450 CYP 3A like Ketoconazole and Itraconazole (5). Fluvoxamine “doubles the maximum plasma concentrations of Alprazolam and decreases clearance by forty nine percent, increases half-life by seventy one percent, and decreases measured psychomotor performance” (4).

This drug is also contraindicated in pregnant or breast-feeding women and patients with myasthenia gravis. Alprazolam should be used carefully in bipolar patients because mania and hypomania could result. This medication should be used cautiously in patients with respiratory depression, pulmonary disease like chronic obstructive pulmonary disease or sleep apnea because it can trigger ventilatory failure. Though rare, incidents of death have been reported in some cases of patients with severe pulmonary disease following the administration of Alprazolam (2).

Alprazolam may worsen symptoms of patients with late stage Parkinson’s disease, impair a patient’s ability to operate machinery, and should be used with extreme care in patients with renal impairment due to possibility of adverse reactions from drug accumulation. Reduced elimination of the drug has also been reported in obese patients (2).

Patients with severe hepatic disease and Geriatric patients run a risk of toxicity due to the prolonged half-life of the drug. A major food interaction is grapefruit juice, which
adversely increases peak serum concentrations. Smoking reduces the drug plasma concentration by approximately fifty percent (2).

SIDE EFFECTS

Side effects of Alprazolam include an extension of its pharmacological effects like drowsiness, light-headedness, convulsions, tremors and insomnia.

Alprazolam can cause psychological and or physical dependence, especially if administered in large doses over a long period of time (6).

There is risk of seizure following sudden withdrawal or abrupt dosage reduction. The risk of seizures has been reported to be greatest twenty four to seventy two hours after discontinuation (2).

Children born of women on the medication may suffer withdrawal symptoms like neonatal flaccidity and respiratory problems. Continuous administration to nursing mothers could lead to loss of weight and lethargic infants. (4).

Paradoxical reaction, hypotension and increased liver enzymes are also possible side effects. Other side effects include allergic reactions, hives, fatigue, blurred vision, decreased libido, anorexia and akathisia (6).

The table below is from a clinical study of some untoward effects of Alprazolam administered over a short period of time to treat anxiety with doses of upto four milligrams a day. Alprazolam relieved some symptoms in some patients, but induced the same symptoms in others (Table 1), (7).
DATA

Table 1 Anxiety Disorders

<table>
<thead>
<tr>
<th>Treatment-Emergent Symptom</th>
<th>Incidence</th>
<th>Incidence of Intervention Because of Symptom</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Alprazolam</td>
<td>Placebo</td>
</tr>
<tr>
<td>Number of Patients</td>
<td>565</td>
<td>505</td>
</tr>
<tr>
<td>% of Patients Reporting</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drowsiness</td>
<td>41%</td>
<td>2.6%</td>
</tr>
<tr>
<td>Light-headedness</td>
<td>20.8%</td>
<td>19.3%</td>
</tr>
<tr>
<td>Depression</td>
<td>13.9%</td>
<td>18.1%</td>
</tr>
<tr>
<td>Headache</td>
<td>12.9%</td>
<td>19.6%</td>
</tr>
<tr>
<td>Confusion</td>
<td>9.9%</td>
<td>10%</td>
</tr>
<tr>
<td>Insomnia</td>
<td>8.9%</td>
<td>18.4%</td>
</tr>
<tr>
<td>Nervousness</td>
<td>4.1%</td>
<td>10.3%</td>
</tr>
<tr>
<td>Syncope</td>
<td>3.1%</td>
<td>4%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>1.8%</td>
<td>0.8%</td>
</tr>
<tr>
<td>Akathasia</td>
<td>1.6%</td>
<td>1.2%</td>
</tr>
<tr>
<td>Tiredness/ Sleepiness</td>
<td>*</td>
<td>*</td>
</tr>
</tbody>
</table>

* Events not reported by Alprazolam patients.

CONCLUSION

In these modern times come complications and more demand in life. This is a positive contribution by scientists to help people keep up with these changes and keep living full, productive lives. I believe Alprazolam will be around for a long time and if anything, will continue evolving into even more effective formulae that will eliminate some of the side effects and produce improved outcome.
BIBLIOGRAPHY

1.) Hoover, E. J. Et. al. (2000). Rxemington. The Science and Practice of Pharmacy (pp. 1408-1409).


3.) McEvoy, G. K., & Miller, J. American Society of Health-System Pharmacists (pp. 2360-2361).


Vaccine Preservatives, Specifically Thimerosal as a Possible Cause of Autism

Emily Oliver

April 16, 2004
Abstract:

Autism is an increasingly prevalent disorder that is characterized by abnormal social relatedness, language and communication, a need for routine sameness, abnormal movements and sensory dysfunction. Mercury is a heavy metal that is toxic and can cause immune, sensory, neurological, motor, and behavioral dysfunctions similar to those found in children with autism. Thimerosal is a mercury-based preservative used in vaccines and has frequently become a major source of mercury in human infants and toddlers. The use of this preservative in routine childhood vaccinations is possibly causing mercury poisoning in children and contributing to a soar in the occurrence of autism.

Introduction to Thimerosal:

Thimerosal, 2-[(ethylmercury) thio] benzoic acid, sodium salt (C9H9HgNaO2S) is an organic mercury compound that is about 49% mercury by weight. It is used most often for its antibacterial properties. It has been widely used since the 1930’s as a disinfectant and preservative in vaccines particularly those packaged in multi dose containers (1). Thimerosal has a molar mass of 404.81. Its structure appears in figure 1 below:

Figure 1:

MSDS Information for Thimerosal:

Thimerosal comes in a white fine crystalline powder with a characteristic odor. It has a pH value of 6.7-8.2 in water. The melting point is 232°C-233°C. Thimerosal is soluble in water at 1 gram per 1 mL of water. It is soluble in ethanol at 1 gram per 8 mL of ethanol. It is practically insoluble in ethyl ether and benzene at any weight. According to Material Safety Data Sheet (MSDS) for thimerosal it is considered very toxic by inhalation, contact with skin and if swallowed. There is a danger of cumulative effects. Respiratory, eye and hand protection are required for handling. Substances to be avoided include aluminum and any reducing agents. The acute toxicity for thimerosal is LD50 of 75mg/kg. The warning as applies to organic mercury compounds in general states that long-term exposure leads to disorders/damage of the nervous system(2).

Thimerosal as a Vaccine Preservative:

Thimerosal as stated above is used in vaccines as a compound that kills and prevents the growth of microorganisms. Such a preservative is needed due to possible contamination of vials especially those who allow for multi dosing. Historically the necessity for such additives was due to an incident in Australia in which several children given a vaccination died with the cause found to be living staphylococci that had contaminated the vial as a result of repeated puncturing for multi doses. Thimerosal is extremely effective as such a preservative in that it kills the specified organisms and prevents growth of fungi. At concentrations of 0.001% to 0.01% there is seen an effective clearing of a broad spectrum of pathogens. In a vaccine containing 0.01% thimerosal it contains 50 micrograms of thimerosal per .5mL dose or 25 micrograms of mercury per .5mL dose(3).
Thimerosal Toxicity:

Thimerosal is degraded into ethylmercury and thiosalicylate. Ethylmercury is an organomercurial meaning it is mercury in the organic form. Organic forms of mercury are more easily absorbed when ingested and are less readily eliminated from the body than inorganic forms. Methylmercury is another form of organic mercury that is toxic and exposure to humans usually occurs from the consumption of seafood. The guidelines for mercury toxicity are based on epidemiological and laboratory studies of methylmercury. Thimerisol is a derivative of ethylmercury so different toxicological profiles would be expected. However there is little definitive data on the toxicity of ethylmercury therefore the FDA considers both ethyl and methylmercury as equal in risk evaluations. Methylmercury is a neurotoxin that was first discovered during the 1950’s in Minamata Bay Japan in which there was an industrial discharge of mercury into the bay which resulted in mercury contaminated fish that were consumed by the public. During this epidemic it was found that fetuses are more sensitive to the effects of the mercury than the adults. Sensory and motor neurological dysfunction and developmental delays were observed in children exposed in utero. Based on studies such as this a “safe” exposure level was created for mercury. These exposure levels range from 0.1μg/kg body weight/day to 0.47μg/kg body weight/day. These levels are applied as well to safe levels for thimerosal.(3)

Physiological Reactions with Mercury:

Once mercury enters the blood it binds to hemoglobin in red blood cells. Mercury binds to cysteine residues in the hemoglobin molecule because they lie on the surface of the molecule. Mercury ions are hydrated in aqueous solutions. There are pH dependant reactions that form mercury-substituted oxonium ions, these reactions are seen in figure 2:(4)

Figure 2:

\[ \text{CH}_3\text{Hg(OH)}_2^+ + \text{OH}^- \leftrightarrow \text{CH}_3\text{HgOH} + \text{H}_2\text{O} \]

\[ \text{CH}_3\text{Hg(OH)}_2^+ + \text{CH}_3\text{HgOH} \leftrightarrow (\text{CH}_3\text{Hg})\text{OH}^* + \text{H}_2\text{O} \]

\[ \text{CH}_3\text{HgOH} + (\text{CH}_3\text{Hg})\text{OH}^* \leftrightarrow (\text{CH}_3\text{Hg})\text{O}^* + \text{H}_2\text{O} \]

Researchers state that the types of complexes formed by the two ions differ greatly; The Hg2+ compounds of amino acids containing SH groups are polymeric and polar and the CH3HgR species are nonpolar and monomeric. The cysteinate is with a linear C-Hg-S. The chemical formation of these oxonium complexes may affect the mercury transport in the bloodstream(4). Approximately 10% of the body’s burden from mercury poisoning is in the brain where it is demethylated to inorganic mercury. Mercury is also easily transferred to the fetus and fetal brain with permeability across the blood-brain barrier through a mercury-f-cysteine complex which transports it to the amino acid carrier(4). In the human brain mercury reduces the viability of a major brain protein called tubulin but has no effect on another major protein called actin. Both tubulin and actin are necessary for the growth of dendrites and maintenance of axon structures in neurons. Exposure to mercury results in the stripping of tubulin from the axon and leaves bare neurofibrils that tangle causing neurodysfunction. Thimerosal not only reduces the viability of tubulin but also destroys the viability of actin causing great damage to the central nervous system. In
a study conducted by Dr. Boyd Haley from University of Kentucky, Lexington, it was found that the presence of thimerosal is severely toxic to numerous brain proteins. The toxic effects were also seen at levels 10,000 times less than the thimerosal concentrations found in most vaccines. The most common symptoms of mercury poisoning are psychiatric disturbances, speech language and hearing deficits, sensory abnormalities, motor disorders, cognitive impairments, unusual behaviors, visual impairments, physical disturbances, gastrointestinal disturbances, abnormal biochemistry, immune dysfunction, Central nervous system pathology, abnormalities in neurochemistry, EBG abnormalities, and epilepsy(5).

**Diagnosing Mercury Poisoning:**

Mercury poisoning is often difficult to diagnose and is often mistaken as a psychiatric disorder. This difficulty can be attributed to two characteristics of mercury poisoning, the latent period between exposure and symptoms onset and the widespread manifestations of the disease. Currently criteria exist to distinguish the poisoning. An observation of impairments in motor/movements, sensory abnormalities, psychological and behavioral disturbances, neurological and cognitive deficits, impairments in language, hearing, and vision and miscellaneous physical presentations such as rashes or strange reflexes. Known mercury exposure at impairing level. Detectable levels of mercury in blood, urine, or hair(6).

**Mercury Poisoning and Autism:**

Medical literature has found that the characteristics of autism and mercury poisoning are extremely similar. The parallels found between these two diseases have led researchers to suggest that some cases of autism are actually forms of mercury poisoning. Autism is considered to be a neurodevelopmental disease that emerges early in life and has an extreme variation in symptom expression and levels of severity for those symptoms. To diagnose autism there is a variety of criteria including qualitative impairments in social relatedness, deficits in verbal and nonverbal communication and the presence of repetitive and restricted behaviors or interests. Other traits associated with autism include movement disorder, sensory dysfunction, cognitive impairments as well as gastrointestinal difficulties and immune abnormalities. The onset of autism occurs before 36 months of age and can appear sooner. In most cases there is normal development followed by regression and then a failure to properly progress normally. In a symptom comparison done by the Autism research Center the following tables were compiled showing the irrefutable likeness between possible autism and mercury poisoning symptoms:

**Table 1:**

<table>
<thead>
<tr>
<th>Mercury Poisoning</th>
<th>Autism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extreme shyness, social withdrawal</td>
<td>Social deficits, social withdrawal</td>
</tr>
<tr>
<td>Mood swings, laughing crying without provocation</td>
<td>Mood swings, flat affect, no facial expression, laughing/crying without reason</td>
</tr>
<tr>
<td>Obsessive compulsive traits</td>
<td>OCD traits, repetitive thoughts and behaviors</td>
</tr>
<tr>
<td>Lack of eye contact, less talkative</td>
<td>Lack of eye contact, gaze avoidance, conversation avoidance</td>
</tr>
<tr>
<td>Irritability, aggression, anger, tantrums</td>
<td>Irritability, aggression severe tantrums</td>
</tr>
<tr>
<td>------------------------------------------</td>
<td>------------------------------------------</td>
</tr>
<tr>
<td>Impaired face recognition</td>
<td>Impaired face recognition</td>
</tr>
<tr>
<td>Complete loss of speech in adults or</td>
<td>Delayed language onset; failure to</td>
</tr>
<tr>
<td>failure to develop speech in children</td>
<td>develop speech</td>
</tr>
<tr>
<td>Difficulties in verbalizing, word</td>
<td>Echolalia, limited speech production</td>
</tr>
<tr>
<td>retrieval problems</td>
<td></td>
</tr>
<tr>
<td>Auditory disturbances, difficulties</td>
<td>Difficulties following conversational</td>
</tr>
<tr>
<td>differentiating voices in a crowd</td>
<td>speech with background noise</td>
</tr>
<tr>
<td>Sound sensitivity</td>
<td>Sound sensitivity</td>
</tr>
<tr>
<td>Poor performance on standardized</td>
<td>Poor performance on verbal IQ tests</td>
</tr>
<tr>
<td>language tests</td>
<td></td>
</tr>
<tr>
<td>Abnormal sensation or numbness around</td>
<td>Abnormal sensation in mouth and</td>
</tr>
<tr>
<td>mouth and extremities, burning feet</td>
<td>extremities, excessive mouthing of</td>
</tr>
<tr>
<td></td>
<td>objects, toe walking</td>
</tr>
<tr>
<td>Excessive pain when bumping abnormal</td>
<td>Insensitivity or overreaction to pain</td>
</tr>
<tr>
<td>touch sensations, touch aversion</td>
<td>and touch, touch aversion, stiff to hold</td>
</tr>
<tr>
<td>Loss of position in space</td>
<td>Vestibular system abnormalities</td>
</tr>
<tr>
<td></td>
<td>difficulty orienting self in space</td>
</tr>
<tr>
<td>Normal pinprick tests</td>
<td>Normal pinprick tests</td>
</tr>
<tr>
<td>Involuntary jerking movements, rocking,</td>
<td>Stereotyped movements such as arm</td>
</tr>
<tr>
<td>purposeless movement, twitching,</td>
<td>flapping rocking, jerking</td>
</tr>
<tr>
<td>shaking</td>
<td></td>
</tr>
<tr>
<td>Unsteadiness in handwriting deficits in</td>
<td>Difficulty in writing poor hand-eye</td>
</tr>
<tr>
<td>hand eye coordination, loss of fine</td>
<td>coordination, limb apraxia, problems</td>
</tr>
<tr>
<td>motor skills</td>
<td>carrying out intentional movements</td>
</tr>
<tr>
<td>Gait impairment, incoordination,</td>
<td>Abnormal gait and posture, clumsiness,</td>
</tr>
<tr>
<td>clumsiness, loss of motor control</td>
<td>incoordination, difficulties sitting</td>
</tr>
<tr>
<td></td>
<td>standing, and crawling in infants and</td>
</tr>
<tr>
<td></td>
<td>toddlers</td>
</tr>
<tr>
<td>Toe walking</td>
<td>Toe walking</td>
</tr>
<tr>
<td>Difficulty chewing or swallowing</td>
<td>Difficulty chewing or swallowing</td>
</tr>
<tr>
<td>Unusual postures</td>
<td>Unusual postures</td>
</tr>
<tr>
<td>Difficulty carrying out complex commands</td>
<td>Difficulty carrying out multiple</td>
</tr>
<tr>
<td></td>
<td>commands</td>
</tr>
<tr>
<td>Restlessness, hyperactivity</td>
<td>Hyperactivity ADHD traits</td>
</tr>
<tr>
<td>Agitation</td>
<td>Agitation</td>
</tr>
<tr>
<td>------------------------------------------------</td>
<td>------------------------------------------------</td>
</tr>
<tr>
<td>Insomnia</td>
<td>Insomnia</td>
</tr>
<tr>
<td>Eating disorders, anorexia, food aversion</td>
<td>Eating disorders, anorexia, restricted diet feeding problems</td>
</tr>
<tr>
<td>Unintelligible cries, unprovoked crying</td>
<td>Unprovoked crying</td>
</tr>
<tr>
<td>Self injurious behavior, including head banging</td>
<td>Self injurious behavior, including head banging</td>
</tr>
<tr>
<td>Grimacing</td>
<td>Grimacing</td>
</tr>
<tr>
<td>Staring spells</td>
<td>Staring spells</td>
</tr>
<tr>
<td>Lack of eye contact</td>
<td>Lack of eye contact</td>
</tr>
<tr>
<td>Gastroenteritis, diarrhea, abdominal pain, constipation, colitis</td>
<td>Diarrhea, constipation, gaseousness, abdominal discomfort, colitis</td>
</tr>
<tr>
<td>Lesions of the ileum and colon</td>
<td>Leaky gut syndrome</td>
</tr>
<tr>
<td>Damage to purkinje and granular cells</td>
<td>Damage to purkinje and granular cells</td>
</tr>
<tr>
<td>Causes demyelating neuropathy</td>
<td>Demyelation in brain</td>
</tr>
</tbody>
</table>

**Possible Source of Mercury Exposure:**

Vaccine injections are a known source of mercury. The mercury found in vaccinations is thimerosal which is 49.6% mercury by weight. This preservative is found in DtaP, HIB, and Hepatitis B. According to the national vaccination program there are 20 injections of 8 different vaccinations recommended for children under the age of 2 years. Since 1977 thimerosal has been suspected to be potentially dangerous especially in long-term exposure cases. According to the CDC a typical vaccinated two-year-old child born in the 1990's would receive 237.5 micrograms of mercury. Because thimerosal is injected during vaccinations the mercury is given in a bolus dose starting at birth, then 2, 4, 6 and 15 months. Four government agencies have set safety thresholds for daily mercury exposure based on methylmercury. In applying these guidelines to a bolus scenario the sum of mercury doses at 6 months of age or younger correlated to infant weights, exceed all of the mercury total guidelines for all infants. The 2-month dose is especially high being calculated as over 30 times the recommended daily maximum exposure level. The babies in the smallest weight category would receive almost three months worth of daily exposures in a single day. This observation was important in that doses that were previously thought to have no adverse affects resulted in damage to humans. The potential of this mercury-induced harm is compounded in the vulnerability of infants. Mercury is most toxic to the developing brain, neonates that are exposed show more accumulation in the brain than in other tissues. In infants mercury is more likely to enter the brain because the blood-brain barrier is not completely closed, and infants are unable to excrete mercury due to their inability to produce bile which in adults is the main excretion route for mercury. It was found that the longer the mercury is in the neurons the more is converted to inorganic mercury and therefore greater neurotoxicity(6).
The Possible Thimerosal – Autism Link:

In the late 1930’s, Leo Kanner a child psychologist first began to notice a type of child that he later called autistic. He had said this type of child has never been described previously and since 1938 there are a number who now fit this new category. Thimerosal was first introduced as a component of vaccine solutions in the 1930’s. At this time no correlation was made between vaccinations and this mysterious new disease. Thimerosal and the effect of mercury vary in a dose-dependant manner, in that the higher the exposure level the more that are affected. At higher levels those who are more sensitive become severely impaired and the less sensitive only slightly impaired and the majority exhibiting no symptoms. The vaccination rate has steadily gone up and therefore so has the rates of mercury exposure through thimerosal. In 1999 it was at its highest at close to 90% depending on the vaccine. The rate of autism has also steadily gone up since its discovery in the 1930’s. Earlier than 1970 shows a prevalence of 1 in 2000 of autism and after 1970 the rate doubled to 1 in 1000 in 1996 the estimated occurrence was 1 in 500.

The large increase in prevalence can supposedly be attributed to the increase in mandatory inoculations, with two more being added to the schedule in 1991 both containing thimerosal.(6). In a case study documented by a mother of an autistic boy it was mentioned that her son progressed normally developmentally for the first year of life but began to regress at one year. His regression was evaluated with MRI’s and blood tests but was unexplained. She had given up hope when she linked his vaccinations to the regression through research on thimerosal toxicity. She found that she could have her son’s hair tested and the results showed an extremely high level of mercury in her son with the results being 4.8 ppm of mercury and the 5 ppm being the mercury toxicity level. She began calculating the amount of thimerosal given to her son and found that at 18 months he had been given 237.5 micrograms of mercury, which according to her sons weight was 125 times the safe allowable daily exposure. She also found that the immune globulin injections for Rh compatibility that she had received when she was pregnant also contained thimerosal.(7). Can this be coincidence?

The future of vaccines:

Currently the FDA has addressed the issue of thimerosal as a preservative in vaccines. In 1997 under the FDAMA act comprehensive reviews were carried out on the use of thimerosal in childhood vaccines. These reviews have supposedly found no evidence of harm from thimerosal exposure in vaccines. The FDA states “however, depending on the vaccine formulations used and the weight of the infant, some infants could have been exposed to cumulative levels of mercury during the first six months of life that exceed EPA recommended guidelines for the safe intake of methylmercury.” As a precautionary measure the FDA, CDC, NIH, HRSA, and the American Academy of Pediatrics, released statements urging manufacturing companies to reduce or eliminate thimerosal in vaccines as soon as possible. Several FDA approved thimerosal free vaccines are now on the market including hepatitis B and DtaP. Vaccines are also being routinely repackaged into single dose vials to prevent the need of thimerosal like preservatives(3).

Conclusions:

This issue is one that is near to my heart in that I work with an autistic child and have researched the cause of her disorder as well as battled the decision to vaccinate my own child with the data available about the incidence of mercury poisoning possibly
diagnosed as autism in more and more children each day. I was fortunate enough that my
daughter suffered no adverse affects from vaccinations. I do however feel that the
correlations presented in this study are too strong to deny it as a possible causative agent
for some cases of autism. I feel that there are many different forms of the autism disorder
and those forms indefinitely have different causes, including environmental exposures
and genetic predispositions and mutations. While to date I stand a supporter of
vaccinations for children, I feel that thimerosal free vaccinations are a smarter choice.
The scientific field would be ignorant to not acknowledge a strong correlation in this
area. I feel further research is needed on the toxic effects of ethylmercury in humans as
well as well documented data on children diagnosed with autism either without being
vaccinated or vaccinated using thimerosal free vaccines. The possibility of future studies
in this area is immeasurable. Children are suffering and we as scientists need to remain
open-minded to the possible causes and preventions for such sufferings.
Bibliography


Concerta
(Methylphenidate HCl)

May I Have Your Attention Please?

Prepared by Kyle Ong
For Dr. Hank Mancini
Organic Chemistry 236
April 14, 2004
Abstract

This paper is to inform the reader about a prescription attention-deficit hyperactivity disorder pill called Concerta (methylphenidate HCl). Basic knowledge and history of ADHD and methylphenidate HCl will be given as well as an overview of the manufacturing process. The reader will also be informed about various pharmacology aspects of Concerta.

Definition of ADHD

ADHD or attention-deficit hyperactivity disorder can be also called attention deficit disorder or ADD. ADHD is a syndrome affecting children, adolescents, and rarely adults characterized by leaning and behavior disabilities. This disorder affects approximately 3% to 7% of school-aged children. This number may be ill represented due to the current diagnostic techniques, which are largely subjective.

ADHD has three main types of symptoms: inattention, hyperactivity, and impulsiveness. Symptoms of inattention include not paying attention, not listening, not finishing tasks on time, not following directions, making careless mistakes, and being easily distracted. Symptoms of hyperactivity and impulsiveness include fidgeting, talking excessively, and interrupting others. There are patients that have more symptoms of hyperactivity and impulsiveness while others have more symptoms of inattentiveness. Some patients have all three types of symptoms. Currently there is no scan procedure or test to diagnose ADHD.

The exact pathophysiology of ADHD is not yet determined. This disorder is considered heterogeneous due to variance among individuals. It is also considered multifactorial, consisting of both neurobiological and genetic components. There is several hypotheses on the actual mechanism ranging from neurotransmitter imbalances to brain malformations. Catecholamine, especially dopamine and norepinephrine seem to be the primary set of neurotransmitters in question. It is thought that deficits in inhibitory control contribute to the behavioral problems. Genetic mutations may also interfere with the receptors binding the neurotransmitters, contributing to the problem. This can be the cause of the dysfunction prefrontal cortex and basal ganglia which are critical in the system that controls attention, motor function, and behavior. Brain scans have shown that these areas and also the cerebellum are smaller in ADHD patients. The posterior parietal cortex, that processes visual and spatial information, has also shown to be smaller. This leads to an inability to adequately process information thus leading to ADHD.

History of Methylphenidate

Methylphenidate was first synthesized in the 1940s and was first marketed in Ritalin in 1960s, a drug very similar to Concerta. In the 1930s, methylphenidate and other amphetamines were prescribed as barbiturate antidotes in very high dosages. Complications arose due to the high amount of usage. Barbiturate overdose was calculated to be as high as 45 percent and amphetamines were not far behind. Barbiturates and amphetamines fell out of favor but methylphenidate still remained to treat ADHD. Methylphenidate’s peripheral pharmacologic actions are milder than those of the amphetamines; the agent has more noticeable effects on mental function than on motor activities. Methylphenidate is clinically used in the treatment of narcolepsy and
primarily used in the treatment of attention-deficit hyperactivity disorder (ADHD) with children.

In 1971, methylphenidate was categorized in the United States as a Class II Controlled Substance. The United States production of methylphenidate increased by 500% to 10,410 kilograms, between 1991 and 1995 such a high increase is very rare for a Class II Controlled Substance. The rate of production of methylphenidate in the United States has continued to grow and in 2001 was reported to be 17,618 kilograms.

**Raw Materials**

| Phenyl Acetonitrile | Sodium Amide       | Methanol       |
| Hydrogen Chloride   | 2-Chloropyridine   | Sulfuric Acid  |
| Hydrogen            |                     |                |

**Inert Ingredients**

| Butylated Hydroxytoluene | Carnauba Wax      | Cellulose Acetate |
| Hydroxypropyl           | Methylcellulose   | Lactose          |
| Phosphoric Acid         | Poloxamer         | Polyethylene Glycol |
| Polyethylene Oxides     | Povidone          | Propylene Glycol  |
| Sodium Chloride         | Stearic Acid      | Succinic Acid    |
| Synthetic Iron Oxides   | Titanium Dioxide  | Triacetin        |

**Manufacturing Process**

In finding the manufacturing process of methylphenidate HCl a Walgreens Pharmacy program was used. This is a direct citation from the program. 80 grams of crushed sodium amide are gradually added to 117 grams of phenyl-acetonitrile and 113 grams of 2-chloropyridine in 400 cc of absolute toluene while stirring and cooling are performed. The mixture is then slowly heated to 110° to 120° C and maintained at this temperature for 1 hour. Water is added there to after cooling, the toluene solution is shaken with dilute hydrochloric acid and the hydrochloric acid extracts are made alkaline with concentrated caustic soda solution. A solid mass is separated thereby which is taken up in acetic ester and distilled, α-phenyl-α-pyridyl-(2)-acetonitrile passing over at 150° to 155°C under 0.5 mm pressure. When recrystallized from ethyl acetate it melts at 88° to 89°C, the yield amounting to 135 grams.

100 grams of α-phenyl-α-pyridyl-(2)-acetonitrile are introduced into 400 cc of concentrated sulfuric acid, allowed to stand overnight at room temperature, poured into ice and rendered alkaline with sodium carbonate. α-PHENYL-α-pyridyl-(2)-acetamide is precipitated thereby which melts at 134°C after recrystallization from ethyl acetate.

100 grams of the resulting α-phenyl-α-pyridyl-(2)-acetamide, when dissolved in one liter of methyl alcohol and treated for 6 hours at water-bath temperature with hydrogen chloride, and after concentrating, diluting with water and rendering alkaline with sodium carbonate, yield 90 grams of the α-phenyl-α-pyridyl-(2)-acetic acid methylester of MP 74° to 75°C (from alcohol of 50% strength).

The α-phenyl-α-pyridyl-(2)-acetic acid methylester of BP 135° to 137°C under 0.6 mm pressure is obtained in theoretical yield by hydrogenation of 50 grams of α-phenyl-α-pyridyl-(2)-acetic acid methylester in glacial acetic acid in the presence of 1 gram of platinum catalyst at room temperature, while taking up 6 hydrogen atoms. Reaction with
HCl gives the hydrochloride. Resolution of stereoisomers is described in U.S. Patent 2,957,880.

Description-Structure and Properties

Concerta is a central nervous system (CNS) stimulant. Concerta is available in four tablet strengths, each extended release tablet for a once-a-day oral administration contains 18, 27, 36, or 54 mg of methylphenidate HCl USP and is designed to have 12-hour duration of effect. Chemically, methylphenidate HCl is d,l (racemic) methylα-phenyl-2-piperidineacetate hydrochloride. The d-isomer is pharmacologically more active than the l-isomer. Its empirical formula is C₁₄H₁₅NO₂·HCl. The structural formula is as follows:

![Structural formula of methylphenidate HCl]

Methylphenidate HCl is a white, odorless crystalline powder and its solutions are acid to litmus. It is freely soluble in water and in methanol, soluble in alcohol, and slightly soluble in chloroform and in acetone. Methylphenidate HCl has a molecular weight of 269.77.

Mechanism

Methylphenidate HCl exhibits activity similar to that of the amphetamines, although the pharmacology for these two drug classes may differ. Methylphenidate HCl exerts many of its effects through dopamine uptake blockade of the central adrenergic neurons, in contrast to the amphetamines and cocaine that increase catecholamine release as a primary mechanism. Methylphenidate HCl blocks dopamine transport or carrier proteins and as a result, sympathomimetic activity in the central nervous system is increased. Because methylphenidate HCl slowly blocks the dopamine-transport proteins, methylphenidate HCl appears to be less likely than the amphetamines or cocaine to increase systolic and diastolic blood pressure or cause respiratory stimulation. There is some evidence that the alteration of dopamine transport systems by methylphenidate HCl may indirectly augment the action of serotonin, but further pharmacologic research is needed to understand these processes. At higher dosages and in overdose, heart rate may increase or reflexly decrease in response to blood pressure; cardiac arrhythmias may occur secondary to increased sympathomimetic effects.

The main sites of the central nervous system (CNS) activity appear to be the brain stem arousal system and the cerebral cortex, including the subcortical structures of the
thalamus. Methylphenidate HCl induces CNS stimulation producing a decreased sense of fatigue, an increase in motor activity and mental alertness, mild euphoria, and brighter spirits. Although, a mild anorexic effect may occur. Unlike the amphetamines and cocaine, physical dependence is infrequent with normal usage at therapeutic dosages.

**Development of Formulation**

Methylphenidate HCl has a short duration of action of about 3 hours, requiring administration of two to three times a day with the immediate-release (IR) formulation. This delivery of the drug not only results in plasma level fluctuations but also social stigma for the children taking the drug. A sustained-release (SR) formulation of methylphenidate with the drug being embedded in a wax matrix was developed with the hopes of creating a single daily dose tablet. This dosage form has a slower onset and longer duration of action of 8 hours. The SR formulation was developed to improve compliance and reduce drug concentration fluctuations. Unfortunately, there have been reports of a slower onset of effects with the SR formulation in addition to a shorter duration of action compared to the twice daily dosing of the IR formulation.

As a result, Concerta developed a new extended-release tablet formulation employing the OROS osmotic technology. The new tablet was designed to have a 12-hour duration of effect after a once-daily dosing. This dosage form provides a rapid onset of action followed by continuous delivery to provide a similar concentration-time profile to the three times daily dosing of the IR formulation.

**OROS System Technology Improves Methylphenidate HCl**

Concerta is a new extended release tablet formulation for methylphenidate HCl that uses the OROS System technology developed by Alza. This technology utilizes the osmotic gradient established between the inside and outside of the tablet to deliver the drug.

![Figure 1](image)

*Figure 1*

The outer coat of the capsule-shaped tablet (Figure 1, Number 1) is composed of an immediate release layer of methylphenidate HCl. This layer accounts for 22% of the total dose. After this layer dissolves, the semipermeable “rate-controlled” membrane allows the transport of water from the gastrointestinal fluids into the core of the tablet.
The core of the tablet consists of three layers: a "push" layer and two drug layers containing the remainder of the dose (Figure 1, Number 2). As water enters the tablet the osmotically active push layer composed of hydroxypropyl methylcellulose begins to expand. As it expands it forces the drug out of the exit port. The membrane controls the rate at which the water enters the core in turn controlling the rate of drug release. This results in minimizing the peak and the plasma concentrations associated with the immediate-release formulations. The table shell and inert components of the dosage form remain intact during gastrointestinal transit and are eliminated in the stool (Figure 1, Number 3).6

"Concerta is designed to have a 12-hour duration of effect. Peak plasma methylphenidate concentrations are achieved about 6 to 8 hours after administration and are followed by gradual decrease in plasma concentrations. This results in a prolonged duration of action after a once-daily morning dosing."

Pharmacokinetics of Absorption

Methylphenidate HCl is absorbed readily from the gastrointestinal tract in both adults and children.2,5 After oral administration of Concerta, plasma levels of methylphenidate HCl increase rapidly to an initial peak plasma level in 1 to 2 hours. This peak is due to the dissolution of the drug's outer coat immediate-release layer of methylphenidate. Once the system's core has been osmotically activated and the drug is being released, the drug plasma concentration increases gradually over the next few hours. This drug system releases the methylphenidate HCl regardless of the pH of the stomach or the state of motility of the gastrointestinal tract. Peak plasma concentrations are achieved 6 to 8 hours after which a gradual decrease in plasma levels occur.2

In order to assess the validity of this new dosage form, the plasma concentration-time profile and rate and extent of absorption of methylphenidate given as a single 18 mg dose of Concerta was composed with that of three 5 mg immediate-release tablets given every 4 hours and a single 20 mg dose of sustained-release tablet in an open labeled, randomized, crossover study of 36 health adult volunteers.6 The results showed a comparable relative bioavailability of Concerta once daily, immediate-release (IR) methylphenidate three times daily and sustained-release (SR) methylphenidate once daily.6 In addition, subjects taking Concerta did not experience the fluctuations between peak and trough concentrations that the IR methylphenidate subjects experienced and the duration of action was longer for Concerta and IR when compared to the SR methylphenidate subjects. (Figure 2) "The dose-normalized peak plasma concentration of methylphenidate was significantly lower for Concerta than for IR methylphenidate."1
The mean pharmacokinetics parameters in 36 healthy adults following the administration of Concerta 18 mg (once daily), IR methylphenidate 5 mg (three times daily), and SR methylphenidate 20 mg (once daily) are summarized in Table 1.

### Table 1
Mean SD Pharmacokinetic Parameters

<table>
<thead>
<tr>
<th>Parameters</th>
<th>CONCERTA™ (18 mg qd) (n=35)</th>
<th>Methylphenidate (5 mg tid) (n=34)</th>
<th>Methylphenidate (20 mg qd) (n=33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C(_{\text{max}}) (ng/mL)</td>
<td>3.75 ± 1.0</td>
<td>4.17 ± 1.0</td>
<td>4.84 ± 1.6</td>
</tr>
<tr>
<td>T(_{\text{max}}) (h)</td>
<td>6.7 ± 1.8</td>
<td>6.5 ± 1.8</td>
<td>3.7 ± 1.6</td>
</tr>
<tr>
<td>AUC(_{\text{inf}}) (ng*h/mL)</td>
<td>42.0 ± 14</td>
<td>38.0 ± 11.0</td>
<td>46.7 ± 16</td>
</tr>
<tr>
<td>t(_{1/2}) (h)</td>
<td>3.5 ± 0.4</td>
<td>3.0 ± 0.5</td>
<td>3.9 ± 0.6</td>
</tr>
<tr>
<td>Relative BA (%)</td>
<td>--</td>
<td>91.4 ± 0.8</td>
<td>101 ± 10</td>
</tr>
</tbody>
</table>

Source: Reference 2
The pharmacokinetics of repeated once daily dosing of Concerta was also evaluated. The results showed no significant drug accumulation and the area under the plasma concentration time curve (AUC) and terminal half-life were similar after single multiple doses of Concerta 18 mg.\(^1,2\) Concerta has predictable pharmacokinetics demonstrated by the low variability in the AUC.\(^6\)

**Dose Proportionality**

"Methylphenidate is a racemic mixture comprising d- and l- isomers. The d-isomer is more pharmacologically active than the l-isomer."\(^1\) When examining the proportionality of the isomers to the dose, the peak plasma concentration and AUC of the d-isomer were found to be proportional to the dose.\(^4\) The single doses of 18, 36, and 54 mg were studied for these results.

**Distribution**

Methylphenidate's volume of distribution is 1.1 to 3.1 liters/kilogram (L/kg).\(^8,9\) Its distribution also includes penetration into the blood-brain barrier readily.\(^1\) The plasma protein binding of methylphenidate is 15.2%.\(^8,9\) Plasma methylphenidate concentrations decline biexponentially after oral administration. The half life of Concerta is approximately 3.5 hours.\(^1,2\)

**Metabolism and Excretion**

"The metabolism of methylphenidate is stereospecific, resulting in substantially higher plasma concentrations of the more pharmacologically active d-isomer than the less l-isomer."\(^1\) In humans, the primary route of methylphenidate metabolism is via de-esterification into an essentially inactive metabolite called α-phenyl-piperidine acetic acid (PPA).\(^2\) The metabolism of Concerta (assessed by PPA levels) is essentially the same as IR methylphenidate tablets whether it was administered as a single or repeated dose.\(^2\) Methylphenidate is mostly excreted in the urine with less than 1% unchanged.\(^8\) "After oral dosing of radiolabeled methylphenidate in humans, about 90% of the radioactivity was recovered in urine. The main urinary metabolite was PPA, accounting for approximately 80% of the dose."\(^2\)

**Special Populations**

There are no differences in Concerta pharmacokinetics regarding gender and race. No studies have been carried out in children less than 6 years of age. There is no experience with the use of Concerta regarding renal or hepatic insufficiency. However, since renal clearances is not an important route of methylphenidate clearance, renal insufficiency is expected to have little effect on the pharmacokinetics of Concerta.\(^2\)

**Dosage and Administration**

Concerta is administered orally once daily in the morning. The tablet must be swallowed whole with the aid of liquids. It cannot be chewed, crushed, or divided. Concerta may be administered with or without food. "Dosage should be individualized according to the needs and responses of the patient."\(^2\)
Patients New to Methylphenidate HCl

"The recommended starting dose of Concerta for patients who are not currently taking methylphenidate, or for patients who are on stimulants other than methylphenidate is 18 mg once daily." Dosage may be adjusted to a maximum of 54 mg a day taken once daily in the morning. "Dosage adjustment may proceed at approximately weekly intervals." 

Patients Currently Using Methylphenidate HCl

The recommended dose of Concerta for patients who are currently taking methylphenidate HCl twice a day, three times a day, or sustained-release (SR) at doses of 10 to 60 mg a day is depicted in Table 2. Dosages may be titrated in weekly intervals in 18 mg increments to a maximum of 54 mg a day.

<table>
<thead>
<tr>
<th>Previous Methylphenidate Dosage</th>
<th>Immediate-Release Tablets</th>
<th>Sustained-Release Tablets</th>
<th>Recommended Concerta Starting Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 mg twice or three times daily</td>
<td>23 mg/day</td>
<td>18 mg once daily in the morning</td>
<td></td>
</tr>
<tr>
<td>10 mg twice or three times daily</td>
<td>43 mg/day</td>
<td>35 mg once daily in the morning</td>
<td></td>
</tr>
<tr>
<td>15 mg twice or three times daily</td>
<td>63 mg/day</td>
<td>54 mg once daily in the morning</td>
<td></td>
</tr>
</tbody>
</table>

*Adapted from Concerta package insert: Children aged 6-12 years of age may be started at 18 mg once daily for 1 week with careful monitoring and dosage titration to 36 mg once daily or 54 mg once daily in the morning over 3-4 weeks.

Table 2

Recommended Concerta Starting Dosage in Patients Previously Treated With Methylphenidate Immediate- or Sustained-Release Tablets

Concerta should be discontinued if there is a paradoxical aggravation of symptoms and if there are other adverse events. In addition, it should be discontinued if no improvements are seen within 1 month after an appropriate dosage adjustment is made. There are no controlled studies or trials available to indicate how long a patient with ADHD should be treated with methylphenidate HCl. However, it is of general consensus that a patient may need pharmacological therapy for ADHD for extended periods of time. During these extended periods of Concerta usage, its efficacy should be periodically re-evaluated by a drug free period.

Directions and Precautions for Methylphenidate HCl

Patients who are under six-years of age, severely depressed, prone to seizures, or prone to Tourette's syndrome should not use methylphenidate. Pregnant women or women in child bearing age should also avoid use due to teratogenic effects seen in animal studies. Common side effects seen with the use of Concerta are headache, abdominal pain, anorexia, dizziness, insomnia, nervousness, rash, and cardiac abnormalities such as angina and tachycardia. The incidence of new onset of tics has
been seen in 8% of patients after 10 months of treatment. Concerta should not be used in conjunction with anticonvulsants, tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), or selective serotonin reuptake inhibitors (SSRIs). There have also been reports of serious adverse reaction with concomitant use of Concerta with Clonidine.

Conclusion

ADHD is a disorder that affects many people today. Methylphenidate HCl is a stimulant drug used to treat ADHD. This treatment has been successful for ADHD but its pharmacokinetics make it difficult for patients to keep up with a three times a day dosage when using immediate-release methylphenidate. A sustained-release formulation was developed to resolve this problem but was unsuccessful and fell short of its expectations.

Concerta (methylphenidate HCl), an extended-release osmotic drug delivery system is the new and improved modern day treatment for ADHD. Concerta demonstrates comparable relative bioavailability and plasma concentration profile as an immediate-release methylphenidate with only a single daily dosing and the advantage of not experiencing plasma fluctuations in drug concentrations.

After all my research and findings I have concluded that Concerta has its good and bad traits but with all drugs this is inevitable. The future of Concerta is promising. I believe that Concerta will continue to be prescribed due to its beneficial formulation in treating ADHD.
References

2. Concerta (methylphenidate HCl). Package Insert
GLEEVEC®: THE REVOLUTIONARY THERAPY FOR
CHRONIC MYELOGENOUS LEUKEMIA

Prepared for
Dr. Mancini
Organic Chemistry 236
Paradise Valley Community College

Prepared by
Shelley Ostlund

April 16, 2004
Abstract- Chronic Myelogenous Leukemia is a rare, myeloproliferative disease linked to gene abnormalities. This paper investigates the enthusiasm surrounding the pathogenesis of Chronic Myelogenous Leukemia, and the revolutionary therapy, Gleevec®, that targets the protein responsible for the progression of the disease. Gleevec®, also known as Imatinib Mesylate, is still under clinical investigation, yet, has surpassed the efficacy of conventional therapy, and has become the therapy of choice for medical providers and patients throughout North America.

History

Chronic Myelogenous Leukemia (CML) is a slowly progressing, fatal cancer of the blood and bone marrow, in which white blood cells proliferate abnormally and suppress healthy red and white blood cells. Originating in abnormal stem cells in the bone marrow, it is also referred to as granulocytic leukemia or chronic myeloid leukemia, which represents the type of white blood cells affected. Although initially thought to be an infection, the disease was named Leukemia in 1845, coined from the Greek words Leukos “white” and haema “blood.” Later, in 1870, it was found to originate in the bone marrow. Nearly a century later, in 1960, two Philadelphia researchers regularly observed “an abnormally small chromosome” in the cells of CML patients, resulting in the name, the Philadelphia chromosome. Incidentally, “this was the first time that a chromosomal abnormality had been associated with a malignant disease.” In 1973, new staining techniques allowed researchers to examine the rearrangement or translocation of chromosomes 9 and 22, producing the Philadelphia chromosome.

Technological advancement such as cytogenetic studies, various blotting or staining techniques, polymerase chain reaction (PCR), and fluorescence in-situ hybridization (FISH) has since allowed the observation of the ABL proto-oncogene translocation. The ABL gene, normally located on chromosome 9, fuses to variable sequences of the BCR (Breakpoint Cluster Region) gene on chromosome 22, yielding the abnormal BCR-ABL fusion gene. (Fig. 1) The BCR-ABL proto-oncogene directs the production of an abnormal protein, specifically, a hyperactive (“turned on all the time”) enzyme. This enzyme (kinase) is responsible for converting the marrow stem cells, from normal white blood cells to leukemic cells, established in CML patients.

Epidemiology and Etiology

Approximately 4500 (15%) of the 30,000 new cases of Leukemia diagnosed each year in the United States are CML. Research has shown CML occurs after birth, therefore, is not an inherited disease. While it does occur in children, more than 95 percent of cases occur in middle-aged adults, with a slight male predominance. Environmental risk factors including benzene, cigarette smoke, radiation exposure, and prior exposure to chemotherapy drugs have been linked to CML. Those at risk to substantial benzene exposure are industrial workers, particularly those dealing with gasoline fumes, industrial solvents, oil and coal emissions, and paint, who consequently, inhale and/or absorb it through their skin. In any case, the predisposing factors to CML are unknown, and the only known causative agent is the BCR-ABL fusion gene.
Figure 1. Panel A, Karyotype [46,xy, t(9;22)(q34;q11)] of a patient with CML.
Panel B, Schematic Illustration of the Philadelphia Chromosome translocation.
Clinical Features

Chronic Myelogenous Leukemia is a triphasic disease determined by the blast cell count and the austerity of the symptoms present. However, symptoms associated with CML are due to the suppression of healthy blood cells, caused by an increase in blast cells in the blood or bone marrow. As the disease progresses, phase transformation transpires, as do the subsequent symptoms:

- Lethargy due to anemia
- Unexplained weight loss
- Bone pain
- Fever
- Pain or fullness below the left side of the ribs

Symptomatic patients will undergo a series of tests (physical exams, blood tests, and bone marrow aspiration) to examine the blood and bone marrow to test for CML. Diagnosis of the disease is dependent upon the presentation of the distinguishing features of the disease: an enlarged spleen (Splenomegaly), the Philadelphia chromosome (Ph+), and an increased or abnormal white blood cell count.

The Three Phases of CML are as follows:

1. The characteristic chronic phase lasts for approximately 3-5 years, with few or no symptoms, and 5% or fewer blast cells in the blood and bone marrow.4

2. The accelerated phase, demonstrated by an increase in spleen size and rapid blast proliferation (6% to 30% blast cells in blood or bone marrow) propels patients to a more symptomatic disease, for an approximate 2-year interval.

3. The terminal blast phase is exemplified by the extramedullary blast proliferation present. In other words, blast cells spread to the tissue, skin and organs. In the blast crisis phase, sometimes called the acute phase, there are more than 30% blast cells in the blood or bone marrow. As a result, severe anemia and bleeding can occur due to low red blood cell and platelet counts. Median survival is three to six months.

Clearly, the prognosis varies in CML patients according to overall physical health, age, and phase at diagnosis. In practice, some oncologists use the Sokal system to develop a score to predict a patient’s prognosis. Patients are divided into risk categories (low, intermediate, and high) based on a mathematical score that accounts for factors such as the patient’s age, blast percentage, spleen size, and complete blood count. Accordingly, treatment is more or less aggressive according to risk category and progression of the disease.
Pathogenesis

The discovery of the Philadelphia chromosome assisted in understanding the cause, development, and effects of chronic myelogenous leukemia. As previously noted, the ABL proto-oncogene, normally located on chromosome 9, is translocated and fuses to variable sequences of the BCR gene on chromosome 22, yielding the Philadelphia Chromosome. The abnormal BCR-ABL fusion oncogene (Ph+) directs the production of a particular abnormal protein. Utilizing the "Central Dogma" of Gene expression, the first step in the BCR-ABL process is transcription, in which an mRNA copy of the gene is produced. The information on the newly assembled RNA copy directs the assembly of a chain of amino acids to produce the abnormal protein, an enzyme, called a tyrosine kinase. (Fig. 2)

Figure 2. A schematic process of the BCR-ABL mutant gene (oncogene) expression.

The active cytoplasmic enzyme behaves incompetently, by generating cell signals that cause the stem cell to behave in an unregulated manner. Tyrosine kinase is the principal factor in reducing apoptosis, or programmed cell death, and ultimately converting the marrow stem cell from normal to leukemia. (Figure 3) Although a great deal is known of the abnormal interactions between the BCR-ABL onco-protein and other cytoplasmic molecules, the specific details of the pathways are incomplete.
Conventional Therapy

Therapy in CML is aimed at eliminating or reducing the leukemia cells (cytogenetic response) to relieve suppression of healthy blood cells (hematologic response) thus, improving the patient's symptoms. There are different therapy options for patients with CML depending on the phase and prognostic factors at diagnosis.

Chemotherapy is a standard treatment used to treat CML since the 1800's. While the active components differ from arsenic, "the first effective treatment," the effect remains the same. Chemotherapy, or cytotoxic therapy, is administered orally or intravenously to destroy the leukemia cancer cells or stops them from dividing. Consequently, while attacking cancer cells, normal white blood cells are damaged in the process, increasing the risk of infection. Other side effects of chemotherapy include hair loss and nausea.

Interferon-alpha(α) Therapy also called biotherapy or immunotherapy was introduced in the 1980's, as a therapy for CML. Interferon-α is a natural substance produced by the body to boost the natural defenses (immune system) against cancer. Interferon is an engineered injection dispensed daily by the patient, often used in conjunction with a supplemental chemotherapy. This is not a curative therapy. While it does prolong life, the intolerable side effects (muscle and bone pain, headaches, fatigue, and nausea) often force patients to relinquish therapy.

Bone Marrow Transplant (BMT) offers a potential curative therapy for CML, although, it is not common due to the immaturity and complexity of the procedure. In the BMT process, the patients infected marrow cells are removed with chemotherapy and radiation, and then, replaced with uninfected marrow cells. There are two different approaches to BMT:

1. Autologous- marrow cells are taken from the patient, and
2. Allogenic- transplant marrow cells are taken from a donor.

In fact, in the latter approach, it is difficult to find a matching donor, related or unrelated. More often than not, CML patients are not candidates for BMT due to physical health and age. Furthermore, the risk associated with BMT is lack of marrow compatibility and loss of life as a result of infection.
Gleevec®: The Revolutionary Therapy

Gleevec® (Imatinib Mesylate), approved by the FDA in 2001, has revolutionized the approach to treating CML. Unlike conventional therapy, in which normal cells and tissues are destroyed while attacking cancer cells, Gleevec targets the cause of CML. The fact that CML is caused by abnormal interactions between the BCR-ABL protein and other cytoplasmic molecules, encouraged scientists to create a new class of drugs called tyrosine kinase inhibitors. Also known as Signal Transduction Inhibitors (STIs), tyrosine kinase inhibitors interfere with the pathways (abnormal interactions) that signal proliferation. Thus, STI 571, commonly called Gleevec or Imatinib Mesylate, was synthesized based on the phenylamino-pyrimidine template and the Adenosine Triphosphate (ATP) binding site on the BCR-ABL tyrosine kinase.¹⁰

Fig. 3. The phenylamino-pyrimidine lead structure and the synthesis of STI571. “Fig. 3A). This template allowed simple chemistry to be applied to produce compounds with potent activity against protein kinase C (PKC). One key observation from analysis of structure activity relationships was that no substitution in the 6-position of the anilino phenyl ring was tolerated for PKC inhibition. However, the introduction of a simple ‘fagmethyl’ led to a loss of activity against PKC, while the activity against protein tyrosine kinases was retained or even enhanced (Fig. 3C). Enhanced activity against protein tyrosine kinases was further achieved by the introduction of a benzamide group at the phenyl ring (Fig. 3B). The original compound that was produced had poor oral bioavailability with low solubility in water. Eventually, it was found that the introduction of a highly polar side chain, i.e. N-methylpiperazine, dramatically increased aqueous solubility and oral bioavailability. From this, STI571 was identified as the most promising compound for clinical development (Fig. 3D).”¹⁰
Gleevec® Chemistry

Gleevec®, (Imatinib Mesylate) is chemically designated 4-[(4-Methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]benzamide methanesulfonate. It has a molecular formula of C_{22}H_{21}N_{7}O_{6}CH_{4}SO_{3} and its molecular weight is 589.7. Prior to tablet form, it is a white to off-white to brownish or yellowish crystalline powder that is soluble in aqueous buffers ≤ pH 5.5 but is slightly soluble to insoluble in neutral alkaline aqueous buffers. The drug is soluble in non-aqueous solvents such as methanol and ethanol but is insoluble in acetone. The structural formula is

\[ \text{Chemical Structure} \]

Clinical Pharmacology

Gleevec is administered orally and completely absorbed within 2 to 4 hours. The half-life elimination for Imatinib is 18 hours, and 40 hours for the N-desmethyl metabolite, which enables the once daily administration. Imatinib is metabolized in the liver, primarily via the enzyme CYP3A4 and the primary active metabolite is the N-demethylated piperazine derivative. Bioavailability is 98%. Imatinib is excreted predominantly in the feces, primarily as metabolites, but elimination in the urine does occur.

Mechanism of Action

The BCR-ABL tyrosine kinase causes proliferation of leukemia cells by binding ATP and transferring a phosphate (phosphorylation) to tyrosine residues on protein substrates. Gleevec® binds to the Bcr-Abl kinase at the ATP binding site, thus, preventing the phosphorylation of tyrosine residues. By interrupting phosphorylation, Gleevec® inhibits the signal transduction pathways responsible for transformation in CML. (Fig. 4) "This specific action is referred to as molecular-targeted therapy because of the specific drug action on the protein that induces the leukemia."
Figure 4A. BCR-ABL Tyrosine Kinase Activity

Figure 4B. Inhibited BCR-ABL Tyrosine Kinase Activity
Clinical Trials

In Phase I patient trials, 31 patients received an introductory dosage of at least 300 mg, all of whom experienced a complete Hematologic response. Not one therapy had ever proven to be that effective on CML patients. To date, Imatinib Mesylate continues to expose significant therapeutic standards in clinical trials.

Table 1. Clinical Response of Ph-Positive Disease to Imatinib Mesylate

<table>
<thead>
<tr>
<th>Stage and Status of Disease</th>
<th>Complete Hematologic Remission, a/n (%)</th>
<th>Complete Cytogenetic Remission, a/n (%)</th>
<th>Comment</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic-phase CML; interferon-α failure</td>
<td>55/54 (98)</td>
<td>71/84 (112)</td>
<td>Dosages 300 mg/d orally; results shown are daily; full responses not yet evident</td>
<td>104</td>
</tr>
<tr>
<td>Chronic-phase CML; interferon-α failure</td>
<td>490/494 (99)</td>
<td>351/454 (44)</td>
<td>Dosage, 400 mg/d</td>
<td>105</td>
</tr>
<tr>
<td>Chronic-phase CML; no previous therapy</td>
<td>522/553 (94)</td>
<td>302/553 (55)</td>
<td>transformed trial of imatinib mesylate vs. interferon-α plus cytarabine induction</td>
<td>109</td>
</tr>
<tr>
<td>Accelerated-phase CML</td>
<td>61/101 (59)</td>
<td>50/101 (49)</td>
<td>Dosage, 400 or 600 mg/d</td>
<td>106</td>
</tr>
<tr>
<td>Lymphoblastic blast crisis: Philadelphia chromosome-positive ALL</td>
<td>4/39 (10)</td>
<td>2/39 (10)</td>
<td>Median response duration, 3 mo for CML lymphoblastic blast crisis and ALL, 6 mo for CML myeloid blast crisis</td>
<td>1</td>
</tr>
</tbody>
</table>

* Results of selected representative studies are given. ALL = acute lymphoblastic leukemia; CML = chronic myelogenous leukemia.
† Refer to remissions sustained for at least 4 weeks.

In patients who had not responded to interferon-α (IFN-α), a daily dose of Imatinib at 300 mg or more produced hematologic response within days. At 400 mg patients were experiencing a cytogenetic response within 3 months. Patients who are resistant to Interferon therapy have complete hematological remission in both the accelerated phase and the blast phase on Imatinib. In clinical studies by Druker et al., comparing Gleevec with interferon, Gleevec has higher remission rates and longer lengths of remissions. The effect of Imatinib on survival has not yet been determined. However, studies controlled with interferon therapy confirmed prolonged survival upon complete cytogenetic remission.

Dosing and Interactions

- Chronic phase patients are ingesting 400 mg once daily, and in the event of disease progression dosage may be increased to 600mg.
- Accelerated or blast phase patients are taking 600 mg once a day with a possible increase to 800 mg daily.

Although there is potential for drug interactions between Gleevec and other substrates or inhibitors, drug interaction data is limited due to the lack clinical studies. It is recommended that patients avoid ethanol and St. John’s Wort.
Side Effects

In comparison to the conventional therapy of CML, the side effects associated with Gleevec® are mild and tolerable. The side effects that do emerge are nonhematological and predictably, due to toxicity. However, unlike immunotherapy, CML patients rarely discontinue therapy due to the side effects. Of course, as the disease progresses, side effects increase as a result of patient prognosis. Although the pathogenesis of these effects is unknown, common signs of Toxicity are:

- Edema and Fluid Retention,
- Gastrointestinal Side Effects,
- Skin Rash,
- Bone, Joint, and Muscle Pain.

There are patients who are resistant or acquire resistance to Gleevec® therapy. These patients commonly express mutations of the Abl kinase domain that affect residue interaction with Imatinib.

Conclusion

Understanding the pathogenesis of CML has enabled therapeutic strategies, such as Signal Transduction Inhibitors to revolutionize the management of CML. I imagine it will change disease therapy, as we know it. With unprecedented response rates, and mild symptoms, Gleevec is mounting first line therapy. Before long, conclusive clinical studies will convey critical effects including drug interactions, long term effects, and mean survival measures. Until then, testimony is forced to carry the immaturity and investigative stages of Gleevec®. As the daughter of a CML patient, I have witnessed the symptoms, of both CML, and the subsequent chemo and interferon therapies. I have watched a man, who was larger than life itself, deteriorate, and cave in to those effects. A man who had conquered colon cancer and a heart attack was welcoming his mortality. He can testify for Gleevec®. What was a thin and weak man, tied down to side effects and symptoms; is now a substantial and resonant man, with life, not death, surging his body. Thanks to this innovative therapy, a man that was hoping for death to catch him has regained the strength to chase life. As a scientist and future physician, it was exciting to investigate and identify with the activity of Gleevec®. But, what I will take with me into my professional life is the quality of life gained, if not the quantity, that I witnessed as a daughter.
BIBLIOGRAPHY

Chemical and Biological Aspects of Anthrax Vaccine Absorbed

Prepared for
Dr. Mancini
CHM 236/Organic Chemistry II

Prepared by
Crystal Palermo

April 5, 2004
Abstract

Research into the protective factors of vaccines that are effective against lethal dosages of *Bacillus anthracis* were conducted by the US Army Medical Research Institute of Infectious Disease. The focus was on the role of the protective antigen (PA) portion of the anthrax toxin. Studies of this immunogen included the results from various animals inoculated with vaccines such as Anthrax Vaccine Absorbed (AVA.) Research can only speculate that this vaccine is effective in humans as it is in animals because exposing humans to live inhalation anthrax is unethical and illegal. Though the data supports that the vaccine would be successful in humans it cannot explain the list of adverse effects that have occurred in those inoculated with the AVA.

I. Introduction

Anthrax is a bacterial infection caused by *Bacillus anthracis*. The bacteria itself is an aerobic, gram positive, rod shaped spore-former. (Fig 1) Under adverse conditions, the vegetative bacteria transforms into a dormant stage as an endospore and can survive in this state for great lengths of time. When the endospores come into contact with a nutrient rich environment, they germinate back into the vegetative state and rapidly multiply. In this highly active phase of germination, the vegetative bacteria release proteins that form an exotoxin as metabolic waste. Though it is the bacteria that cause the infection, it is the exotoxin that causes the symptoms of the anthrax disease.

There are three forms of the anthrax disease, cutaneous, gastrointestinal and inhalation. Inhalation anthrax is the most lethal and is easy to reproduce. For these reasons it is an attractive biological weapon for terrorists. In its dry powder form it can be stored for many years and when put into an easy to disperse aerosol form, the airborne anthrax can travel great distances and remain virulent for decades. This biological threat has created the desire to produce a preventative vaccine. The first American vaccine was FDA approved in the early 1970’s. This vaccine was called Anthrax Vaccine Absorbed and was designed to prevent cutaneous anthrax in workers that worked with sheep in wool mills.

In 1998 the Department of Defense initiated a mandatory program called the Anthrax Vaccine Immunization Program in which every member of the Armed Forces was required to be inoculated with the vaccine. The DOD contracted with a company called BioPort to manufacture the vaccine similar to the original AVA, named Biothrax. Much controversy over the effectiveness, legality and safety of the vaccine has since ensued. The data and research that has been reported varies from source to source. The only consistent information comes from the Department of Defense and it’s affiliated agencies. The DOD swears to the vaccines ability to protect military troops in the event of exposure and it’s safety in those vaccinated but admits that no long-term studies have been conducted. Because it would be unethical to expose a human test group to the deadly bacteria, there is no way to be certain that the vaccine which is proven effective against the lesser cutaneous form would be effective against the more virulent inhalation anthrax. These problems are
compounded by the purported problems with BioPort’s use of the old FDA approved license for the first AVA vaccine for the newly developed version Biothrax (also still referred to as AVA) and questionable manufacturing, packaging and storing practices. The vaccine Anthrax Vaccine Absorbed (AVA) and its newest rendition Biothrax utilization of the Protective antigen (PA) protein as a method of protection against exposure to inhalation anthrax is not sound because of its inability to prevent infection, test for effectiveness in humans and high incident of adverse reactions.

Figure 1

II. Synthesis

The package insert provided with the Biothrax vaccine states that it’s biological and chemical constitution is composed of a “sterile, milky-white suspension made from cell-free filtrates of microaerophilic cultures of an avirulent, nonecapsulated strain of Bacillus anthracis.” It continues to read that a culture from which the sterile suspension is filtrated from is a “chemically defined, protein-free medium consisting of a mixture of amino acids, vitamins, inorganic salts and sugars.” The finished product contains no living or dead bacteria cells and is formulated with the 83kDa protective antigen (PA) protein (altered in it’s gene sequence) and 1.2mg/ml aluminum (derived from aluminum hydroxide in 85% sodium chloride.) It is suspended in 25 µg/ml benzethonium chloride and 100 µg/ml formaldehyde as preservatives.² (Fig. 2)

Figure 2

Culture production and protein isolation
(1) Non-encapsulated strain Bacillus anthracis + Al(OH)₃ + NaCl \rightarrow 83kDa (PA) protein + Al

Active agent plus preservatives
(2) 83kDa (PA) protein + Al + C_{27}H_{48}ClNO₂ + H₂CO
III. Mechanism

When a human is exposed to *B. anthracis* spores through inhalation, the body responds by sending macrophages to the site of infection and the invading bacteria spores are engulfed and carried away for phagocytosis and eventual elimination from the body. However, *B. anthracis* is surrounded by a nontoxic capsule of a single poly-D-glutamate polypeptide that acts to protect it from phagocytosis. So once inside the macrophage, the spore does not undergo phagocytosis but instead germinates into its vegetative form that can then emit the anthrax toxins. The toxins consist of three individual proteins, the protective antigen (PA) protein, the edema factor (EF) protein and the lethal factor (LF) protein. After the toxins are released into the bloodstream, they begin the process of attaching and entering the surface of the host cell. The toxin proteins alone are not pathogenic. It is only when the protective antigen (PA) is present with either the edema factor (EF) or the lethal factor (LF) that the primary virulence factor is the protective antigen (PA) because without it neither the edema factor protein (EF) or the lethal factor (LF) protein could attach to the receptor sites on the host cell or enter into it. (Fig 3)

As seen in Figure 3, it is only after the protective antigen (PA) has attached itself to the receptor site (1) and the protease enzyme cuts the protein into two parts, one that is released back into the blood stream and the other that remains attached to the host cell that the invasion into the host cell can occur (2). The single monomer (protein piece) is then joined by six others to form a single 7-unit protective antigen (PA) heptamer (Fig 4) (3). The heptamer provides an opening that will allow the toxins to enter the host cell (4). At this point either the edema factor (EF) protein or the lethal factor (LF) protein binds to the heptamer (5). The now complete toxin is enclosed by the cell membrane through endocytosis (6). Due to the low pH of the cytoplasm in the cell, the PA/EF or PA/LF heptamer is able to intercalate into the host cell (7). Once inside the cell, the PA heptamer releases the lethal factor (LF) or edema factor (EF) which act as enzymes to throw off the cell’s biochemistry thereby killing the host cell and eventually the host itself (8).
Figure 3

Figure. Construction of anthrax toxin on host cell surface followed by internalization and release of the lethal factor to kill the cell.

Help find a molecule which can bind here and stop the next step!

Figure 4

Heptamer
The design of the vaccine is to inhibit either the lethal factor (LF) protein or the edema factor (EF) protein from binding to the protective antigen (PA) heptamer. The recent scientific breakthrough in gene technology has given the medical community the ability to map the anthrax genome. Having this information allows the crucial protective antigen (PA) protein to be genetically altered through bioengineering. Research has shown that "a PA heptamer is deactivated by the presence of even a few mutant subunits" in the gene sequence. The original AVA vaccine and its newest version, Biothrax, both utilize the altered protective antigen (PA) heptamer.

The anthrax immunization regimen consists of a total of six subcutaneous shots. Shots are administered at two-week intervals for the first three shots. The remaining shots are given at six, twelve and eighteen months after the vaccination series has begun. To maintain the maximum level of immunity, annual booster shots are given.

Though it cannot be explained based on known physiological effects of the components found in the AVA vaccine, adverse reactions are widespread in those who have taken it. The most commonly reported reactions are muscle ache, fatigue, headache, swelling and lumps, itching and inflammation. The data also reflects that the rate of adverse reactions are significantly higher in women than in men. The research gathered also shows that the rate of incidence did not significantly decrease in time. (Fig 5) The research provided by government agencies cannot justify or account for the cause of these reactions.

**Figure 5**

| Incidence of Reported Events in TAMC 601 Cohort members Who Reported They Could Not Perform All Activities |
|-------------------------------------------------|---|---|---|---|---|---|
| Any event—male* | #1 | #2 | #3 | #4 | #5 | #6 |
| Any event—female* | 6.0% | 4.3% | 2.7% | 2.4% | 4.0% | 3.4% |
| Muscle aches | 12.2% | 5.8% | 3.2% | 5.1% | 1.9% | 6.1% |
| Fatigue | 4.1% | 3.1% | 1.3% | 1.7% | 1.0% | 1.7% |
| Headache | 2.9% | 1.4% | 0.6% | 1.1% | 0.8% | 1.7% |
| Joint aches | 3.1% | 1.4% | 1.3% | 1.1% | 1.5% | 1.7% |
| Loss of appetite | 2.6% | 1.5% | 0.9% | 1.1% | 0.8% | 1.0% |
| Nausea or vomiting | 0.3% | 0.3% | 0.2% | 0.4% | 0.0% | 0.0% |
| Fever | 1.4% | 1.2% | 0.6% | 0.4% | 0.8% | 0.5% |
| Itching over entire body | 0.2% | 0.9% | 0.0% | 0.4% | 0.3% | 0.3% |
| Chills | 0.7% | 0.7% | 0.4% | 0.0% | 0.2% | 1.0% |
| Diarrhea | 0.9% | 0.3% | 0.0% | 0.9% | 0.3% | 0.3% |
| Shortness of breath | 0.7% | 0.7% | 0.0% | 0.4% | 0.5% | 0.3% |

* Individuals with at least one reported event (over 11 possible symptoms, counting only once per individual for each immunization).
IV. Conclusion

After researching this vaccine, I do not feel it is a safe or effective means of protection against anthrax. The original vaccine, AVA, is effective in its original use against cutaneous anthrax in wool workers because the exposure is only to the skin and in low amounts. Infection of inhalation anthrax is not only more pathogenic than cutaneous anthrax, exposure to it would not be accidental so it would most certainly be in higher doses. The design of the newest version of this drug, Biothrax, has little to no differences from the original AVA yet it is intended or a completely different use than its predecessor. Our Armed Forces are being inoculated with this vaccine as a measure against bioterrorism. Because the *B. anthracis* is in its spore form so terrorists can easily disperse it as an aerosol, it is protected from our immune system by its poly-D-glutamate polypeptide capsule that prevents phagocytosis. The bacteria itself cannot be destroyed by this vaccine. So even though the series of shots given build up some immunity to the effects of the toxins, it’s limited. The vaccine works similar to all other vaccines in that it builds cells in our own immune system to recognize and mimic (without the virulence factor) the invading element. Not all of our cells will carry the ability to mimic the protective antigen (PA) (but with a missing binding element so that the (LF) and (EF) proteins cannot bind to it) so at some point after exposure, because the bacteria itself is not being destroyed, the anthrax will multiply until it tips the balance between the amount of protective cells from our immune system and the number of bacteria. This means that after exposure to a lethal amount of inhalation anthrax you would have to be treated with antibiotics at some point thereafter to survive. The vaccine alone would not protect you. It is not realistic to say that troops in the middle of foreign countries would have timely access in adequate amounts to these antibiotics. If there were no side effects to this vaccine, little protection would better than no protection at all. But that is not the case, and throughout my research the issues of adverse side effects are well documented but no clear explanations are ever given to explain what the cause is. No long-term research has been done on fertility or why women have more adverse effects than men. There are too many unexplainable medical conditions and I believe at some point in the future this will be the next “Gulf War Syndrome.”
References:


(4) Institute of Medicine of the National Academies. An Assessment of the CDC Anthrax Vaccine Safety and Efficacy Research Program 2002, 24


(6) Koehler, T. Anthrax 2002, 65

(7) Ariel, N. Infection and Immunity 2003, General information

(8) Fellows, P. Microbiology 2001, General information
ABSTRACT:

Currently one of the common treatments for lung cancer is chemotherapy, using drugs that are unable to discriminate cancerous cells from rapidly reproducing healthy cells. The resulting side effects of chemotherapy often further ravage the patient's physical condition. A new approach to lung cancer treatment, aimed at minimizing these side effects, targets specific enzymes associated with the proliferation of the cancer cells and leaves the healthy cells unharmed. Gefitinib (Iressa ®) is a new drug recently approved by the US Food and Drug Administration for treating advanced non-small cell lung cancer (NSCLC) by inhibiting the activity of epidermal growth factor receptor (EGFR) tyrosine kinase. With tyrosine kinase inhibited, the cascading events within the cancer cells are interrupted, causing the excess proliferation of cancer cells to cease and a subsequent reduction of the tumor in some patients. Targeted therapy is very much at its infancy, since much of the mechanism at the molecular level is not well understood; it is, however, emerging as one of the most promising fields in cancer treatment.

BACKGROUND ON LUNG CANCER

The human lungs are spongy organs composed of three lobes on the right lung and two on the left lung. A thin moist membrane, the pleura, surrounds the lungs. Only about 10% of the lungs are solid tissue, the rest is air space. Air enters the lungs through the trachea, then through flexible airways called bronchi, which divide successively into over a million smaller airways called bronchioles. At the end of each bronchiole are clusters of microscopic sacs called alveoli. Oxygen and carbon dioxide pass through the thin membrane of the alveoli to and from capillaries, which carry blood throughout the body.

Lung cancer occurs when normal cells within the lung become genetically mutated, having abnormal shapes and behavior and begin to reproduce rapidly to form cancerous tumors. Tumors spread to other parts of the body by invading blood vessels and lymph nodes. The cancer may metastasize and travel to other parts of the body.

Lung cancers are divided into two major categories: small cell lung cancer and non-small cell lung cancer (NSCLC). Most of lung cancers are NSCLC, which are classified into three different types: squamous cell carcinoma, adenocarcinoma, and large cell carcinoma.

Squamous cell carcinoma, making up 25% to 40% of all lung cancer, is mostly caused by smoking. Squamous cells are developed from reserve cells that are used to replace damaged cells in the lining of the bronchi. This type of cancer is often found in one of the main airways or in a major lobe. It can metastasize to the brain, the adrenal glands, the liver, the bone, and the small intestine.

Adenocarcinoma is now considered the most common type of lung cancer, accounting for 30% to 50% of all lung cancers. Adenocarcinomas form from the mucus-producing cells within the lung. About two thirds of adenocarcinomas are found in the outer regions of the lung and one third occurs toward the center. This type of cancer is difficult to detect early since it often develops slowly and causes no or few symptoms. But it can quickly become unpredictably aggressive and fatal. When adenocarcinoma metastasizes, it infects the brain about 50% of the time. It also travels to the other lung, liver, the adrenal glands, and bone.
Large cell carcinomas are comprised of malignant cells that are not identified as squamous or adenocarcinoma. About 10% to 20% of lung cancers are classified as large cell carcinoma.

The following staging system is used to identify the progress of the disease:

Occult Stage: cancer cells are found in a sample of a patient's coughed-up sputum but no cancer cells have yet been detected in the lung.

Stage 0: noninvasive cancers and only a few layers of cancer cells are detected within one local area. The cancer has not grown through to the top lining in the lung and can be surgically removed. There is a high risk for development of a second tumor, however. Often results in complete cure.

Stage I: The cancer has reached higher layers of the lung but has not spread into the lymph nodes or beyond the lung. Stage IA: 5year survival rate as high as 80%. Stage IB: 5year survival rate can be better than 60%.

Stage II: The cancer cells have spread to nearby lymph nodes. Stage 2A: survival rate is as high as 60%; stage 2B: survival rate can be better than 40%.

Stage III: The cancer cells have spread beyond the lung to the chest wall, diaphragm, or further lymph nodes, such as those in the neck. Stage 3A survival rate is as high as 30%. Stage 3B: one year survival rate 20-25% (improve to 35-40% after chemotherapy treatment).

Stage IV: The cancer has spread to other parts of the body. [1]

CURRENT TREATMENT OPTIONS

The preferred treatment for Stage I and earlier is to remove the tumor by surgery. The removal of a lobe or part of a lobe is a common treatment for Stage I cancer. Radiation and/or chemotherapy are used on patients with inoperable conditions. At Stage II, surgery to remove an entire lobe or one lung is standard treatment. Radiation and chemotherapy could also be administered postoperatively. At Stage 3, surgery is no longer an option for some of the cases due to lymph node involvement. Chemotherapy is the preferred treatment option. At stage 4 when the cancer has spread to other parts of the body, radiation is used for symptom control and chemotherapy could also be used, depending on the overall condition of the patient. Treatment at late Stage 3 into Stage 4 is quite limited due to the adverse side effects of the heavy doses of chemotherapy required to treat the metastasized cancer.

The drugs used for chemotherapy were designed to work against cells that divide rapidly, one of main characteristics of cancer cells. These drugs also affect healthy cells that also divide rapidly such as blood cells and cells that line the digestive tract. Consequently, patients who undergo chemotherapy are more likely to get infections due to severe drops in white blood cells, have liver and kidney damage, abnormal blood clotting, bruise or bleed easily, loss of appetite, nausea and vomiting, hair loss, or mouth sores. [2].

TARGETED TREATMENT – A NEW APPROACH

A new class of drugs - targeted therapies - has been introduced to treat cancer without these devastating side effects. The pharmacology of targeted therapy drugs is cancer-cell
specific, sparing normal cells from the toxicity often seen with chemotherapy and radiation. The drugs work specifically on cancer cells, blocking their means of proliferation.

"While each targeted therapy may work a little bit differently, most focus their activity on proteins that stimulate cancer cell growth, such as epidermal growth factor (EGF). These growth-stimulating factors act by either binding to specific receptors on the cell's surface or by using the receptor as an entry point, disrupting molecular signals that stimulate cell growth. A wide variety of cancers, such as lung, breast, ovarian, bladder, prostate, colorectal, kidney and head and neck cancer overproduce EGF proteins and some of these tumors may be especially dependent on those proteins to maintain viability." [3]

Iressa joins two other smart cancer drugs which are changing the way certain cancers are treated. Herceptin and Gleevec, used to treat breast cancer and chronic myeloid leukemia, respectively, target receptors similar to EGF receptor. [3]

Iressa® (gefitinib) is the first agent in its class to be tested in clinical trials that shows the highest efficacy against NSCLC. The antitumor effects of gefitinib are observed in the reduction of cell proliferation, increasing in apoptosis (programmed cell death), inhibiting angiogenesis and metastasis. This paper addresses Iressa® as targeted therapy for non-small cell lung cancer.

**WHAT IS IRESSA® AND HOW DOES IT WORK?**

According to the US Food and Drug Administration (FDA), Iressa® (active ingredient gefitinib) is an anilinoquinazoline with the chemical name 4-Quinazolinamine, N-(3-chloro-4-fluorophenyl)-7-methoxy-6-[3-4-morpholin) propoxy]. Its structural formula is as follow:

![Iressa molecular structure](image)

Its molecular formula is C_{22}H_{24}ClFN_{4}O_{3} with molecular mass of 446.9. [4]

Iressa® (also designated ZD1839, active ingredient gefitinib) is a white colored powder in a brown film coated tablet, manufactured by AstraZeneca, London, UK. It has been approved by the US FDA in May 5, 2003 for use as targeted monotherapy (to be used by itself and not in combination with other drugs) for the treatment of advanced NSCLC after failure of both conventional platinum-based and docetaxel chemotherapies. Japan was the first country to approve gefitinib for NSCLC treatment in July 2002. Six months following the approval in Japan, approximately 19,000 people with inoperable treatments had been given the drug. Some of the patients developed complications (Interstitial Lung Disease)
promoting US FDA to delay the approval in the US from February 2003 to May 2003. Iressa® has also been approved in Australia. [5]

According to the researchers at AstraZeneca, the epidermal growth factor receptor (EGFR) is a promising target for anticancer therapy because of its role in tumor growth, metastasis, and angiogenesis (growth of new networks of blood vessels to support newly reproduced cells), and tumor resistance to chemotherapy and radiotherapy. “The researchers have developed a low-molecular-weight EGFR tyrosine kinase inhibitor: (EGFR-TKI), ZD1839 (Iressa®). ZD1839, a substituted anilinoquinazoline, is a potent EGFR-TKI (IC₅₀= 0.033 microM) that selectively inhibits EGFR-stimulated tumor cell growth (IC₅₀= 0.054 microM) and that blocks EGF-stimulated EGFR autophosphorylation in tumor cells.” [6]

According to Shah, et al., the growth factor and signaling pathway studied most extensively is the epidermal growth factor (EGF) and its receptor (EGFR). Activation of EGFR leads to receptor-associated tyrosine kinase activity, which initiates a cascade of intracellular events. This leads to cell cycle progression as well as a number of other processes crucial to cancer progression. EGFR is expressed, overexpressed, or deregulated in a variety of human solid tumors, resulting in an enhancement of tumor growth. Gefitinib is a selective reversible inhibitor of EGFR that has shown activity in several tumor types. EGFR activation seems to enhance tumor growth by increased mitogenesis (stimulating transit through the cell cycle), cell proliferation and upregulating growth factors for sustained survival. In addition, EGFR activation promotes tumor progression and invasiveness by stimulating transcription genes that regulate cell motility, cell adhesion, and angiogenesis. As an oral agent, gefitinib is extensively metabolized in the liver. In the phase II trials, gefitinib has shown a response rate of 8.8%-18.4% in refractory lung cancer. Clinical trials in various other nonlung cancer patients include studies of gefitinib as a monotherapy or in combination with various chemotherapy, radiation, and/or hormone therapy regimens. Skin and gastrointestinal toxicities are the most frequent side effects of gefitinib. Recently, interstitial pneumonia has emerged as one of the serious adverse effects among gefitinib patients. [7]

Unlike other targeted drugs that have larger molecular structures that work by binding to a receptor site on the exterior cell wall, Iressa®, having a relatively small molecular structure, penetrates into the cell through the EGF receptor sites located on the cell wall. Once inside the cell, these molecules disrupt the cascade of signals found along the critical pathways, preventing intracellular communication downstream, thus minimizing the ability of cancerous cells to proliferate.

**THE SIDE EFFECTS OF IRESSA®**

The most common drug-related side effects associated with Iressa were diarrhea (48%) sometimes associated with dehydration, skin rash (43%), acne (25%), dry skin (13%), nausea (13%), and vomiting (12%). These conditions generally occurred within the first month of therapy and usually were mild to moderate. 2% of patients stopped taking Iressa due to an adverse drug reaction.

About 1% of patients receiving Iressa developed interstitial lung disease (ILD-described as interstitial pneumonia, pneumonitis, and alveolitis). Approximately 1/3 of the
ILD cases were fatal. When ILD occurred, it was often accompanied by acute onset of breathing difficulty with cough or low-grade fever requiring hospitalization.

The reported incidences of ILD in the 23,000 patient U.S. expanded access program was about 0.3%. In Japanese post-marketing experience the reported rate of ILD was about 2%. In the phase III controlled studies in combination with chemotherapy, there were similar rates of ILD (about 1%) reported in both the placebo and Iressa arms of the study. [8]

THE EFFICACY OF IRESSA ®

It was reported in Drug Week that “AstraZeneca’s new anti-cancer pill Iressa (gefitinib) shrunk tumors in a number of non-small cell cancer patients who previously not responded to standard chemotherapy, according to phase II study results published in The Journal of the American Medical Association (JAMA).

“There is an urgent need for new treatments for persons with lung cancer who often have few options available to them,” explained lead author Mark G. Kris, MD, chief of thoracic oncology, Memorial Sloan-Kettering Cancer Center.

The final published results showed that 12% of 102 patients who received the recommended dose of 250mg of Iressa once daily demonstrated at least a 50% reduction in tumor size.” [9]

“Iressa is the kind of treatment that oncologists dream of – a pill that can be swallowed once a day, a nontoxic therapy that causes few side effects. For 10% of the patients who have tried it, people who have no other options left for them, Iressa seems to make the difference between life and death. Another 30-40% of patients who have used the drug have a better, if not a longer, life. But for most patients, Iressa does not shrink their cancer. That fact has become a challenge to researchers at the University of Texas M.D. Anderson Cancer Center. They are dedicated to solving the central puzzle that Iressa, and similar other targeted therapies, pose – what are the cancers that may best respond, and which patients will benefit?” [10]

FUTURE DIRECTION OF TARGETED THERAPY

Targeted therapy is at its early development and its approval as a monotherapy is a giant step forward for this new therapeutic class. “Still these drugs, even Gleevec (used for treating chronic myeloid leukemia), are not yet the Holy Grail that cancer researchers seek. Most cancers employ multiple pathways to grow and survive but targeted therapies tend to focus on a single pathway. Even Gleevec, which has initial high response rates in the relatively rare cancers it treats, cannot affect cancer cells that have mutated in order to use other pathways to grow. That’s why many researchers believe future use of targeted therapies will involve “bundling” these drugs together to treat cancer that is early in its development – cancer which has not developed multiple survival mechanisms.” [11] There have been attempts to combine Iressa ® with other conventional treatments such as chemotherapy in chemo-naïve patients but they have not demonstrated a survival advantage with the addition of gefitinib to standard platinum-based chemotherapy regimens. [12]
Research is currently underway to determine the role genetic makeup plays in the response to targeted therapy. Some patients may not benefit from these new treatments. Researchers at Cedars-Sinai Medical Center identified that a genetic test of patients’ tumors would be helpful in finding the best drug for an individual patient. Their investigation used tumor samples from 39 patients with NSCLC, looking for the expression of numerous genes associated with EGFR. The researchers identified patterns of genes linked to different types of tumors. These specific genes were able to be correlated with a response or failure of the drug Iressa. In their study, seven of the 39 patients responded to treatment with Iressa, while the remaining 32 did not. The investigators were able to link the genes that correlated with this response or lack of benefit. This study reinforced the need for genetic profiling of patients who want to try Iressa as a treatment for their lung cancer. [13]

Up to now, the effectiveness of Iressa @ is based on the objective response rates. Controlled trials need to be conducted to show clinical benefits such as improved in disease-related symptoms or increased survival. [14]

Researches are being conducted to determine the effects of Iressa @ on tumors other than lung cancers. Recent studies have shown that Iressa @ is effective in suppressing enzymes that are vital to transformation and survival of cancer cells in the head, neck and breast tissues [15]. Iressa @ is also found to be effective against colorectal tumor cells that express high levels of EGFR. [16] Results of studies of the efficacy of Iressa @ on renal cell carcinoma also indicated that the antitumor activity of Iressa @ was due to the inhibition of cell proliferation as well as tumor angiogenesis. [17]

According to Langer, we have reached a therapeutic plateau with the existing chemotherapy regimens, with the response rate seldom exceeding 30-40%. He expresses doubt that substituting one agent for another in various combinations will lead to any further improvement in these rates. The thrust of current research has focused on targeted therapy, and EGFR inhibition is one of the most promising clinical strategies. [18]

The Chemical Market Reporter showed that Iressa @ recorded first half 2003 sales of $66 million, including $18 million sales in the US, where the product was only approved 6 weeks earlier. Wall Street analysts estimate peak sales to range from $500 million to $1 billion. [19] The current cost of Iressa @ is approximately $60 per tablet, designed to be taken once daily.

CONCLUSION

Due to the toxic side effects of conventional chemotherapy, researchers have been focusing on a new class of drugs for targeted therapy, also known as smart cancer drug. This type of drug targets the intracellular pathways or extracellular cell molecules to inhibit EGF tyrosine kinase receptors, which are identified as regulators of tumor and its growth. The ability to direct its action only against cancerous cells makes this type of drugs to be “the” cancer drugs of the future. Much challenge still lies ahead since the underlying mechanism of targeted therapy is not yet well understood. Many of the patients on Iressa @ did not show improvement, perhaps due to the advanced nature of their tumors and the possibility of cancer cells to develop multi-pathways, out-smarting the new smart cancer drug. I believe that targeted therapy in the future will combine a number of different inhibitors as more will be known about cancer and its inner workings. The approval of Iressa @ as monotherapy,
focusing on a single pathway, now serves as an open door to many more future drugs that will be capable of inhibiting multiple pathways. This will be a wide open field of research indeed given the sheer number of different types of cancer in existence and their ability to mutate to survive. In the meanwhile, the current therapeutic strategy based on indiscriminate cytotoxic activity will continue to serve the needs of cancer patients.
SELECTED BIBLIOGRAPHY


2) Website: http://seniorhealth.about.com/cs/cancer/a/cancer_treat_se.htm


6) “Orally active inhibitor of EGF signaling has potential for cancer therapy” Drug Week, 1/3/2003, p3.


9) Ref. 8.

10) Ref. 3.

11) Ref. 3.


15) Yang Z, Bagheri-Yarmand R; Wang RA; Adam L; Papadimitrakopoulou VV; Clayman GL; El-Naggar A; Lotan R; Barnes CJ; Hong WK; Kumar R. “The epidermal growth factor receptor tyrosine kinase inhibitor ZD1839 (Iressa) suppresses c-Src and Pak1 pathways and invasiveness of human cancer cells.” Clinical cancer research: an official journal of the American Association for Cancer Research. Jan 15, 2004; pp 658-67.


Vitamin E
Is it a Powerful Antioxidant
or a Waste of Money?

Prepared by

Todd S. Reese

For

Dr. Hank Mancini

Chemistry 236
Paradise Valley Community College

April 16, 2004
VITAMIN E: IS IT A POWERFUL ANTIOXIDANT OR A WASTE OF MONEY?

ABSTRACT

Vitamin E is an antioxidant touted as vital to the human body. For more than twenty years, scientists have worked to improve the antioxidant ability of this molecule. Vitamin E has become important both to the people who believe it helps their body and to the economy. Recent work has delivered a promising enhanced antioxidant version of vitamin E. Yet, other research questions the validity of antioxidants in the body altogether. Consumers should be wary of the remarkable claims of this molecule.

HISTORY

The “discovery” of vitamin E is unclear. Humans have been ingesting plants containing the molecule for thousands of years unaware of the benefits of the vitamin. However, researchers credit Herbert McLean Evans (1882-1971) and Katharine Scott Bishop (1889-1976) with the discovery of vitamin E and its benefits while working at the University of California, Berkeley.¹

The common chemical name for vitamin E is α-tocopherol. It has a molecular weight of 430.719 grams per mol, a formula of C_{90}H_{190}O_2, a melting point of 2.5-3.5°C and a boiling point of 350°C. It has a density of 0.95 and is insoluble in water. It is a phenol comprised of a ring of six carbon atoms with a hydroxyl (OH) group attached (see figure).

Vitamin E is actually four naturally occurring tocopherols (α-, β-, γ-, and δ-tocopherol) which differ in the number and position of the methyl substituents on the aromatic ring. Experts consider the α-tocopherol form as the most important to human health.² Although it is synthesized in labs, plant oils represent the major source for vitamin E. The U.S. recommended daily allowance (RDA) indicates that Americans consume 15 mg of α-tocopherol on a daily basis³, and the average diet usually meets this criteria.²

Antioxidants are chemicals/molecules that inhibit oxidation.⁴ In humans, these are substances, such as vitamin E, vitamin C, or beta carotene, which researchers believe to protect body cells from the damaging effects of oxidation. In the commercial sector, many materials such as plastics, rubber, fuels, lubricants, cosmetics, and agricultural feed can be damaged by oxygen.⁵ The value of antioxidant agents is extremely important to human health and the economy. Vitamin E and other antioxidants are useful for the termination of Free Radicals. Free radicals are formed when weak chemical bonds split in a manner which leaves one with an odd, unpaired electron. These free radicals are extremely unstable and react quickly with other molecules in an attempt to gain stability.
In chemistry, the free radical propagation or chain reaction follows this format: 1. Initiation (radicals form), 2. Propagation (radical makes new radical), 3. Termination (all radicals terminate). See the following text box for an illustration:

**Free Radical Chain Reaction:**

<table>
<thead>
<tr>
<th>Step</th>
<th>Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Radicals form:</td>
<td>( XX \rightarrow X_1^\cdot + X_2^\cdot )</td>
</tr>
<tr>
<td>2. Radical makes new radical:</td>
<td>( RH + X_1^\cdot \rightarrow X_1H + R^\cdot ) or ( RX_1 + H^\cdot )</td>
</tr>
<tr>
<td>3. Radicals terminate:</td>
<td>( R^\cdot + X_1^\cdot \rightarrow RX_1 ) or ( H^\cdot + X_2^\cdot \rightarrow HX_2 )</td>
</tr>
</tbody>
</table>

Typically free radicals attack the nearest stable molecule to grab an electron. When this electron is grabbed, the molecule which was attacked loses an electron and becomes a Free Radical itself (radical makes new radical). The problem is that in the human body, the chain reaction can take place where radicals make new radicals and continue doing damage until finally the reaction is terminated.

Usually the body’s immune system handles free radicals, and sometimes the body makes its own free radicals to fight off viruses and bacterial infection. However, outside influences such as radiation, pollution, and carcinogens such as cigarette smoke and herbicides can create free radicals. If left unchecked, this free radical chain reaction continues and can cause cellular disruption and mutation, especially with age. Experts have linked the chain reaction of free radicals to cancer, arthritis, and heart disease. Experts also believe that antioxidants such as vitamin E protect the body against the effects of free radicals. By donating one of their own protons, antioxidants neutralize free radicals. Since the antioxidant is stable with or without the proton, it does not become another free radical, thereby terminating the chain reaction (see figure below).

![Resonance-stabilized radical](image)

**Figure - Mechanism of Vitamin E radical termination**

**RECENT RESEARCH**

In 1983, three chemists in the Division of Chemistry at the National Research Council of Canada in Ontario published a paper in the *American Chemical Society* journal discussing the possibility of better antioxidants than vitamin E. In their paper, "Antioxidant Activity of Phenols Related to Vitamin E: Are there Chain-Breaking Antioxidants Better than..."
α-tocopherol?'” Graham Burton, Lise Hughes, and Keith Ingold compared the antioxidant scavenging ability of vitamin E with various molecules added at the X, R1, and R2 positions as shown in the diagram to the right. Their work demonstrated that the best antioxidant ability occurs when the long vitamin E tail \((C_{16}H_{33})\) at R2 is replaced with a Methyl group and R1 is replaced with Hydrogen. Their work also indicated that at the X position, the attachment of Nitrogen groups (such as NH, NC(O)CH\(_3\), and NCH\(_2\)CH\(_3\)) to the Carbon did not have improved effects on antioxidant ability as they expected. The researchers had hoped that Nitrogen’s lone pair of electrons would be better able to stabilize a free radical. Their research discovered that the axial position of the Nitrogen group was too close to the plane of the aromatic ring giving it an unfavorable stabilization position.

Despite this unfavorable outcome from their work, the research of Burton, Hughes, and Ingold had profound effects on future research into enhancing vitamin E. One very important discovery they found that was that reducing the lower ring from six members to five members reduced the dihedral angle with respect to the axis of the main six member ring. This and the substitution of R1 and R2 with H and CH\(_3\) led to a large jump in antioxidant ability. These discoveries opened the door for the improvement of vitamin E through chemical substitution.

Burton, Hughes, and Ingold’s work greatly influenced the recent work done by Derek Pratt at Vanderbilt University Medical Center. Obviously influenced by the vitamin E research, Pratt developed an idea while working with Ingold at the National Research Council in Canada. His idea: In addition to adding a Nitrogen group to the ring, he had the novel idea to substitute a Nitrogen atom in the carbon ring itself. With the two changes, he predicted that the new molecule would be more stable in air.

Theoretical analyses of the proposed new molecules, called Pyridinols (see text box), confirmed that they would have the same properties as existing antioxidants. Pratt considers synthesizing pyridinols as a “simple substitution.” However, it took him a year to work out the 12-step substitution process that would enable him to synthesize large quantities for testing. Pratt sent samples of the new pyridinols to Dr. Luca Valgimigli in Professor G. F. Pedulli’s lab at the University of Bologna, the premiere
testing site for antioxidants. Valgimigli determined that the new pyridinols are as much as one hundred times more effective as antioxidants than vitamin E.\(^4\)

Pratt has discovered other exciting possibilities. He proposes that by attaching a “greasy” chemical group to the pyridinols, it will give them affinity for fatty acids and can protect LDL (the “bad” cholesterol) from oxidation. Thus, the pyridinols are more effective inhibitors than vitamin E.\(^5\) Pratt also looks to the possibility of synthesizing a watersoluble pyridinol which he hopes will have similar antioxidant abilities to vitamin C.

**MARKET FORCES**

In the United States, an estimated 35 million Americans take vitamin E supplements\(^6\), which explains the fact that there is an $800 million per year market for this vitamin.\(^5\) In addition to the proposed benefits of preventing cancer, arthritis, and heart disease, vitamin E is touted as reducing the risk of asthma in children\(^1\) and when linked with Selenium, prevents allergies.\(^2\) Doctors also believe that vitamin E can protect the body from LDL (the “bad” cholesterol) oxidation and that vitamin E may slow down the progression of Alzheimer’s disease and Parkinson’s disease.\(^3\) There is no doubt that the public is sold on the proposed health benefits of this molecule. The question is, does vitamin E really have all these health benefits? Will changing the structure of vitamin E improve its antioxidant ability?

**Efficacy of Vitamin E**

As mentioned, the work of Burton, Hughes, and Ingold was instrumental. However, these researchers were quite surprised to find that their initial hypothesis of adding Nitrogen groups to vitamin E did not turn out as expected. Often in science it is common to focus so heavily on the minutia that the overall picture is overlooked. For example, one reason that the Nitrogen addition did not yield the expected results is likely due to the fact that antioxidant activity depends on the “localization of the antioxidant” and its “inherent chemical relativity.”\(^4\) In other words, how well vitamin E works depends on the form it is in (α-, β-, γ-, or δ-tocopherol) and what surrounds it.

The work of Etsuo Niki and Noriko Noguchi at the University of Tokyo indicates that vitamin E behaves quite differently in test tube solutions as opposed to the membranes of the body (see figure at right).\(^5\) The accessibility of the radicals, the mobility of the antioxidant in the membranes, and the chemical reactivity of the antioxidant form are all key factors in how well the antioxidant scavenges free...
radicals. As pointed out by Niki and Noguchi, “It is known that the phytol side chain of α-tocopherol is required for incorporation and retention in the membranes and lipoproteins. This is a dilemma, because the side chain reduces the mobility and efficiency of radical scavenging in the domain.” In other words, vitamin E works best in the phospholipid cellular membranes of the body, but being stuck in the membranes keeps it from aggressive radical scavenging. This notion of correct positioning was suggested a few years ago by Wilhelm Stahl and Helmut Sies. In their article, “Antioxidant Defense: Vitamins E and C and Carotenoids,” they point out that when α-tocopherol is optimally positioned in membranes by its phytol side-chain, it increases the radical scavenging properties. This does not necessarily negate the work of Burton, Hughes, Ingold, and later work by Derek Pratt. While they found that vitamin E works best without the phytyl tail, it is important to point out that these were test tube studies. As pointed out by Niki and Noguchi, “…the dynamics of antioxidant action of vitamin E in vivo have not been well elucidated yet.”

There is a growing community of researchers and scientists who deride the proposed benefits of vitamin E as an antioxidant. A recent meta-analysis of several clinical trials (81,000 total patients) looked at the effectiveness of vitamin E. The results show that vitamin E is a weak antioxidant. The authors conclude that there is “little reason” to take vitamin E for the prevention of heart disease. “Future trials looking at new drugs that have a stronger antioxidant effect may show that true antioxidants are helpful - but right now we just don’t have good evidence that available antioxidants offer much benefit.”

This research is supported by the work of other scientists. The article, “Doubt Cast on Free Radical Theory” reports that researchers at University College London deem that it is time to rethink the role of free radicals and disease. Their research indicates that “the basic theory underlying the toxicity of oxygen radicals is flawed.” Professor Tony Segal at the Centre for Molecular Medicine at UCL claims that his team’s laboratory experiments indicate that enzymes released by leukocytes, not free radicals, are responsible for killing microbial infections. In other words, white blood cells kill off bacteria and fungi with enzymes, not with free radicals. The fundamental theory was that white blood cells create free radicals to ward off infection, and left unchecked these free radicals also damage human tissues. The new research suggests that that theory is invalid. Professor Segal worries that “Many patients might be using expensive antioxidant drugs based upon completely invalid theories.”

Another article entitled “FDA Finds Antioxidant Vitamin Health Claim Misleading,” points out that the FDA has concluded that the phrase, “consumption of antioxidant vitamins may reduce the risk of certain kinds of cancer” printed on dietary supplement labeling is misleading. The article points out that the FDA has determined:

“There is no significant scientific agreement for a relationship between antioxidant vitamins (vitamin C or vitamin E, alone or in combination) and certain cancers, such as cancer of the bladder, breast, cervix, colon and rectum, oral cavity/pharynx/esophagus, lung, prostate, pancreas, skin, stomach.”
There are others who are concerned that research into making a better vitamin E is fueled by the over-the-counter drug industry which wants to sell more antioxidants. For example, a misleading advertisement appeared in several health-food industry publications during 1994. While the small print at the bottom cited the Medical Tribune as the source, "no survey on antioxidant usage had actually been done; the editor had merely asked for opinions on the use of vitamin E." (see advertisement at right).{20}

THE FUTURE

The future of vitamin E and antioxidants in general is unknown. There is no doubt that chemists can create antioxidants that work better in the test tube, and these antioxidants may have valid uses in industry with rubber, plastics, and cosmetics. This research has shown that there are exciting new advances in the technology of building a better vitamin E, but these advances may be built on faulty premises as far as the human body is concerned. The findings by the FDA and researchers show that the efficacy of vitamin E, in human biological/chemical reactions, does not agree with the work of other researchers and what profit-motivated advertisements tell us.

CONCLUSION

Vitamin E and antioxidants in general are exciting molecules. They represent the possibility for healthier, longer-living humans. The incredible research by a number of chemists show that there are tremendous advancements in antioxidant properties in vitro. However, the work done by others suggests that there are many, many questions which must be answered when considering these molecules in the human body. This research has shown that vitamin E may not do everything that numerous business and research facilities claim that it does. It is likely that sales of antioxidants will continue to surge as drug companies bring this profitable molecule to market. Eventually, the truth of the research will bear out. Until that time, consumers should be wary of the remarkable claims and benefits of vitamin E.
Works Cited

15. 10.1021/ai030059m S0001-4842(03)00069-4, November 19, 2003.

Citation and image from:
http://www.quackwatch.org/01QuackeryRelatedTopics/PhonyAds/antioxid.html,
accessed on the Internet, April 9, 2004.
Carcinomas and other health concerns

and their possible links to MTBE

Irene Robinson

For

Dr H Mancini

Organic Chemistry 236

16th April 16, 2004
Abstract

Methyl tertiary-butyl ether (MTBE) is the predominant component in reformulated gasoline that was added to replace tetra-ethyl lead and still maintain high automobile engine combustion efficiency. Numerous investigations have attempted to categorize MTBE definitively as a human carcinogen. Other studies claim that MTBE is a contributor to other minor yet debilitating health symptoms. This paper reviews the current information that is available in relation to the question of whether or not MTBE is a component in health issues and if indeed it should be banned as a gasoline additive.

Introduction

Methyl tertiary-butyl ether (MTBE) is an oxygenated compound and it is the main additive to gasoline that creates reformulated gasoline (RFG) (1). This measure was required in order to comply with one specific section of the Clean Air Amendments Act of 1990 which determined that specific regions, within the United States, with less than desirable air quality needed to add a minimum of 2% oxygen to fuels year round. Other regions where pollution is only a seasonal problem must also comply with the act during those times (2). The composition of MTBE is such that an 11%, by volume, amount is required to be added to gasoline to ensure the correct percentage of oxygen is present. Although the Act does not state that MTBE is the only member of the group of oxygenates that can be added, many oil companies have chosen it because of its relative low cost to produce and ease of distribution. However, in a chemical summary report written by the U.S. Environmental Protection Agency, it states that “The Clean Air Act Amendments of 1990 list MTBE as a hazardous air pollutant”.

The purpose of RFG is to replace the use of “leaded” gasoline. Lead was added to petrol to improve the octane rating but also to reduce the incidences referred to as “knocking” and thereby improve engine combustion efficiency. Unfortunately it has been determined that the lead component decomposes into vapour form and enters the environment (3). MTBE is thought to still maintain the ability for fuel to power the high-compression engines that automobiles now use and reduce the production of these and other dangerous emissions. Although there are concerns expressed by the Environmental Protection Agency that as MTBE was categorized in the Federal Register in 1992 as a volatile organic compound substance, it could play a part in creating photochemical smog when mixed with other volatile organic compounds.

MTBE is produced as a result of methanol undergoing an acid-catalysed addition reaction with methylpropene, as shown below.

\[ \text{CH}_3\text{OH} + \text{CH}_3\text{C}-(\text{CH}_3)=\text{CH}_2 \rightarrow (\text{CH}_3)_3\text{C-O-CH}_3 \]
MTBE, also known as 2-methoxy-2-methyl-propane (4), has the molecular formula of C$_3$H$_8$O. Its geometrical configuration is shown in Figure 1 as a totally saturated ether with the carbons on either side having a tetrahedral arrangement consisting of a t-butyl group on one and a methyl group attached to the other. It has a melting point of 109°C and a boiling point of 55.2°C. The U.S. Environmental Protection Agency states that “At room temperature, MTBE is a volatile, flammable and colorless liquid that dissolves rather easily in water.” It also has a distinctive taste and pungent odour that can be detected when the level of contamination reaches 15 parts per million in water. An advisory on drinking water levels of MTBE produced by the Environmental Protection Agency recommends that the range should be between 20-40 micrograms per litre as they believe this will reduce the smell, the taste and the risk that the consumer will find the contaminated water unacceptable. It also hopes that at this level of contamination the likelihood of toxicity will be low (5).

![MTBE](image)

**Figure 1: A three dimensional representation of MTBE.**

Cancer or more specifically, a tumour is the result of one individual cell’s unconstrained growth pattern that creates many more cells, identical to itself, through its own division. Normally this process is ongoing over a long period of time before the mass of cells is large enough to be detected and categorized (6). There are three primary pathways that encourage conditions that help to damage a cell’s genes and create cancerous cells. The first set of conditions emanates from the environment. These consist of radiation from both the sun and ionizing radiation agents, also genotoxic chemicals. Secondly are the numerous components that are linked with the body’s own metabolism and replication of its DNA. Thirdly is the spontaneous deterioration or induced destruction on the chemical bonds between the nucleotides under natural conditions over time. These pathways are illustrated in Figure 2 (7).
Figure 2: The main pathways to damage a cell’s genes and their possible results.

There are several ways to test for a substance for carcinogenic properties. One way involves the use of rodents as test subjects and either direct or indirect controlled doses of the compound in question are administered and the results are analysed and recorded. Another way is epidemiological methods in which large human populations are observed and variables are minimized or accounted for. The Ames test is one method that tests a compound for mutagenic properties without using mammals. This test involves subjecting a colony of bacteria to measured volumes of a substance. If the substance causes mutation within the bacteria population then there is a high probability that it will do so in mammal DNA as well. Although not 100% true, this test does provide a quick and economical starting reference for recently synthesized chemicals. It was also discovered that chemicals could be carcinogenic not by damaging DNA but rather promoting replication thereby enhancing the possibilities for mistakes to be made. These chemicals are called “Promoters”.

Robert A. Weinberg states that “the ability of a chemical to induce cancer is derived from its ability to damage genes in the body’s cells” (6). But in order for this to happen the chemical must first enter the body.
Routes of Entry

The opportunities for MTBE to enter the environment are numerous and include emissions from the exhaust pipes of vehicles, evaporation from open storage containers and leaks from pipelines into the ground. Once this chemical reaches the soil and leaches in the ground water, it is almost impossible to extract and difficult to biodegrade. The greatest risk for daily exposure to humans not directly working in the petro-chemical industry is at the gas station, in parking garages and while driving where inhalation of the exhaust fumes is possible (8). In the paper produced by Prah, Ashley et al. it was determined that levels of MTBE in the blood, after inhalation, peaked at between 15 to 20 minutes after the termination of exposure. However the levels of its metabolite tert-butyl alcohol (TBA) continued to rise and remained in the body for a considerable period of time. They also state in their paper that "this study demonstrated that MTBE can be absorbed dermally from an aqueous medium in measurable quantities" (9). In another study by Prah, Blount et al., they developed a specific system to saturate a human limb with MTBE and it was determined that a constant temperature of around 38.5°C – 41°C was required for optimal dermal receptiveness (10). According to the study done by Amberg, Rosner and Dekant MTBE is taken up quickly in the gastrointestinal tract from both oral exposure and inhalation and peak blood and breath levels are reached around 10 to 20 minutes after exposure (11). The end products present in the urine of rodents also indicate that metabolism of MTBE is not dependant upon the form of exposure but is related to the quantity of exposure.

The experiment conducted by Mathies on the absorption of MTBE into edible vegetation, found that because MTBE is hydrophilic and difficult to decompose it was present in all sections of the plant due to the contents of the soil. However the leaves of the plant were the clearance house for the compound and should enough time lapse between harvesting and consumption and an MTBE-free environment be available the chemical is evaporated into the air with a half life of 3 days. It is also stated that the predominant route of daily ingestion of MTBE by humans is through polluted drinking water, followed by polluted organic food and finally temperate air-conditions (12).

Possible Mechanisms of Metabolism

MTBE undergoes oxidative demethalization via the human liver enzyme P450 2A6 in a reaction that requires NADPH, to form TBA and formaldehyde in equimolar volumes according to the research performed by Le Gal, Dreano et al. (13). Dekant, Bernauer et al. explain that formaldehyde continues on to undergo reduction to methanol or it is oxidized to create formic acid and CO₂, with the remaining single carbon joining the one-carbon physiological pool (14). Williams and Borghoff surmised that the MTBE encourages the liver enzymes to clear testosterone from the body and thereby increase the production of the lutainizing hormone from the pituitary gland which in turn creates over stimulation of the liver cells. This creates a negative feedback mechanism that requires excessive cell divisions hence the promotion of cancer in male Sprague-Dawley rats (15).
Nihlen, Sumner and Johanson documented the presence of two previously undetected MTBE-derivatives in human urine, 2-methyl-1,2-propanediol (MPB) and α-hydroxyisobutyric acid (HBA)(16). These compounds had already been identified in rodent’s urine after administration of MTBE. A suggested progression of MTBE’s metabolism through the body is illustrated in Figure 3 below.

The Chemical progression of MTBE in the Body

\[
\text{CH}_3\text{C}==\text{C}==\text{O} \quad \rightarrow \quad \text{CH}_3\text{CH}_2\text{OH} \quad \text{methyl tert-butyl ether (MTBE)}
\]

\[
\text{CH}_3\text{CHO} \quad \rightarrow \quad \text{CO}_2 \quad \text{formaldehyde}
\]

\[
\text{CH}_3\text{CO}_2\text{H} \quad \rightarrow \quad \text{CH}_3\text{CH}_2\text{OH} \quad \text{tert-butyl alcohol (TBA)}
\]

\[
\text{CH}_3\text{CHO} \quad \rightarrow \quad \text{CH}_3\text{CO}_2\text{H} \quad \text{acetone} \quad \text{formaldehyde}
\]

\[
\text{CH}_3\text{CO}_2\text{H} \quad \rightarrow \quad \text{CH}_3\text{CH}_2\text{OH} \quad \text{2-methyl-1,2-propanediol (MPD)}
\]

\[
\text{CH}_3\text{CO}_2\text{H} \quad \rightarrow \quad \text{CH}_3\text{CH}_2\text{OH} \quad \text{α-hydroxyisobutyric acid (HBA)}
\]

\[
\text{CH}_3\text{CO}_2\text{H} \quad \rightarrow \quad \text{CH}_3\text{CHO} \quad \text{acetyl}
\]

\[
\text{CH}_3\text{CHO} \quad \rightarrow \quad \text{CH}_3\text{CHOH} \quad \text{1,2-propanediol}
\]

\[
\text{CH}_3\text{CHO} \quad \rightarrow \quad \text{CH}_3\text{CH}_2\text{OH} \quad \text{methylglyoxal}
\]

\[
\text{CH}_3\text{CH}_2\text{OH} \quad \rightarrow \quad \text{CH}_3\text{CHOH} \quad \text{D-lysine}
\]

\[
\text{CH}_3\text{CH}_2\text{OH} \quad \rightarrow \quad \text{CH}_3\text{CH}_2\text{OH} \quad \text{L-lysine}
\]

\[
\text{CH}_3\text{CH}_2\text{OH} \quad \rightarrow \quad \text{CH}_3\text{CH}_2\text{OH} \quad \text{pyruvate}
\]

\[
\text{CH}_3\text{CH}_2\text{OH} \quad \rightarrow \quad \text{CH}_3\text{CH}_2\text{OH} \quad \text{glucose}
\]
De Peyster, MacLean et al. also indicate in their research that MTBE restricted the synthesis of testosterone in male rats and encouraged the break down of estrogen in female mice. They composed their findings of similarities and differences between MTBE and other known carcinogens of Leydig cells into a summarized Table that is presented below (Table 1) (17).

<table>
<thead>
<tr>
<th>MTBE effects reported in DePeyster and Williams et al.</th>
<th>DePeyster, MacLean et al.</th>
<th>MacLean et al.</th>
</tr>
</thead>
<tbody>
<tr>
<td>circulating T</td>
<td>circulating T</td>
<td>circulating T</td>
</tr>
<tr>
<td>T production in vivo</td>
<td>T production in vivo</td>
<td>T production in vivo</td>
</tr>
<tr>
<td>LH results vary depending on dose and sampling time</td>
<td>LH results vary depending on dose and sampling time</td>
<td>LH results vary depending on dose and sampling time</td>
</tr>
<tr>
<td>Acute testicular shrinkage was statistically significant after one month of daily oral dosing</td>
<td>Acute testicular shrinkage was statistically significant after one month of daily oral dosing</td>
<td>Acute testicular shrinkage was statistically significant after one month of daily oral dosing</td>
</tr>
<tr>
<td>LH results vary depending on dose and sampling time</td>
<td>LH results vary depending on dose and sampling time</td>
<td>LH results vary depending on dose and sampling time</td>
</tr>
<tr>
<td>Decreased immunotoxic activity in liver and testis microtome</td>
<td>Decreased immunotoxic activity in liver and testis microtome</td>
<td>Decreased immunotoxic activity in liver and testis microtome</td>
</tr>
</tbody>
</table>

**Similarities and Difference between MTBE and other Known Carcinogens**

**Other Health Effects**

In a study by Martin, Bilgin and Iba it was shown that MTBE and its derivatives bind to the GABA_A receptors in the brain and that this is the source of reported neurological disorders in the presence of reformulated gasoline. It is also a possibility that these compounds could remain in the brain and build up over time with constant exposure (18).

It has been recorded that when MTBE was first added to commercially available gasoline in 1992 in the two major cities of Alaska, a large number of the population began to experience physical discomfort. These symptoms included ear, nose and throat irritation, nausea, headaches and dizziness. This phenomenon has also been reported in many other locations world wide upon the introduction of reformulated gasoline with MTBE. In studies done in Finland on the drivers of Tankers it was noted that around 20% complained of nausea and disturbances to the central nervous system. No definitive link could be shown however and therefore it has been suggested that a small percentage of the community are highly sensitive to MTBE and others simply wish to exhibit hypochondriac behavior with relation to the chemical based on media reports or the objectionable odour of the chemical heightened awareness of it and this manifested into an awareness of already present physical conditions (8).
Although acute quantities of MTBE have been used in medical procedures to dissolve gallstones within the human body, it has been noted that intravascular hemolysis and renal failure has occurred due to the mistaken administration of too large a dose (4).

In a report published by Buckley, Pleil et al for the US EPA in response to discussions held by New Jersey government representatives, it was shown that metabolism of MTBE into TBA in expelled air can skew the results of breathalyzer tests. Older breathalyzer machines process gas samples in a potassium dichromate mixture and when ethanol is oxidized, it is analyzed through this solution within the machine, after a predetermined time frame. MTBE is able to be concentrated in the blood and consequently the breath at much lower exposure levels and therefore it has been suggested that motor vehicle drivers and petrochemical industry employees may be disadvantaged. The results from the breathalyzers were even higher when ethanol had been consumed. The newer machines rely on detecting infrared light absorption and electrochemical data. These instruments can differentiate between the two chemicals. However, both types of machines are still considered, in the legal system, to provide adequate singular proof of intoxication. (19)

It has also been suggested that as tert-butyl alcohol (TBA) one of the major metabolites of MTBE should be considered as a marker for MTBE saturation because it has a longer half-life within the body. However TBA is a compound that is present in many diverse products such as perfumes, drugs and paint removers and so would be difficult to isolate as a sole source from MTBE.

Current Status

To date most short term MTBE exposure and rodent studies state that there is no conclusive and definitive evidence categorizing MTBE as a carcinogen, even in those studies that do find a possible connection between MTBE and carcinogenic properties. However, historically a substantial number of chemicals had been categorized as rodent carcinogens in the period of time from the end of World War II to the 1960s. These chemicals were normally removed or limited in their use based on the assumption that rodents and humans had similar biological responses and epidemiological studies were not considered an option (6).

A report for Congress on Renewable fuels and MTBE dated November 18th 2003 highlights the major issues of the current energy bill that had been proposed. This recent bill proposed to modify the existing Clean Air Act requirement for RFG that requires at least 2% oxygen. This requirement had led to the gasoline refiners adding MTBE to RFG. The new modification proposed that 5 billion gallons of renewable fuels such as ethanol would have to be added to motor fuels over the next 10 years. This would double existing ethanol production. However the main controversial aspect of the bill would require MTBE producers' immunity from product liability lawsuits. It had also proposed to ban MTBE over 11 years not 4 years as the Senate bill had proposed and had even given the President the authority to not ban it at all! This bill recently failed to pass through congress (19).
Conclusion

In short there have been a number of studies of MTBE and its adverse effects on rodents. In the past these types of studies have been sufficient to limit or remove a substance from general use. Although the studies on humans have been limited in both exposure and time, they too show a disturbing trend toward abnormalities due to the presence of the chemical within the body. The properties of MTBE may not be those of a mutagen but perhaps a promoter. Whilst the current studies are not conclusive I believe that it is essential that further detailed and independent investigations continue to establish definitive links to cancer and other health concerns.

Concurrently the new energy bill must provide stimulus for the eventual replacement of MTBE with the provision for the addition of renewable fuel sources, such as ethanol, as quickly as politically and practically possible. This move will not only reduce public health risk but will provide the impetus for less reliance on pure sources of fossil fuel and non-renewable motor fuel supply. The technology for us to move away from fossil fuel dependency is available but until such times as the public demands this change or it is forced on them, the current situation will remain. This bill should not provide for a ‘safe harbour’ for MTBE producers. This measure would seem obsolete if indeed there was no real question of the damaging effects of the chemical.

The introduction of MTBE was essentially an economical one but not necessarily an ethical one. I believe in the long run it will become a very expensive venture – not only as we attempt to clean up the environmental damage but as we also come to terms with the costs to our health.
Bibliography

1) “Methyl Tertiary Butyl Ether (MTBE)” U.S. Environmental Protection Agency. Online. 1 Apr. 2004 http://www.epa.gov/mtbe/gas.htm


The Carcinogenic Effects of Benzene

Kelly Schmidt
April 2004
Mancini – Chemistry 236

'Don't try this in the lab, kids!"
This report is on the carcinogenic effects of benzene. This report will cover how the chemical is ingested, what happens biologically to the body, and the effects it has on the body in general. Also, it will cover short and long-term effects when being exposed and nomenclature of the chemical Benzene.

First, we must establish what is benzene. Benzene is an aromatic compound that is colorless with a sweet odor. It evaporates quickly and dissolves in water very fast. This chemical is also highly flammable. Benzene is found in the air, water, and the soil. Benzene was first discovered by Michael Faraday in 1825 from liquid condensed by compressing oil gas but is now taken from petroleum, which started in 1937. It was first synthesized in 1833 by distilling benzoic acid with lime. The structure for Benzene was discovered by Kekule. It was widely known that Benzene came to him from a dream of a snake eating its own tail. This inspired him to deduce the ring structure of benzene. The chemical formula for benzene is C6H6 and is an aromatic ring. Its molecular weight is 78.11 and its density is 0.8787. The boiling point is 80.1°C and the melting point is 5.5°C. (1,5,4)

The uses of Benzene vary but are widely used for commercial purposes. The major uses of benzene are in the production of ethyl benzene, cumene, and cyclohexane. Ethylbenzene is an intermediate of styrene (Styrofoam), which makes plastics. Cumene is
used to produce acetone and phenol. Cyclohexene is used to make nylon resins. Benzene is also a component of gasoline since it comes naturally from crude oil. 1-2% of unleaded gasoline contains benzene. This chemical makes rubbers, lubricants, dyes, detergents, drugs, and pesticides. The carcinogenic effects only occur when benzene is alone, if it is attached to another element of chemical the carcinogenic properties become inert. Benzene was used as a pesticide but this was stopped because it became classified as an air pollutant. Benzene ranks in the top 20 for chemicals produced in the United States. 98% of manufactured benzene comes from petroleum refining industries. Natural sources for benzene also include volcanoes, forest fires, crude oil and cigarette smoke. The major impurities of commercial Benzene can include Toluene, Xylene, Phenol, Thiophene, and pyridine. (1,5)

Benzene is mostly found in the environment due to industrial processes. It can pass into air from water and soil surfaces and can hook onto rain and snow to be passed back into the ground. It breaks down quicker in the air than in the soil and water. (1)

Benzene is classified as a hazardous air pollutant and a hazardous waste. Most exposure to benzene occurs through the skin or by inhaling it. Benzene is fatal within 5-10 minutes of exposure usually if the content is higher than 20,000 ppm. The results are asphyxiation, respiratory arrest, the central nervous system stops working, and the heart stops pumping. Leukemia is the usual result of long-term exposure to benzene. Most people are exposed to some amount of Benzene on a daily basis. About 50% of the entire nationwide exposure of Benzene comes from cigarette smoke. This includes secondhand smoke. 20% is caused of nationwide exposure comes from vehicle emissions. If you touch gasoline benzene can enter though your skin and also breathing in the exhaust fumes. The EPA estimates that benzene emissions from pharmaceutical, resin, plastics, and rubber plants release 495 tons of benzene per year into our air. The EPA also estimates that 3 people die annually from cancer caused from benzene exposure. Though, an estimated 3 million people get regular benzene exposure in the production of this chemical. Eating or drinking foods with high levels of benzene cause vomiting and even in severe cases convulsions, coma, and death. If you spill benzene onto your skin redness and sores can occur, and exposure of benzene in your eyes can damage the cornea. Exposure is also harmful to the reproductive organs as well. Women who were exposed showed a decrease in ovary size and studies in pregnant animals showed harmful effects to the developing fetus. These effects included low birth weight, delayed bone formation, and bone marrow damage. Finally exposure of Benzene has also been linked to damage of chromosomes, which contain the cells hereditary information otherwise known as DNA. (2,3,5)
Benzene enters the body in three ways: inhalation, orally, and through the skin. When they enter the bloodstream, benzene is temporarily stored in the bone marrow and in the liver. Benzene is converted to metabolites and some of the harmful effects of benzene are caused by these. Certain metabolites of benzene, such as phenol, muconic acid, and S-phenyl-N-acetyl cysteine (PhAC) can be measured in the urine. The amount of phenol in urine has been used to check for benzene exposure in workers. The test is useful only when you are exposed to benzene in air at levels of 10 ppm or greater. However, this test must also be done shortly after exposure, and it is not a reliable indicator of how much benzene you have been exposed to, since phenol is present in the urine from other sources (diet, environment). Measurement of muconic acid or PhAC in the urine is a more sensitive and reliable indicator of benzene exposure. Measurement of all parts of the blood and measurement of bone marrow are used to find benzene exposure and its health effects. These metabolites usually will leave the body through urine is 48 hours or less. (1,3)

Long-term exposure causes problems with the blood. People who have been exposed experience effects in the tissues that form blood cells such as bone marrow. This can cause anemia and excessive bleeding. Benzene causes cancer to the blood-forming organs otherwise known as leukemia. Exposure has been linked to a specific type of leukemia known as acute myeloid leukemia. This type of leukemia affects various white blood cells including granulocytes, monocytes, and platelets. The leukemic cells accumulate in the bone marrow and spread to the liver, spleen, lymph nodes, CNS, kidneys, and gonads or sexual organs. Treatments include chemotherapy, and blood stem cell replacement therapy from a donor. One optional treatment is a drug therapy called arsenic trioxide. This is an anticancer drug that kills the leukemic cells and stops them from dividing. This is usually used in combination to chemotherapy. (1,5)

resonance of benzene
OSHA otherwise known as the occupational safety and health administration has made rules for safe use of benzene. All workers that may be exposed to benzene must wear special breathing equipment called a respirator when the levels of benzene are out of safety range, and the EPA requires that all companies let them know how and where they are dumping and storing benzene waste. Other protective equipment includes goggles, boots, gloves, aprons etc. So that no benzene can become in contact with the skin. (4) EPA regulates benzene under the Clean Air Act (CAA), Toxic Substances Control Act (TSCA), Clean Water Act (CWA), Superfund Amendments and Reauthorization Act (SARA), Food, Drug, and Cosmetic Act (FD&CA), Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA), Resource Conservation and Recovery Act (RCRA), and Safe Drinking Water Act (SDWA).

OSHA has several plans of actions if you become exposed. If benzene is splashed in the eyes, wash out and see a dr. as soon as possible for suspected damage. For skin spills use soap and water and immediately wash the area and contaminated clothing.. If benzene is inhaled expose the person to fresh air immediately and apply artificial respiration if breathing has stopped. Call for medical assistance as soon as possible. If benzene is swallowed and the patient is conscious do not induce vomiting and call 911. (4)

As you well know by now benzene is highly flammable and should be stored in tightly closed containers in a cool and well ventilated area. All sources of ignition around this substance should be controlled. Smoking and using tools that spark is greatly prohibited when working with benzene. (4)
Benzene Structures

Kekulé structure ↔ hybrid structure

ethylbenzene → styrene

cumene → phenol + acetone
The Molecule Benzene is dangerous but fascinating. When alone it is a dangerous human carcinogen but when attached to certain substituents becomes docile. Several government agencies have put up many regulations for the use and disposal for benzene and that is good. Benzene is not a molecule that I would want my children to be inhaling or ingesting. I think though that benzene should be watched more carefully that it is. Since it is the 20th top most made chemical in the United States there must be a lot of it being manufactured where does it go and does the FDA, EPA, or OSHA do all they can to regulate it. Probably not. Benzene is also exported from our country to others. I read nothing about the safety precautions on the ships or travel equipment used to transport benzene. I find that interesting. I also noticed many law firms are suing large corporations for workers needing to be compensated from long-term exposure to the chemical. Apparently hasn't been that long known that benzene is a human carcinogen. I hope our government gets into gear and helps to regulate all chemicals and such that pose a threat to Americans. I don't believe you can ever be too careful when dealing with dangerous chemicals.
Bibliography Works Cited Page

1. http://www.eco-usa.net/toxics/benzene.html
2. www.osha.gov/sitc/benzene.html
Caffeine – Just Another Happy Drug

Prepared for
Dr. Hank Mancini
Chemistry 236
Paradise Valley Community College

Prepared By
Krissie Sesi

April 15, 2004
Abstract

Who would have thought the world's most widely used addictive drug could be purchased on virtually every street corner and grocery store? It is quite possible since the drug is caffeine. Caffeine uses range from athletic stimulation, staying awake, helping maintain better physical and mental endurance as well as aiding in weight loss. Unfavorable side effects to caffeine include headache, lethargy, and poor sleep. Although caffeine is a drug and does have addictive properties, there are some misconceptions as to the safety of it.

1. Introduction:

"Caffeine, by any measure is the world's most popular drug, easily surpassing nicotine and alcohol". Chemically, caffeine is 1,3,7-trimethylxanthine — meaning it is a xanthine molecule with methyl groups replacing the three hydrogens bound to nitrogens in the xanthine ring. Caffeine is metabolized (demethylated) in the liver by cytochrome P450 enzymes known as 1A2. When it is in pure form, caffeine appears to be a white crystalline powder that has a bitter taste. Figure 1 depicts the structure of xanthine and caffeine with imidazole being the circled portion.

![Figure 1](image)

II. History

Caffeine is most commonly found in coffee, and was first extracted from coffee in 1521. Coffee originated in Ethiopia and by the fourth century it was introduced to Arabia and the rest of the east. It is believed that Ethiopian nomads discovered coffee through their animals. After the animals would eat the fruits from the trees they would have an energy boost, so the nomads tried eating the seeds and they too had an increase in energy. Coffee has since been used in religious ceremonies so the people involved in the rituals could stay up and pray the entire night. In 1573 coffee was introduced to the Europeans and authorities attempted to ban it but they could not do it. Tea was later introduced in 1657 and became very popular. Milk chocolate was introduced into Switzerland in 1876, and near the end of the 19th century cola products started to appear around the world. The United States alone imports almost 30% of the world's coffee supply where daily consumption averages 2-3 cups.
When caffeine is in the body, it acts as a stimulant and increases metabolism, heart rate, and accelerates breathing. The effects of caffeine are felt about 15 minutes after consumption and can last several hours. Athletes tend to be large supporters of caffeine as ingestion will improve endurance performance as well as "increase lipolysis and fat oxidation, decrease muscle glycogen breakdown, and lessen the subjective perception of effort". Caffeine can increase plasma levels of free fatty acids, cortisol and epinephrine which are thought to improve athletic performance. But effects on the brain may be more important for improving endurance -- such as increased dopamine signaling in the basal ganglia and reduced serotonin signaling (insofar as serotonin mediates fatigue).

III. Advantages to Caffeine

Although caffeine is considered a drug, it does have many benefits to it. Caffeine will increase alertness and reduce fatigue. This particular upshot becomes especially advantageous in situations of not enough sleep, i.e. doctors, truck drivers, students, etc. That extra burst of energy offsets the consequence of lack of sleep. Caffeine is also known to improve performance on tasks that require prolonged endurance, whether mental or physical. Some research indicates that a few daily cups of coffee may prevent episodes of gallstones, asthma, diabetes, and contain antioxidants that fight cancer and heart disease. Besides coffee and energy drinks, caffeine is largely found in products that aid in weight loss. It serves as a diuretic and increases metabolism, as well as frees stored fat so that the body can use it for energy. In studies done at Emory university where caffeine and a placebo was given to subjects over a period of 21 days, the subjects who maintained the best results were those given caffeine.

Time course of caffeine withdrawal symptoms.
The key to upholding the benefits of caffeine is moderation. Too much of anything will have negative consequences but Mooney also states that 250 – 300 milligrams of caffeine daily is safe, even healthy for the average person. Caffeine regularly increases energy metabolism throughout the brain while decreasing cerebral blood flow -- and there is no tolerance for these effects. According to Fredholm, vasoconstriction due to 250 milligrams of caffeine can decrease central blood flow by 20-30%, which is why caffeine has been used to treat migraine headaches and is found in over the counter medications such as Excedrin, Anacin and Midol. See table 1 for caffeine content.

<table>
<thead>
<tr>
<th>Beverage</th>
<th>Caffeine content per serving (milligrams)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Coffee</strong></td>
<td></td>
</tr>
<tr>
<td>Brewed (8 ounces)</td>
<td>85</td>
</tr>
<tr>
<td>Instant (1 rounded teaspoon, dry)</td>
<td>75</td>
</tr>
<tr>
<td>Espresso (1 fluid ounce)</td>
<td>40</td>
</tr>
<tr>
<td>Decaffeinated, brewed (8 ounces)</td>
<td>3</td>
</tr>
<tr>
<td>Decaffeinated, instant (8 ounces)</td>
<td>3</td>
</tr>
<tr>
<td><strong>Tea (8 ounces)</strong></td>
<td></td>
</tr>
<tr>
<td>Black tea</td>
<td>40</td>
</tr>
<tr>
<td>Green tea</td>
<td>40</td>
</tr>
<tr>
<td>Decaffeinated black tea</td>
<td>4</td>
</tr>
<tr>
<td>Iced tea, ready to drink</td>
<td>30</td>
</tr>
<tr>
<td>Iced tea mix, unsweetened</td>
<td>13</td>
</tr>
<tr>
<td><strong>Carbonated beverages (12 fluid ounces)</strong></td>
<td></td>
</tr>
<tr>
<td>Coca-Cola Classic, Cherry Coca-Cola</td>
<td>34</td>
</tr>
<tr>
<td>Diet Coke</td>
<td>45</td>
</tr>
<tr>
<td>Mello Yellow (regular and diet)</td>
<td>51</td>
</tr>
<tr>
<td>Pepsi-Cola, Wild Cherry Pepsi</td>
<td>38</td>
</tr>
<tr>
<td>Diet Pepsi-Cola</td>
<td>36</td>
</tr>
<tr>
<td>Sunkist Orange Soda</td>
<td>41</td>
</tr>
<tr>
<td>Surge</td>
<td>51</td>
</tr>
<tr>
<td>Red Flash</td>
<td>40</td>
</tr>
<tr>
<td>Mountain Dew (regular and diet)</td>
<td>55</td>
</tr>
<tr>
<td>Code Red Mt. Dew</td>
<td>56</td>
</tr>
<tr>
<td>Royal Crown Edge</td>
<td>70</td>
</tr>
<tr>
<td>Red Bull</td>
<td>80</td>
</tr>
<tr>
<td>Planet Java Caramocha (9.5 ounces)</td>
<td>65</td>
</tr>
<tr>
<td>Planet Java Tremble (9.5 ounces)</td>
<td>123</td>
</tr>
<tr>
<td>KMX Orange, KMX Blue (8.4 ounces)</td>
<td>38</td>
</tr>
<tr>
<td>SoBe Adrenaline Rush (8.3 ounces)</td>
<td>79</td>
</tr>
<tr>
<td>SoBe No Fear (8 ounces)</td>
<td>158</td>
</tr>
<tr>
<td>Excedrin</td>
<td>65</td>
</tr>
<tr>
<td>Anacin; Midol</td>
<td>85</td>
</tr>
</tbody>
</table>

Table 1 Sources: National Soft Drink Association (1999), www.nsda.org; SoBe Beverages (2003); American Dietetic Association (2004)
There is ample evidence that lower doses (20-200 mg) of caffeine are reliably associated with "positive" subjective effects even in the absence of acute withdrawal effects. The subjects report that they feel energetic, imaginative, efficient, self-confident, and alert; they feel able to concentrate and are motivated to work but also have the desire to socialize. Griffiths also states that schoolchildren consuming more that 50 mg of caffeine per day, mainly from soft drinks, report higher wakefulness than a control group consuming less than 10 mg per day. Performance, such as when driving a car, appears to be improved by caffeine in doses corresponding to 1 to 2 cups of coffee. There is also evidence that caffeine improves work performance during night shift work, without severely compromising daytime sleep. The combination of a prophylactic afternoon nap and caffeine appears to maintain performance at a high level even for prolonged periods without sleep. Some of the negative mood effects of prolonged sleep deprivation are also reduced by caffeine.

When people are interviewed about psychoactive substance use disorders, seven criteria are used: 1) tolerance; 2) withdrawal; 3) substance often taken in larger amounts or over a longer period than intended; 4) persistent desire or unsuccessful efforts to cut down or control use; 5) a great deal of time spent in activities necessary to obtain, use, or recover from the effects of the substance; 6) important social, occupational, or recreational activities given up or reduced because of substance use; 7) use continued despite knowledge of a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by substance use. Because coffee or caffeine-containing nutrients or drinks are widely available and culturally accepted, their consumption does not usually have negative social consequences. Indeed, in the studies on caffeine dependence, criteria 3, 5, and 6 are usually excluded. Especially in the US there is no doubt that many individuals reduce or try to reduce their caffeine intake due to perceived health problems. This relates to criterion 7 if these individuals have difficulties in reducing intake. One interesting question is therefore if caffeine poses a real health hazard or if the negative association between health and caffeine is a perceived one.

It is generally admitted that important variations in individual sensitivity to the effects of caffeine exist, but abuse of caffeine represents a minimal risk, particularly when compared with other stimulant drugs. Recently, the effects of an i.v. administration of caffeine were tested in 10 subjects with histories of stimulant drug abuse. In that study, caffeine dose-dependently increased ratings of positive mood, and the higher doses of caffeine were more frequently identified with other stimulant drugs like amphetamine and cocaine. While the effects of i.v. administration of caffeine on mood were similar to those previously reported for cocaine in the same subjects, the physiological effects were different. In other respects as well, caffeine differs from other drugs and there is little evidence for compulsive use of caffeine. The great majority of consumers drink caffeinated beverages in a controlled manner, although a small minority uses caffeine compulsively, such that they have difficulties in reducing or stopping intake.

Because the drug is consumed by a majority of the adult population in most countries, it is clear that caffeine use does not introduce major social problems. In fact, there is even some, albeit weak, evidence to suggest that caffeine can improve social interactions. It is also widely accepted that compared with other commonly used drugs
such as nicotine (in smoked tobacco) or alcohol the social consequences of caffeine use are negligible. Thus, caffeine does not impose a potential health hazard or a polluted environment on fellow citizens as does smoking. Similarly, the behavioral changes are not nearly as great as those seen after use of alcohol, but caffeine does have a specific mode of attack when it enters the body.

IV. Mechanism of Action in the Body

The chemical structure of caffeine has a lot to do with how it will act in the body. Nitrogen atoms that are part of aromatic rings, such as pyridine, pyrrole & imidazole, have planar configurations ($sp^2$ hybridization), and do not have stereogenic centers. Nitrogen atoms bonded to carbonyl groups, as in caffeine, also tend to be planar. More than 99% of orally ingested caffeine is absorbed -- with peak plasma levels obtained in 15 to 45 minutes. Caffeine is soluble in both water & oil and can readily cross the blood-brain barrier. Adenosine is an adenine molecule attached to a ribose or deoxyribose sugar molecule. The similarity in chemical structure between the adenine portion of adenosine and the caffeine molecule is the key to how caffeine works. Cells -- including neurons -- have adenosine receptors. The caffeine molecule is similar enough to adenine to fit into adenosine receptors, but is not similar enough to stimulate those receptors. So the main action of caffeine is to block adenosine receptors. Caffeine is similar enough to adenine that it binds to phosphodiesterases, but it can inhibit phosphodiesterase molecules preventing them from hydrolyzing (inactivating) cAMP, which is where we get our energy when it is converted to ATP. Practically speaking, Fredholm affirms that this effect is rarely seen in the body because the amounts required are much greater than the plasma levels of caffeine achieved by coffee-drinking. Caffeine is metabolized by the liver to form dimethyl- and monomethylxanthines, dimethyl and monomethyl uric acids, trimethyl- and dimethylallantoin, and uracil derivatives. The demethylation, C-8 oxidation, and uracil formation occur mostly in liver microsomes. Metabolism in humans is characterized by the quantitative importance of the 3-methyl demethylation leading to the formation of paraxanthine. In his study, Arnaud states that the “first metabolic step represents up to 72 to 80% of caffeine metabolism”. Many of the metabolic steps may be saturable in humans as the elimination half-time for not only caffeine, but also some of its metabolites, is dose-dependent.

Caffeine is absorbed through the stomach and small intestine into the bloodstream. The amount of caffeine in the blood reaching the brain determines the severity of its effects on the body. The metabolites of caffeine are excreted in urine, although caffeine can also be secreted in saliva, semen, and breast milk. Caffeine will continue to have an effect on the body as long as it remains in the blood. The time required for the body to eliminate one-half of the total amount of caffeine consumed this varies from several hours to several days. For the average non-smoking adult the effects last about five to seven hours. Several factors can lengthen caffeine’s half-life, such as some medications, liver diseases, and pregnancy.
V. Adverse Reaction to Caffeine

There are well-documented effects of caffeine on anxiety in humans, and it is well established that caffeine delays the onset of sleep. It can first be noted that effects on sleep are quite variable. It has been suggested that the subjects most sensitive to the effects of coffee on sleep might metabolize caffeine more slowly than the others. There are however major differences in the sensitivity to caffeine among individuals. According to Bonnet, there is some evidence to suggest that one may "pay" for the benefit of increased alertness and awareness with a lower restorative capacity of a nap after sleep deprivation. Caffeine in doses corresponding to one cup of coffee taken at bedtime increases sleep latency and decreases the reported quality of sleep in parallel with small changes in the EEG pattern during sleep, especially in the non-REM deep sleep. On the other hand, a dose of caffeine taken in the morning can have such effects the following night. Generally, more than 200 mg of caffeine is needed to affect sleep significantly, yet concentrations as low as 3 μM can influence sleep. Sleep problems tend to be one of the major reasons why people, of their own initiative, cease drinking coffee. Conversely, there are many people that seem to have no sleep problems despite taking a regular evening dose of caffeine. This clearly emphasizes that caffeine interferes with a modulatory mechanism in sleep regulation, not with a fundamental sleep regulatory brain circuit. It probably also reflects on the fact that regular sleeping habits are of fundamental importance in ensuring suitable sleep. If regular caffeine intake is part of such a normal diurnal pattern, it is easy to understand how it could contribute to satisfactory sleep. The most prominent effects are shortened total sleep time, prolonged sleep latency, increases of the initial light sleep EEG stages, and decreases of the later deep sleep EEG stages, as well as increases of the number of shifts between sleep stages. Subjective sleep quality decreases in parallel to the lengthening of sleep latency, the duration and number of periods of wakefulness, and the shortening of total sleep time. REM sleep is hardly decreased in relation to total sleep time, but the latency to the first REM period is shortened. However, the practical importance of these findings is limited by the fact that most coffee is consumed in the morning and by the question as to what extent tolerance might develop to the sleep-disturbing effects, particularly in heavy consumers. Other negative changes obtained, particularly with higher doses or in nonusers, include having the jitters, nervousness, anxiety, tension, and restlessness. Negative social consequences of coffee drinking are not claimed, but DSM-IV 1994 lists caffeine intoxication, caffeine-induced anxiety, and sleep disorders as caffeine-induced disorders.

VI. Withdrawal/Dependency

Drug dependence may be used to denote "a state of affairs when administration of the drug is sought compulsively, leading to disrupted behavior if necessary to secure its supply, and use continues despite the adverse psychological or physical effects of the drug." In the study that Griffiths conducted, he found that humans can experience a variety of withdrawal symptoms. These include weariness, apathy, weakness and drowsiness, headaches, anxiety, decreased motor behavior, increased heart rate, and
increased muscle tension and, occasionally, tremor, nausea, vomiting, and flu-like feelings. Several reports on caffeine abstinence and postoperative headaches reported that, in high but not in low caffeine consumers, abstinence was followed by marked increases of blood flow in the frontal lobes\textsuperscript{16}. Hughes also found two studies which insisted that caffeine withdrawal should be included in the list of diagnoses recognized by the American Health System.

Anecdotal reports on complaints induced by caffeine withdrawal go far back into the last century. The first controlled study was carried out by Dreisbach and Pfeiffer in 1943 who gradually increased the dose of caffeine across 7 days up to 850 mg/day and then substituted this medication with placebo capsules. Fatigue, disinclination to work, mental depression, and headache appeared in most subjects. Headache was alleviated by reinstatement of caffeine but hardly by conventional analgesics. This may be related to changes in blood flow. Caffeine has central vasoconstrictive properties, which lead to a 20 to 30% decrease in cerebral blood flow in humans and in animals. This decrease can be achieved in humans after the absorption of 250 mg of caffeine\textsuperscript{17}. Thus, blood flow velocity in the middle cerebral, posterior cerebral and basilar arteries is increased during withdrawal, and decreased within 30 min after intake of caffeine, returning to baseline values after 2 hours\textsuperscript{18}.

Withdrawal symptoms generally begin about 12 to 24 hours after sudden cessation of caffeine consumption and reach a peak after 20 to 48 hours. Nonetheless, in some individuals, these symptoms can appear within only 3 to 6 hours and can last for 1 week\textsuperscript{19}. Thus, even a short abstinence, equivalent to missing the morning cup of coffee, can lead to significant unpleasant effects. There were generally more complaints in the afternoons than in the mornings. All complaints tended to be more severe on the second than on the first day of abstinence, but had nearly vanished by the third day. Most complaints were correlated with the headache reports, suggesting that they were secondary to headache. Furthermore, in a group that alternated between 1 day of caffeine consumption and 2 caffeine-free days, the complaints decreased from the first period of abstinence to the next and vanished almost completely by the third one, demonstrating that more than 1 day of previous caffeine exposure is needed to induce withdrawal symptoms\textsuperscript{20}. The syndrome is specifically due to the discontinuation of caffeine intake, because it persisted regardless of the increased consumption of over-the-counter analgesics that closely paralleled the intensity of the headache complaints.

\textbf{VII. Misconceptions}

While it is commonly believed that caffeine causes high blood pressure, a study done in Zurich may show otherwise. Subjects given coffee exhibited "elevated blood pressure and increased nervous system activity...regardless of whether or not the coffee contained caffeine"\textsuperscript{21}. The results suggested that since coffee contains hundreds of ingredients, any one of them could be the cause of an increase in blood pressure, not the caffeine. Unlike cocaine, amphetamine, morphine, alcohol and nicotine, caffeine does not activate dopamine release (to D\textsubscript{2} receptors), in the "pleasure centers" (the shell) of the
nucleus which are associated with addiction. The "addictive" properties of caffeine seem to be almost entirely connected to withdrawal symptoms.

VIII. Conclusion

Caffeine affects the human body in many different ways, with sensitivity and amounts varying in each individual. Although caffeine is rated and studied differently than other drugs, it does have adverse effects and withdrawal symptoms when consumption ceases. This leads me to believe that it is an addictive drug and potentially has more harm than what is currently believed. I also believe that in the future, things like increased metabolism and heart rate, as well as the blockage of adenosine will cause more long term damage than just the 3 day to week long withdrawal period. I don't think that the long term or short term affects of caffeine will be as harmful as other drugs such as nicotine, alcohol, marijuana and more, but I do think that anything that alters the natural mechanisms of the body will prove to be harmful. If caffeine is not addictive, then that leads us to wonder why Starbucks is a multi-million dollar corporation, with lines of people at the door practically every morning.
References

(1) Bealer, Bonnie K. *Journal of American Sleep Foundation* 2001, 1
(2) Fredholm, Bertil B. *Pharmacological Reviews* 1999, 51 83-133
(3) Hartley, Terry R. *American Journal of Cardiology* 2004, 93 1022-1026
(5) Linda, Mooney J. *Prevention* 2000, 52 7
(8) Bonnet, M H. *Physiological Behavior* 1996, 59 777-782
(9) Hughes, J R. *Experiments in Clinical Psychopharmacology* 1997, 5 393-398
(12) Kaplan, G B. *Journal of Clinical Pharmacology* 1983, 37 693-703
(13) Levy, M. *Clinical Pharmacol Ther* 1983, 33 770-775
(14) Landolt, H P. *Neuropsychopharmacology* 1995a, 12 229-238
(15) Ran, H P. *Pharmacology* 1995, 1-855
(16) Fenely, M. *Anesthetic Analgesic* 1991, 72 449-453
(17) Mathew, R J. *Headache* 1985, 25 305-309
(18) Couturier, E G. *Cephalalgia* 1997, 17 188-190
(19) Barone, J J. *Food Chemical Toxicology* 1996, 34 119-129
(20) Hofer, I. *Pharmacol Biochemical Behavior* 1994a, 48 899-908
Antidepressants
and
Wellbutrin

Sneha Shah

Chemistry 236

April 16, 2004
Abstract

Depression is a disorder in the brain. There are many antidepressants available in the market right now. Wellbutrin is antidepressant medication in the aminoketone class. Wellbutrin is chemically unrelated to selective serotonin reuptake inhibitors (SSRI), tricyclics, or tetracycline. Wellbutrin is very commonly used as an antidepressant and smoking cessation treatment, and it includes bupropion hydrochloride crystalline and highly soluble in water substance.

Depressant

Depression has been a very common problem in the United States for decades. Approximately sixteen percent of the population will be suffering from significant depression period in their lifetime by year of 2020. The National Institute of Mental Health calculates around over eighteen million American adults of age eighteen and older, or ten percent of the U.S population, were affected by depression last year. Nearly twelve percent of women and six percent of the men are found to be depressed each year. More than three-fourths of the patients with depressive disorders are afflicted with one or more depressive conditions, such as anxiety disorder, panic disorder, substance use disorder, and impulse control disorder. (1)

Depression is a disease that happens in a particular part of the brain called the limbic system. This is the area of the brain, which regulates the activities such as emotions, physical and sexual drives, and stress response. Within the brain, there are special chemicals called neurotransmitters that carry out many very important functions. They help transfer messages through structures of the brain’s nerve cells. These nerve cells, called neurons, are organized to control specialized activities. Each person has somewhere between 10 and 100 billion neurons within our brains.

Symptoms of the depression

Most people who have not experienced depression do not properly understand depression. Many individuals with the disorder are left untreated. Depression is a mood disorder that is analyzed by some primary symptoms like the shortness of concentration, missing deadlines, or drop in standards, change in personality, cranky behavior, or loud voice and negative statements. Sleep disturbance or unable to fall back to sleep, feeling fatigue after long sleep, and sleep eating habits are noticed in depressed people. Thoughts of suicide, increased isolation, increased sexual promiscuity, or increase alcohol drugs uses are very common in today’s life and may indicates a depression disorder. (2) There are significant numbers of the depressed people that contemplate suicide, or attempt suicide, and some of them are succeed.

Biological causes of depression
Depression is a serious disorder and is considered life threatening. The cause of depression was not clearly understood for a long time. Nowadays depression has been treated very carefully and seriously. It is important for the psychologists or the doctors to understand whether or not it is a physical illness or depression.

Experts have made great progress in understanding the functions of the brain, the influence of neurotransmitters and hormones, some other biological processes, and the development of depression. The limbic system of the brain and hypothalamus, the small structure located at the base of the brain controls the activities in the brain. There are special chemicals in the brain called neurotransmitters, which help transfer the messages through the structures of the nerve cells. (3)

The major depression and depressive indication, although commonly come across in medical population, are under diagnosed and under treated in patients with cardiovascular disease because several studies have shown depression and its associated symptoms to be a major risk factor for both the development of cardiovascular disease and death after an index myocardial infarction. (4) Treatment of depression in patients with cardiovascular disease improves their dysphoria and other signs of depression, improve quality of life, and increases longevity.

**Antidepressants**

Antidepressants were made for the first time about fifty years ago. Antidepressant interacts to depress the activities of the central nervous system. Antidepressants are only prescription drugs that come with risk as well as benefits. Most of them are class III and IV narcotic drugs. Antidepressants are differentiated by their chemical structures and mechanism of action. The individual classes of antidepressants like tricyclics, tetracyclics, monoamine oxidase inhibitors, SSRI, Aminoketone, and Triazolopyridines are prominent antidepressants.

**Tricyclics**: This class of drugs is effective in combating depression. Tricyclic drugs are still extensively prescribed world wide. Amitriptyline, the brand name Elavil, clomipramine, Doxepin, Nortriptyline, Imipramine are good examples of tricyclics. (5)(6)
Tetracyclines: Most of the tetracyclic antidepressants are not very common in U.S. However, Amoxapine and maprotiline are good tetracycline medications. Amoxapine is antidepressant of the dibenzoxapine class, chemically distinct from the dibenzazapines, dibenzocycloheptenes, and dibenzoepinines. One tetracyclic antidepressant mianserin, the brand names are Tolvon and Lumin are very popular in Australia.

Amoxapine

Selective Serotonin Reuptake Inhibitors (SSRIs): Serotonin (5-hydroxytryptamine) found in all tissues and body fluid in humans. Serotonin provides many of the biological functions and behavioral functions including sex, memorizing, reply or response to situation, locomotors, aggression and sleep hormonal secretion. It causes variety of human disorders such as depression, anxiety, anorexia nervosa, and schizophrenia. Serotonin receptors found in both central and peripheral nervous system as well as number of non-neuronal tissues in the gut, cardiovascular system and blood cells. Serotonin has been used to treat many diseases such as migraine, hypertension, anxiety, eating disorder, and vomiting. (7)

Celexa, Lexapro, Fluoxetine, Prozac, Paxil, Zoloft, Fluvoxamine are very common types of SSRIs are treated for depressant in the market.

Prozac
Aminoketone Class

There is only one drug is officially found in aminoketone group, which is used as antidepressant. It is very interesting to learn about it because it is used as smoking cessation as well.

Wellbutrin: Wellbutrin used as an antidepressant, non-nicotine aid to smoking cessation, and sometimes ADHD treatment. It is an Aminoketone class medication, which chemically unrelated to tricyclic, tetracyclic, SSRI, or Monoamine Oxidase inhibitors. Bupropion is the generic name of the wellbutrin. Bupropion Immediate Release has been on the market since 1988 and is effective and usually used as antidepressant. The Department of Federal Food and Drug approved Wellbutrin Sustained Release (Bupropion hydrochloride SR) as an antidepressant on November 27, 1995. Wellbutrin is designated as a racemic mixture of \((\pm)\)-1-(3-chlorophenyl)-2-[(1,1-dimethyllethyl)amino]-1-propanone hydrochloride. The empirical molecular formula of wellbutrin is \(C_{13}H_{18}ClNO\cdot HCl\) and the molecular weight are 276.2. Bupropion hydrochloride powder is white, crystalline, and highly soluble in water. (8)

Bupropion does not stop on Monoamine Oxidase. Bupropion is a weak blocker of the neuronal uptake of serotonin, dopamine, and norepinephrine comparable to tricyclic. Dr. J. A. Johnston, the head of psychiatric clinical development, said in a personal communication on December 14, 1998, that many smokers taking bupropion reported that after one or two weeks their craving for tobacco seemed to fade and they were able to quit smoking with fewer symptoms. (9) The University of Pennsylvania's Tran disciplinary Tobacco Use Research Center surveyed 418 smokers in a clinical tria
using the Antidepressant bupropion plus psychological counseling as an aid to cease smoking. After six months, the researchers found that participants with variants of two genes, a dopamine transporter gene known as SLC6A3 and a dopamine receptor gene known as DRD2, had higher abstinence rates and were able to hold off from lighting up longer than smokers carrying other gene variants. (8)

The structure of the bupropion closely looks like that of diethylpropion and related to the phenylethylamines. The mechanism of bupropion's antidepressant activity is unknown but appears to mediate by noradrenergic and possibly dopaminergic, rather than serotonergic mechanisms. Study has shown the bupropion blocks noradrenalin reuptake and dopamine reuptake. Its major metabolite blocks only noradrenalin reuptake. (11)

Bupropion and its major metabolites had essentially no affinity for b-adrenergic, dopaminergic, GABA, benzodiazepine, glycine and adenosine receptors, and only weakly inhibited a-adrenergic receptor in rat brain, a2-adrenergic, 5HT2, and muscarinic cholinergic receptors. High concentrations of bupropion and its major metabolites did not inhibit MAO-A or MAO-B activity. Bupropion and its major metabolites had no significant affinity for the 5HT transport system. (11) Bupropion is magnificently metabolized in humans. Hydroxybupropion and the amino-alcohol isomers threo-hydroxybupropion and erythro-hydroxybupropion which are formed via hydroxylation of the tert-butyl group of bupropion. In addition, reductions of the carboxyl group are three active metabolites. Oxidation of the bupropion side chain results in the formation of a glycine conjugate of metachlorobenzoic acid, which is excreted as major urinary metabolite. The preclinical trials used to predict antidepressant activity, have been observed that hydroxybupropion is comparable in potency to bupropion, while the other metabolites are one half to one tenth as potent. (11)

**Synthesis of Wellbutrin**

The short and one-pot mechanisms are used to make bupropion. The synthesis of bupropion can be carried out in less than two hours and give material 98% pure in an average overall yield at about 80%. The chemicals used in the procedure of bupropion are bromoketone, t-butylamine, N-methylpyrrolidinon, α-halogenated ketone, m-chloropropiophenone, CH₂Cl₂, Bromine, Na₂SO₄, and ether. (13) The overall synthesis is as
Development of Wellbutrin:

The condition and duration of exposure to Wellbutrin shows some adverse events reported in clinical trials and post marketing experiences with the sustained-release formulation of bupropion in depressed patients and non-depressed smokers, as well as in clinical trials and post marketing clinical experience with the immediate-release formulation of bupropion.

The substantial proportion of patients treated with Wellbutrin experience some degree of increased restlessness, agitation, anxiety, and insomnia. Patients treated with wellbutrin have been reported to show a variety of neuropsychiatric signs and symptoms including delusions, hallucinations, psychotic episodes, confusion, and paranoia. Antidepressants can precipitate manic episodes in bipolar manic-depressive patients during the depressed phase of their illness and may activate latent psychosis in other susceptible patients. A weight loss of greater than five pounds occurred in twenty-eight percent of patients receiving Wellbutrin, which is almost double than comparable to tricyclics or placebo. In addition, almost nine percent of people treated with Wellbutrin gained weight, compared to thirty-four percent patients treated with tricyclics or placebo. (12)

The possibility of suicide attempt is inherent in depression and may persist until significant remission occurs. The smallest numbers of the Wellbutrin tablets consist with good patient management. Anaphylactoid reactions characterized by symptom such as urticaria, edema, and dyspnea requiring medical treatment have been reported in clinical trials with bupropion. There have been rare spontaneous post marketing reports of erythema multifforme, Steven-Johnson syndrome, and anaphylactic shock associated with bupropion. Arthralgia, myalgia, and fever with rash and another symptom suggestive of delayed hypersensitivity have been reported in associated with Wellbutrin. These symptoms may resemble serum sickness. (12)

Wellbutrin Strength and Dosage

There are many different strength of the Wellbutrin available in bazaar. The Wellbutrin Immediate Release, Wellbutrin Suspended Release, and the Wellbutrin Extended Release are famous prescription medications. Wellbutrin SR tablets are prescribed for oral administration as 100-mg, 150-mg, and 200-mg of sustained releases. The Wellbutrin XL tablets are oral administration as 150-mg and 300-mg of extended release tablets. (8)

Drug Interaction

The lower seizure threshold should be undertaken only with extreme caution. There are some reports of adverse neuropsychiatry events reduced alcohol tolerance in patients who were drinking alcohol during the treatment of Wellbutrin; therefore, the use of alcohol during the treatment of Wellbutrin should be avoided. The pregnancy category reproduction studies has been performed in rabbits and rats have revealed no definitive evidence of impaired fertility or harm to the fetus due to bupropion. There are no
adequate, well-controlled studies on pregnant women. Because animal reproduction studies are not always predictive of human response, these drugs are used in pregnancy only if clearly needed. The effect of labor and delivery is unknown. Bupropion and its metabolites are secreted in human milk, raising the potential for serious adverse reactions in nursing infants from Wellbutrin. The drug may be discontinued the drug, taking into account the importance of the drug to the mother. The safety and effectiveness of Wellbutrin in pediatric patients under eighteen years old have not been established. (12)

Conclusion:

After all this research, it seems the treatment of depression has been handling very carefully and seriously. Although all drugs have different drug interactions, we found many different choices as antidepressants. Wellbutrin has fewer interactions than many other drugs. I personally think that Wellbutrin will be used for smoking cessation more than as an antidepressant.

2) Mark, Francis. (June, 2000). Mondimore: Depression in adolescence-popular works (pp. 45-55).


5) Amitriptiline packet insert

6) Doxapin packet insert


11) Dr. C.A.P. Kenyon. (March, 2004) The catecholamine theory of depression (pp. 65-78) University of Plymouth Department of Psychology.


Chinese Restaurant Syndrome: Monosodium Glutamate

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{OH} & \quad \text{OH} \\
\text{O} & \\
\text{NH}_2 & \\
\end{align*}
\]

Prepared for
Dr. Hank Mancini
Chemistry Instructor
PVCC

Prepared By
Matt Sloan

April 16, 2004
Abstract

This report investigates the role of monosodium glutamate in the Chinese Restaurant Syndrome. Monosodium glutamate, also known as MSG, is a food enhancer found in a variety of foods. This paper includes research of monosodium glutamate from a variety of peer reviewed journals, magazines, and books. This paper explains the background and history of monosodium glutamate, how monosodium glutamate is used, in what foods it is found, and any adverse reactions caused by monosodium glutamate in the human body.

Introduction

The Chinese Restaurant Syndrome occurs when some people have reactions to food containing monosodium glutamate (MSG). The Chinese Restaurant Syndrome is a set of symptoms that occur after consumption of foods containing MSG. MSG is a common flavor enhancer used in foods to stimulate taste buds and make a variety of foods taste better. Those who have a reaction to MSG commonly refer to it as an allergic reaction. Some of these reactions include burning sensations on the neck, chest, and abdomen, pressure or tightness in the face, nausea, vomiting, and sweating. A person who consumes MSG on an empty stomach increases the risk of Chinese Restaurant Syndrome.¹

Monosodium glutamate is a source of glutamate, amino acid that the body uses as a nerve impulse transmitter in the brain. Glutamate-responsive tissues also exist in other parts of the body. When abnormal functions of the glutamate receptors occur, illnesses like Alzheimer's disease and Huntington's chorea happen to be an outcome. But consumption of glutamate itself does not promote this threat.

Background

Glutamic acid was first found as a pure and isolated substance by a German chemist named Ritthausen. He found (S)-glutamic acid through acidic hydrolysis of gliadin, which in fact is wheat gluten. Years later, a Japanese chemist named Kikunae Ikeda of Tokyo Imperial University, found that glutamic acid was responsible for the flavor-enhancing properties of kelp like seaweed called, “konbu.” This seaweed had been used in Japan for many centuries in the preparations of soups. By extracting 40 kilograms of the seaweed in water, there could be 30 grams of glutamic acid.¹

He once said, “There is a taste which is common to asparagus, tomatoes, cheese and meat but which is not one of the four well-known tastes of sweet, sour, bitter and salty.” ² He noticed this taste in a seaweed broth and ran many chemical tests to find what could be this different taste on normal foods used today. he named this taste “umami.” He found that 100 grams of dried konbu yielded about 1 gram of pure monosodium glutamate.
A couple of years later, Ikeda patented a process of obtaining monosodium glutamate from wheat flour. The first batch of monosodium glutamate was produced commercially in 1909 and was sold under a Japanese name, Ajinomoto. This means “at the origin of flavor.” It has a solubility in water and is not absorbed in humidity or solidifies. Monosodium glutamate has no smell and can be used in a kitchen or wherever accessible.

Since that day, MSG has become a staple in foods today. It is used all around the world as a food additive or seasoning to enhance the foods that are produced. It has become a trillion-dollar worldwide industry and a prominent staple in the diet of many throughout the world.\(^1\)

There are also other similar forms of glutamic acid that are used in animal feed: (S)-lyosine, (S)-methionine, and (r)-methionone are very common amino acids that are very similar to (S)-glutamic acid; (S)-monosodium glutamate is a form of (S)-glutamic acid without a hydrogen group (or proton).\(^1\) Glutamic acid would be compared to a carboxylic acid and an amide. Monosodium glutamate would be a very similar structure without hydrogen group on the carboxylic acid. The structures are:

![Chemical structures of glutamic acid and monosodium glutamate (MSG)](image)

**MSG in the Human Diet**

Amino acids are added to many foods from hydrolyzed vegetable proteins such as soy or wheat proteins. Soy sauce is hydrolyzed soy protein. Hydrolyzed vegetable protein is a commonly used flavor component in snack foods like potato chips, corn nuts, and soy sauce. Glutamic acid ranks first in production among other amino acids in the world when it comes to food production.

Monosodium glutamate is said to stimulate glutamate receptors in the tongue to augment meat-like flavors.

In 1959, the Food and Drug Administration (FDA), classified monosodium glutamate as a safe food ingredient under the Food, Drug, and Cosmetic Act. In 1980, the FDA research showed that free glutamate played an important role in the normal
functioning of the nervous system and further questioned if manufactured MSG could in fact be harmful.³

Later, in 1995, the FDA and the Federation of American Societies for Experimental Biology (FASEB) presented a study that stated if “...MSG is consumed at usual levels by the general population, ...there is no evidence to suggest that dietary MSG or glutamate contributes to Alzheimer’s disease, Huntington’s disease, or any other long-term or chronic diseases.” ...No evidence suggests that “MSG causes brain lesions or damage to the nerve cells in humans.”³

Free glutamate is a natural occurrence of glutamate that is found in a variety of items. A mother’s milk can be the most important food in an infant’s diet. Glutamate is found ten times more in a human mother’s milk than a cow’s milk. Free glutamate plays an important role in human metabolism. “Almost 2 kilograms of naturally occurring glutamate are found in muscles, in the brain, in kidneys, in the liver, and other tissues.”²

Figure 2²

<table>
<thead>
<tr>
<th>Free Glutamate in Mothers’ Milk</th>
<th>Mg/100 Grams</th>
</tr>
</thead>
<tbody>
<tr>
<td>Humans</td>
<td>21.6</td>
</tr>
<tr>
<td>Chimpanzees</td>
<td>38.9</td>
</tr>
<tr>
<td>Rhesus monkeys</td>
<td>4.6</td>
</tr>
<tr>
<td>Cows</td>
<td>1.9</td>
</tr>
<tr>
<td>Sheep</td>
<td>1.4</td>
</tr>
</tbody>
</table>

Items that Contain MSG

Monosodium glutamate can be found in a variety of places. Many foods are produced and grown to have monosodium glutamate. Also, dietary supplements, cosmetics, and pharmaceutical drugs carry with them monosodium glutamate. It is also placed in the waxes that help keep fruits and vegetables fresh. It can be found in pesticides, fungicides, fertilizers, and plant growth enhancers.
If monosodium glutamate is dissolved in water and drank, it does not have a very appealing taste. But when MSG is placed in soups, it improves the taste, mouth feel, and smoothness. It also adds to the meaty flavor by making the soup taste have a stronger meat flavor. As the graphs show most people enjoy soups that contain MSG at a moderate level. This means that adding anything more to the appropriate amount does not make the soup more appealing.

Of all the items listed above, the items with the freest glutamate are the ones that contain a type of fish or sea animal. These sauces have dated back to the 7th centuries. Most of the people then knew that the tastes of these sauces were enhanced.

Monosodium glutamate is found naturally in many protein-containing foods like cheese, milk, meat, peas, and mushrooms. Glutamate is released during the breakdown of a protein molecule such as meat, milk, tomatoes or mushrooms. Most of the time our nerves use this form of glutamate in nerve impulse transmittance.
Today a fermenting process using starch, sugar beets, sugar cane, or molasses creates MSG. The FDA shows that MSG is, "...added to Asian cuisine, canned vegetables, soups, and processed meats." MSG is sold as a white crystalline substance that could be similar to salt or sugar. Foods that contain monosodium glutamate as a natural component are not required to list MSG on its label. These ingredients are said to carry with them MSG and most should know that this could be a natural ingredient. These items are meats, cheeses, soy sauce, and yeast extracts. But if MSG is added to give a certain flavor enhancement, it is required to be listed on that food’s ingredient list. This list cannot bunch together MSG in “spices” or “natural flavoring.”

Figure 5

Glutamate in a ripening tomato

The graph shows how glutamate levels in tomatoes rise during the ripening process to over 100 milligrams per 100 milliliters of juice.

As a tomato ripens, the overall percentage of glutamate increases. As the tomato is more and more appealing as it ripens many believe it is because of the free glutamate that naturally occurs in this process of nature.

Adverse Reactions in the Human Body

Monosodium glutamate can cause adverse reactions inside the body. These reactions include burning sensations on the back of the neck, chest, shoulders, abdomen, thighs, and forearms. Also included is pressure, tightness, or numbness in the face, headache, sweating, palpitations, flushing and wheezing.

Most adverse reactions will happen because of a certain type of allergy or personal reaction. According to WEBMD, an online health organization dedicated to those with medical questions, “an abnormal reaction to a food is considered an adverse
reaction.” It goes on to say, “Adverse reactions are classified as either food intolerance or a food allergy.” A food allergy is “an overreaction by the body’s immune system to proteins in foods that are usually safe or harmless.” It also states, “Your doctor can perform specific tests on your skin to determine whether you are sensitive to certain foods. WEBMD goes on to state, “food intolerance is an abnormal response of the body to an ingested food that is not an allergy. Examples of this are food poisoning and reactions to chemicals in food or drinks like caffeine.”

The Food and Drug Administration has identified two groups that would develop a condition called, “monosodium glutamate symptom complex.” One of those groups would be classified to be intolerant to MSG when eaten in a very large quantity. The other group would be classified.

Figure 6

![Our bodies naturally contain about 10 grams of free glutamate](image)

**Conclusion**

Chinese Restaurant Syndrome can exist to a point of the symptoms that were discussed. High consumptions of monosodium glutamate will add to these symptoms of nausea, sweating, vomiting, and burning sensations. These symptoms can be serious if not taken in consideration with food allergies, intolerances, or an adverse reaction.

MSG could be harmful in the diet if not taken seriously. Items that contain MSG show how they are found in a normal diet and even those who wish to live extremely healthy. There exist adverse reactions in the human body when it comes to many things
like MSG and highly overproduced foods that contain more chemicals than pure food product.

Since free glutamate is needed in human bodies to help with the nervous system, it is important to always take information in moderate forms. Always intake chemicals and produced foods in moderation. This will give the feeling of a healthy life and body.
Figure 7.3

NIST Chemistry Webbook (http://webbook.nist.gov/chemistry)
Wavenumber (cm⁻¹)

IRFARED SPECTRUM
L (+)-GLUTAMIC ACID, Alpha-FORM

TRANSMTTANCE
References:

2. The International Glutamate Information Service www.glutamate.org
   Dues, P.; Cynober, L. Digestion 1999, 60 (4), 349-357
   Metabolism 2003, 16 (7), 965-958
   489
10. Takahasi. Drug Week 2004 620, 2p
11. Yeung, Chi Kong; Chiang, Sylvia; Pang, Chi Pui; Lam Dennis. Journal of
    Toxicology 2004, 23 (1), 41
14. Heyer, BR.; Taylor-Burds, CC; Tran, LH; Delay, ER. Chemical Senses 2003, 28
    (7), 631-641.
   M. European Journal of Clinical Nutrition 2000, 54 (11), 822-827
Anthrax: A Way To Find A Vaccine

Prepared for
Dr. Mancini
Paradise Valley Community College
Organic Chemistry
CHM 236

By: Charles Sovetsky
April 16, 2004
ABSTRACT

Anthrax has been a threat to human society for thousands of years. However, in the modern era, the threat of anthrax as a biological weapon is much more of a reality now that the United States is defending itself against terrorist attacks. Though there are vaccines that have been made to fight anthrax, there are none void of side effects and none that have been determined to be 100% effective. Nations across the world are organizing together to find a cure and a way to protect people from any possible attack using anthrax as a weapon. By understanding the exact process that anthrax spores attack the body, a vaccine should be quick to arrive on the horizon.

BACKGROUND

Anthrax is one of the most widely known infectious diseases that have affected humans and animals for thousands of years. It is believed that anthrax was the cause of the fifth and sixth plagues written in the Bible’s book of Exodus (1) which killed large numbers of cattle and humans. It is also believed that the “Black Bane,” a disease that swept through Europe during the 1600s, killing hundreds of humans and cattle, was most likely anthrax. During these times, it was believed that anthrax was exposed due to skinning of animals and livestock, such as sheep and cattle (2). In 1876, Robert Koch recognized the bacterial origin of anthrax and four years later, in 1880, the first successful immunization of livestock against anthrax was discovered (3).

During World War I, it is believed that German agents in the United States injected cattle with anthrax on their way to Europe in order to infect the Allies. In 1936, the Japanese began a biological warfare program in Manchuria that consisted of tests on anthrax. Soon to follow, the United States and the United Kingdom began tests starting in 1942 and 1943, respectively. During the 1950s, the Soviet Union and Iran admitted their investigation into the use of anthrax in biological warfare (3). Although the United States and United Kingdom halted offensive biological programs regarding anthrax, both countries still are pursuing defensive mechanisms against the disease.

In the modern era, anthrax has run a very hard course. In 1978-80, a large outbreak of anthrax occurred in Zimbabwe, infecting more than 6,000 people and killing more than 100 people (3). In 1979, the Soviet Union accidentally released anthrax into the air, killing more than 68 people and infecting many others (3). The most recent scare of anthrax occurred in 2001. One week after the September 11 terrorist bombing attacks on the World Trade Center and the Pentagon, a letter was mailed to NBC containing anthrax spores. This led to many other incidents of anthrax being mailed to different organizations and companies around the United States.

The United States began a complete investigation into who was sending the contaminated letters. The time was one of confusion and disarray. People would cautiously look up at the sky constantly and handle each letter as if it were a fragile egg. Unfortunately, no one was found guilty of sending the contaminated letters and few clues
were left behind. Events were occurring at an alarming rate during that time in the United States.

There are many investigations into anthrax, more now than ever, as terrorist threats seem to be lurking right around the corner against the United States. However, anthrax is a main concern. It is estimated by the World Health Organization that three days after the release of 50 kg of anthrax spores along a five-mile line upwind of a city with a population of 500,000 would affect 125,000 people, resulting in 95,000 deaths (3). Biological weapon attacks will continue to pose a threat and investigations into anthrax will occur until a cure and a proper vaccine will be discovered without side effects. Though vaccines have been tested, none have proven 100% guaranteed. Though many antibodies can be used to stop the disease once affected, there are so many different strains of anthrax that just one drug cannot stop all forms.

**ORIGIN OF ANTHRAX-Bacillus Anthracis**

![Image](image_url)

**Figure 1. Bacillus Anthracis. Ellipsoidal Shaped cells with square ends.** (6)

*Bacillus anthracis* was the first bacterium found to be the cause of anthrax in 1877 by Robert Koch (4). The bacterium is a very large and Gram-positive rod structure (4). Koch grew the organism in pure culture and eventually showed the ability of the bacteria to form endospores. The bacterium can be cultivated in nutrient medium conditions and can also be grown in aerobic and anaerobic conditions (4). This would concur with the thought that anthrax had the ability to be dormant for years in soil. The most ‘friendly’ conditions for the spores to germinate occurred in the soil, and this later led to the spread of the spores into cattle and later humans.

There still is much more information to be found regarding *Bacillus anthracis*. The spores have been found naturally in soil around the world, and yet the organisms cannot be cultivated where there is no endemic anthrax (4). This causes some confusion in how a proper vaccine can be made for anthrax.

**TYPES OF ANTHRAX**

There are three types of anthrax. The first, cutaneous anthrax, is the most common form found in humans, though anthrax infecting humans from animals or soil is very rare. Contamination usually occurs with a scratch or slight abrasion on an exposed area of the
body and is inoculated by spores from the soil or a contaminated animal or carcass (4). Once in the body, the spores germinate, and the cells multiply and edema (swelling) occurs at the site. Later it evolves into a papule 12-36 hours after infection. The papule changes to a pustule and eventually a necrotic ulcer where the infection spreads throughout the body and causes septicemia (blood poisoning). In the most severe cases, the disease can be fatal if not treated before the infection hits the blood and weakens the body (4).

The second type of anthrax is gastrointestinal anthrax. It is very similar to cutaneous anthrax, except that it occurs within the intestinal mucosa (6). “Intestinal anthrax occurs from the ingestion of poorly cooked meat from infected animals” (6). This normally happens in underdeveloped countries where the mortality rate, if infected, is very high.

The third type of anthrax, and most important in understanding anthrax as a biological weapon, is inhalation anthrax (woolsorts’ disease). A biologist from Harvard University, Dr. Matthew S. Meselson, noted that the spores can only really do harm to people if they are sprayed in ‘an extremely fine mist that can penetrate deep in the lungs’ (5). After the spores are inhaled, they enter the airways of the lung and later the immune system transports them to the lymph nodes, where they can germinate. The most common form of contamination of inhalation anthrax occurs when someone inhales spore-containing dust where animal hair or hydes are handled. High-fever and chest pain occur almost instantly and progresses very rapidly to a ‘systematic hemorrhagic pathology’ (4). If there is no treatment of the disease before it invades the blood, then this form of anthrax can be very fatal.

ANTHRAX TOXINS

Many types of bacterial toxins specifically bind to receptors on a target cell, and after engulfing the toxin via receptor-mediated endocytosis, the translocation occurs of the biological active proteins to the cytosol (6). In replacing the catalytic domain with a DNA-binding domain of a DNA-binding protein would result in a system having the bacterial toxins deliver the DNA to the cytosol of cells (6). This is the basis of what occurs with anthrax.

There are three protein components of the anthrax toxin in which the catalytic and binding parts are released from the bacteria as separate monomeric proteins. These three proteins gather on the surface of mammalian cells into receptor bound structures which are internalized by endocytosis. The three distinct antigenic proteins of anthrax are: Protective antigen (PA), lethal Factor (LF), and edema Factor (EF).

EF causes edema (swelling) wherein the activity of the toxins are produced. LF is essential for the lethal effects of the anthrax toxin, and PA produces protective antitoxic antibodies. Therefore, the incision of anthrax ‘trick’ the PA into helping administer LF and EF into the body.

PA is the most important of the three toxins because of its ability to bind the other two proteins. Without the binding of all three proteins, there would be no active site for the disease to occur. In 2002, a very important discovery was made when the cellular
receptor of PA was discovered, for this allowed scientists to exam the point where all three bind together; this cellular receptor was termed “ATR” (6).

![Diagram of Anthrax toxins into mammalian cells](image)

**Figure 2. Anthrax toxins into mammalian cells (7).**

At the ATR, the PA binds to the target cell and is cleaved by a cellular enzyme (protease furin—an integral membrane protein) as shown in figure 2 (8). The fragmented PA (PA20) leaves allowing the PA that is left over looking to replenish itself. Thus, the PA, which is now receptor-bound, forms a heptamer at the target cell and binds the EF and LF toxins (7). The complex of PA+LF+EF enters the cell by receptor-mediated endocytosis. This results in a low pH balance within the endocytotic compartment. It is here that exposure to the acidic environment results in the PA undergoing conformational changes in the formation of a membraneous pore (channel) that allows the EF and LF to diffuse into the cytosol of the target cell and produce their toxins. EF and LF intoxicates the target cells by elevating concentrations of cAMP (cyclic AMP) (7). By causing the rise of cAMP within the body, the cells become susceptible. It is believed that by changing levels of cAMP within a cell will affect changes in membrane permeability, resulting in edema (4). By increasing the levels of cAMP, the body does not have enough ATP for phagocytosis of the infected cell to occur. Therefore, it is believed that one effect of the toxin is to impair the process of phagocytosis during the infectious process.

This impairment of phagocytosis occurs because of a poly-D-glutamyl capsule which is found in *Bacillus anthracis*. This capsule is a single antigenic type of capsule consisting of a polypeptide chain. The poly-D-glutamyl capsule itself is not toxic, but it protects the organism from phagocytic engulfment. Though this capsule is not very
important in the mediation of the anthrax toxins during the final phases of the disease, it is very important in establishing the infectious process.

It is important to note that each of the three proteins, EF+LF+PA, do not affect the body separately; they do form together in combinations of two or three to yield the toxin components:

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>PA+LF =</td>
<td>produce lethal activity</td>
</tr>
<tr>
<td>EF+PA =</td>
<td>produce edema (swelling)</td>
</tr>
<tr>
<td>EF+LA = no reaction</td>
<td></td>
</tr>
<tr>
<td>PA+LF+EF =</td>
<td>produces edema and cellular death. Can be very lethal</td>
</tr>
</tbody>
</table>

*Figure 3. Combinations of the toxin components*

**CHEMICAL STRUCTURE OF BACILLUS ANTHRACIS EDEMA FACTOR (EF)**

In order to find a vaccination or cure for anthrax, the infectious process of the edema factor must be chemically understood. If scientists are able to understand what is causing the swelling of the cells, then that will help further the study in possible antibiotics for all the strains of anthrax.

There are two major steps involved in the catalytic mechanism for Bacillus anthracis EF as shown if figure 4 (9). First, acting as a base, His(nistamine)351, withdraws hydrogen from the 3'-hydroxyl group of ribose (9). This leads to the second step where the remaining oxygen performs a nucleophilic attack on the a-phosphate of the ATP substrate. This results in the cleaving of the a-phosphate to b-phosphate bond and forms cAMP and PPI(2 phosphates). Activation of the a-phosphate occurs when Mg$^{2+}$ combines with Lys 346, stabilizing the α-phosphate and β-phosphate groups of the substrate.

*Figure 4. The catalytic mechanism for B. anthracis EF (9)*
CURRENT VACCINES AND ANTIBIOTICS

Since the beginning of biological warfare, there has been much investigation in finding a proper vaccine and cure for anthrax. It is of utmost importance for the development of a novel anti-anthrax vaccine without the current side effects of some of the current vaccines. Currently there are few antibiotics, that when affected, are deemed suitable in fighting the disease. Many have side effects, and the problem is that all are not made to fight against all strains of the virus.

One of the drugs used is Penicillin VK 500 MG. This drug is used once a victim is infected. This medicine must be taken until the patient is told to stop by a physician. Side effects are wheezing, skin rash, swelling of face, lips, or throat, and severe diarrhea. Sore throat and itching of the mouth might also occur (10).

Another drug used during the infection stage is Ciprofloxacin (Cipro) 500 Mg. This drug is specifically used to fight anthrax spores, and then no other bacteria forms. It has been FDA approved. Side effects include vomiting, diarrhea, fatigue, dizziness, or headache. Mental changes also might occur. Cipro can also increase sensitivity to sun. This drug would seem not very plausible for soldiers if they are to be out most of the day (10).

The final drug to mention and most important in finding a vaccine isAVA (Anthrax Vaccine Absorbed) (16). This has been licensed by the FDA. During the early 1990s, this was given to the military to fend off a possible biological attack of anthrax. Unfortunately, since it is very difficult to use human models, this drug has only been tested on animals. A study in the US military was done in 1999. Though there were some side effects such as malaise, fever, and chills, the US Army Medical Research Institute of Infectious Diseases noted that no one had enough of the side effects to miss work (11). So far, no long term effects have been noted. The vaccines seemed to have worked at a 90% rate regarding cutaneous anthrax (tests were done on fur and food handlers), though it is still difficult to find the results against inhalation anthrax against humans.

FINDING A PROPER VACCINE AGAINST ANTHRAX

The most important idea is for scientists to find a vaccine against anthrax without any of the side effects. In one scenario, scientists are currently trying to understand the two iron-binding proteins of Bacillus anthracis (12). It is believed that the uptake of iron by the bacteria helps it to grow and germinate once inside the body. In the immunogenic bacterial proteins, there are two Dps (DNA binding proteins) genes present in the Bacillus anthracis genome (12). The two structures of these proteins are called Dlp-1 and Dlp-2. Acting like ferritins (iron-containing protein complex), these proteins are involved in iron regulation which is a fundamental function during the growth of bacteria (12).
Figure 5. Stereo View of Fe(II) site of Dlp-1(A) and Dlp-2(B) (12).

It is important to understand the structure of Dlp-1 and Dlp-2 in order to inhibit the uptake of iron in the body. In figure 5, notice that both proteins exhibit a tetrahedral shape. By looking at the structure of Dlp-1 of Part A, we can compare it to the building of a four-room in a house. The iron is securely nestled in the middle of Dlp-1. Dlp-1 and aspartate(salt or ester of aspartic acid) make two walls of the room. A nitrogen from a histidine makes up another wall. Finally, an oxygen from water makes the fourth and final wall of the room. Notice in Part B that Dlp-2 and glutamate(a salt or ester of glutamic acid) combines with oxygen to build two of the walls. Once again, a nitrogen from a histidine makes another wall. The final wall is made from an oxygen from water. Therefore, the Fe is boxed in this tetrahedral shape using both Dlp-1 and Dlp-2. These bonds stay together by using the hydrogen bonds of water molecules. If scientists can somehow inhibit this uptake of Fe and find a weakness in one or both of the proteins to prevent Fe uptake of the bacterium, then this would slow or prevent the bacteria; resulting in a vaccine which can be further explored (12).
Another powerful technique for structure-based drug discovery is NMR spectroscopy. In order to achieve a proper structure, *Bacillus anthracis* PA must be isolated. One of the products of PA, when broken down, PA-D4 gives an amenable structure for NMR studies (8). It is believed that PA-D4 is expressed as a fusion protein. The PA-D4 has been shown to have a function in the binding of PA to the ATR of the targeted cell; therefore in one study, the description of the preparation of the PA-D4 was used. In figure 5a, the spectrum indicates that a secondary structure has been formed. The elliptical mean residual can be seen at 220nm resulting in 17% of the helical content (8). In figure 4b, the downfield structure of PA-D4 is presented. According to the source, spectral dispersion and line-weights indicate the PA-D4 structure. This, in turn, suggests that PA-D4 is monomeric in solution and can be used for high NMR studies (8). Finally, 5c dictates the ability of PA-D4 to bind with HeLa cells, which holds the ATR receptor.
known to bind with the PA. It is shown that PA-D4 is structural and functional to bind with the ATR of the cell. This leads to the idea that finding where the PA attaches with the ATR will result in the ability of drug discovery using NMR spectroscopy.

CONCLUSION

Anthrax has been a threat to humans since we started farming thousands of years ago. From livestock to the land being farmed, anthrax spores have found a way to become effective against humans. In our modern day world, anthrax used as a biological weapon has become more and more of a threat. Since WWI, anthrax has been used in battle, and though many countries have stopped producing and testing anthrax, the threat still looms, now more than ever. The United States is in a battle against terrorists and a proper vaccine with no side effects must be produced and must be effective in fighting the disease.

Ever since 9/11, it seems as if there is much more investigation into anthrax. I believe that in due time, there will be a cure and there will be a vaccine void of side effects. As the United States and other countries become increasingly aware of the possible attack using anthrax, it is imperative that a vaccine be made. Though I believe that a vaccine will soon arrive, will it arrive in time?
References

1) Exodus 9: 1-12
6) Gaur, R & Gupta, P. & Goyal, A. (2002). Delivery of nucleic acid into mammalian cells by the anthrax toxin. *Biochemical and Biophysical Research Communications (BBRC)*, 1121-1127
7) Chaudry, G. & Moayeri, M. & Liu, S. (Feb 2002). Quickening the pace of anthrax research: three advances point towards the possibilities towards possible therapies. *TRENDS in Microbiology*, 10, 58-72
Joel Stoker

Evolution of Modern Inhalation Anesthetics

April 15, 2004
Abstract: General anesthetics are used in modern medicine to better facilitate a surgical procedure. Anesthetics have evolved over the centuries from naturally occurring local anesthetics to modern synthetic chemical structures that break down quickly with few negative side effects. Anesthetics are similar in their physiologic effects, yet differ in chemical structure, metabolic pathways and products.

Anesthetic agents covered here are administered through the respiratory system (inhalaion). Each inhalation drug is designed to achieve optimum results in patient care. These drugs have evolved over decades through changes in inorganic and organic chemical research. Through the study of the effects of molecular arrangement and the chemical and physical structure of various ethers and new evolving inhalation agents, anesthesia is becoming more efficient and effective. Anesthetics are becoming faster acting, safer, more analgesic, and more rapidly metabolized medications that prevent surgical complications.

Current knowledge of drug mechanisms and metabolic pathways are theorized to explain how they work. Most current inhalation agents metabolize similarly, but at varying rates. Also, the effects of individual anesthetics on respiratory rates, heart rates, and other physiologic parameters, vary by drug and concentration.

Xenon represents a possible future of inhalation general anesthetic agents. It is currently studied for its minimal side effects. Although many studies have shown its usefulness in the operating room, it has not yet become feasible (nor approved) for mass clinical use.

History of Inhalation Anesthetics

Anesthetic properties of inhalation anesthetics were first observed in the 1840’s (Stoelting and Miller 3). Diethyl ether, nitrous oxide, and chloroform were the pioneering inhalation agents. Chloroform, although effective at rendering unconsciousness, can cause damage to skin, liver, kidneys, and is a carcinogen (CDC). Scientists knew they needed to seek out other agents with less negative side effects. Another agent produced in hopes of escaping the negative side effects was cyclopropane in the 1930s (Stoelting and Miller 5). Other agents used experimentally and clinically include ethylene, vinetene, and trichloroethylene.

It took nearly 80 years from the discovery of the first general anesthetic drug before other inhalation anesthetics were introduced. The problem of toxicity plagued early anesthesiologists. Another significant problem with early inhalation agents was flammability. With the exception of nitrous oxide, all agents were combustible and potentially damaging to the liver. A simple recognition of principle organic chemistry lead researchers to combine carbon atoms with fluorine atoms to decrease flammability.

Most modern inhalation anesthetics used in anesthesia today are fluorine containing compounds with nitrous oxide as the exception. For any performed anesthetic, anesthesiologists use specific agents to achieve a desired result. Halothane (2-Bromo-2-chloro-1,1,1-trifluoroethane) was the first modern inhalation agent prepared for use in 1951, but other agents were sought due to certain undesirable side effects including prolonged recovery (high solubility in the blood and lipids), and increased fluoride-plasma concentrations leading to nephrotoxicity (5-6). Enflurane (2-Chloro-1,1,2-
trifluoroethylidifluoromethyl ether) was then discovered and began clinical use in 1973, but side effects included more problems with fluoride toxicity due to its moderate degree of metabolism (6). An isomer to Enflurane, Isoflurane (1-Chloro-2,2,2-trifluoroethylidifluoromethyl ether), was introduced in 1981, with few fluoride metabolism side effects (7). Desflurane (1,2,2,2-Tetrafluoroethylidifluoromethyl ether), was introduced in 1992 and was quickly followed by Sevoflurane (fluoromethyl 2,2,2-trifluoro-1-(trifluoromethyl) ethyl ether) in 1994 (7). Challenges facing today’s anesthesiologists include minimizing risks to the patient, airway irritation, sympathetic nervous system stimulation, carbon monoxide production, vaporizer technology, and increased expenses associated with modern drugs.

Structure

\[
\begin{align*}
\text{Chloroform} & \quad \text{Cyclopropane} & \quad \text{Ethylene} & \quad \text{Trichloroethylene} \\
\text{N} & = & \text{N} & - & \text{O} & - \\
\text{Or} & \quad \text{F} & \text{Br} & \quad \text{Cl} & \text{F} & \text{F} \\
\text{N} & = & \text{N} & = & \text{O} & - \\
\text{Nitrous Oxide} & \quad \text{Halothane} & \quad \text{Enflurane} \\
\text{F} & \text{Cl} & \text{F} & \text{F} & \text{F} & \text{CF}_3 & \text{H} \\
\text{F} & \text{C} & \text{C} & \text{O} & \text{C} & \text{H} & \text{F} & \text{O} & \text{C} & \text{F} \\
\text{F} & \text{H} & \text{F} & \text{H} & \text{F} & \text{CF}_3 & \text{H} \\
\text{Isoflurane} & \quad \text{Desflurane} & \quad \text{Sevoflurane}
\end{align*}
\]

Physical and chemical properties of inhaled anesthetics (Stoebling 37)

<table>
<thead>
<tr>
<th></th>
<th>N₂O</th>
<th>Halothane</th>
<th>Enflurane</th>
<th>Isoflurane</th>
<th>Desflurane</th>
<th>Sevoflurane</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular weight</td>
<td>44</td>
<td>197</td>
<td>184</td>
<td>184</td>
<td>168</td>
<td>200</td>
</tr>
<tr>
<td>Boiling pt (°C)</td>
<td></td>
<td>50.2</td>
<td>56.5</td>
<td>48.5</td>
<td>22.8</td>
<td>58.5</td>
</tr>
<tr>
<td>Vapor pressure (mmHg, 20°C)</td>
<td>Gas</td>
<td>244</td>
<td>172</td>
<td>240</td>
<td>669</td>
<td>170</td>
</tr>
<tr>
<td>Odor</td>
<td>Sweet</td>
<td>Organic</td>
<td>Ethereal</td>
<td>Ethereal</td>
<td>Ethereal</td>
<td>Ethereal</td>
</tr>
</tbody>
</table>
Metabolic Processes, Bodily Effect, and Mechanisms

The metabolic processes for all inhalation agents are closely related. Although most of the anesthetic is expelled through respiration, the chemical structures of many agents allow for simple breakdown. The ether bonds and carbon-halogen bonds are susceptible to metabolism via oxidation. Although, when a carbon-hydrogen bond is replaced by a carbon-halogen bond, the metabolism of the ether is decreased and becomes more resistant to oxidation. The ideal dehalogenation occurs when two halogens are found on terminal carbons. Because there are no ester bonds in inhalation anesthetics, there are no metabolic hydrolysis reactions.

Enzymatic breakdown of the anesthetic found in the body occurs mostly by a hepatic enzyme. Cytochrome P-450 is the enzyme responsible for the break down of these medications. The metabolic process includes defluorination of the chemical structure with byproducts such as hydrochloric acid and water.

Nitrous Oxide

Approximately 0.004-0.01% of nitrous oxide is metabolically reduced (Morgan et al. 137-9). Therefore it is almost entirely exhaled during respiration. The metabolic breakdown of nitrous oxide occurs in the gastrointestinal tract by anaerobic bacteria (Pseudomonas).

Halothane

Halothane is a multi-halogenated alkane, categorically ancient to the multistructural ether anesthetics (139-40). The remnants of Halothane not exhaled (approximately 15-20%) are metabolized in the liver by isosomes of cytochrome P-450. The final product of metabolism of Halothane is trifluoroacetic acid.

Enflurane

Enflurane is a structural isomer of Isoflurane (142). The major metabolic breakdown of enflurane by Cytochrome P-450 yields organic and inorganic fluorine, although this accounts for only 3% of the enflurane delivered as 97% is exhaled.

Isoflurane

Approximately 0.02% of Isoflurane remains after exhalation to be metabolized by Cytochrome P-450 and yields the intermediate difluoromethanol and progresses to trifluoroacetic acid as its principle metabolic end-product (143).

Desflurane

Desflurane undergoes minimal metabolism in humans (approximately 0.02%) as it breaks into carbon dioxide which is absorbed by lime in an anesthesia breathing circuit system (144-5). However, Cytochrome P-450 does catch some remnants and breaks them into inorganic fluorine, trifluoroacetic acid, and water.

Sevoflurane

The structure of sevoflurane does not allow it to be metabolized to an acyl halide, whereas halothane, enflurane, isoflurane, and desflurane all do (145-6). Cytochrome P-450 is still primarily responsible for the metabolism into fluorinated products. The 5% of Sevoflurane not exhaled will metabolize to hexafluorisopropanol glucuronide (1,1,1,3,3,3-hexafluoro-2-propanol). This end product is then excreted in the urine.
Percent Metabolite in Body Used to Break Down Inhalation Anesthetic

<table>
<thead>
<tr>
<th>Agent</th>
<th>% Metabolite in Body</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitrous Oxide</td>
<td>0.004-0.01</td>
</tr>
<tr>
<td>Halothane</td>
<td>15-20</td>
</tr>
<tr>
<td>Enflurane</td>
<td>3</td>
</tr>
<tr>
<td>Isoflurane</td>
<td>0.02</td>
</tr>
<tr>
<td>Desflurane</td>
<td>0.02</td>
</tr>
<tr>
<td>Sevoflurane</td>
<td>5</td>
</tr>
</tbody>
</table>

Structural Metabolism of Halothane (Stoelting 61)

\[
\begin{align*}
\text{F} & \quad \text{H} & \quad \text{F} & \quad \text{OH} & \quad \text{F} & \quad \text{O} & \quad \text{F} & \quad \text{O} \\
\text{F} & \quad \text{C} & \quad \text{C} & \quad \text{Br} & \rightarrow & \text{F} & \quad \text{C} & \quad \text{C} & \quad \text{Br} & \rightarrow & \text{F} & \quad \text{C} & \quad \text{C} & \quad \text{Cl} & + & \text{HBr} & \rightarrow & \text{F} & \quad \text{C} & \quad \text{C} & \quad \text{O} & \quad \text{H} \\
\text{F} & \quad \text{Cl} & \quad \text{F} & \quad \text{Cl} & \quad \text{F}
\end{align*}
\]

Structural Metabolism of Enflurane (Stoelting 61)

\[
\begin{align*}
\text{F} & \quad \text{F} & \quad \text{H} & \quad \text{F} & \quad \text{F} & \quad \text{O} & \quad \text{F} & \quad \text{F} & \quad \text{F} & \quad \text{F} & \quad \text{F} \\
\text{H} & \quad \text{C} & \quad \text{O} & \quad \text{C} & \quad \text{C} & \quad \text{Cl} & \rightarrow & \text{H} & \quad \text{C} & \quad \text{O} & \quad \text{C} & \quad \text{C} & \quad \text{Cl} & \rightarrow & \text{H} & \quad \text{C} & \quad \text{O} & \quad \text{C} & \quad \text{C} & \quad \text{F} & + & \text{HCl} & \rightarrow & \text{H} & \quad \text{C} & \quad \text{O} & \quad \text{C} & \quad \text{C} & \quad \text{O} & \quad \text{H} \\
\text{F} & \quad \text{F} & \quad \text{F} & \quad \text{F} & \quad \text{F} & \quad \text{F} & \quad \text{F}
\end{align*}
\]

Structural Metabolism of Isoflurane (Stoelting 61)

\[
\begin{align*}
\text{F} & \quad \text{F} & \quad \text{H} & \quad \text{F} & \quad \text{F} & \quad \text{F} & \quad \text{O} & \quad \text{F} & \quad \text{O} & \quad \text{F} & \quad \text{F} & \quad \text{F} & \quad \text{F} \\
\text{H} & \quad \text{C} & \quad \text{O} & \quad \text{C} & \quad \text{C} & \quad \text{F} & \rightarrow & \text{H} & \quad \text{C} & \quad \text{O} & \quad \text{C} & \quad \text{C} & \quad \text{F} & \rightarrow & \text{H} & \quad \text{C} & \quad \text{O} & \quad \text{C} & \quad \text{C} & \quad \text{F} & + & \text{HCl} \\
\text{F} & \quad \text{Cl} & \quad \text{F} & \quad \text{F} & \quad \text{Cl} & \quad \text{F} & \quad \text{F} & \quad \text{F} & \quad \text{F} & \quad \text{F} & \quad \text{F}
\end{align*}
\]

\[+ \text{CF}_2\text{OH} \text{ or } \text{Cl} \quad \text{C} \quad \text{C} \quad \text{F} \rightarrow \text{HO} \quad \text{C} \quad \text{C} \quad \text{F} \]
Structural Metabolism of Desflurane (Stoelting 61)

\[
\begin{align*}
F & \quad H & \quad F \\
\rightarrow & \quad H & \quad C & \quad O & \quad C & \quad C & \quad F \\
& \quad F & \quad F & \quad F & \quad F & \quad F & \quad F
\end{align*}
\]

\[
\begin{align*}
F & \quad O & \quad F \\
\rightarrow & \quad H & \quad C & \quad O & \quad H & \quad + & \quad H & \quad O & \quad H & \quad C & \quad C & \quad F & \quad + & \quad H & \quad F \\
& \quad F & \quad F & \quad F & \quad F & \quad F & \quad F
\end{align*}
\]

Structural Metabolism of Sevoflurane (Stoelting 62)

\[
\begin{align*}
CF_3 & \quad H & \quad CF_3 & \quad O & \quad CF_3 \\
\rightarrow & \quad H & \quad C & \quad O & \quad C & \quad H & \quad + & \quad C & \quad F & \quad F & \quad + & \quad C & \quad O & \quad H & \quad Glucuronide & \quad CF_3 & \quad F & \quad CF_3
\end{align*}
\]

All of the inhalation anesthetics currently in use increase the rate of breathing at a dose-dependent rate (meaning the rate at which the anesthetic is delivered to the patient according to their respective mass). Isoflurane differs only in that there is no significant increase in respiratory rate after a level of 1 Minimum Alveolar Concentration [MAC—“the concentration of an inhaled anesthetic at 1 atmosphere that prevents skeletal muscle movement in response to a noxious stimulus (surgical skin incision) in 50% of patients” (Stoelting and Miller 24)]. Nitrous oxide, however, continues to increase the breathing rate at concentrations higher than 1 MAC. This increase in respiratory rate is caused primarily by stimulation on the central nervous system (CNS) by the anesthetic. Although respiratory rate is increased, tidal volume decreases, resulting in a net decrease in minute ventilation, which is why oxygen gas is added to the concentration. The volatile anesthetics are all smooth muscle relaxants, which results in bronchodilation (the opening of the bronchial air passages). Each of the inhaled anesthetics is somewhat an irritant to the airway. Isoflurane and Desflurane are known to increase coughing and breath-holding for the patient, whereas Halothane and Sevoflurane are less irritating.

Each of the anesthetic agents differs to how it affects heart rate. Halothane has a direct myocardial depressant effect (Barash 367–8). Desflurane leaves the cardiac rate unchanged also until 1 MAC, after which the higher the concentration, the higher the cardiac rate. Isoflurane is known to increase the heart rate of young adults, but leave older adults’ rates unchanged. Enflurane increases the heart rate as its concentration increases.
The actual mechanism of action of volatile anesthetics in the CNS is unknown. How inhaled agents "produce reversible and sometimes selective depression of the CNS" is greatly unknown (Stoelting and Miller 25). However, certain mechanisms including "neurotransmitter activity, receptor responsiveness, chemical and voltage gated ion channels and enzymes" have been presumed (25). Factors including genetic variability and the genetic predisposition to produce certain anesthesia destructing or metabolizing enzymes will ultimately affect the individual patient's anesthetic. Therefore, much attention must be paid to acknowledge this variability.

Many hypotheses have arisen in regards to the mechanisms by which general anesthesia is achieved with volatile anesthetics. The Meyer-Overton Theory (Critical-Volume Hypothesis) explains how lipid solubility of the drug and individual patient mass factor into an anesthetic. Also, Proteins (Receptor) Hypothesis deals with how certain regions of the CNS's hydrophobic proteins are regions for anesthetic variability. An alteration in neurotransmitter availability and the activation of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) achieves anesthesia. Ultimately, each inhalation agent is subject to an elimination half-life ("the time necessary for the plasma concentration of drug dose to decline 50% during the elimination phase" Stoelting and Miller 28). This can be optimized by higher initial doses at the beginning of the anesthetic followed by lower doses near the end of the procedure.

**Future Ideal Inhalation Anesthetic Medications**

For decades now, inhalation anesthetic medications have progressed from explosive, flammable, unpredictable agents to more volatile, rapidly metabolized predictable compounds. Much of this progression has been due to altering chemical structure of ether and thereby altering its metabolic pathways and solubility. However, questions of toxicity, cost and recovery time constantly have anesthesiologists seeking new inhalation agents. The most recent studies are on Xenon.

Xenon may represent the future of general anesthetic inhalation agents. It is highly sought after for its rapid inductive effect, short recovery period, and minimal side effects (Del Turco et al. 1-2). Also, volatile anesthetics are known to restrict the body's "chemotaxis, phagocytosis, respiratory burst activity, cytokine release, and modulation of platelet-monocyte adhesion" (Barderschneider et al. 1007). Conversely, xenon presents no restrictive properties on monocyte activity, which shows promise for patients presenting infection prior to surgery. Xenon has shown to have minimal side effects on cardiac anesthetics (Bedi et al. 2556-7), which are considered to be one of the most difficult anesthetics to perform. Xenon differs encouragingly from other volatile anesthetics in that it inhibits "excitatory NMDA (N-methyl-D-aspartate) receptor channels" rather than the GABA receptors (Dickson 1).

Xenon, despite its highly desired properties, is still years away from wide spread use as a clinical general anesthetic. It is much more expensive than the cost of current anesthetics, and the delivery method must still be custom made to suit the individual anesthesia machine desired. Xenon's chemical and physical properties (including heavy mass, low critical temperature) and lack of natural abundance (Garrett) make it difficult to efficiently produce this anesthetic drug.

Anesthesia, although advancing in drug capability, is more focused on patient safety and operative care along with better technology in the operating room. The
ultimate combination of which will allow for the most efficient drugs in a perfectly monitored anesthetic.
Bibliography


*Special thanks are given to Dr. Chad Stoker and Dr. Reuben Turner, Anesthesiologists.*
Mitoquinone in the Mitochondria

Prepared for
Dr. Hank Mancini
Organic Chemistry instructor
Paradise Valley Community College

Prepared by
Brian Szumarski

April 16, 2004
Abstract

Mitoquinone is a mitochondria-targeted antioxidant that selectively blocks mitochondrial oxidative damage, enabling the roles of mitochondrial oxidative stress in different types of cells to be inferred. This antioxidant named mitQ, is a ubiquinone derivative targeted to the mitochondria by covalent attachment to a lipophilic triphenylphosphonium cation through an aliphatic carbon chain. Which allows the cation to accumulate within the mitochondria inside cells. Thus allowing the antioxidant to protect the mitochondria against oxidative damage.

Background

The uses of the antioxidant up to this point in the human body has not yielded much success because they were not very bio-available to the cell especially the mitochondria. The mitochondria were most of the damaging ROS (reactive oxygen species) are formed, needed a targeted antioxidant to successfully penetrate the lipid bi-layer of the cell to gain access to the mitochondria. This was accomplished by the attachment of a lipophilic triphenylphosphonium cation to an antioxidant derived from ubiquinone. This mad it possible to deliver bioactive molecules to the mitochondria in vivo. This being done it is theorized that the new molecule will be an affective tool in treating a wide range of diseases including Friedreich’s ataxia, Parkinson’s disease, Diabetes, Huntington’s disease, disorders associated with mitochondrial DNA mutations, defective apoptosis in cancer and degenerative disease, and the pathophysiology of aging.

This antioxidant was named Mitoquinone ([10(4,5-dimethoxy-2-methyl-3,6-dioxo-1,4 cyclohexadien-1-yl)decyltriphenylphosphonium bromide or [10-(6'-ubiquinonyl) decyltriphenylphosphonium bromide]

There are several new variations of antioxidants being tested but to date mitoquinone has been the strongest and the most effective at stopping oxidative damage.

How it works to counter disease (FRDA)

This mitochondria-targeted antioxidant (mitoQ) protects Friedreich Ataxia fibroblasts from endogenous oxidative stress effectively. Friedreich ataxia (FRDA), the most common inherited ataxia, arises from the defective expression of the mitochondrial
protein frataxin, which leads to increased mitochondrial oxidative damage. Therefore antioxidants targeted to mitochondria are particularly more effective at slowing the disease progression than non-targeted antioxidants. This hypothesis was tested by comparing the efficacy of mitochondria-targeted and untargeted antioxidants derived from coenzyme Q10 at preventing cell death due to endogenous oxidative stress in cultured fibroblasts from FRDA patients. The mitochondria antioxidant mitoQ was several hundredfold more potent than the untargeted analog idebenone.

This is the first demonstration that mitochondria-targeted antioxidants prevent cell death that arises in response to endogenous oxidative damage. Targeted antioxidants may have therapeutic potential in FRDA and other disorders involving mitochondria oxidative damage.

Friedreich Ataxia which is the most common of the recessively inherited ataxias, with a onset in early adulthood leading to the progressive loss of neuromuscular function that usually culminates with death in the forth or fifth decade (1,2). FRDA is caused by intronic GAA triplet expansion in the gene for the mitochondrial protein frataxin that significantly decreases the amount of frataxin (1). This causes mitochondrial dysfunction in FRDA patients, increasing oxidative stress, decreasing the activity of iron-sulfur cluster containing enzymes, and causing the accumulation of iron in the mitochondria (2,3). Deletion of the yeast frataxin homologue and tissue-specific deletions of frataxin in mice lead to defects in iron-sulfur proteins and increased mitochondria oxidative stress and iron accumulation (4,5). Although the function of frataxin is uncertain, it is clear that its impaired expression in FRDA patients increases mitochondria oxidative stress, which is a major cause of the pathophysiology of FRDA (4) and the other diseases that were listed in the above pages.

Antioxidants that decrease mitochondria oxidative damage should delay the onset or slow the progression of FRDA in the body. Supporting this, idebenone, a short chain analog of coenzyme Q10, decrease oxidative damage and improves disease-related parameters in FRDA patients (6,7). However these untargeted antioxidants distribute through the extracellular and intracellular compartments, with only a very small proportion accumulating in the mitochondria, the principle site for oxidative damage.
Thus by targeting these molecules to mitochondria may improve their effectiveness. Mitochondria-targeted antioxidants were then developed by covalently coupling antioxidants to the triphenylphosphonium cation (8). The delocalized positive charge of these lipophilic cations enables them to permeate lipid bilayers easily and to accumulate several hundredfold within the mitochondria because of the large membrane potential (150-10 mV, negative inside; 8,9). Furthermore the plasma membrane potential (30-60 mV, negative inside) also drive the accumulation of these molecules from the extracellular fluid into isolated cells, from there they are concentrated further within mitochondria, with >90\% of intercellular lipophilic cations being present in the mitochondria (9,10). Once inside the cell the antioxidant (ubiquinol) donates a hydrogen atom from one of its hydroxyl groups to a lipid peroxyl radical, which decreases lipid peroxidation within the mitochondria inner membrane. This selective uptake by the mitochondria should greatly increase the efficacy and specificity of molecules designed to interact with mitochondria while also decreasing harmful side reactions.

In order for these mitochondria-targeted molecules to have therapeutic potential then they must be taken up selectively by the mitochondria in vivo. In particular, they must accumulate at high enough concentrations in the organs most affected by mitochondrial dysfunction, i.e., the heart, skeletal muscle, and the brain.
The accumulation into the heart of the central nervous system after feeding mitoQ to mice indicates that this is an efficient way of increasing the antioxidant content in the mitochondria in those tissues most affected by oxidative damage. These lipophilic cations pass directly through the lipid bi-layer; they do not utilize specific uptake systems and have the potential to distribute to mitochondria in all organs, including the brain.

Effects of mitoQ on telomere shorting (Anti-aging)

Oxidative damage is thought to be a major factor for replicative senescence and human aging (11). Leakage of superoxide from the mitochondrial respiratory chain is an important source of oxidative stress (12). Targeting antioxidants to the mitochondria is an effective way to attenuate oxidative damage in mitochondria due to the production of ROS (reactive oxygen species) in isolated mitochondria and in mitochondria within cells (13). MitoQ reduces oxidative damage and decreases ROS-induced apoptosis in short-term experiments. As high concentrations of mitoQ is located within mitochondria cells due to its accumulation by the mitochondrial membrane potential, it affects on cells is largely due to the prevention of mitochondrial oxidative damage, also mitoQ decreases the release of ROS from the mitochondria into the surrounding cells.

Telomeres act as ‘mitotic clocks’ in human fibroblast because they shorten with each round of replication due to both the inability of DNA polymers to replicate the very ends of chromosomes (11) and the specific accumulation of stress-induced DNA damage (14). ROS production accelerates replicative senescence via its contribution to telomere shorting under conditions of mild stress. MitoQ will prolong the replicative lifespan of human fibroblast under mild stress conditions, and correlates to a reduction in the rate of telomere shorting.

MitoQ in micromolar concentration block mitochondrial oxidative damage and prevents apoptosis induced by acute treatments with hydrogen peroxide (13). MitoQ decreases the cellular peroxide content and prolongs replicative lifespan of MRC-5 cells under hyperoxia. Treatment of MRC-5 cells under these conditions with mitoQ significantly elongated the replicative lifespan by an average of 40% (ranging from 15% to 70%) in four independent experiments whereas the lifespan of the DPPT-treated control cells remained unchanged.
this is in agreement with effects of other potent antioxidants on the replicative lifespan of human cells. MitoQ treatment also minimized telomere shorting under hyperoxia.

MitoQ treatment completely prevented the rise in telomere shorting rate due to hyperoxia and instead gave a negligible rate of telomere shorting. As opposed to the control cells that were treated with DPPT. The DPPT treated cells had an increased rate of telomere shorting per population doubling.

Together, this data indicates that minimizing oxidative stress significantly slows down telomere shorting and prolongs replicative lifespan. Moreover they suggest that it is accelerated telomere shorting in response to increased mitochondrial ROS production that induces premature senescence-like arrest under conditions of mild stress such as chronic hyperoxia. Thus, telomeres appear to act as cellular sentinels for oxidative damage under near-physiological conditions by limiting cell proliferation if and when stress and thus greater mutational risk accumulate (14). MitoQ was shown to be an effective molecule at protecting the mitochondria against oxidative stress and elongating the life span of our cells.

Mitochondria have a range of defense mechanism against oxidative stress, but there is still room for crn and oxidative damage still occurs. Oxidative damage leads to decreased mitochondria ATP synthesis, cellular calcium dyshomoeosais and induction of
the mitochondrial permeability transition, all of which predispose cells to necrosis or apoptosis. In summary, many diverse and pro-oxidant and antioxidant process occur in the mitochondria. Oxidative damage results whenever the ROS produced by the mitochondria evade detoxification. The steady-state level of oxidative damage depend on the relative rates of damage accumulation, repair and degradation (10). In addition, this ROS production may be involved in redox signaling from the mitochondria to the rest of the cell. There are still considerable uncertainties that remain about the nature of and significance of ROS signaling in the cell.

Tests & Synthesis

Female Swiss-Webster mice (8-10 weeks old) were fed mitoQ in their drinking water for 43 days then analysis of their tissue was done to determine the distribution of the compound. Mice were killed by cervical dislocation and bled, the liver, brain (cerebrum, cerebellum, and brain stem), kidneys, heart, adipose tissue and skeletal muscle (gastrocnemius and quadriceps) were collected and weighed. For mitoQ fed mice, tissue were homogenized in 4ml of ice cold methanol by using and ultraturax homogenizer, (2 X 30s) and then debris was pelleted by centrifugation (10,000 X g for 10 min). The methanolic supernatant was transferred to scintillation vial, the solvent was evaporated under a stream of nitrogen, and scintillant was added to the residue. The specific activity of administered compound was used to calculate the tissue content in nanomoles per gram of wet weight tissue.
Synthesis of mitoquinone, crude mitoquinol (200mg) was oxidized to 10-(6'-ubiquinonyl)decylyriphenylphosphonium bromide by stirring in CDCl₃ at room temperature under an oxygen atmosphere. The solvent was removed under reduced pressure, the residue was dissolved in CH₂Cl₂ (5ml), diethyl ether (15ml) was added, and the resultant suspension was stirred for 5 min. the supernatant was decanted, and the CH₂Cl₂/diethyl ether precipitation was repeated twice more. Residual solvent was removed under reduced pressure, giving crude mitoquinone as a sticky brown solid (173mg). IR (film) 3357, 2927, 1650, 1609, 1438, 1266, 1113 cm⁻¹. NMR (299.9 MHz) 7.9-7.6 (m, 15H-P+Ph₃) 3.98 (s, 6H 2X -OCH₃), 3.93-3.8 (m, 2H -CH₂-P+Ph₃) 2.42 (t, J = 7.4 Hz 2H ubiquinone-CH2-), 2.00 (s, 3H CH₃), 1.6-1.2 (m, 16H (CH₂)₈) ppm; ¹³C NMR (75.4 MHz) 184.8 (C=O), 184.2 (C=O), 144.3 (2C ring), 143.1 (ring), 138.8 (ring), 135.0 (d, J = 2.4 Hz -P+Ph₃ para), 133.8 (d, J = 85.0 Hz -P+Ph₃ ortho/meta), 130.5 (d, J = 13.3 Hz P+Ph₃ ortho/meta), 118.6 (d, J = 85.0 Hz P+Ph₃ ipso); 30.4 (d, J = 15.8 Hz -CH₂-CH₂-CH₂-P+Ph₃), 29.8 (CH₂), 29.3 (d, J = 48.5 Hz CH₂-P+Ph₃), 22.7 (d, J = 4.9 Hz CH₂-CH₂-P+Ph₃), 11.9 (CH₃) ppm. NMR (121.4 MHz) 25.1 ppm. Anal. calcd. For C₃₇H₄₄O₄PBr: C, 66.97; H, 6.68; found: C, 66.69; H, 6.99; mass spectrum: calcd. for C₃₇H₄₄O₄P 583.2977; found 583.2972. (10).
Looking Towards the Future

Even though mitoquinone is still in FDA testing and will not be available to the general public for two more years the idea of being able to radically reduce oxidative damage in the mitochondria is remarkable. In the long term oxidative damage is responsible for a host of problems even in healthy subjects, and for FRDA patients it opens up a new avenue to elongate their lives previously not available to them. As we age our bodies become less efficient at detoxifying our cells and preventing oxidative damage, this drug and drugs like this are on the cutting edge of anti-aging research.
References


Antabuse (Disulfiram)

By

Farid Torabi
Abstract:

Alcohol has been and will be one of the vast used drugs around the world. It is used to warm up parties and make things more interesting at times. It is used for celebration, but it could also lead to many physical and emotional damage including, liver failure and alcoholism which could ruin not only the life of the abuser but his or her whole family. Many clinics and medications are available to deal with alcoholism and one of these little helpers is a white pill called Antabuse.

Antabuse (Disulfiram)

Alcoholism is a disease characterized by impaired control over the consumption of alcoholic beverages. Alcoholism is a serious problem worldwide; in the United States the wide availability of alcoholic beverages makes alcohol the most accessible drug, and alcoholism is the most prevalent of the nation’s additions. The understanding of alcoholism, and hence its definition, continues to change. Many terms, often with hazy differences in meaning, have been used to describe different stages and manifestations of the disease. According to Long, Phillip W., M.D., in 1992 the National Council on Alcoholism and Drug Dependence and the American Society of Addiction Medicine published a definition reflecting the current understanding of the disease: “Alcoholism is a primary, chronic disease with genetic, psychosocial, and environmental factors influencing its development and manifestations. The disease is often progressive and fatal. It is characterized by impaired control over drinking, preoccupation with the drug alcohol, use of alcohol despite adverse consequences, and distortions in thinking, most notably denial. Each of these symptoms may be continuous or periodic.”.1 This definition recognizes alcoholism as a disease, i.e., as an involuntary disability. It accepts a genetic vulnerability in some people and identifies the phenomenon of denial as both a psychological defense mechanism and a physiological outcome of alcohol’s effect on the memory.1.

Alcohol, like all addictive drugs, produces physical dependence in the habitual user. A hangover, a combination of headache, nausea, fatigue, and depression, may be a mild type of withdrawal from alcohol. Sudden abstinence by the chronic alcoholic produces a severe withdrawal syndrome, including tremors, vomiting, and convulsions resembling those of epilepsy, that is more likely to cause death than withdrawal from narcotic drugs. The final and most dangerous phase in this withdrawal pattern is delirium tremens, a toxic psychosis characterized by insomnia, hallucinations, seizures, and maniacal behavior.1.

Treatments

According to Menichol, R, in the book “Disulfiram (Antabuse) A Unique Medical Aid to Sobriety”, the treatment of alcoholism depends on how far the disease has progressed. Treatment typically begins with professional advice or self-motivation to abstain, often coupled with medical efforts to achieve sobriety. In the presence of withdrawal symptoms, antianxiety drugs such as benzodiazepines may be prescribed. A next step is often enrollment in a treatment program suitable to the severity of the
disease and patient's social stability. Residential programs offer a supportive atmosphere and a structured environment in which the patient can begin to learn how to restructure his or her life and develop new habits. Many programs educate the family as well, alerting them to patterns within the family that may have enabled the patient to keep drinking. Because alcoholism is a chronic recurring and relapsing disease, treatment programs are usually followed by membership in a support group such as Alcoholics Anonymous.2.

According to Meyers, Robert J. in "Clinical Guide to Alcoholic Treatment", there are Medical treatments to help ensure continued sobriety, and they include self-administration of drugs such as Antabuse, which produces severe discomfort if present in the system when alcohol is consumed. The therapeutic use of Antabuse was discovered in the 1930s when workers exposed to tetraethylthiuram disulfide, a chemical used in the rubber industry, became ill after drinking alcoholic beverages.3.

**CHEMICAL NAME:** “bis(diethylthiocarbamoyl) disulfide, C10H20N2S4. M.W. 296.55”.1.

![Figure 1: 3 dimensional or an Antabuse molecule.](image)

**Antabuse** is a trade name for the drug tetraethylthiuram disulfide (C10H20N2S4), used in the treatment of alcoholism. Also called sulfinyl, Antabuse is nontoxic, but it alters the metabolism of alcohol in the body, making it impossible for one who is taking the drug to drink without experiencing severe discomfort. When alcohol is present the
drug increases the concentration of acetaldehyde (C2H4O) in the body, causing symptoms resembling those of a bad hangover: the individual feels hot, the face becomes flushed, the neck and head throb, and nausea, vomiting, headache, thirst, chest pain, palpitation, dyspnea, hyperventilation, tachycardia, hypotension, syncope, marked uneasiness, weakness, vertigo, blurred vision, and confusion.3. From the information gathered from the “Medical Consequences of Alcohol Abuse” by Clark, P.M.S.; Kricka L, in severe reactions, there may be respiratory depression, cardiovascular collapse, arrhythmias, myocardial infarction, acute congestive heart failure, unconsciousness, convulsions, and death. The intensity of the reaction may vary with each individual but is generally proportional to the amount of disulfiram and alcohol ingested. In the sensitive individual, mild reactions may occur when the blood alcohol concentration is increased to as little as 5 to 10 mg/100 mL. At a concentration of 50 mg/100 mL symptoms are usually fully developed, and when the concentration reaches 125 to 150 mg/100 mL unconsciousness may occur. Small quantities of alcohol, such as from food sauces and cough medicines, and even inhaled traces from shaving lotions and varnishes, may induce the same symptoms. The drug Temposil, or citrated calcium carbamimde, has the same function as Antabuse, but is weaker and safer.4.

Antabuse + drinking alcohol (ethanol or ethy alcohol) equals in high levels of acetaldehyde in the body;

\[
\text{C10H20N2S4} + \text{C2H6O} \rightarrow \text{high levels of C2H4O}
\]

Ethanol is toxic, and the body begins to dispose of it immediately upon its consumption. Over 90% of it is processed by the liver. In the liver, the alcohol dehydrogenase enzyme converts ethanol into acetaldehyde, which is itself toxic.2.

\[
\text{CH}_3\text{CH}_2\text{OH} \rightarrow \text{CH}_3\text{C} = \text{H} + 2 \text{H}
\]

Figure 3: Conversion of ethanol into acetaldehyde 1.

This is destroyed almost immediately by the aldehyde dehydrogenase enzyme, which converts it to acetate ions.2.

\[
\text{CH}_3\text{C} = \text{H} + \text{H}_2\text{O} \rightarrow \text{CH}_3\text{C} = \text{O}^- + 3 \text{H}
\]

Figure 4: Conversion of acetaldehyde to acetate ions.1.

During alcohol metabolism after disulfiram intake, the concentration of acetaldehyde occurring in the blood may be 5 to 10 times higher than that found during metabolism of the same amount of alcohol alone. The duration of the reaction is
variable, from 30 to 60 minutes in mild cases, up to several hours in more severe cases or as long as there is alcohol remaining in the blood. In severe reactions, supportive measures to restore blood pressure and treat shock should be instituted. Other measures such as the administration of oxygen or carbogen (95% oxygen, 5% carbon dioxide), massive i.v. doses of vitamin C (1 g), ephedrine sulfate, or antihistamines i.v. might be indicated. Potassium levels should be monitored particularly in patients on digitalis since hypokalemia has been reported.

Disulfiram is slowly absorbed from the gastrointestinal tract and is slowly eliminated from the body. Ingestion of alcohol may produce unpleasant symptoms 1 or even 2 weeks after a patient has taken his last dose of disulfiram. Prolonged administration of disulfiram does not produce tolerance. The longer a patient remains on therapy the more sensitive he becomes to alcohol. Patients who are receiving or have recently received metronidazole, paraldehyde, alcohol, or alcohol-containing preparations such as cough syrups, elixirs, should not be given disulfiram. Severe myocardial disease or coronary occlusion; diabetes mellitus; hepatic cirrhosis or insufficiency; hypothyroidism; epilepsy; cerebral damage; chronic and acute nephritis; psychoses; and hypersensitivity to disulfiram or other thiram derivatives used in the manufacture of items such as pesticides or vulcanized rubber.

Precautions

Patients should be informed of the type of reaction which will be encountered if alcohol is taken overtly or as a component of food or other products. Patients having a history of industrial contact dermatitis who currently work or have previously worked in the rubber industry should be evaluated for hypersensitivity to thiram derivatives before receiving disulfiram. Patients exposed to organic solvents which may contain alcohol, acetaldehyde, paraldehyde or structural analogues are at risk of experiencing disulfiram alcohol reactions. Such exposure should be eliminated prior to treatment.

It is suggested that every patient under treatment carry an identification card stating that he is receiving disulfiram and describing the symptoms most likely to occur as a result of the disulfiram-alcohol reaction. In addition, this card should identify the attending physician or institution to be contacted in emergency.

Alcoholism may be associated or followed by dependence on narcotics or sedatives. Barbiturates have been administered concurrently with disulfiram without untoward effects, but the possibility of initiating a new dependence should be considered. Patients taking disulfiram should not be exposed to ethylene dibromide or its vapors. This precaution is based on animal studies which have suggested a possible toxic reaction between inhaled dibromide and ingested disulfiram. Rats exposed to this regimen have shown a higher incidence of tumors and mortality. Correlation of this finding in humans however has not been demonstrated.

Since disulfiram-alcohol reactions could aggravate some medical conditions such as diabetes mellitus, hypothyroidism, epilepsy, cerebral damage, chronic and acute nephritis, hepatic cirrhosis or hepatic insufficiency, disulfiram should be used with extreme care in patients having such a medical history. Baseline and follow-up transaminase tests (10 to 14 days) are suggested to detect any hepatic dysfunction that may be associated with disulfiram therapy. In addition, a complete blood count and a
sequential multiple analysis-12 test (SMA-12) should be carried out every 6 months. Disulfiram inhibits enzyme induction and may thus interfere with the metabolism of drugs taken concomitantly. It enhances the effects of the coumarin anticoagulants and phenytoin.3.

Pregnancy and Lactation

It is not known whether disulfiram can cause fetal harm when administered during pregnancy, but one report of limb reduction anomalies in infants born to disulfiram-treated mothers has been published. Because of these findings, extreme care should be exercised before administering disulfiram during pregnancy.

It is not known whether this drug is excreted in human milk. Since many drugs are, and because of the potential for serious adverse reactions in the nursing infants, before administering disulfiram to a nursing mother it would appear advisable to discontinue nursing.2.

Symptoms and Treatment

Severe cases of disulfiram poisoning have been reported mainly in children. Within a few hours of ingestion of a large amount, drowsiness followed by coma develops accompanied by persistent nausea, vomiting, aggressive and psychotic behavior, and ascending flaccid paralysis which can reach the cranial nerves. Treatment consists of administration of oxygen therapy, glucose 5% i.v., and sodium ascorbate 1 g i.v. Patient should be kept in bed and as quiet as possible with appropriate symptomatic treatment.2.

Dosage

Should never be administered until the patient has abstained from alcohol for at least 12 hours.1.

Initiation of therapy

A maximum of 500 mg daily in a single dose should be given for 1 to 2 weeks, preferably taken in the morning. Patients experiencing a sedative effect may take the drug at bedtime or, if necessary, dosage may be adjusted downward. Average maintenance dose is 250 mg daily (range 125 to 500 mg) but should not exceed 500 mg.2.

Duration of therapy

Daily, uninterrupted administration of disulfiram must be continued until the patient has established a basis for permanent self-control. Depending on the individual patient, maintenance therapy may be required for months or even years.2.
Conclusion

I decided to use Antabuse as my projects topic since one of my friends was the victim to alcoholism, and I just wanted to learn more about the drug. Throughout the research I learned a great quantity on how the medication assists patients who are trying to quit their habits of drinking. I also learned that this medication does not cure or prevent alcoholism, it is merely a tool in helping individuals who are willing to quit and sober up. This drug has been around for a good amount of time and has helped out a lot of people in their recovery, and will do so in the coming years, but good results will not be achieved unless the patient has all the intentions of kicking the habit.
Work Cited

   http://www.mentalhealth.com/drug/p30-a02.html
   http://newtraditions.chem.wisc.edu/FPTS/fbform/forchalf.htm#antabuse


Silicone and Saline Breast Implants

My Truong

April 14, 2004
Abstract. Breast implants have raised some controversial argument over the year. How safe are the implants. The history of silicone and saline breast implants, and how silicone and saline breast implant are made? How does the chemical structure and properties of the silicone gel and rubbers work?

History of Breast Implants

Breast implants were first introduced to America by Dow Corning in the 1960s. “In the 1940’s, Japanese prostitutes had their breasts injected with substances such as paraffin, sponges and non-medical grade silicone to enlarge their breasts. This was done by the fact that they thought American servicemen favored women with large breasts.”(9). In the 1940’s in America, doctors injected silicone liquid without a shell, directly onto the body to fill up gaps or smooth out facial wrinkles. That is how they got the idea to use silicone to make breasts fuller. Because it was just liquid, it soon spread out and lost its form in the body. Next, the concept of the shell was introduced by the manufacturers Dow Corning and Bristol Meyers Squib.

From the very beginning, the implants were popular. Women accepted the fact that they would get scarring from the surgery to increase their breast size. At thirst, the thick shelled implants were introduced to the public by the company, but complications were discovered. Between the sixties and seventies, three models were produced to try to prevent leakage. The second model had a thinner shell. They were supposed to look more natural and decrease in bleeding of the silicon gel, but they still leaked. Therefore, the third model was introduced. This model had a thicker shell and did produce a lower rate of gel bleed.

Silicone

Until the 1980’s, silicone were the only breast implants available. They were extremely popular in the seventies and no complications were found during that decade. A few complications developed in the early eighties for women who had their implants in more than a period of ten years. Some minor complications, if left untreated can lead to life threatening conditions.

Although available since the late 1960’s, saline implants were not approved by the FDA until 20 years later. Silicone implants were still more popular in the eighties because they felt and looked more similar to the natural breast tissue. Doctors preferred to work with silicon more so than saline so that patients would be more satisfied with the results.

However, in 1992, the FDA banned silicon and recommended saline as the implant of choice because of the complications such as cancer, hardening, leaking, scar tissue, and difficulty breast feeding. In the late 1990’s, it was discovered that saline and silicone both harden and gave some of the same complications. That is why FDA approved silicone again at that time. Now, it is common for the first surgery to implant saline and the second surgery to implant silicone.

Silicones are an inorganic compound. That means there are no carbon atoms in the backbone chain of the molecules. Silicone’s backbone is made up of oxygen and alternating silicones atoms. That is where the name “polysiloxane” (3) came from, with
the thought that silicone was in the backbone. The real structure was discovered later, but the name stuck. (3) The silicone structure looks somewhat like the following picture.

![Chemical structure of silicone]

What is a silicone breast implant?

A silicone breast implant is a vulcanized rubber shell filled with silicone gel or oil. It is pre made and sealed. It can be ordered according to desired size.

The shell or jacket of the implant is made up of silicone elastomer, that has been vulcanized. Silicone elastomer is a polymer of silicone that is formed by cross linking and treatment with amorphous silica to increase strength. (2) Most elastomers are organic because they have carbon as a main chain. Silicone is among the best elastomers for both high and low temperature resistance. It can survive in an environment of -100°C-200°C. Silicone rubber has excellent ozone weather resistance. Its properties change very little in contrasting environments.

The silicone that is used in an implant is a type of silicone gel made from the silicone polymer. The scientific name for the chemical that made up of the silicone gel is called PDMS (polydimethylsiloxane). “A copolymer in which the methyl groups have been partly or entirely replaced by phenyl groups.” (2) The physical properties of PDMS are governed by their structure, the flexibility of the methyl groups are the reason for the extremely low surface tension of PDMS. These copolymers are divided into three different groups known as Di-block, Tri-block and star polymers. They are synthesized sequentially; cyclic dimethyl compounds are polymerized by anionic ring opening, followed by polymerization of the second component, as shown below in Fig.2. The triblock will used lithium diphenyldisilanolate to attack the Di-block, then add another group at the end of the chain and in the termination state to create the polymer of polydimethylsiloxane.
Complication of silicon

Silicone breast implants have a history of complications. Women in the sixties did not develop complications from the silicone implants until years had passed. The reason they did not know about the complications sooner was that there was a lack of study and research of the implants. The focus was on aesthetics, not technology. The women did not care because they were very happy with their new image. The company which produced the implants did not take initiative to find its faults with the product at the time.

Some complications develop at an earlier phase as due to surgical procedures, such as infection and anesthesia swelling, redness and bleeding. These minor complications can be treated with antibiotics. There are several other major complications which have developed as a result of the implants. One is the capsular contracture which is when the implant hardens. Capsular contracture "Occurs when the scar tissue or capsular that normally forms around the implant tightens and squeezes the implant."(4) According to the author of the book What Women need to know. She wrote that her implant started to harden fifteen months after the surgery. It caused her body to develop other disorder that nobody would have suspected was influenced by the implants. Symptoms included major back pain and migraine and headaches that, which over a period of ten years caused her so much pain that she was ready to commit suicide. (5) This happened back in the seventies. Today if this complication occurs most doctors would advise a patient to have the implants surgically removed.

Deflation or rupture of the implant is another complication in which the breast implant begins to leak. Other signs of deflation or rupture are swelling, tenderness, or changes in sensation. This complication can be detected by an MRI scan. In the case of deflation, the silicone gel will escape into the body and can cause granulomas of lumps to form in places such as breasts, the chest wall, arm pits, arms or abdomens. (4)
Another major complication is necrosis. This is the formation of dead tissue (scar tissue) around the implants, which may prevent the wound from healing. A permanent scar may form as a result of necrosis. Undergoing any surgical procedure can cause nerve damage which may lead to blood clotting and later be a result of organ damage. This is a concern for all patients.

Another concern for all surgical patients is the risk of developing infection. There are two types of infection: internal and external. The internal infection is the type created when the implant is in the body and is very difficult to treat, sometimes due to the body’s rejection of antibiotics.

In 2002 the British Association of Plastic Surgeons did a study on why implant rupture when women swim and sleep. It was due to misleading news in the lay press concerning breast implant rupture due to changes in pressure, altitude, and sleeping position. Scientists did a study “To ascertain whether mammary implants are prone to changes in conformation or structure if they are submitted to recreational dives and constant simulated with movement.” (6) The Tc scan was used to detect changes. As a result none of the implants showed shell ruptures, but were not able to retain their shape after several years. This study shows that rupture can happen even if woman does not do all the things mentioned above, mostly because of the age of the silicone implants.

**Fig. 3**

**Figure 5**—Tc scan of the McGhan expendable breast implant subjected to the simulated dives. The implant is unbroken after completion of the test; but tiny bubbles of air can be seen inside the inner chamber of the device.

**Figure 4**—Tc scan of the McGhan implant explanted after 2 years and submitted to the simulated dives. The implant is unbroken after completion of the test; but a hyperdense profile can be seen inside the implant.

**Figure 3**—Imaging of three Style 410 McGhan implants by Tc scanning. The leftmost implant was used as a control; the middle and rightmost implants were submitted to the simulated dives. The implants submitted to the simulated dives have changed shape. There are no differences in gel density between the three implants.
Saline

Saline implants have been available since the 1960's; however, they were not the implant of choice until the early 1990's. In 1992, as previously mentioned the FDA approved the saline implants due to the rising complications and several lawsuits with the silicone implants. Saline implants were chosen as an alternative implant for women who did not want silicone breast implants. The shell of the saline implants are made from a silicone elastomer, which is the exact same material used to make the silicone implant shell. The liquid inside of the shell is a solution that is made of salt and water. The physiological saline solution is made up of 0.9% of NaCl in water.

![Fig. 5](image)

H₂O salivates Na⁺ and Cl⁻ to create saline solution

What is saline breast implant?

Since saline is a natural substance easily absorbed, scientists have proven that it does not harm the human body if it is released into the body. Like most medical devices, saline filled implants have evolved from two different designs. Production of these mentioned models has been modified based on the complications found with the silicone implants. Though no breast implants are guaranteed to last a lifetime, saline filled implants are far more reliable today than they were thirty years ago.(8)

Cosmetically speaking the saline implant is not as pleasing to most women because it can ripple given that it is a liquid form. The rippling effect is due to the implant being under-filled. Under-filling can be associated with premature failure due to rubbing of the folded elastomer against itself. The folding is called the “fold flaw” (9). Saline implants are vulnerable to complications when that the saline is injected through a valve after it has been inserted into the body. The valve through which the implant is filled is often identified as a weak point (9). The concern for this complication was found to be valid from the beginning, unlike the silicone complications.
Complications of saline implant

As with silicone, saline implantation risk developing similar side effects. Capsular contracture, nerve damage, breast pain are just to name a few possible results of this the surgical procedure. One risk that is found to be more profound in the saline implant is the risk of microbes entering into the implant through an area which as developed a leak. Due to the warm environment of the human body, the organism can reproduce into a colony which can lead to other health issues. (9)

Women experience pain and implant shifting. There is no evidence that breast implants interfere with lactation, but recently there have been some complaints about how lactation affects the implants. The FDA is currently studying whether there is evidence of silicone in the breast milk of lactating women. Some where out there a major myth of silicone implants influence progression of cancer. There is no scientific evidence that silicone gel-filled implants can increase the risk of cancer in women. (4) Because the implant is a foreign object, the body typically form a defense mechanism to protect itself, but can create harm like developing cancer cell or capsular contracture to itself with out knowing. Both saline and silicone implant interfere with mammography and delay or hinder the early detection of breast cancer by hiding suspicious wound, in injury or tumors. (10). It is difficult to include them in the image. Recent studies have shown benefits of different models. New, improved saline implants “high profile saline” made by Mentor Corp comes pre filled like the silicone implants. Doctors do not recommend pumping up or refilling the new model after implantation to prevent and avoid leaking through the valve. This model does not leak easily when maintained properly.

Even with the new improved models, scientists have proved that saline implants will only stay good for a period of ten years. After that they must be taken out and replaced with a new one. This is a constant maintenance job, but due to the popularity of breast implants today, Most women would gladly take risks and attentively maintain themselves to enhance their image, women who choose breast implant surgery should consult with more than one physician to be educated in the risks and side effect of the surgery and the implants. Most likely breast implant will only be more popular in the future due to the effect of Hollywood movie actresses. Every woman wants to look perfect like their favorite star. As for the risk of complications some women do not care if they could die from breast cancer only if they can have their image improved to the perfection of Hollywood standards. They would die happy with the years that they can live. More to the technology side I believe that in the future scientist will be able to improve the MRI scan to detect early sign of cancer. The scan will be able to screen through the implant and give a better image of the cells. Furthermore, manufacture like Mentor Corp are more careful these day when they develop a new model of an implant they would have to study it more accurately to avoid lawsuits. They constantly give their implants makeover to stay in business and steer clear of complications. Due to this reason I think breast implants these days are much safer and will be even more safe in the future. Women will never stop perfecting their image no matter how dangerous the procedure can be.
A 175cc high profile implant has the equivalent projection of a 475cc standard saline implant with much less anterolateral width.

High profile saline implant compared to a standard saline implant of the same size. Note the increased projection of the high profile implant on the left.

Photos courtesy of:
Barry DiBernardo, MD, FACS
Director, New Jersey Plastic Surgery
Montclair, New Jersey
www.plasticsurgerynj.com
973-509-2000
(3) Institute of Medicine, Safety of Silicone Breast Implants, National Academy Press, 2000, 4.
Anti - Anxiety Medications
Prozac and Ativan

Stephanie Velasquez

April 16, 2004
The purpose of this paper is to provide some insight into two widely prescribed anti-anxiety medications. The topics covered include: biological applications (uses), biological reactions (action mechanisms), chemical structures, chemical synthesis, stereochemistry, and cautions and dangers. The subject of the following report is Prozac (fluoxetine), which is a selective serotonin re-uptake inhibitor, and Ativan (lorazepam), which is a benzodiazepine.

"Anxiety disorders, as a group, are the most common mental illness in America. More than 19 million American adults are affected by these debilitating illnesses each year (1)." We have all experienced anxiety of one form or another during our lifetime weather it be test anxiety, butterflies in the stomach, or stage fright. Anxiety disorders, however, are classified as "illnesses that fill people's lives with overwhelming anxiety and fear that is chronic, unremitting, and can grow progressively worse (1)." Without recognition and proper treatment the results can be both mentally and physically devastating. Anxiety disorders are classified into five major groups including: panic disorders, which are reoccurring and sudden episodes of fear; obsessive-compulsive disorder (OCD), which is an overwhelming want to repeat certain activities or thoughts; post traumatic stress syndrome (PTSS), which are reoccurring thoughts or physical symptoms that are initiated after a traumatic event in an individual's life; phobias, which include social phobia, or a fear of social situations and possible embarrassment; and specific phobias or fear of particular people, places, or situations, such as, a fear of heights or spiders. Finally, there is general anxiety disorder (GAD), which is a consistent fear or anxiety of daily events which lasts more then a month, and an overwhelming habit of always expecting the worse in every situation (1). While many of us have experienced one or more of these symptoms on occasion, a person suffering from an anxiety disorder is a prisoner of their persistent and reoccurring thoughts or behaviors. It takes a great deal of mental and physical energy for these individuals to lead a normal and fulfilling life. Fortunately, several medications and forms of psychotherapy have been developed to aid anxiety sufferers in leading a less stressful lifestyle. The four most common classifications of drug therapy used to treat anxiety are benzodiazepines, tricyclics (TCAs), selective serotonin re-uptake inhibitors (SSRIs), and azaspirones. These medications are used either as the sole form of therapy or in conjunction with some form of psychotherapy. While there are several forms of anxiety treatments, medication drug therapy is increasingly on the rise and continues to be a popular form of therapy among anxiety sufferers. However, with an increase in drug therapy and constant development of new prescription medications, it is often times mind boggling and confusing for consumers to make a well informed medication selection. While drug selection is ultimately up to the discretion of a qualified medical professional, it is becoming quite common for patients to request certain medications. Communication between physician and patient is on the rise and is important when developing a medication regimen that will be most beneficial for the patient (2). For this reason, it is also important for consumers to be well informed and aware of all their options. Countless drugs flood the market often times making a decision very confusing and difficult. Understanding the
basics about anti-anxiety medications will enable consumers and physicians to collaborate in making an appropriate and beneficial drug selection. There are several options when choosing medication so it is important and essential that patients openly communicate with their physician. While only two anti-anxiety drugs will be compared in this report, there are numerous options if health conditions or personal preference do not permit the use of the medications in this comparison. Patients should always consider drug allergies, existing medical conditions, and possible adverse drug interactions; and only after careful review and consideration of a patient’s current condition and medical information should a drug selection be made (2).

**Biological Applications (uses):**

The most common use for Prozac (fluoxetine) is to treat depression. However, it is also often prescribed to treat anxiety disorders, bulimia, obsessive-compulsive disorder (OCD), anorexia, obesity, alcoholism, attention-deficit hyperactivity disorder (ADHD), narcolepsy, schizophrenia, Tourette's, headaches, and other personality or emotional disorders determined by a doctor (3). In placebo-controlled trials over a period of 5 to 6 weeks patients with diagnosed depression, anxiety, and sleep disorders were given 20 mg of fluoxetine daily. A significant improvement in symptoms and a decrease in relapse was noticed in the fluoxetine group when compared to the placebo group (4). Similarly, in the treatment of obsessive compulsive disorder 28% of the patient pool reported substantial improvement in symptoms when given 20 mg of fluoxetine daily, whereas, only 8% of the placebo group reported improvement (5). On the other hand, Ativan (lorazepam) is most often prescribed for anxiety but can also be used to treat muscle spasms, seizures, tension, agitation, insomnia, and irritable bowel syndrome (3). In a week long, double-blind, placebo controlled trial lorazepam proved extremely effective in relieving anxiety when administered in a twice daily dose of 3.2 mg with little adverse side effects reported. Studies have also shown that the administration of lorazepam before medical procedures helps reduce anxiety before and through the duration of the procedure (6). While both drugs are effective in treating anxiety Prozac is generally administered over a long period of time as part of an ongoing drug therapy program or as a maintenance medication. The onset of effectiveness is normally 28 days from the start of therapy. On the other hand, lorazepam is used as a temporary form of therapy generally lasting 2 to 4 weeks. The onset of drug efficacy is within hours of administration and lasts 12 to 16 hours (7).

**Biological Reaction (action mechanism):**

Both Prozac and Ativan are popular medications for treating anxiety, however, each drug performs differently in the brain to help stabilize chemical imbalances, or by enhancing certain chemical reactions. Prozac is classified as a selective serotonin reuptake inhibitor (SSRI). SSRIs work by blocking the re-absorption of serotonin by nerve endings in the brain (8). Serotonin is an important neurotransmitter that regulates mood, sleep, and appetite. In normal circumstances, when stimulated, neurons in the brain release serotonin into the synapse between two neurons. Some serotonin is then
absorbed by the nerve ending of the receiving neuron, and the excess serotonin is reabsorbed by the secreting neuron. This secretion and absorption of serotonin is what dictates mood and emotion. In an individual suffering from depression, there is a chemical imbalance in the brain which affects the amount of serotonin available for absorption. When the neuron is stimulated, a less than normal amount of serotonin is secreted then partially absorbed by the receiving neuron while the rest is reabsorbed by the secreting neuron. This less than normal amount of serotonin absorption by the receiving neuron has an adverse effect on mood and emotion. SSRIs work by blocking the re-absorption of serotonin by the secreting neuron. This forces the serotonin to remain in the synapse for a prolonged amount of time increasing the absorption of serotonin by the receiving neuron, thus balancing or compensating for the lack of serotonin produced. This helps to stabilize mood and emotional state (8). While SSRIs work by correcting or compensating for a chemical imbalance within the brain, Ativan (lorazepam), which is a benzodiazepine, combats anxiety by enhancing naturally occurring brain chemicals. Gamma-amino butyric acid (GABA) is a neurotransmitter within the brain which is responsible for inhibitory actions, or a natural tranquilizer. When GABA is released from a neuron into a synapse, it binds to specialized sites on the receiving neuron which then allows the passage of Cl- ions through chloride specific channels and into the neuron. These Cl- ions in turn inhibit nerve impulses causing a state of relaxation or sedation. Benzodiazepines work by enhancing the effects of GABA. For example, benzodiazepines bind to the same site as GABA molecules, this addition of the benzodiazepine and GABA on the same neuron site causes an increased amount of Cl- ions to flow through the neuron channel and thus increases the natural sedative affect of the GABA molecule (9).

**Chemical Structures:**

The following chemical structure is borrowed from the Prozac (Eli Lilly) package insert (Figure 1).

\[
\text{F}_3\text{C}-\text{O}-\text{CHCH}_2\text{CH}_2\text{NHCH}_3 \quad \bullet \text{HCl}
\]

(Figure 1)

Prozac: \((\pm)-\text{N-methyl-3-phenyl-3-[(alpha,alpha,trifluoro-p-tolyl)oxy]proplyamine hydrochloride}

Empirical formula: \(\text{C}_{17}\text{H}_{18}\text{F}_{3}\text{NO} \bullet \text{HCl}\)
The following chemical structure is borrowed from the Ativan (Sandoz) package insert (Figure 2).

(Figure 2)

Lorazepam: 7-chloro-5-(o-chlorophenyl)-1,3-dihydro-3-hydroxy-2H-1,4-benzodiazepin-2-one

Empirical formula: C18H10Cl2N2O2

Chemical Synthesis:

Prozac (fluoxetine): In the Perrine Laboratory procedure the following methods of synthesizing Prozac (fluoxetine) are shown as follows. (Figure 3)
Ativan (lorazepam): In the MedChem document the synthesis of Ativan (lorazepam) is shown as follows. (Figure 4)

![Diagram of Ativan synthesis](image)

(Figure 4)

**Stereochemistry:**

The stereochemistry and chirality of drugs is becoming an area of increasing importance. "Approximately 50% of marketed drugs are chiral, and of these approximately 50% are mixtures of enantiomers rather than single enantiomers (12)." Studies have shown that a pair of enantiomers within a drug can have substantially different effects in the body's chiral environment. For the purpose of this explanation, we will use a fictional drug, DRUGRX. When DRUGRX is tested for the presence of enantiomers it is found to contain a racemic mixture of both the R and S configurations. When the R and S configurations are tested separately in the body it is determined that the R configuration achieves the desired pharmacologic effects. When the S configuration is tested in the body it is discovered that it has no therapeutic effect due to its molecular arrangement. Similarly, while one enantiomer is reactive and provides a pharmacologic effect the other may be responsible for a drug's adverse side effects. On
the other hand, a chiral drug may contain enantiomers that provide equal therapeutic results. Individual studies must be conducted on a drug by drug basis to determine the effects of enantiomers within a chiral drug. Presently, the FDA does not require stereochemical testing of all drugs, it is up to the discretion of each drug manufacturer (12). As a result, the importance of stereochemistry for each drug on the market remains unknown. Further testing in stereochemistry has the potential for development of drugs that are more therapeutically beneficial with less side effects. This, however, presents an extra cost to drug companies and manufacturers.

Prozac (fluoxetine) is a chiral drug that contains a racemic mixture of both the R and S enantiomers. There have been attempts to develop a single enantiomer formulation but these attempts proved unsuccessful. Further studies showed that both the R and S enantiomers produce similar therapeutic effects but are metabolized differently (7). Presently, Ativan (lorazepam) is also sold as a mixture of enantiomers, however, more studies must be conducted to determine the therapeutic effects of the individual enantiomers within the mixture.

Cautions and Dangers:

People taking or considering Prozac (fluoxetine) or Ativan (lorazepam) should be aware that both drugs present potential dangers and should be taken with caution. It should be noted that patients allergic to certain medications should avoid taking the drug and inform both their physician and pharmacist. One out of twenty five patients taking Prozac develop a rash that may be accompanied by fever, joint pain, swelling, wrist and hand pain, breathing difficulties, or swollen lymph glands. These adverse symptoms disappear in most patients who discontinue use of the drug (3). Weight loss has also been linked to Prozac (fluoxetine) use. As many as 9% of patients experience appetite loss, and 13% lose more than 5% of their body weight (3). People with certain pre-existing medical conditions should use caution when taking Prozac as it may aggravate some current medical ailments. Prozac is largely metabolized in the liver, so individuals with liver dysfunction should take extra caution when taking this or any other medications (2). If patients suffer from seizures, Prozac should be administered with great care.

Patients taking Ativan (lorazepam) should avoid alcohol, tranquilizers, and other depressants. Taking additional barbiturates (depressants) can accelerate or enhance, to a potentially harmful extent, the sedative effects experienced by the central nervous system. Individuals suffering from severe depression, lung disease, narrow-angle glaucoma, kidney or liver disease, or alcoholism should avoid the use of lorazepam or any other benzodiazepines (3). Lorazepam's sedative effects coupled with the above conditions may lead to serious health conditions that could be fatal. In addition, lorazepam should always be administered with great care, it can be a potentially addictive substance if abused. “About 2% of the adult population of the US (around 4 million people) appear to have used prescribed benzodiazepine hypnotics or tranquilizers regularly for 5 to 10 years or more....Many studies have shown 50 to 100% of long-term users have difficulty in stopping benzodiazepines because of withdrawal symptoms... (9)”
Conclusion:

In conclusion, while both medications have been proven effective for treating anxiety I believe that SSRIs such as Prozac (fluoxetine) will eventually become more widely prescribed than benzodiazepines for the treatment of anxiety disorders. Prozac (fluoxetine) provides a means of long term treatment that is effective with less potential side effects. The risk of chemical dependence with the use of Prozac is rare, while, the potential for dependence and symptoms of withdrawal are common adverse side effects associated with the use of benzodiazepines. Benzodiazepines should be used only occasionally for quick relief of anxiety disorders associated with isolated stressful situations, such as, medical procedures or severe and sudden panic attacks. Prozac is a more suitable and safe option for a long term medication regimen. As patients and medical professionals become increasingly aware and knowledgeable of their medication options I anticipate a significant rise in the amount of SSRIs and a decrease in the amount of benzodiazepines prescribed to treat long term anxiety disorders.
Bibliography


High Cholesterol and the Class of Statin Drugs

Prepared for
Professor Dr. Hank Mancini
Organic Chemistry Instructor
Paradise Valley Community College

Prepared by
Christy Wilmoth

April 16, 2004
Abstract

High cholesterol is a deadly disease and if not monitored correctly, it can be life threatening. This report includes a description of high cholesterol, the synthesis of cholesterol, and the prescription cholesterol lowering class of statin drugs. How statin drugs work, their differences, and side effects will be discussed. Chemical structures and mechanism of action of each drug will be explained as well as the future outlook of statin drugs.

Introduction

Cholesterol is a fatty substance that is important to the membrane of cells in the body. It is found in the blood stream and comes from two places, dietary ingestion and liver production. The liver is able to remove cholesterol from the blood as well as manufacture cholesterol and secrete it into the blood stream. The liver removes cholesterol after eating and secretes it between meals. Cholesterol cannot dissolve in the blood without attaching to lipoproteins. Cholesterol secreted by the liver is either combined with very low-density lipoproteins (VLDL) or high-density lipoproteins (HDL) producing LDL cholesterol or HDL cholesterol. LDL cholesterol is considered the bad cholesterol because at abnormal levels it can cause a risk of heart disease. LDL lipoproteins deposit cholesterol on artery walls causing a hard thick substance called cholesterol plaque. The liver removes LDL cholesterol from the blood by proteins called LDL receptors. A deficiency of LDL receptors contributes to high LDL cholesterol blood levels. When the plaque ruptures, a blood clot forms on the plaque blocking the artery and reducing the blood flow. If a clot forms in the heart the result is a heart attack.\(^1\)

Synthesis of Cholesterol

"The liver is the primary body site of beta oxidation (breakdown of fatty acids to acetyl-CoA)."\(^1\) "Acetyl-CoA and acetoacetyl-CoA condense to form $\beta$-hydroxy-$\beta$-methylglutaryl-CoA (HMG-CoA)."\(^2\)
“Enzymatic reduction of the thiol ester group of HMG-CoA reduces to a primary alcohol of mevalonic acid. The enzyme that catalyzes this step is called HMG-CoA reductase. Mevalonic acid is an intermediate and is then transferred into 3-methyl-3-butenyl pyrophosphate by phosphorylation and decarboxylation.”

3-Phospho-5-pyrophosphate

3-Methyl-3-butenyl pyrophosphate

“3-methyl-3-butenyl pyrophosphate isomerizes to produce and equilibrium mixture that contains 3-methyl-2-butenyl pyrophosphate, and these two compounds condense to form geranyl pyrophosphate. This condenses with 3-methyl-3-butenyl pyrophosphate to form farnesyl pyrophosphate.”
"Two molecules of farnesyl pyrophosphate undergo reductive condensation to produce squalene."

![Chemical structure of squalene]

"Squalene is the direct precursor of cholesterol. Oxidation of squalene yields squalene 2,3 epoxide, which undergoes a series of ring closures to yield lanosterol. Lanosterol is converted to cholesterol through a series of enzyme-catalyzed reductions."

![Chemical structures of lanosterol and cholesterol]

**Desirable and Undesirable Levels of Cholesterol**

According to the National Cholesterol Education Program (NCEP), the normal level of LDL cholesterol is <100. 100-129 is near or above normal, 130-159 is borderline high, 160-189 is high and > 190 is very high. If LDL cholesterol levels are elevated, medications such as statin drugs may be needed.

**Statin Drugs**

Statin drugs are the most widely used medications in lowering LDL cholesterol. Statins are well tolerated with low side effects when used long term. They not only lower LDL cholesterol levels, they also help increase HDL cholesterol levels. The statin medicines that are now on the pharmacy shelves used to lower LDL cholesterol include Lipitor (atorvastatin), Zocor (simvastatin), Mevacor (lovastatin), Pravachol (pravastatin) and Crestor (rosuvastatin).
How Statin Drugs Work

Statins are a class of drugs that lower the level of cholesterol in the blood by reducing the production of cholesterol by the liver. They block the enzyme in the liver that is responsible for making cholesterol. This enzyme is called β-hydroxy-β-methylglutaryl-coenzyme A reductase (HMG-CoA reductase). Scientifically, statins are called HMG-CoA reductase inhibitors. By reducing the cholesterol manufactured by the liver statins are able to reduce the formation of new plaque and can reduce the size of plaque that already exists. They also stabilize plaque and make them less prone to rupturing and forming clots. Statins not only return cholesterol to normal levels, they also prevent atherosclerosis, angina, stroke, blood clots, and death.

Differences Among Statin Drugs

Statin drugs differ in many ways. The most obvious is their ability to reduce cholesterol. Some of them are more potent than others. Statins also differ in the way they interact with other drugs. They differ in the way they reduce heart attacks and the ability to reduce death as well. Some statins are derived from natural sources and have similar chemical structures. Others are completely synthetic and have chemical structures that differ greatly from the natural statins. They differ in the frequency with which they cause rhabdomyolysis (a condition in which muscle damage occurs). The statins on the market are considered safe. If they cause rhabdomyolysis, they are taken off the market. Baycol is a statin drug that was taken off the market because of this side effect.

Side Effects Of Statin Drugs

The most common side effects are headache, nausea, vomiting, constipation, diarrhea, rash, weakness, and muscle pain. The most serious and fortunately rare effects are liver failure and rhabdomyolysis. Rhabdomyolysis begins with muscle pain; however, it can develop into muscle loss, kidney failure and death. The rare side effects happen if statins are used in combination with other drugs that increase statin levels in the blood.

Statistics Relating to Statin Drugs

According to a Pharmacy Times magazine, “An estimated 12 million Americans are currently on statins. Statins are the biggest selling class of prescription drugs in the nation, but even so, the market is far from saturated. According to some estimates, 34 million Americans have cholesterol levels that are higher than current federal guidelines, leaving an untapped market of about 24 million potential customers for statin drugs. The statin drug Lipitor, lead Unites States sales of nearly $7 billion in 2003. The second biggest seller was Zocor, adding nearly $5 billion in sales to the public’s overall statin bill, which came in at more than $15 billion.” This article suggests a promising outlook for future sales of the cholesterol lowering statin drugs Lipitor, Zocor, Mevacor, Pravachol, and Crestor.
Description of Lipitor

Lipitor (atorvastatin) blocks the body’s ability to make cholesterol and can prevent the risk of heart disease and stroke. “Lipitor is a synthetic cholesterol lowering agent.” It’s unique structure and long half-life may explain its greater LDL lowering potency compared to other HMG-CoA reductase inhibitors. The FDA approved Lipitor on December 18, 1996.” The empirical formula for Lipitor is (C33H46FN3O8)2Ca-3H2O, and the molecular weight is 1209.42. The structural formula of Lipitor is:

\[
\begin{array}{c}
\text{[R-(R*,R*)]-2-(4-fluorophenyl)-\beta,\delta-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenyl amino)carbonyl]-1H-pyrrole-1-heptanoic acid, calcium salt (2:1) cryohydrate]} \end{array}
\]

Mechanism of Action

“Lipitor is a HMG-CoA reductase inhibitor. The enzyme catalyzes the conversion of HGM-CoA to mevalonate, an early and rate-limiting step in cholesterol biosynthesis.” This, in turn, results in upregulation of LDL-receptors and increased uptake of LDL cholesterol from circulation. Lipitor ultimately reduces the levels of circulating total cholesterol and LDL cholesterol. Doses of 10-80 mg once daily result in mean LDL reductions ranging from 43-60%. Lipitor is administered orally. Following oral administration, the drug is rapidly absorbed with peak plasma concentrations occurring within 1 to 2 hours. The extent of absorption increases in proportion to the dose of Lipitor.”
Description of Zocor

Zocor (simvastatin) is a cholesterol lowering agent, which similar to Lipitor, is derived synthetically. "The FDA approved Zocor for use on July 5, 1995." The empirical formula is C_{23}H_{36}O_{3}, and its molecular weight is 418.57. The structural formula of Zocor is:

```
\begin{center}
\includegraphics[width=0.5\textwidth]{zocor_structural_formula.png}
\end{center}
```

"2,2-dimethyl-1,2,3,7,8,8a-hexahydro-3,7dimethyl-8-[2-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]-ethyl]-1-naphthalene ester"

Mechanism of Action

"Zocor is a HMG-CoA reductase inhibitor. It is a methylated form of Mevacor (lovastatin). Both Zocor and Mevacor are prodrugs and require hydrolysis for activation. The 6-membered lactone ring is hydrolyzed to generate mevinolinic acid. Mevinolinic is structurally similar to HMG-CoA. Once hydrolyzed Zocor competes with HMG-CoA for HMG-CoA reductase and the interference with the activity of this enzyme reduces the quantity of mevalonic acid, a precursor of cholesterol. Synthesis of cholesterol is then impaired causing cholesterol uptake to be augmented. Doses of 5-80 mg once daily reduces mean LDL concentrations by 26-47%. Absorption of Zocor is about 85%. Peak plasma concentrations are reached in 1.3-2.4 hours."
Description of Mevacor

"Mevacor (lovastatin) is a cholesterol lowering agent and represents the first HMG-CoA reductase inhibitor to be introduced. It was approved by the FDA in August 1987. The empirical formula is C_{29}H_{46}O_{5} and the molecular weight is 404.55. The structural formula for Mevacor is:"

```
```

"[1 S-\{1α(R^*),3α,7β,8β(2S^*,4S^*),8αβ\}]1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalene 2-n-methylbutanoate"

Mechanism of Action

The mechanism of action of Mevacor is exactly like Zocor. "Mevacor is a prodrug and is hydrolyzed to mevinolinic acid. Mevacor will compete with HMG-CoA for HMG-CoA reductase, and the interference with the enzyme reduces mevalonic acid, therefore reducing total cholesterol and LDL cholesterol. Doses of Mevacor are 10, 20, 40, and 80 mg once daily with reductions ranging from 21-42%. It is taken orally and is incompletely absorbed from the GI tract and undergoes extensive first-pass extraction in the liver. Peak plasma concentration occurs within 2-4 hours after oral administration."
Description of Pravachol

"The HMG-CoA inhibitor, Pravachol (pravastatin) was approved by the FDA in October 1991."\(^{12}\) "The empirical formula is C\(_{22}\)H\(_{32}\)NaO\(_7\), and the molecular weight is 446.52. The structural formula of Pravachol is:"\(^{1,13}\)

\[\text{1-Naphthalene-hepinoic acid, 1,2,6,7,8,8a-hexahydro-\(\beta,\delta,6\)-trihydroxy-2-methyl-8-(2-methyl-1-oxobutoxy)-, monosodium salt}"\(^{13}\)

Mechanism of Action

"In contrast to Zocor and Mevacor, Pravachol does not require hydrolysis of activation."\(^{12}\) Pravachol is efficient in lowering cholesterol in two ways. The first way is the same as Lipitor. "It will inhibit HMG-CoA reductase, the enzyme necessary for the intracellular synthesis of cholesterol. Inhibition of HGM-CoA lowers the amount of mevalonate, the precursor of sterols including cholesterol, and reduces cholesterol levels in hepatic cells."\(^{12}\) This mechanism increases LDL receptors which will increase the capture of the amount of LDL cholesterol in the blood.\(^{12}\) "Second, Pravachol inhibits hepatic synthesis of VLDL, the precursor for LDL. The result is the reduction of circulating total cholesterol and LDL cholesterol. Pravachol is administered orally with doses of 10, 20, 40, and 80 mg once daily. It is rapidly absorbed by the GI tract. Peak plasma concentrations occur in 1-1.5 hours with LDL reductions of 22-34%."\(^{12}\)
Description of Crestor

"Crestor (rosuvastatin) is a synthetic cholesterol lowering agent which inhibits HMG-CoA reductase."\textsuperscript{14} It is the newest statin drug on the market. "The FDA approved Crestor on June 10, 2002."\textsuperscript{15} "The empirical formula for Crestor is (C_{32}H_{27}FN_{3}O_{6}S)_{2}Ca, and its molecular weight is 10001.14. The structural formula of Crestor is:"\textsuperscript{14}

\begin{center}
\includegraphics[width=0.5\textwidth]{structure.png}
\end{center}

"Bis[(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino] pyrimidin-5-yl]-(3R,5S)-3,5-dihydroxyhept-6-enoic acid] calcium salt]\textsuperscript{14}

Mechanism of Action

"Crestor, because of its chemical structure binding sites and relatively greater hydrophilicity, appears to better penetrate the hepatocyte and bind to HMG-CoA reductase with a higher affinity than the other statins. This makes Crestor more potent than currently available HMG-CoA inhibitors. Crestor is administered orally in doses of 5, 10, 20, and 40 mg reducing cholesterol by 45, 52, 55, and 63% respectively with peak plasma concentration reached within 3-5 hours."\textsuperscript{15}

Conclusion

In conclusion, high cholesterol is a deadly disease and if not monitored, it can cause heart attack, stroke, and even death. An awareness of the desirable and undesirable cholesterol levels is important in maintaining a healthy life. Statin drugs are widely used and well tolerated with low side effects. The number of Americans in the Unites States with high cholesterol makes the future outlook for statin drugs promising. An over the counter statin drug could be a possibility for the future.
References

(7) *Atorvastatin*. Pfizer Ireland Pharmaceuticals. Parke-Davis Division of Pfizer Inc, NY, NY.
(9) *Simvastatin*. Merck & CO, Inc. April 2003. Whitehouse Station, NJ.
(11) *Lovastatin*. Mylan Pharmaceuticals Inc. Morgantown, WV.
(14) *Crestor*. AstraZeneca Pharmaceuticals LP 2003. Wilmington, DE.
Fructose: Sweet or Sour

Prepared for:
Dr. Hank Mancini
Chemistry Instructor

Prepared by:
Jeremy Witt

April 16, 2004
Abstract:

Fructose is used in many different types of health food sweeteners and is being consumed in too high of portions. The amount of fructose found in the average diet is higher than recommended by nutritionists and the government. New research developed facts that fructose promotes insulin resistance, impairs glucose tolerance, leads to high insulin levels, high blood pressure and can increase the risk of Type 2 diabetes. Other hormonal factors show that fructose is directly metabolized into fat in the liver and promotes disease more readily. The differences between sugars in the diet will be analyzed, along with the future of fructose.

Background:

Fructose is a simple sugar found in honey and in the fruit of plants. Fructose is also known as levulose or fruit sugar. Fructose can also be found in High Fructose Corn Syrup (HFCS), which is widely used in many foods and beverages. Most fructose is consumed into the diet in the forms of sucrose and HFCS. Most HFCS consists of 55 percent fructose blended with 45 percent glucose. 1 There are several types of sugars found in diets which include sucrose, glucose, and galactose. Fructose is the third most common sugars found in the diet. 1 Fructose and glucose are isomers of each other and they share the same empirical formula which is C₂H₁₂O₆. The difference between fructose and glucose is a ketone instead of an aldehyde as seen in figure 1. Glucose and galactose have very similar structures, and only differ in the arrangement of the hydroxyl group on the fourth carbon. Fructose looks more like glucose than galactose, but it differs from glucose by having a hydroxyl group on the first carbon, with its second carbon having the double bond with oxygen. 1

![Chemical Structures](image-url)
Glucose and fructose are carbohydrates, which are monosaccharides. Fructose can not be hydrolyzed into smaller units. Fructan, for instance, is a polysaccharide made up of a glucose molecule linked to many fructose molecules. When fructan is hydrolyzed, it will break up into simple carbohydrate units, which is glucose and fructose. When sucrose is hydrolyzed by the enzyme invertase or by heating with dilute acid, glucose and fructose will be formed in equal amounts. Fructose is obtained by hydrolysis of inulin, a polysaccharide.

Most monosaccharides that are synthesized in nature have the same stereochemical configuration at the chiral carbon farthest from the carbonyl group. The natural monosaccharides are called D-sugars, (D coming from dextrorotatory). The non-natural form is called the L-sugar, (L coming from levorotatory). D is also called right turning, and L is called left turning. Using Fisher projections, most naturally occurring sugars have the hydroxyyl group at the lowest chiral carbon pointing to the right. Only a very small percentage of the monosaccharides exist in the open-chain form with a free aldehyde or keto group. In solution the open-chain forms spontaneously form cyclic structures, in which the carbonyl group is involved. This is called the hemiacetal formation. Hemiacetal formation is an addition reaction between a carbonyl and a hydroxyl group. The reaction is catalyzed by a base or acid. In sugars the carbonyl and hydroxyl groups are both present, and can therefore form a cyclic structure. The addition of the hydroxyl group to the carbonyl group can lead to two mirror stereo configurations. These are called alpha and beta. In Fisher projections, the molecule is called alpha if the newly formed hydroxyl group on the carbonyl group is on the same side as the lowest chiral atom. If the hydroxyl group is on the opposite side, it is called beta.

**Isomeric Forms of Fructose**

![Diagram of Isomeric Forms of Fructose](image)
To determine whether fructose is a reducing sugar, a certain test can be performed. The test uses Fehling's Reagent which is Cu(NH₃)₄(OH)₂. Fehling's solution is a deep-blue, alkaline solution used to test for the presence of aldehydes. Fehling's reagent is like Tollens' Reagent, which oxidizes an aldehyde to a carboxylic acid. Simple sugars like fructose and glucose give a positive test, which identifies that a reducing sugar is present. This test can also be used to look for glucose in urine, which is a symptom of diabetes. Another test can be used to differentiate glucose from fructose. When reacting glucose with lime water, a water-insoluble precipitate will form called calcium fructosate.¹

Fructose Metabolism:

Fructose has a different metabolism than glucose. The enzyme required to initiate fructose metabolism is called fructokinase. Fructose metabolism begins with phosphorylation by fructokinase. Fructokinase is only found in the liver. Fructose carbon enters the glycolytic pathways at the phosphate level which consist of dihydroxyacetone phosphate and glyceraldehydes-3-phosphate.² Fructose bypasses the major control point by which glucose carbon enters glycolysis. This allows fructose to serve as an unregulated source of both glycerol-3-phosphate and acetyl-CoA.² Fructose is not a direct energy source for other tissues as glucose. Fructose metabolism is not controlled like glucose. This results in an increased synthesis of lipids and increased serum lipoproteins. When fructose is metabolized it creates the following products: glucose, glycogen, lactate, and pyruvate.³ Fructose consumption results into a large increase of circulating lactate than it does for the comparable amounts of glucose.

![Fructose Metabolism Diagram](Image)

When large amounts of fructose are consumed be high fructose corn syrup sweetened beverages, a triacylglycerol product is facilitated because fructose continues to
enter the glycolytic pathway and produce phosphofructokinase. In glucose metabolism the uptake of glucose is negatively regulated at the level of phosphofructokinase. Unlike glucose metabolism, high concentrations of fructose can serve as a relatively unregulated source of acetyl-CoA(2). Fructose does not stimulate the product of the two key hormones which is insulin and leptin. Insulin and leptin are involved in the long term regulation of energy. Therefore, large consumptions of high fructose corn syrup will lower energy levels and have long term effects due to the lack of insulin and leptin.  

In solution, fructose exists as a ring compound in equilibrium with a straight chain form. Carbons one and six are not involved in the central ring, and this effects both intestinal uptake and metabolism of fructose. Fructose is not handled as other monosaccharides in the body. Fructose is 30-40% sweeter than table sugar or sucrose. The increased sweetness of fructose is a feature of the 5-ring. When fructose in solution is heated to a higher temperature, it changes to a 6-ring form. When baking foods or drinking tea and coffee, fructose loses its sweetness and has a form similar to sucrose. This equilibrium can be represented with the alpha and beta forms. Furanose is a 5-ring form which is in equilibrium with the pyranose 6-ring form. The equilibrium reaction speeds up as the temperature increases. The pyranose forms of fructose are not sweeter than table sugar, and one must use just as much fructose as sucrose in warm drinks and baked goods if equal sweetness is desired.

Health Effects of Fructose:

Many people believe that they do not consume large amounts of fructose. The truth is that they consume more than they think. Fructose is hidden in the food that is eaten everyday. Fructose can be found in foods like potato chips, yogurt, breads and through the HFCS and sucrose in processed foods. There are many reasons why high fructose corn syrup is used in today’s foods. From the standpoint of food manufacturing, HFCS is: much sweeter than sucrose, easier to handle during processing, has a longer shelf life, and is cheaper than sucrose. HFCS may be better than sucrose for manufacturing, but it is not any better for health when consumed in larger portions than necessary. The body can not handle such large quantities of sugar, particularly fructose. Recently more research is being performed to prove that fructose poses a health hazard.

A recent study from the American Journal of Clinical Nutrition examines how fructose promotes insulin resistance, impairs glucose tolerance, leads to high insulin levels, high blood pressure and can increase the risk of Type 2 diabetes. Other hormonal factors show that fructose is directly metabolized into fat in the liver and promotes disease more readily. High fructose consumption has also been a factor in heart disease. It raises blood levels of cholesterol and another type of fat, triglyceride. It makes blood cells more prone to clotting, and it may also accelerate the aging process. A little fructose will not hurt your body, but fructose is needed to perform
everyday functions. Many people do not know the limit of how much should be consumed, which is why there is many growing problems that need more extensive research.

Fructose has been touted for years as a safe sugar for diabetics because it does not trigger a rapid rise in blood sugar. On the contrary, the cardiovascular consequences may outweigh the benefits for diabetics, who already face a higher than average risk of developing heart disease. In a recent study, 18 Type I (insulin-dependent) and Type II (nonsulin-dependent) diabetics were laced on two diets. The first diets contained carbohydrate as starch, which is digested as glucose, and the other contained carbohydrate as fructose. When they consumed the fructose, the diabetics had fewer spikes in blood sugar levels. On the other hand, the diabetics' total cholesterol rose an average 7 percent, and their low-density lipoprotein cholesterol rose almost 11 percent. The fructose increased their risk of heart disease.

In another study with non-diabetic people, similar effects were found. With 14 healthy volunteers, a high-fructose diet was consumed. With the fructose diet, the subjects' total cholesterol levels increased by 9 percent and their low-density lipoprotein cholesterol increased by 11 percent. With the added fructose to the typical American high-fat diet, the risk of heart disease increases even more. Sheldon Reiser, Ph.D., of the U.S. Department of Agriculture's Human Nutrition Research Center studied 21 men eating two kinds of high-fat diets. The diets were the same except for the carbohydrate. The first carbohydrate was simple starch, the other used fructose. The cholesterol and triglyceride levels of all the men increased while they consumed the high-fructose/high-fat diet, but not while they ate a high-starch/high-fat diet.¹

From a study done by Thrombosis Research, fructose promotes abnormal clotting much more than any other common sugar does. Recent research by Forrest Nielsen, Ph.D., of the USDA's Human Nutrition Research Center, found that fructose interferes with absorption of copper, an essential mineral needed to create hemoglobin in red blood cells. With a high intake of high-fructose corn syrup, people might show signs of a copper deficiency and may need to take more copper.

Conclusion:

Fructose will continue to be found in different types of health foods sweeteners for a while. The problem is not directly with fructose, but the fact that it is being consumed in too high of portions. Much of the high consumption is due to hidden fructose in foods. Since fructose is used as a sugar preservative, and a strong sweetener, it is found in many different types of food. The amount of fructose found in the average diet is much higher than recommended by nutritionists and the government. The amount of sweeteners consumed increased by 22% from 1970 to 1995. Cane and beet sugar declined in the 1980's due to high fructose corn syrup being added to beverages and baking goods. With fructose consumption on the rise there will be health related consequences for eating too much.
New research developed facts that fructose promotes insulin resistance, impairs glucose tolerance, leads to high insulin levels and high blood pressure, and increases the risk of Type 2 diabetes. Other hormonal factors show that fructose is directly metabolized into fat in the liver and promotes disease more readily. These short-term studies showed that fructose was responsible for adverse health effects. When more research is done on the long-term effects of fructose the health effects may be totally different. The future of fructose will depend on more research proving that it is truly harmful to the body. Up to this point in time, the food and drug administration finds that fructose and high fructose corn syrup are totally safe to consume in proper amounts.

Fructose is sweeter than sucrose, and is being substituted in place of sucrose for this reason. There are a lot more different sweeteners that are sweeter than fructose like splenda, neotame and aspartane. The sweeter the compound the less of it is needed to add to food and beverages. The problem facing researchers is finding a sweetener with the cheapest cost, lowest health affects, and lowest calories. There are more sweeteners on the horizon, and they may replace fructose overall, just as fructose has started to substitute sucrose.
Bibliography


Rohypnol
The Date Rape Drug

Prepared for
Dr. Hank Mancini
Organic Chemistry 236 Instructor
Paradise Valley Community College

Prepared By
Bertina Bedah Yellowhair

April 16, 2004
Abstract

This report will cover the drug known as Rohypnol (Flunitrazepam). It will talk about the background, pharmacodynamics, pharmacokinetics, and some of its adverse effects on individuals. This paper will also discuss predictions about the future of the drug.

I. Introduction

In recent years date rape incidences have been on the rise. The perpetrators committing these crimes have used prescription drugs on their victims as a weapon to carry out their crime. As a result, the misuse of the drugs has increased; therefore, date rape has increased. The drugs most commonly used are the benzodiazepines.

<table>
<thead>
<tr>
<th>TABLE: Drugs Used to Facilitate Sexual Assault</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol (in fruit drinks, beer, wine, spirits)</td>
</tr>
<tr>
<td>Alprazolam</td>
</tr>
<tr>
<td>1,4 Butanediol (BD)</td>
</tr>
<tr>
<td>γ-Butyrobutyric acid (GBL)</td>
</tr>
<tr>
<td>Cannabis</td>
</tr>
<tr>
<td>Chloral hydrate</td>
</tr>
<tr>
<td>Cinazepam</td>
</tr>
<tr>
<td>Diazepam</td>
</tr>
<tr>
<td>Flunitrazepam (Rohypnol)</td>
</tr>
<tr>
<td>γ-Hydroxybutyric acid (GHB)</td>
</tr>
<tr>
<td>Ketamine</td>
</tr>
<tr>
<td>Meprobamate</td>
</tr>
<tr>
<td>Midazolam (Versed)</td>
</tr>
<tr>
<td>Oxazepam</td>
</tr>
<tr>
<td>Phencyclidine (PCP)</td>
</tr>
<tr>
<td>Scopolamine</td>
</tr>
<tr>
<td>Secobarbital</td>
</tr>
<tr>
<td>Temazepam</td>
</tr>
<tr>
<td>Triazolam</td>
</tr>
<tr>
<td>Zolpidem</td>
</tr>
</tbody>
</table>

Table 1.

The benzodiazepines are among the most frequently prescribed drugs for the treatment of sleep disturbance and anxiety, and can be used as tranquilizers. They act on the central nervous system (CNS), by inducing a "sedative-hypnotic, muscle relaxant, anxiolytic and anti convulsive effects, as well as cognitive impairment (eg., psychomotor, subjective effects, and memory)." A benzodiazepine now growing in popularity as the date rape drug of choice is Flunitrazepam or Rohypnol.

II. Background

Flunitrazepam was first introduced in 1975, in Switzerland, with the brand name Rohypnol. Since its introduction it has been marketed in 80 countries and has been prescribed for over 200 million treatments of insomnia and as a preoperative anesthetic. This drug is manufactured in Europe and Latin America. It is not sold or prescribed in Canada or in the United States. Despite it being banned in the United States, it has made
its way into the country through smuggling. Findings and use of the drugs have been reported in Florida, Texas, and California. This has lead to the US Drug and Enforcement Administration to place Flunitrazepam into Schedule I of Controlled Substance Act of 1970, which allows prosecution of any person(s) who sells or manufactures the drug. The drug is reported as being used at parties, nightclubs, and rave dances. Some street names for Flunitrazepam include Mexican Valium, circles, roofies, la rocha, roche, R2, “rope” and forget-me pills. Rohypnol is sold in 1 and 2 mg tablets and has a street value ranging between $0.50 to $5.

III. Structure

![Chemical structure of Rohypnol](image)

**Flunitrazepam (INN); Rohypnol**
7-a-methyl-5-(2'-thiomephenyl)-1,3-dihydro-1-methyl-(CH)-1,4-benzodiazepine-2-one

C$_{16}$H$_{12}$F$_{1}$N$_{2}$

m.wt. 313.3

CAS-no. 1622-62-4

pKa 1.82 [5,21]

Solubility in water 6.0 µg/ml (pH 7.4, 37°C) [14]

Figure 2. Chemical characteristics and metabolic pathways of flunitrazepam.

The Rohypnol compound contains two aromatic rings connected to a cycloheptane. The presence of the nitro group at C-7 of the Rohypnol molecule and the α-fluoro substituent of the phenyl group at C-5 is known to contribute to the enhanced hypnotic effects of Rohypnol compared to the other benzodiazepines.

III. Pharmacodynamics

Rohypnol affects the brains synaptic processes through the central nervous systems neurotransmitter known as γ-aminobutyric acid (GABA). The synaptic process involves the transmission of the nerve impulses to the neurons. The neurons then in turn send the impulses to the effector cells. The effector cells include the cells of the organ, gland, and muscle. These cells are activated by an impulse leading to the desired physiological effect.

GABA is the brain major inhibitor of neurotransmission. Their are three different GABA receptors: GABA$_{A}$, GABA$_{B}$, and GABA$_{C}$. The three GABA receptors have different chemical structures and serve different functions. GABA$_{A}$ is coupled to a
chloride channel, GABA_\textsubscript{A} is coupled to cationic channels (K^+, Ca^{2+}) via G-proteins and second messenger systems, and GABA_\textsubscript{B} are chloride channels.\footnote{Cl\textsubscript{ions}} Chloride channels allows negatively charged Cl\textsubscript{ions} to enter the neurons and lower the resting membrane potential (hyperpolarization), resulting in a less excitable tissue and decreased neuronal function.\footnote{Cl\textsubscript{ions}} GABA_\textsubscript{A} receptors are the most common CNS receptors because they have many available binding sites for flunitrazepam.\footnote{Cl\textsubscript{ions}} When GABA_\textsubscript{A} is released it “blocks the arousal of higher brain centers.” Rohypnol, increased the force of attraction between GABA_\textsubscript{A} to its receptors, causing the nervous system to become less stimulated, leading to a decrease in anxiety and alertness.\footnote{Cl\textsubscript{ions}} Rohypnol also alters peptide chain formation of certain neurons, which leads to memory loss.\footnote{Cl\textsubscript{ions}}

V. Pharmacokinetics

In clinical settings when Rohypnol is administered orally or intravenously at 0.5-2mg doses it is absorbed quickly and almost completely.\footnote{Cl\textsubscript{ions}} Rohypnol is first metabolized in the liver where 85-90% of it becomes available to the physiological system. The onset of action depends on how quickly the gastrointestinal tract absorbs the drug.\footnote{Cl\textsubscript{ions}} Rohypnol is then absorbed by the brain and is distributed through the central compartments. This distribution lasts up to 20 h, with an initial half-life of 2-4 h. “After a single oral dose of 2mg, plasma peaks of 8.8 ± 3.0 ng/ml” of flunitrazepam “occur 1.90 ± 1.38 h after administration.” Ninety-five percent of Flunitrazepam administered intravenously showed attachment to plasma proteins. Flunitrazepam that was administered orally was detected in plasma and blood,\footnote{Cl\textsubscript{ions}} with a higher concentration in plasma. Based on this the therapeutic plasma range for rohypnol is 0.005-0.015 mg/L. These levels may be exceeded with patients with chronic therapy, dysfunctional liver or kidney, and those who have developed tolerance. The duration of action of flunitrazepam depends on half-life of the drug, rate of metabolism, the formations of active metabolites and the rates of brain distribution.\footnote{Cl\textsubscript{ions}} Table 2\footnote{Cl\textsubscript{ions}} shows more pharmacokinetics of oral and intravenous Flunitrazepam.

<table>
<thead>
<tr>
<th>Pharmacokinetics of Oral Flunitrazepam (14-16, 23, 27, 30, 31)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Absorption</strong></td>
</tr>
<tr>
<td><strong>Bioavailability</strong></td>
</tr>
<tr>
<td><strong>Plasma peaks</strong></td>
</tr>
<tr>
<td><strong>Plasma elimination half-life</strong></td>
</tr>
<tr>
<td><strong>Distribution</strong></td>
</tr>
<tr>
<td><strong>Plasma protein binding</strong></td>
</tr>
<tr>
<td><strong>Blood-to-plasma ratio</strong></td>
</tr>
<tr>
<td><strong>Plasma clearance</strong></td>
</tr>
</tbody>
</table>

Table 2\footnote{Cl\textsubscript{ions}}

<table>
<thead>
<tr>
<th>Pharmacokinetics of Intravenous Flunitrazepam (17)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Plasma elimination half-life</strong></td>
</tr>
<tr>
<td><strong>Distribution</strong></td>
</tr>
<tr>
<td><strong>Plasma clearance</strong></td>
</tr>
</tbody>
</table>
The chemical alteration of Rohypnol within the body occurs through biotransformation in the liver. Three major biotransformation reactions that occur are \(N(1)\)-desmethylation, \(C(3)\) -hydroxylation, \(O\)-glucuronidation. Biotransformation occurs readily at \(N\)-demethyl and hydroxylation at the carbon 3 and the reduction of carbon 7 occur slowly. 45

A process known as glucuronidation can stop the biotransformation of these substances. Glucuronidation is a conjugation reaction that displaces "uridine diphosphate (UDP) from uridine diphosphate-\(\alpha\)-D glucuronate (7, UDP-GA)." The 7-UDP-GA is a derivative of UDP-glucose. The glucuronidation reaction is similar to a SN2 displacement reaction "because it involves inversion of configuration at the anomeric carbon (C-1) of the glucuronate (GA) moiety." The \(O\)- and \(N\)-glucuronides have the \(\beta\) configuration and not the \(\alpha\) configuration like the UDP-GA. 5

The GA of the UDP-GA comes from the oxidation of glucose on the UDP-glucose molecule. The \(-\text{CH}_2\text{OH}\) group at C-5 of the UDP-glucose is oxidized to a carboxylic group and is later ionized to \(-\text{COO}\text{-carboxylate}\). The carboxylate group at \(\beta\)-D-\(O\)-glucuronide and \(\beta\)-D-\(N\)-glucuronide increase the solubility, which helps in excretion of rohypnol through the liver. 5

---

Figure 1. Biotransformation pathways of Rohypnol (5, 39).

Figure 3. Biotransformation Pathways of Rohypnol 5
VI. Affects and Future

Figure 4a,4 Figure 4b,4 Plasma levels of oral and intravenous flunitrazepam versus sedative effects
Figure 5,4 Correlation between plasma concentration and ability to concentrate.

After examining the pharmacokinetics and pharmacodynamics of the drug it has been determined that there is considerable correlation between impairment and memory and the use of the drug. Flunitrazepam can cause anterograde amnesia,13,14 which is "lack of memorization by the individual from the time of administration of the drug (parenteral) or after adequate absorption of the drug (oral)."14 But there is no affect on previous memory. This may be the reason this is becoming the drug of choice or date rape. Flunitrazepam is also known to cause muscle relaxation, drop in blood pressure, increase in heart rate, and a euphoric feeling. When taken alone it has not been proven to be deadly.4

When flunitrazepam is combined with alcohol it is known to increase intoxication.6 It can also increase the effects of amnesia and loss of inhibition. Some other effects that have been observed with concurrent use of alcohol, in clinical studies, include "hypotension, dizziness, confusion, visual disturbance, urinary retention, and in some users aggressive behavior."7 Some withdrawal symptoms include headache, tension, extreme anxiety, restlessness, muscle pain, photosensitivity, numbness, tingling of extremities, and seizures.7

Some common methods of a detection for rohypnol are spectrophotometry, electrochemical methods, liquid chromatography, capillary electrophoresis, gas chromatography, and thin layer chromatography. All these methods are considered as time consuming, tedious, and lack specificity.6 Detecting rohypnol through urine samples has not been easy either. This is due to the fact that rohypnol is a "faster clearing benzodiazepine."4 This creates a problem in many date rape cases because the victims report the crime too late, and often do not remember right away what has happened to them.11

The company, F. Hoffman-LaRoche Ltd. that manufactures the drug has taken new measures to stop date rape before the victims are slipped the pill. These measures include changing the shape, color, coating, marking of the pill. It has also added a dye to the pill to give clear beverages a blue color and adds a haziness to colored beverages.13
VII. Conclusion

Drugs always have a potential for abuse. Based on the research I have done on this drug I am glad to see that it is banned in the United States. I believe when a drug is used for its intended purposes such as in clinical settings it is a helpful and I have no objections for its uses. But when it is used to commit crimes it is unfortunate. I think this drug will continue to be banned in the United States but I don’t think it will stop it from being smuggled unless we find a better method of detection and have harsher punishments for the abuse and distribution of the drug. I think that because there are many other drugs in benzodiazepine family that can perform similar functions as the drug that it could eventually be replaced by one that is better regulated.
References

(1) Schechter, M. D. Pharmacology Biochemistry and Behavior 1993, 59, 19-25
(2) Hindmarch, I., Brinkmann, R. Human Psychopharmacology: Clinical & Experimental 1999, 14, 225-231
(3) Schwartz, R. H., MD, Meteer, R., MD, Lebeau, M. A., MS Southern Medical Journal 2000, 93, 558-561
(4) Benzodiazepines and GHB Humana Press: Totowa, 2001; p 1-16
2003, 31, 1185-1189
(5) Labianca, D. A. Journal of Chemical Education 1998, 75, 719-722
(7) Bakavoli, M., Kaykhah, M. Journal of Pharmaceutical and Biomedical Analysis
Namenda

Timothy Youkhana
April 16th, 2004
Organic Chemistry 236
Dr. Hank Mancini
Abstract: Since the discovery of the debilitating disease of Alzheimer’s in 1906, science has struggled to find a method to treat patients with the ailment. One of the worst symptoms of AD is severe long-term memory loss, which was found in moderate to severe phases in the dementia. One drug that has been FDA approved to treat this moderate to severe phase memory loss is Namenda, or also known as its generic name, memantine HCL.

Drug Description: Memantine is an oral, non-competitive antagonist at N-methyl-D-aspartate (NMDA) receptors. It is being studied for the treatment of moderate to severe Alzheimer’s disease (AD) and in the treatment of mild to moderate vascular dementia. Pivotal placebo-controlled trials have been completed for the AD indication. Memantine’s chemical formula is C_{12}H_{21}N with a molecular weight of 215.76. Its chemical name is 1-amino-3,5-dimethyladamantane^1.

When first synthesized by Eli Lilly in the 1960’s, it was thought to be a potential anti-diabetic agent; however, it was ineffective at lowering elevated blood sugar^2. When tested for CNS activity, it tested positive and further research showed its relationship to prevention of memory loss.

Memantine would be the first therapy approved for the more advanced stages of AD when difficulty with daily activities, behavioral problems and caregiver burden become significant. It may have neuroprotective effects due to a novel mechanism of action distinct from the currently available cholinergic therapies for AD. Memantine has also been investigated for dementia syndromes due to AIDS, cerebral ischemia and neuropathic pain associated with diabetes. The investigations for neuropathic pain use however, have not been positive according to controlled trial data. Memantine has been marketed in Germany since the 1980’s for the management of dementia and the drug itself has been available for treatment of moderate to severe AD in the European Union since June of 2002. The FDA finally approved memantine for the treatment of moderate to severe AD on October 17, 2003. Although it has been in use in Germany since the 1980’s, research on its effectiveness has not been required until the FDA approved it in the United States. This research may show the overall potential that memantine has to offer on helping with patients in the moderate to severe stage of Alzheimer’s.
a) Model of the NMDA receptor. The NMDA receptor is where the memantine molecule’s mechanism of action takes place.

Mechanism of Action: Glutamate Activation at the NMDA receptor is needed for learning and memory processes in the brain. There is evidence that the chronic excitatory activity of the neurotransmitter L-glutamate may play a role in the demoting property of AD and other neurological disorders. Glutamate, the dominant excitatory amino acid in the brain, (shown in the lower right side of the illustration) stimulates the NMDA receptors, which in turn leads to increased intraneuronal concentrations of calcium. Excessive glutamate in the CND can lead to neuronal damage. This flooding of glutamate is the main source of concern for patients with AD, and causes memory loss. For example, persistently elevated synaptic glutamate levels during hypoxia and ischemia can lead to cell death due to excess calcium influx via NMDA receptor channels. Under normal resting conditions, NMDA receptor channels do not allow chronic calcium influx because they are blocked by magnesium. Depolarization of the membrane allows the calcium to bypass the magnesium blockade, and influx through the NMDA receptor channels.

Because memantine is an antagonist at the NMDA receptor sites, it has a low-moderate affinity for the receptor. Blockade of the NMDA receptors by memantine slows the intracellular calcium accumulation and helps to prevent further nerve damage, thus causing less memory loss. A low affinity antagonist like memantine may prevent excitatory amino acid neurotoxicity without interfering with the physiological actions of glutamate required for memory and learning. High affinity NMDA antagonist such as ketamine and dextromethorphan, are associated with excessive psychotomimetic effects at dosages needed for dementia treatment.

Although memantine does affect neurotransmitter receptor sites, it does not affect the release of dopamine or serotonin. Studies demonstrate that memantine lacks affinity for most serotonin receptor subtypes such as muscarinic acetylcholine, alpha and beta adrenergic, dopaminergic, histaminic, and glycine receptors.

![Chemical structure of memantine HCl](image)

Chemical structure of memantine HCl

Pharmacokinetics: Memantine is administered orally and is rapidly and completely absorbed with 100% bioavailability. Food does not alter the extent of absorption either and may be taken with or without food. The pharmacokinetics of memantine is linear in
the range of 5-40mg single oral doses. The time to maximal concentration ranges from 4-6 hours. The serum concentration of memantine is roughly double that found in the cerebrospinal fluid, or CSF. It rapidly crosses the blood brain barrier and can be detected in the CSF within 30 minutes of an IV infusion.

Memantine undergoes little metabolism and is primarily (75-90%) excreted unchanged in the urine. The remaining 10-25% of memantine is converted to the inactive metabolites, memantine N-glucuronate conjugate and 6-hydroxy memantine. Increases in urinary pH may decrease the elimination of memantine, resulting in drug accumulation and the potential toxicity. Renal clearance can drop to roughly 65% under urinary alkaline conditions. Alternatively, acidification of the urine may increase the elimination of memantine. The extended half-life of memantine is 60-80 hours.

Memantine did not produce any psychological or physical dependence when administered to 2,504 patients. There was no evidence of drug-seeking behavior or withdrawal symptoms. The effectiveness of memantine does not appear to be reliant upon age of the patient. When gender was taken into consideration, females had about 45% higher exposure than males did. When body weight was taken into account, there was no difference in exposure to the medication.

Dosages: Among the adults and elderly patients, memantine HCl should be prescribed as one 5 mg tablet once daily. The initial dosage is titrated slowly over weeks. At this time, increase the dose by 5mg for each week over a 3-week period to a target dose of 10 mg twice daily at week 4. In studies, it has taken roughly 15 days to reach steady state plasma concentrations. Periodic evaluation of the patient may be helpful to decide on the treatment duration. The maximum dosage for adults and elderly patients is no more than 20 mg per day. The study has not been conducted amongst the effect of memantine on adolescents nor children so there is no dosage pattern established.

Over dosage: When 400 mg of memantine was administered to a patient, they experienced restlessness, psychosis, visual hallucinations, somnolence, stupor and loss of consciousness. The patient did however recover without permanent damage.

Contradictions and Precautions: There is definite contradictions with memantine if the patient is breast-feeding, a child, or has renal failure. Suspected precautions with taking memantine are with the elderly, if the patient is pregnant, have renal disease, renal impairment, seizure disorders or experiences seizures. The dosing procedure of memantine is an on an escalating dose, and thus caregivers should be instructed on this procedure. Patients with renal impairment or renal disease leading to renal impairment may be at risk for accumulation of memantine resulting in toxicity. Memantine is eliminated primarily by the kidneys with a half-life of 60-80 hours. Dosage adjustments are not needed in patients with mild to moderate renal impairment; dose adjustments are required with severe renal impairment and memantine should not be prescribed to patients with renal failure at all. The elderly may be at greater risk for renal impairment due to age-related changes in renal function, concomitant medications or other risk factors. Memantine is partly eliminated via renal tubular secretion and thus may be susceptible to drug interactions involving these processes. Cationic drugs that are
eliminated by renal tubular secretion may compete with memantine for common renal tubular transport systems, thus possibly decreasing the elimination of one of the drugs. Although many interactions are theoretical, careful patient monitoring of response to memantine and the potentially interacting drug is recommended to assess for needed dosage adjustments.

There have not been any studies of memantine used in pregnant women and memantine should only be used during pregnancy if the potential benefit justifies the potential risk to the fetus.

Interactions: Memantine reacts with several amounts of medications ranging from morphine to metformin. Another drug memantine interacts with is triamterene and hydrochlorothiazide (HCTZ). Triamterene is a drug excreted in part by renal tubular secretion. At normal doses, the combination of HCTZ, triamterene did not alter the bioavailability of memantine at steady state. Memantine did not affect the bioavailability of triamterene either; however, it did reduce the effectiveness of HCTZ by roughly 20%, however the significance of the loss of effectiveness is unknown. Other cationic drugs known to undergo renal tubular (RT) secretion include adeovir, amiloride, cimetidine, digoxin, doxetilide, midodrine, morphine, procainamide, quinidine, quinine, ranitidine, trimethoprim, or vancomycin. These drugs may decrease memantine elimination or vice versa, by competing for common RT transport systems.

Amantadine, dextromethorphan and ketamine are also NMDA antagonists, and may lead to additive adverse effects if combined with memantine. Until further data is available, it may be prudent to the patient to avoid coadministration of either with memantine.

Adverse Reactions: -agitation -fatigue
-back pain -hallucinations
-confusion -headache
-constipation -hypertension
-cough -infection
-diarrhea -insomnia
-dizziness -nausea/vomiting
-drowsiness -toxic epidermal necrolysis
-dyspnea -urinary incontinence

In general, memantine is very well tolerated amongst individuals. In a controlled trial, adverse effects were found commonly within the placebo and memantine groups (84% in memantine and 87% in placebo). The most common reactions occurring in at least 10% of the study patients were agitation, urinary incontinence, urinary tract infection, insomnia, and diarrhea. Agitation seems to be more controlled in patients receiving memantine as opposed to placebo. While the study was being conducted however, there were seven deaths. Whether the deaths were caused by the memantine was uncertain however. All other adverse reactions occurred in less than 10 percent.
The manufacturing process is conducted through a series of refluxing and cooling. Here is a direct copy of the reaction needed to create memantine taken from the Pharmaceutical Manufacturing Encyclopedia:

**Raw materials:**

- 1,3-Dimethyladamantane
- Acetonitrile
- Sodium hydroxide
- Bromine
- Sulfuric acid
- Hydrogen chloride

**Manufacturing Process:**

A mixture of 24 g of 1,3-dimethyladamantane and 80 ml of bromine was refluxed for 6 hours. The reaction product mixture was cooled, taken up in about 200 ml of chloroform, and poured onto ice. The excess bromine was removed by adding sodium hydrosulfite. The chloroform layer was separated from the aqueous layer, dried, concentrated in a vacuo, and distilled at reduced pressure to yield 30.5 g of product having a boiling point of 118 degrees C. The product was identified by NMR and elemental analyses as 1-bromo-3,5-dimethyladamantane.

A mixture of 20 g of 1-bromo-3,5-dimethyl adamantane, 75 ml of acetonitrile, and 150 ml of concentrated sulfuric acid was allowed to react overnight at ambient room temperature. The red reaction product mixture was poured over crushed ice, the white solid that precipitated was taken up in benzene, and the benzene solution dried over sodium hydroxide pellets. The benzene solution was filtered from the drying agent and evaporated to dryness in vacuo to yield 18.2 g of product having a melting point of about 97 degrees C and identified by IR to as 1-acetamido-3,5-dimethyladamantane.

A mixture of 18 g of 1-acetamido-3,5-dimethyladamantane, 38 g of sodium hydroxide and 300 ml of diethylene glycol was refluxed for a period of 6 hours. The reaction product mixture was cooled and poured onto about 2,000 ml of crushed ice. The basic solution thus obtained was extracted five times with 250 ml portions of benzene and the aqueous layer was discarded. The combined benzene extracts were dried over sodium hydroxide and the dried benzene solution concentrated in vacuo to give a crude oil weighing 14 g. A 4 g sample of the crude oil was dissolved in ether and the solution saturated with anhydrous hydrogen chloride. The solid that precipitated was filtered off and re-crystallized from a mixture of alcohol and ether to yield product weighing 3.5 g and melting at 258 degrees C. It was identified by analysis as 1-amino-3,5-dimethyladamantane hydrochloride.  

A company called Merz introduced the first public release of memantine in 1983 to the European nation. Although memantine HCl has just recently been available in the United States this past year, the European pharmaceutical industry has been selling the product for more than 20 years now. Its ability to relieve the memory loss in Alzheimer’s disease patients has been tested and approved by the FDA. Although memantine retards the memory loss process in AD patients, it has not been found to reverse the effects of memory loss completely. It is being studied however to see if it can be used with patients
with early signs of dementia, if so, it may be prescribed with other early AD sign
medications to lessen the harsh effect AD has on the nervous system. This drug still
requires further research to express its full potential.

Overall, I believe that memantine does help in the prevention of further memory
loss in AD patients, however, the studies conducted upon it seem somewhat shaky. The
basis of a 52-80% non-metabolized drug in the urine is very misleading and probes the
question of “Is that non-metabolized portion effective or useless material that is
discarded?” Although memantine does offer an optimistic approach in slowing memory
loss, its foundation is not supported by factual evidence. Even though it has been sold in
Europe for more than 20 years now, the future of memantine may be shaky since more
and more research is being conducted to see if it’s truly a possible drug used to cure a
once hopeless disease. The market analyses however differ from my opinion as shown in
this graph:

The “Market to treat Alzheimer’s disease” shows the potential sales of memantine and
other drugs in the next 10 years. Memantine sales are shown in the middle range in each
bar of the graph. The expected growth of memantine alone seems extremely optimistic in
the fact that everything goes as planned and all research conducted proves memantine to
be one of the key agents in preventing memory loss in moderate to high AD patients. In
a recent study however, the combination of memantine with another Alzheimer’s
disease medication called Aricept, has shown improved scores on thinking tests, thus
adding more evidence that memantine may help more with intellectual functioning than
first suspected. I believe that one of these days a cure will come for Alzheimer’s disease,
and memantine will be considered as one of the forefathers of the discovery.
Bibliography

Cited sources:


Non-Cited References:


HERMANSKY-PUDLAK SYNDROME

A TRIAD OF DEFECTS \(^{(1),(2)}\)

Prepared for
Professor Hank Mancini
Chemistry Instructor
Paradise Valley Community College

Prepared by
Rosanna Diana Zvonek

April 15, 2004
ABSTRACT

This article pertains to an autosomal recessive disorder called Hermansky-Pudlak Syndrome (HPS) first diagnosed by Dr. Hermansky and Dr. Pudlak.\(^6\) The three primary characteristics of HPS are oculocutaneous albinism, low platelet dense bodies, and hemophilia. There are a multitude of causes regarding the affects of HPS; therefore, the disease has been categorized into seven types, HPS 1 through HPS 7.\(^7\) Due to the various pathways that produce the disabilities of HPS, there have not been any specific conclusions or resolutions for any of the HPS types; therefore, this paper will focus primarily on research involving HPS 4. HPS 1 and HPS 4 have the highest degree of similarities between all of the HPS Types.\(^2\),\(^3\) Hermansky-Pudlak Type 4 involves the destruction of three major organelles: melanosomes which produce melanin, giving pigment, lysosomes (which are enzymes that breakdown lipids) and storage pool disorders which control blood coagulation.

I. INTRODUCTION

Hermansky-Pudlak Syndrome is a genetic disorder brought to the attention of Dr. Hermansky and Dr. Pudlak, when a male and female were presented to the doctors with similar characteristics. Although there was no relationship between either of the patients they both displayed signs of ocular dysfunction, albinism, bleeding diathesis and pulmonary disorders which was the cause of and early death for both patients.\(^4\),\(^6\) Because HPS is a genetic disorder both parents must be heterozygous for the recessive allele to reproduce a homozygous carrier for HPS. Currently the largest population of HPS victims resides in Puerto Rico, although the roots of HPS have been traced back to Spain.\(^4\)

Of the seven different types of HPS, Type 4 is diagnosed due to the three major organelles that are affected: lysosomes, melanosomes, and platelet dense bodies. The lysosomes are overcome with an excessive buildup of celloid tissue throughout the body.\(^1\) Once the celloid buildup attacks the lungs, pulmonary fibrosis sets in becoming the cause of death for the majority of HPS victims. Melanosomes, which assist in pigmentation, are affected by tyrosinase, an enzyme that depletes melanin causing both ocular dysfunction and albinism. All HPS 4 victims are diagnosed as TY-OCA (tyrosinase oculocutaneous albinism) positive.\(^1\) Platelet aggregation is hindered causing disruption in blood coagulation; therefore, hemophilia becomes the effect.

Although there is no cure for HPS, there are precautions and medications that assist in the comfort and extension of the life of the victim. There are ongoing clinical studies in progress requesting volunteers to assist in the research for locating what exactly disrupts normal vesicle trafficking of proteins which is the cause of the defects that HPS maintains. There are also many assistance programs for patients and families dealing with Hermansky-Pudlak Syndrome.
II. GENETICS / STATISTICS

The chances of reproducing offspring with HPS are rare here in the central United States; however, in Puerto Rico the number of heterozygous carriers is 1 in 21 causing a frequency of HPS victims to be 1 in 1800. \(^1\) There is also a small Swiss village in which the gene for HPS dominates the population. It is necessary to have two parents which are both heterozygotes, each parent carries one gene, for a recessive allele. As a homozygote for HPS the offspring has obtained an identical recessive allele, (mutated gene) from each parent. Because of the biological background there is only a 25% chance for two heterozygote carriers of the HPS gene to produce a homozygous carrier, which is increased through reproduction within the same family.\(^2\) Interbreeding is a common practice in many countries other than the United States, therefore the number of HPS victims in the U.S is rather low, approximately 400.

The recessive allele transferred from each parent produce genes which hinder the production and transport of vesicle and organelle trafficking.\(^3\) The alleles which determine characteristics for an offspring are located on each of one of the homologous chromosomes received from the parents. The chromosome affected by HPS 4 is chromosome 22.\(^4\) HSP 4 also contains 13 exons with mutation in both the heterozygous and homozygous amino acid chain sequences in the areas: Q698insAAGCA, A631X, Q181X, and A316.\(^5\) Additional research performed by doctors Anderson, Claassen, Huizing, White and Gahi reveal that HPS 4 produces a chain of 708 amino acids with a difference of 5 more expressions in the forward N-terminus versus the reverse N-terminus.

III. CLINICAL

There are three lysosome organelles indirectly affected by the HPS 4 mutation: platelets, melanosomes, and the lysosomes themselves. Lysosomes contain hydrollic enzymes and lysosomal functions that are dependent upon a vesicles path.

Hemophilia A is one characteristic of HPS 4 generated by an x-linked recessive allele carrier which affects the platelets. Hemophilia is an excessive bleeding disorder in which the extent of blood loss is determined by a mutated gene, Factor VIII. However the majority of hemophilia A patients are affected individually due to the deletion of specific exons and introns according to a research where 30 pages of individuals were used in a case study. A few symptoms of hemophilia A are bruising easily, excessive bleeding due to open wounds, epitaxis (nose bleeds), menorrhagia (prolonged menstrual episodes), as well as dental problems. HPS 4 holds a phenotype for all of the above symptoms in hemophilia a. However, it appears that the mutated gene causing the storage pool deficiency in HPS 4 is Rab27a discovered while investigation of Rab proteins for vesicle trafficking with in the platelets was being done.\(^6,7\) Although the mutant Rab27a gene was found, the specific platelets that are affected were not pinpointed.\(^8\)

Platelet aggregation plays a significant role in the formation of haemostatic plugs, when damage to the vascular endothelium causes bruising or open wounds. Various physiological agents play a key role in platelet aggregation, two of which are
In an embedded light microscopy study, performed on mice, of the cappuccino (cno) gene there was a distinct mutation found in the choroid layer. Using an electron photomicrograph a second picture of the choroid layer of the retinal area on the mouse revealed the same mutation (Fig 3).

Figure 3

There is a significant amount of difference between the amount of melanosomes and the appearance of the melanosomes in the choroid layer of a normal mouse and one with HPS.

IV. CONCLUSION

A number of clinical studies have revealed answers to what may cause some of the defects related to Hermansky-Pudlak Syndrome. However, because the defects are genetic in nature it is my feeling that there will never be a cure. Although I do believe that the time and effort Dr. Gahl and his colleagues are putting into discovering new medicines, like pirferidone for pulmonary fibrosis, the life of HPS victims will be prolonged. In the past the average life expectancy for HPS victims was between forty to fifty years old. Today there are survivors that have reached seventy and slightly beyond. In the future I see that HPS will no longer be a debilitating disease only a slight handicap.

REFERENCES

adenotriphosphate (ATP) and adenosine diphosphate (ADP) found stored in dense bodies. However, the ADP is almost nonexistent, indicating a higher percent of ATP which is a main factor in blood coagulation. The ADP triggers the thromboxine A$_2$ which releases the ATP and activates GPIIb-IIIa assists fibrinogen binding. Fibrinogens are fibers that help to rebuild the haemostatic plug. Due to such low densities of ADP there is not enough to trigger and ATP release therefore, the blood does not coagulate.$^{(12),(13),(14)}$

A secondary factor in coagulation is the granule, which secretes fibrinogen. The mutation of Rab27a, the protein spoke of previously hinders the Rab geranylgeranylation transferase activity that regulates the trafficking pathway to release the α granules for secretion of fibrinogen.$^{(14)}$

Melanosomes are found within melanocytes which are formed from melanoblasts that are produced in the central nervous system when the embryo is developing. Tyrosinase, an enzyme that synthesized melanin, is found in melanosomes. Tyrosinase is a protein copper which catalyzes or speeds up the oxidation process in forming tyrosine thus developing brown or black pigment. However, when this reaction is hindered the reaction can not follow its course to completion thereby releasing little or no pigment causing albinism (Fig 2).

Figure 2$^{(15)}$

![Chemical diagram showing the transformation of phenol, c. phenol, o. quinone, and tyrosine](image)

A. Tyrosine (aminoacid)  
B. Simplistic tyrosinase reaction using phenol to represent the tyrosine.


