8th Annual
Science Symposium
Volume I
May 9, 2002
Paradise Valley Community College
And
South Mountain Community College
Foreword

The 8th Annual Science Symposium was held on May 9, 2002. Students enrolled in General Organic Chemistry II, CHM 236 from Paradise Valley Community College (PVCC) and South Mountain Community College (SMCC), participated in the event. I want to thank Dr. Michael Bishop of South Mountain Community College 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 the victims of the tragedy of September 11, 2001. These innocent, normal people sacrificed their lives for democracy. The events of 9/11 will never be forgotten. 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
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Synthesis of Allegra and its effects on allergy suffers

Prepared for
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By
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April 26, 2002
Abstract

This report examines the development of Allegra. It first discusses the definition of allergy and its effect on patients. It also investigates the synthesis of this medicine as well as its general background, medical availability, cautions to patients, clinical pharmacology and reported side effects.
I. Introduction

An allergy is the body’s hypersensitivity to substances in the environment.¹ "When an antibody sites response to pollen or other allergens (such as animal dander, dust, and mold), the antibody immunoglobulin E (IgE) is produced by white blood cells called B-lymphocytes."² The IgE is in search for receptors on mast cells which is an immune system cells in nasal passages, bronchial tubes, and other tissues. "The antibodies then trigger the allergic outburst by docking on mast cells and linking together."³ "The mast cells burst, and release a flood of histamine and other chemicals that cause sneezing, a runny nose, itchy eyes, and shortness of breath. Some allergic reactions can be extremely serious and can result in anaphylactic shock, in which a person's airway swells shut and blood pressure drops."⁴ Antihistamines work by preventing the effects of histamine, which is produced by the body.¹ Fortunately, there are a variety of allergy medications available to allergy suffers presently. One of them is Allegra, a non-sedating antihistamine used to relieve the symptoms of hay fever and hives of the skin"⁵ which is widely used by a large population in United States.

Seldane was the first non-sedating antihistamine and it became very popular in 1985. But in 1991, researchers discovered side effects to this medication, such as abnormal hear rhythms, effects on central nervous system, and diminishing effect when it was combined with the common antibiotics as well as grapefruit juice. The solution to this devastating problem was Allegra "that should not cause dangerous cardiac side effects."⁶ As an alternative, Food and Drug Administration (FDA) approved Fexofenadine a safer form of Terfenadine (Seldane) on July 30, 1996.⁴ Allegra contains Fexofenadine hydrochloride as its active ingredient and it has the following structure:

![Chemical Structure of Allegra](image)

C₃₂H₃₉NO₅·HCl
MW: 538.13
II. Synthesis

Fexofenadine hydrochloride is histamine H1-receptor antagonist and its chemical name is \((\pm)-4-[1\text{hydroxy}4-[4\text{-hydroxydiphenylmethyl}]1\text{-peperidinyl}]-1\text{-butyl}\alpha,\alpha\text{-dimethyl benzeneacetic acid hydrochloride.}^5\) "It is a white to off-white crystalline powder. It is freely soluble in methanol and ethanol, slightly soluble in chloroform and water, and insoluble in hexane."\(^5\) It is a racemate which exists as a zwitterion in aqueous media at physiological pH.\(^5\) It is the oxidized metabolite 10 and "the structure and the purity of the final product is supported by H\(^1\)-NMR, \(^13\text{C}-\text{NMR}, \text{mass spectrometry and elemental analysis, as well as by HPLC comparison with an authentic sample.}^6\) The empirical formula is C\text{32}H\text{39}NO\text{4}\cdot\text{HCl} and the molecular weight is \text{538.13}. The synthesis of metabolite \text{of Terfenadine, Fexofenadine hydrochloride includes the following processes:}

![Chemical structures and reactions]

1. Esterification of 4-bromophenylactic acid
2. Methylation of the Benzylic carbon using NaH/MeI
3. Alkyne formation using Pd\(^0\)/Cu\text{2Br}\(_2\) as a catalyst with 3-butyne-1-ol
Mesylation of the primary hydroxyl using MsCl

Formation of a tertiary amine using piperidine

Formation of Benzylic ketone by mercury-catalyzed hydration (Hg²⁺ / H₂O)
Note: "Ph" indicates Phenyl (Benzene as a substituent)

Formation of secondary alcohol by adding NaBH₄ / MeOH
Finally, this ion was used to form Fexofenadine hydrochloride, the active ingredient of Allegra.

III. Medical Application

Medical availability:
Allegra has been shown to relieve the symptoms associated with seasonal allergic rhinitis in adults and children 6 years of age and older. Symptoms treated effectively were sneezing, itchy nose/palate/throat, itchy/watery/red eyes. It is available in two oral dosage forms, capsules and tablets. Their forms and contents are as follows:

- Allegra 60 mg capsules
  Excipients: croscarmellose sodium, gelatin, lactose, microcrystalline cellulose, pregelatinized starch.
  Capsule shell: gelatin, iron oxide, silicon dioxide, sodium lauryl sulfate, titanium dioxide, and other ingredients.
- Allegra 30 mg tablets
- Allegra 60 mg tablets
- Allegra 180 mg tablets
  Excipients for 30 mg, 60mg, and 180mg tablets: croscarmellose sodium, magnesium stearate, microcrystalline cellulose, and pregelatinized starch.
  Tablet film coating: hydroxypropyl methylcellulose, iron oxide blends, polyethylene glycol, providone, silicone dioxide, and titanium dioxide.
Directions:

- Adults and children 12 years of age and older:
  60 milligrams twice a day for both hay fever and chronic hives, or 180 milligrams once a day for hay fever.
- Children 6 to 11 years of age:
  30 Milligrams twice a day
- Children younger than 6 years of age:
  The doctor must determine usage and dosage.

Cautions

As with many medications available today, there are some important facts one must consider before taking this medication. These considerations are as follows:

Allergies: It is important to determine if candidates are allergic to any substances, foods, preservatives, or dyes prior to taking medications.

Children: This medicine is for children 6 years of age and older.

Pregnancy: Consultation with a doctor on safety is advisable.

Nursing: Mothers who are taking this medicine and who wish to breast-feed should discuss this with their doctor.

Medical Problems: Kidney disease increases the effects of fexofenadine because of slower removal from the body. If the candidates have this disease or other medical problems, consulting the doctor is crucial since the presence of other medical problems may affect the use of fexofenadine.

Other Medicine: Allegra should not be combined with aluminum and magnesium containing antacids. It was found to decrease the effectiveness of fexofenadine by approximately 41-43%.

Clinical Pharmacology

Mechanism of Action:
Fexofenadine hydrochloride is an antihistamine with selective peripheral H1-receptor antagonist properties. Both enantiomers of fexofenadine hydrochloride displayed approximately equal amount of antihistaminic effects. Fexofenadine inhibited histamine release from peritoneal mast cells in rats. In laboratory animals, no sedative or other central nervous system effects were observed. Also, radiolabeled tissue distribution research in rats indicated that fexofenadine does not cross the blood-brain barrier.

Absorption:
Fexofenadine hydrochloride was rapidly absorbed following oral intake of a single dose of two 60-mg capsules to healthy male volunteers with an average time to maximum plasma concentration occurring at 2.6 hours after the dosage. After oral intake of a single 60-mg capsule to healthy subjects, the mean maximum plasma concentration was 131 ng/mL. Following a single dose oral intake of either the 60 and 180 mg tablet to healthy, adult male volunteers, mean maximum plasma concentrations were 142 and 494 ng/mL, respectively. The tablet formulations are bioequivalent to the capsule when administered in equal amounts. Fexofenadine hydrochloride pharmacokinetics is linear for oral doses up to a total daily rate of 240-mg (120-mg twice daily).
Distribution:
Fexofenadine hydrochloride is 60% to 70% joined to plasma proteins, primarily
albumin and e1-acid glycoprotein.

Elimination:
The average half-life of fexofenadine was 14.4 hours following consumption of
60 mg, twice daily, in normal volunteers. Human mass balance studies documented a
recovery of approximately 80% and 11% of the [14 C] fexofenadine hydrochloride dose in
the feces and urine. Because the absolute bioavailability of fexofenadine hydrochloride
has not been established, it is unknown if the fecal component represents unabsorbed
drug or the result of biliary excretion.

Metabolism:
Approximately 5% of the total oral dose were metabolized.

Hepatic Impairment:
The pharmacokinetics of fexofenadine hydrochloride in patients with hepatic
disease did not vary substantially from those observed in healthy patients.

Effect of Gender, Age, Weight, and Race:
Across several trials, there were no significant differences in the effect of
fexofenadine hydrochloride across subgroups of patients defined by gender, age, weight,
and race.

Seasonal Allergic Rhinitis in Adults:
In three, 2-week, multicenter, randomized, double-blind, placebo-controlled trials
in patients 12 to 68 years of age with seasonal allergic rhinitis (1634 patients),
fexofenadine hydrochloride 60 mg twice daily significantly reduced total symptom scores
(the sum of the individual scored for sneezing, rhinorrhea, itchy nose/ palate/ throat,
itchy/ watery/ red eyes) compared to placebo. Statistically significant reductions in
symptom scores were observed following the first 60-mg dose, with the effect maintained
throughout the 12- hour interval. In these studies, there was no additional reduction in
total symptom scores with higher doses of fexofenadine hydrochloride increased to 240
mg twice daily.

Pediatrics:
Two 2-week multicenter, randomized, placebo-controlled, double-blind trials in
877 pediatric patients 6 to 11 years of age, with seasonal allergic rhinitis were conducted
doses of 15, 30, and 60 mg twice daily. In one of the two studies, conducted with 411
pediatric patients, all three doses of fexofenadine hydrochloride significantly reduced
total symptom scores compared to when a placebo was administered. However a dose
response relationship was not observed. In addition, the safety and effectiveness of
Allegra in pediatric patients less than 6 years of age have not been established.

Side Effects:
Despite the benefits this medicine offers, it may produce unwanted effects as well.
Some of the effects may leave as the body adjusts to this medicine, but some may require
medical attention. Some of the unwanted effects are as follows:

Rare incidence:
Chest tightness; feeling of warmth, redness of the face, neck, arms and
occasionally, upper chest; large, hive-like swelling of the face, eyelids, lips, tongue,
throat, hands, legs, feet, sex organs; shortness of breath, difficult or labored breathing,
nervousness; rash; insomnia; terrifying dreams.
Less common:
Back pain; coughing; dizziness; drowsiness; earache; fever; headache; nausea; pain or tenderness around eyes or cheekbones; painful menstrual bleeding; ringing or buzzing in ears; runny or stuffy nose; stomach upset; unusual feelings of tiredness; viral infection (such as cold and flu).

Clinical Studies on Side Effects:
“Events that have been reported during controlled clinical trials involving seasonal allergic rhinitis patients with incidences less than 1 % and similar to placebo and have been rarely reported during postmarketing surveillance include: insomnia, nervousness, and sleep disorders. In rare cases, rash, urticaria, pruritus and hypersensitivity reactions with manifestations such as angioedema, chest tightness, dyspnea, flushing and systemic anaphylaxis have been reported.

IV. Conclusions

In conclusion, many people in this country suffer from allergies, which are a form of disease, commonly experienced with runny noses, itchy eyes, and sneezing. Not only can the allergy affect a patient’s quality of life, “it may lead to secondary diseases such as ear infections, sinus infections, and asthma.” Therefore Allergy must be taken seriously to prevent other related illnesses that may develop. Despite the benefits of allergy medicines available today, none of them completely cure allergies not to mention the side effects that may follow. Clearly, further research in developing more effective allergy medicines will be greatly beneficial for allergy suffers in the United States. This may bring not only a higher quality of everyday living, but enhanced productivity.
References


The Science of Weight Loss:
A Closer Look at Low-Carbohydrate Diets

By
Robin Bertozzi
4/26/2002
Abstract

This paper will begin by exploring the causes and implications of an increasingly overweight society. It will then explain the role of carbohydrates, proteins, and lipids in weight gain. Finally, several weight loss options will be evaluated including the traditional balanced diet and the increasingly popular low-carbohydrate, high-protein diets.

PART ONE - BACKGROUND

America's Increasing Waistline.

Americans are losing the battle of the bulge. Today in the U.S. approximately 55% of adults are overweight with 20% of men and 25% of women considered obese. While the prevalence of obesity is the same regardless of age, race, geography, and economic status, Native Americans, African Americans and Hispanics are at the greatest risk. Perhaps one of the most troubling statistics is that this trend is being passed on to our children. It is estimated that 4.7 million youths under the age of eighteen are overweight.

Are You Overweight?

Before you step into the shower, stand naked in front of a full-length mirror. One glance should answer the question. However, if there is any ambiguity, or you require a more scientific approach, the National Institute of Health recommends using the Body Mass Index (BMI). An individual's BMI classification is calculated by dividing their weight in kilograms by their height in meters squared.

\[
BMI = \frac{\text{Weight (kg)}}{\text{Height (m)}^2}
\]

A BMI of up to 24.9 indicates a normal weight. An overweight individual will fall between 25.0 and 29.9 and the classification for obesity begins at 30.0.

Another slightly more complicated method focuses on an individual's percentage of body fat rather than their weight. A family physician or dietitian can recommend the best method for determining percent body fat, which could include submersion in a water tank or the use of charts that assign values to various body measurements. For males, up to 15% body fat is considered healthy and for females up to 22%. According to Dr. Berry Sears in his book The Zone, men average 23% body fat, making them 53% fatter than the ideal and women average 32% meaning their body fat is 50% higher than ideal.

What’s The 'Big' Deal?

It's not just a matter of aesthetics, today obesity is defined as a chronic disease. Simply being overweight increases an individual's risk of developing coronary artery disease, high blood pressure, diabetes and several forms of cancer. As a result, over 325,000 deaths in America are annually attributed to obesity. Economically this translates into 6.8% of all U.S. health care costs. Over 100 billion is spent each year treating obesity and obesity related health issues.
Why So Fat?

Factors that contribute to weight gain include genetic, environmental, cultural, economic and psychological issues. However, obesity is a disorder of energy balance. More energy, in the form of food, is consumed than is needed and used by the body and the excess is stored as fat. Age, gender and genetic makeup will influence individual energy needs.

The Centers for Disease Control and Prevention reported a steady increase in the percent of the population that are overweight from 1960 to 1994. However, during the same time period the number of calories being consumed also increased. Not just carbohydrates but fat and protein consumption jumped considerably.

An average person has 25-35 billion fat cells in their body. As food is broken down in the digestive system and enters the bloodstream excess calories, in the form of fat are transferred into cells called adipocytes. The fat stored in these cells is called triglyceride, which is a form of reserve energy for the body. As increasing amounts of fat are stored, the adipose cells will expand to twice their size and then stimulate the growth of new cells called preadipocytes. Cell hyperplasia is the term used to describe an increase in the number of fat cell. The bad news is people can lose weight and shrink their fat cells but they never go away.

PART TWO - MACRONUTRIENTS

Before looking at specific diets to combat weight gain, it is important to understand the science behind the weight. Calories are the measure of the energy value of food. For instance, fat has nine calories per gram and protein has four calories per gram. Food can not be directly utilized by the body as fuel. It must first be broken down into the macronutrients carbohydrates, lipids, and protein, which in turn cause hormonal responses that will influence fat storage.

Carbohydrates

Carbohydrates, meaning hydrated carbon, contain carbon, hydrogen, and oxygen. Two-thirds of normal carbohydrate intake is used solely to maintain proper brain function. They are a group of molecules that include sugars and starches and are classified by their size.

Simple sugars are referred to as monosaccharides because of their single ring structures that contain three to seven carbons. Examples in the body include deoxyribose, a pentose monosaccharide, that is part of DNA and glucose. There are also glucose and fructose, both hexose monosaccharides.

The second form of carbohydrate, a disaccharide, is formed when two monosaccharides are joined by dehydration synthesis. Table sugar is the synthesis of the monosaccharides glucose and fructose to form sucrose as seen in the following reaction.

\[ C_6H_{12}O_6 + C_6H_{12}O_6 \rightarrow C_{12}H_{22}O_{11} + H_2O \]

These sugars are too large to pass through the semi-permeable membrane of a cell so they must be broken down so they can move from the digestive system into the bloodstream.
Through the process of hydrolysis water is added back to the sugars to break the bonds and produce the monosaccharides.

Finally, there are long chains of simple sugars called polysaccharides. These chains of repeating units are referred to as polymers. Carbohydrates provide cellular fuel in the form of simple sugars, the most important being glucose. Glycogen is a polysaccharide the body stores in skeletal muscle and liver cells. As blood sugar levels drop the liver will break down its glycogen stores and release glucose directly into the bloodstream. The bond energy stored in glucose is used to synthesize ATP, which when hydrolyzed, provides the energy source the body uses to function.

\[ \text{monosaccharide (glucose)} \]
\[ \text{disaccharide (sucrose)} \]
\[ \text{polysaccharide (amylose starch)} \]

The 300-400 grams of stored glycogen in the skeletal muscles is not available for conversion to glucose. Only the 60-90 grams of glycogen, a 10-12 hour supply, from the liver can be broken down and returned to the bloodstream. For this reason carbohydrates must be replenished to maintain optimal reserves. However, excessive carbohydrate intake will cause a rapid increase in blood glucose. To compensate the pancreas secretes insulin to decrease the blood sugar levels. Unfortunately insulin also encourages the storage of carbohydrates as fat for later use.

**Lipids**

Lipids are fat-soluble molecules that contain carbon, hydrogen, oxygen, and may contain phosphorus. Of the many categories of lipids an understanding of neutral fats and steroids is important when discussing weight gain. Neutral fats are also known as triglycerides because they are comprised of a chain of three fatty acids and one glycerol molecule that undergo dehydration synthesis. Fatty acids are a hydrocarbon chain with an acid group —COOH, at one end and glycerol, a sugar alcohol, at the other. Stored fat deposits provide energy for the body when oxidized. Fats with a single covalent bond are called saturated. These are animal fats found in butter and meats. Unsaturated fats or oils have a double bond between the carbons and are liquid at room temperature.

It is important to discuss steroids because cholesterol falls into this category of lipids. Cholesterol is a flat molecule with a steroid alcohol attached to four interlocking hydrocarbon rings. Animal products such as eggs, meat, and cheese are high in cholesterol. This steroid is a major component of cell membranes and is responsible for
maintaining various hormone levels yet, elevated levels of cholesterol are associated with heart disease. In order to maintain a healthy heart Americans are advised to limit their intake of these foods. However, lipids are not restricted in many low-carbohydrate diets.

\[
\begin{align*}
\text{3 Fatty Acids + Glycerol} \\
\text{Triglyceride}
\end{align*}
\]

**Protein**

Ten to fifteen percent of cell mass is protein. Their structure consists of carbon, oxygen, hydrogen, nitrogen, and sometimes sulfur and phosphorus. A protein is formed from individual amino acids, which have an amine group \(-\text{NH}_2\), a carboxyl group \(-\text{COOH}\), and various R groups as seen below. Through dehydration synthesis a peptide bond is formed when the amine end of one amino acid joins with the acid end of another. They are the basic structural materials of the body and their functions are the most varied. Examples of proteins include enzymes, hemoglobin of the blood and contractile proteins of muscle.

Excess protein consumption, more that 100 grams a day, leads to excess amino acid accumulation in the bloodstream. This stimulates an increase in insulin levels that rid the body of the acids, but as with carbohydrates, the insulin also converts the excess protein to fat.

\[
\begin{align*}
\text{R} \\
\text{NH}_2-\text{CH-CO}_2\text{H}
\end{align*}
\]

**Amino Acid**

\[
\begin{align*}
\text{R} \\
\text{O} \\
\text{N} \\
\text{C} \\
\text{O} \\
\text{H} \\
\text{R} \\
\text{O}
\end{align*}
\]

**Protein**
PART THREE - TRENDS IN WEIGHT LOSS

The latest trend in weight loss is the advent of the low-carbohydrate, high-protein diets. A few of the most popular include: The Carbohydrate Addict’s Diet, Sugar Buster: Cut Sugar to Lose Fat, Protein Power, and perhaps the best known, Dr. Atkins’ New Diet Revolution. The popularity of these diets is new, however the idea is not. Dr. Atkins first introduced his diet concept twenty-five years ago.

The common theme in all of these books is that excessive carbohydrate intake is the cause of America’s weight problems. The idea is that carbohydrates increase the production of insulin, which is the hormone that transports nutrients into fat cells causing them to produce more fat. If this is true, the books theorize that decreasing carbohydrate intake, and in some cases virtually eliminating them altogether, will lead to permanent weight loss. This is in direct opposition to the traditionally advocated nutrition advice touted for decades that suggests a healthy diet is a balanced diet. This ‘traditional’ or food pyramid diet recommended by the government and nutritionists suggest that 70% of daily caloric intake come from carbohydrates, and 15% each from protein and fat.

The premise behind Dr. Atkins’ New Diet Revolution is simple, if you replace the carbohydrates with protein and fat you will lose weight. The first phase of this diet involves a 14-day induction period that allows dieters to consume no more that 15-20 grams of carbohydrates a day. According to Dr. Atkins, during this phase of his diet “your body converts from being a carbohydrate-burning engine into being a fat-burning engine.” You are establishing an alternative metabolic pathway that conditions your body to use fat as its fuel source rather than carbohydrates.

This induction phase places the body in a state of ketosis. Oxaloacetic acid’s job in the body is to carry acetyl coenzyme A into the Krebs Cycle. When carbohydrate levels are insufficient the body converts oxaloacetic acid to glucose, which provides its needed fuel, but prevents acetyl CoA from entering the Krebs Cycle where it is an integral part of converting macronutrients to ATP. At this point the liver gets involved and converts the excess acetyl CoA into various ketone bodies including acetone, acetoacetic acid, and B-hydroxybutyric acid, which lower blood pH.

Following the restrictive induction phase, dieters progress to the ongoing weight loss and maintenance stages. Depending on one’s metabolic resistance to ketosis carbohydrate intake varies from 25-90 grams a day. In order to maintain weight loss the dieters must keep their carbohydrate intake between these levels indefinitely.

A less restrictive approach is Dr. Berry Sears The Zone. He agrees with Dr. Atkins that it is imperative to lower carbohydrate intake to lose weight. The difference is his diet advocates 40% of calories come from carbohydrates and 30% each from protein and fat.

PART FOUR - ANOTHER POINT OF VIEW

People lose weight on these diets. The books are full of success stories, so why do nutritionists and dietitians continue to recommend the ‘traditional’ diet? There are many critics who insist that low-carbohydrate diets are unhealthy and ultimately
unsuccessful. A report from Cornell University argues that initial rapid weight loss on low carbohydrate diets is due to the depletion of the liver's glycogen stores that are used to maintain normal blood sugar levels. Because glycogen contains water molecules that are also lost, dieters experiences weight loss instead of fat loss. This would seem to be supported by reports that claim it is genetically impossible to lose more than 1-1/2 pounds of body fat per week.

A convenient side effect to high protein diets is a decrease appetite. It would stand to reason that reducing total caloric intake would result in weight loss. Not only are dieters reducing calories they are greatly reducing the variety of foods they can eat. The restrictions of these diet plans make them difficult to stick with long-term. Nutritionists argue that a varied diet prevents nutritional deficiencies and imbalances such as ketosis, which is a symptom of starvation and if not corrected the acidic pH can depress the nervous system causing death in extreme cases.

PART FIVE - CONCLUSION

Statistics on obesity reveal that the 'traditional' diet is not working and must be revised. The catalyst for these changes will be the increasing price tag associated with the health care costs related to obesity. The government, pressured by insurance companies, will be forced to modernize its nutritional guidelines.

In the long run a combination of moderate exercise to increase the metabolism, decreasing carbohydrate consumption, and increasing protein intake will prove to be the healthiest way to loose and maintain weight loss. The Zone diet best represents this balance.

While the various low-carbohydrate diets agree on the need to reduce carbohydrate intake from the recommended 6-11 servings they can not come to a consensus on how low is too low. It is unrealistic and ultimately unhealthy to believe carbohydrates can be eliminated from the American diet. If variety is the spice of life, dieters are destined to stray from these restrictive weight control plans. However, it is clear that carbohydrate intake must be reduced to healthier levels.

It is also curious that many low-carbohydrate diets often neglect to focus on caloric intake. While Dr. Atkins encourages dieters to eat as much protein and fat as they want, you can get too much of a good thing. Neglecting the importance of total caloric intake has contributed to obesity.

One thing all diets and weight loss plans agree on, is the need for exercise. Our ancestors were farmers who in the course of an average day did the equivalent of 15 miles of jogging while plowing their fields and tending the farm. Women jogged over 7 miles managing the house and chasing the kids. Today women still manage the house and chase the kids but with the invention of cars, grocery stores, washing machines, and remote controls, men and women are doing less and eating more. Add to this the bounty of refined, processed, and fast food we so often consume, it is no wonder we are expanding at an alarming rate.

As there are many reasons people become overweight, there are many options for weight loss. The key to success is to find a method that works for you, get medical advice, and start slow. The most important tool is information. Understanding your
body’s unique nutritional needs gives you knowledge, which in turn empowers you to succeed.

It is not realistic to be on any ‘diet’ forever. Each individual needs to find the nutritional and exercises plan that works for them and make it their lifestyle. Change does not come easy and ingrained eating habits are hard to break. Balance and moderation are not popular themes with Americans, but perhaps with diet plans like The Zone we can have our cake and weight loss too.
References


Toxic Alcohols
Patricia Beuhler
April 24, 2002
Abstract

Methanol, ethylene glycol and isopropanol are common alcohols. When the alcohol dehydrogenase enzyme oxidizes them, they form toxic metabolites. In this research paper, the metabolic pathways of the mentioned alcohols are reviewed. The different medical treatments for individuals poisoned by these alcohols are reviewed as well.

Introduction

There are many different types of alcohols used in society today. Three common toxic alcohols covered in this research paper are methanol, ethylene glycol and isopropanol. In order to understand more about the metabolic pathways of these alcohols two essential enzymes are discussed. Alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH) are the two crucial enzyme systems in these metabolic pathways.

Alcohol Dehydrogenase

The alcohol dehydrogenase enzyme plays a very crucial part to the metabolism of alcohols. It is the first conversion step to metabolizing an alcohol to an aldehyde. The alcohol dehydrogenase enzyme (ADH) is actually one of three metabolic systems that carry out ethanol oxidation. This system consists of a series of specialized enzymes known as ADH's and found in the cytosol of the different tissues in the human body. The second system is an oxidation of a molecule of ethanol into acetaldehyde as a simultaneous decomposition of a hydrogen peroxide molecule occurs by the catalase enzyme. The third system is an oxidation system referred to as Microsomal Ethanol Oxidizing System (MEOS). This research paper will only deal with the first system.

The ADH enzymes promote the oxidation of ethanol into acetaldehyde along with the reduction of a nicotinamide adenine dinucleotide (NAD+). The enzymes use the NAD+ as electron accepting coenzyme to catalyze the oxidation of ethanol into acetaldehyde.

Aldehyde dehydrogenase

The aldehyde dehydrogenase enzyme convert the aldehyde formed from the previous step into the corresponding acid. This is the second step in the metabolism of alcohols. Aldehyde dehydrogenase is responsible for the oxidation of aldehyde groups.

Methanol

A primary alcohol, methanol is a clear, colorless volatile liquid. It can be produced from the distillation of wood or synthesized from pressurized mixtures of hydrogen, carbon monoxide and carbon dioxide gases in the presence of
catalysts. Methanol has a mild to weak odor, somewhat sweeter than ethanol. Common names are methyl alcohol, carbinol, wood spirits, and wood alcohol.

Methanol can be found in such products as paints and varnishes, industrial solvents, antifreeze, copier and windshield fluid. It is also used in the synthesizing of formaldehyde and acetic acid. Since the 1980’s methanol has been used as an alternate transportation fuel. It is the only fuel used in Indianapolis type racing cars, and it is now used in passenger vehicles and buses as well.

The metabolic pathway for methanol is depicted in figure 1:

![Figure 1: Metabolism of Methanol](image)

As a result of the metabolism of methanol, formaldehyde and formic acid are produced. Formaldehyde, the first metabolite, is formed by an oxidation reaction with the alcohol dehydrogenase enzyme. Formaldehyde is short lived and does not accumulate to toxic levels in the body.

The next part to this metabolism pathway is a two-step process of formaldehyde to formic acid via the ALDH enzyme. Formation of formic acid in the body has very harmful effects; hence the reason methanol is considered a toxic alcohol. Formic acid will cause a metabolic acidosis, that is when the serum pH falls below the normal 7.4, making the body acidic. ATP production is decreased which contributes to the acidosis and cellular homeostasis is disrupted. This can result in cell death, which leads to tissue damage.

Toxicity may arise from exposure to methanol by three different routes: inhalation, ingestion, and dermal contact. Ingestion is by far the most dangerous exposure.

However, the body can metabolize and eliminate low concentrations of methanol without causing harm. For instance, methanol can be found in cooked vegetables and artificial sweeteners that are in soft drinks (Fig.2) During the digestion process, they are metabolized to methanol and excreted through the kidneys.

![Fig.2 Aspartame](image)
The circled area in figure 2 is the methanol that gets cleaved off during the metabolism of aspartame.

When significant exposure to methanol occurs, treatment is essential. One method is to give ethanol. Ethanol can inhibit the conversion of methanol to its toxic metabolites by blocking the alcohol dehydrogenase enzyme from metabolizing methanol. Ethanol has many side effects. Not only will the patient receiving ethanol be intoxicated for many days, CNS depression may occur as well. Ethanol levels must be monitored at all times.

The other method of treatment is to give the drug fomepizole. This is the preferred method of treatment since there are no harmful side effects and it is easy to administer. A downfall to this treatment is the expense of Fomepizole. It is very expensive and costs up to a thousand dollars a dosage.

When severe cases of ingestion of methanol occur, dialysis must be administered. This process will excrete not only the parent alcohol and its metabolites, but it will excrete the treatment drug as well. This complicates the dosing procedure but it is necessary for some severe ingestions.

**Ethylene Glycol**

Ethylene glycol is a colorless, odorless viscous liquid having a very sweet taste. Produced commercially by the hydrolysis of ethylene oxide it can be found in such products as antifreeze, deicing solutions and brake fluid (hydraulic). More than 25% of the ethylene glycol produced is used in antifreeze and coolant mixtures for cars. Another common name for ethylene glycol is 1,2-ethanediol.

The metabolic pathway for ethylene glycol is depicted in figure 3:

The first step in the metabolizing process of ethylene glycol is to convert it from an alcohol to an aldehyde. This step is completed via the alcohol dehydrogenase enzyme. When the aldehyde is formed it is then converted to an acid by the aldehyde dehydrogenase enzyme. The metabolite that is formed is
called glycolate. This molecule possesses a carboxylic acid and an alcohol group allowing it to be metabolized again by the ADH enzyme. A new aldehyde will form, called glyoxylate. Aldehyde dehydrogenase acts on this molecule to form oxalate or oxalic acid. This is probably the most toxic metabolite compared to the multiple others formed in this pathway.

Treatment for ingestion of ethylene glycol is the same procedure as methanol.

**Isopropanol**

Isopropanol is a clear, colorless, volatile alcohol with a characteristic odor. This alcohol can be found mostly in industrial solvents, paints, inks, thinners, hair tonics and drugs. It is also sold as 70% disinfectant solution as rubbing alcohol. Isopropanol is used to synthesize acetone. Isopropanol is produced through distillation methods. Common names for this alcohol are isopropyl alcohol and 2-propanol. The metabolic pathway of isopropanol is depicted in figure 4.

![Figure 4: Metabolism of Isopropanol](image)

Isopropanol is not nearly as toxic as methanol or ethylene glycol, but it is 2-3 times more intoxicating than ethanol. The less effect of toxicity is due to the acetone production. Acetone is occasionally found in the body. Metabolism of toxic alcohols usually results in a more toxic metabolite. In this case isopropanol metabolite is less toxic than the parent alcohol. When it is metabolized it can be excreted without harmful effects through the kidneys and lungs along with the unchanged alcohol as well. During the metabolism process the isopropyl-intoxicated patient may have a fruity smell about them. This is the metabolized acetone on their breath as well as the unmetabolized Isopropanol.

To treat a severe case of ingested isopropanol, dialysis may be required. However, IV fluids and vitamins may only be the items necessary for treatment purposes.

**Conclusion**

Toxic alcohols are an important part of our industrial society. When ingested, they are metabolized in a fashion similar to ethanol. Without treatment, the consequences of their ingestion may be quite grave.
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The Propagation and Properties of Nanotubes

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Abstract

This report discusses two new structures of pure carbon recently discovered and named nanotubes. It talks about the history and properties of nanotubes and delves into some possible uses for nanotubes. Furthermore, the paper presents the latest theoretical models for the propagation of nanotubes. Lastly, current methods for commercial production of nanotubes are examined.
1) Introduction

The atom carbon has been studied for over a hundred years. The entire branch of chemistry known as organic chemistry has been devoted to carbon based molecules. It was assumed that only two pure forms of carbon were to be found: the ubiquitous graphite, and the valuable diamond. Imagine the surprise and excitement the world of chemistry experienced, when late in 1985, a new configuration of carbon was discovered. The following report is a look at two new forms of pure carbon. These forms of carbon, now known as Fullerenes or nanotubes, come in three categories. The two classes of carbon that this paper will present are the nanotubes known as the Multi-Walled NanoTube (MWNT), and Single-Walled NanoTube (SWNT). This paper will explore the history of nanotubes, the properties of nanotubes, the possible uses of nanotubes and how nanotubes are synthesized. As it is not yet possible to observe the growth of a nanotube because of the extreme temperatures involved, this paper will include the theoretical mechanisms that have the greatest support by the scientific community presently. Next, this paper shall address the bending of nanotubes. The process for weaving nanotubes into ropes, and the method in which a nanotube can be opened and used as a vessel. Finally, some new discoveries in nanotube creation will be discussed.

![Figure 1. The first Fullerene discovered. Now known as the Buckyball or C_{60}.](image)

![Figure 2. The second Fullerene discovered now known as the nanotube. (a) is the zigzag configuration. (b) is the chair configuration.](image)

In 1985, a group of researchers began what is now a famous experiment\(^1\)\(^2\). The team, lead up by Harry Kroto, Robert Curl, and Richard Smalley, blasted a laser at a block of graphite expecting to get long chains of hydrocarbons. Instead, they produced hollow spheres of carbon, each comprised of 60 carbon atoms as shown in Figure 1.\(^3\) This structure of carbon was previously unknown to science but is now commonly found in nature as well as in the laboratory. It is popularly noted in scientific papers as C\(_{60}\). The atoms had aligned themselves in pentagonal designs reminiscent of the shapes that Buckminster Fuller has used to create his geodesic domes, thus, the name Fullerene or Buckyball was born. In 1996, Smalley, Curl and Kroto shared the Nobel Prize for their parts in the discovery of the Fullerene. In 1991, a new and in many respects more exciting class of Fullerene was discovered by the electron microscopist Sumio Iijima. While Iijima was studying the carbon soot produced in the Buckyball creation process, he discovered what has come to be known as the ‘Buckytube’ or more commonly known as the ‘nanotube.’ This class of Fullerene begins with half of the C\(_{60}\) Buckyball shape, but then
rearranges its molecular structure into a tube of hexagonal shapes. The tube will continue for some distance and then terminate, again using a half $C_{60}$ shape. The particular form of nanotube that Iijima found is what is called the Multi-Walled NanoTube or the MWNT. The MWNT is called such because it contains one nanotube within a second larger nanotube. Just as the world of chemistry was settling down from the news of a new class of carbon compound, a third compound was isolated. This time both Sumio Iijima’s lab and a lab in California operated by Donald Bethune simultaneously reported the synthesis of the single-walled carbon nanotube. Of all the Fullerenes, this was the most novel, as it is the only nanotube discovered that has never been found in nature. Once Smalley had reported the $C_{60}$ Fullerene microscopists, all over the world began finding $C_{60}$ Fullerenes and MWNT’s everywhere in nature. This is an exciting feature of the SWNT, it is apparently a stable molecule that has only been created by mankind.

All the properties of nanotubes have yet to be identified. However, some very interesting features have been discovered. The Young’ modulus found on bundles of a few woven nanotubes has ranged around 1800 Gigapascals. This puts the nanotubes ability to resist stretching far beyond the capability of any other known substance. The nanotubes also have a very high shear modulus, meaning that they resist being cut or when twisted, they are less likely to break. Although the actual number for the shear modulus has yet to be satisfactorily determined, it is known that a nanotube is only a few hundred atoms in length and can be tied in knots without shattering. Another feature is the nanotubes ability to resist heat. This may be because SWNT nanotubes are created by temperatures in excess of 3000 degrees Kelvin. However, it has been shown that plastics augmented with between 1-5% nanotubes are capable of sustaining temperatures of up to 70% higher before bursting into flame than plastic without the nanotubes.

Perhaps, the most interesting aspect of carbon nanotubes is their electrical properties. One of the electrical features that has been discovered is that a nanotube will act like a semiconductor, that is, it may be possible to replace silicon with nanotubes in computer chip production. Another electrical feature that is displayed in nanotubes is a behavior similar to a superconductor. Experiments show that in defect free and contamination free nanotubes, electrons moving across the tubes will react in what is known in the electrical engineering community as “ballistic transport.” Ballistic transport is defined as electrons that are encountering no resistance, therefore, no heat is generated and no energy is lost to the conductor. This means that there is a possibility of using nanotubes as a superconductor. Another recently discovered feature of the SWNT is the ability to place something inside the nanotube. Many different atoms have now been successfully encapsulated in nanotubes. In addition, some complex molecules have been placed inside nanotubes.

Many possible applications for nanotubes exist. The plastics industry is expressing great interest in using nanotubes to augment plastics. The nanocomposites will give the plastic greater heat resistance along with durability; it may also lead to the first plastics that conduct electricity. It has been found that plastics formed with 4-7% nanotubes can conduct electricity across their surface. The automotive industry has been eyeing the use of plastic in car bodies to replace metal for years, as a plastic body would be less expensive to manufacture. However, a suitable plastic has never been found for the construction of a car body. Now General Electric Plastics has created a plastic modified with nanotubes that the automotive industry is excited about. One major stopping point with plastic car bodies is the difficulty in painting the exterior. Traditionally, an electrostatic paint would be sprayed, and then the part of the car being painted would be electrified. This process results in the ionized paint being attracted to the electrified
portion of the car much like a magnet is attracted to metal. Now that plastic modified with nanotubes can do the same thing, the automotive industry may be willing to exchange metals for the lighter and less costly plastics. Because the nanocomposites can conduct electricity, they can also block incoming electromagnetic fields. The rapid growth in demand in the materials industry for electromagnetic shielding may well result in the use of nanocomposites for such objects as the shell of a mobile phone, to the housing for a computer monitor.

Drug delivery has always been a tricky process. How can a possible dangerous and expensive drug be introduced directly to the area in the body that requires it without delivering the drug to the entire body? There may be an answer to this problem in the nanotube. It has been proposed that a nanotube could act as a carrier for the drug. The nanotube would be filled with molecules of the drug and one end of the nanotube would be equipped with a chemical “door.” The door, upon finding the correct glycoprotein or glycolipid would dissolve, allowing the drug to escape the nanotube vessel. This would result in the direct delivery of the drug to a specific location in the body. Evidence shows that nanotubes can hold biological enzymes. Therefore, the possibility arises that a nanotube could be filled with an array of enzymes. The enzymes could act as biological sensors or literally, a microscopic laboratory.

2) Synthesis

![Image of nanotube synthesis apparatus]

Figure 3. This illustration shows the apparatus used in the electric arc method of creation of nanotubes.

The most common technique to synthesize the MWNT is called the electric arc method. The electric arc method can be thought of as a welder in a closed and sealed chamber as in figure 3. An anode and a cathode are placed in a sealed vacuum chamber. The electrodes are made of high quality graphite. The air in the chamber is evacuated and replaced with pressurized helium and a direct current is applied. As the carbon anode is vaporized, due to the extreme level of energy coursing through it, the carbon transforms from the solid phase to the gaseous phase. The carbon gas disperses through the chamber with a large quantity landing and recondensing on the cathode. The carbon landing on the cathode is also exposed to a great deal of energy. In order to stabilize itself, it must rapidly shed as much energy as possible and yet fill its electron orbital. To do this, the carbon must form the shortest bonds possible to experience the least strain. Each bonding of the carbon to carbon, if done properly, will decrease the overall energy of the molecule.

The two reoccurring shapes that the carbons will configure themselves to are pentagons and hexagons as shown in Figure 4. The pentagon shape is the less stable of the two forms and will only be found at the ends of the tube, or if the tube is bent, at the point of the curve along its length. The hexagon has the advantage of possessing a conjugated diene. This results in the loss of $\Delta E = -0.54$ eV per extra carbon atom that attaches to create the pentagonal shape. This extreme
loss of energy may make the pentagonal shape favorable initially when the seed or first molecules of the nanotube begin to form. This seed formed initially by the pentagonal shapes is called a yarmulke, named so for its resemblance to the Jewish skullcap. However, the pentagonal shape has a disadvantage at the termination of the reaction. If only pentagonal shapes are used, the overall molecule will quickly form a ball. This may be evidenced by the formation of Buckyballs. Buckyballs, while stable, may have greater overall molecular energy than that of a nanotube. This may be evidenced by the superior ability of the nanotube to resist chemical change, then that of the Buckyball. The nanotubes resistance to chemical change would imply greater stability in the molecule. This is where the hexagonal shapes become useful to the molecule. Although, the hexagonal shape loses less energy individually than the pentagonal shape $\Delta E = -.25 \text{ eV per atom joining the molecule.}$ The addition of many hexagons would create a greater overall loss of energy to the entire molecule. If all these suppositions are correct, then it would lead to the conclusion that the most stable structure that carbon could assume in the electric arc chamber, would be that of a nanotube. Evidence shows that the nanotube growing mechanism releases large amounts of heat, meaning the process is strongly exothermic. This would support the concept of the nanotubes growth being the only stable form of growth, under these extreme conditions.

![Illustrations of the hexagonal and pentagonal rings found in the carbon nanotube. Pentagonal rings will be found at the yarmulkes of the tube and at bends or elbows in the tube. Hexagonal rings will be found in the straight tube walls.](image)

The MWNT has two distinct morphologies. The first is called chair conformation, the second is called zigzag conformation see Fig 2. To see the chair conformation, imagine a Buckyball cut into two halves, but the cut breaks the Buckyball at the hexagonal rings instead of the pentagonal rings. Then, between the Buckyball, imagine a carbon tube made of the hexagonal shaped materials. Attach the halves of the Buckyball to each end, there is now a nanotube in the chair conformation. To see the zigzag nanotubes, again imagine the Buckyball being sliced in half, but this time, cut it along the pentagonal shaped structures. Again, place the carbon tube between the halves and attach the Buckyball to the tube. This will result in the zigzag conformation of nanotube.

The MWNT, as stated earlier will have two or more walls. There is an unresolved debate as to how the extra walls form. The strongest argument that has the most evidence to support it at this time is the Russian doll model for MWNT. The Russian doll argument argues that one nanotube will grow simultaneously within the second nanotube as in Figure 5. This leads to the
analogy of the Russian doll. When the first doll is opened a second, a smaller doll is found inside the original doll, and so on. From an energy standpoint, there has been no satisfactory explanation yet as to why the MWNT will grow simultaneously inside of each other.

![Figure 5. This illustration depicts the Russian doll model for the multi-walled nanotube.]

However, it has been observed that the MWNT undergoes a more thermodynamic reaction than the SWNT. A MWNT without a catalyst will grow in an environment of about 2800° Kelvin while the SWNT, with the catalyst will develop in an environment of about 1500° Kelvin. This lends evidence to the fact that the MWNT undergoes a much more thermodynamic reaction. Therefore, if given enough energy, the nanotube seems to prefer to grow in the multi-walled form to the single-walled form.

![Figure 6. This chart shows the predicted loss of energy the carbon molecule experiences as new hexagonal rings are added to it in the growth process.]

The growth of the SWNT must be done in the presence of a catalyst. The catalysts used are transition state metals. This paper will use nickel as a catalyst, but many of the transition metals will work. Again, like the MWNT, the seed or yarmulke will be created. However, from this point onwards, the SWNT mechanism is different from the MWNT mechanism. Now, instead of the nanotube shedding energy as it grows, the carbons at the end of the yarmulke will form triple bonds with each other as shown in Figure 8. This triple bond is very strained and prone to attack. The steps in the growth process could be summarized in this fashion.

1) An atom of nickel will form two bonds to two different hexagonal atoms.
2) Then an atom of carbon will form two different bonds with two individual carbon atoms.
3) Next, an atom of nickel will form a bond to the attacking carbon and the carbon adjacent to it.
4) Than nickel will then be replaced with a second carbon.
5) At this point, the nickel can move onto the next two hexagonal rings, and the process repeats itself.

This process is so commonly referred to that it has now been given a nickname; it is called 'scooterizing' as shown in Figure 7. Interestingly, too much catalyst seems to impede the growth
of the SWNT, and many experiments have indicated that only about one percent of any catalyst is desired, as more will slow the reaction down or halt it.

**Figure 7.** This illustration is of a nickel atom scooting around the growing edge of a single-walled nanotube.

**Figure 8.** This illustration is of the individual steps that must be taken in the process of the catalytic scooting of the carbon nanotubes growing edge. See steps outlined above.

It is widely agreed upon that the nanotubes bend because of a defect in the construction of the tube. This defect is formed because the mechanism, for some reason as yet unknown, did not create a hexagonal ring, but instead created a pentagonal ring. This will cause the carbon tube to bend in the direction away from the pentagonal shape. This happens simply because of the geometry of the shapes in the tube, as can be observed in Figure 9 a,b. The hexagonal ring will attempt to open the tube while the pentagonal ring on the opposite side will attempt to close the tube. The net result will be an arc formed in the tube.

**Figure 9.** Illustration of a bent nanotube. Notice the darkened pentagonal ring pushing the tube away from it and the hexagonal ring pulling the tube towards itself.

Once the nanotube fibers exist, the question arises if they can be woven into ropes. Early reports are of the belief that they can. However, while this has been done in the lab, it has yet to
be scaled up into useful production. The process that is currently looking feasible works thusly: initially, the nanotubes are dispersed into a surfactant such as sodium dodecyl sulfate. At high levels of concentration, the surfactant will condense the nanotubes into homogenous black mats. The nanotubes are aligned by the slow but constant injection of polyvinalalcohol. This process creates long ribbons of nanotubes that remain stable even in the absence of the flowing solution, the ribbons are then removed from the solution and washed with water. They can be simply dried on a flat surface. Using the above process, ribbons of over a meter long have been created.

Nanotubes can be opened at the ends so materials can be placed inside them. One very simple method to open the nanotubes is to oxidize them. A group of researchers in Oxford developed a technique using CO₂ gas.

\[ C_6(s) + CO_{2(g)} \rightarrow 2CO_{2(g)} \]

This chemical process, along with heating the nanotubes to roughly 900°C, will remove the caps or yarmulkes off the nanotubes which can then be filled. The method of filling the nanotubes is simple. Place the nanotubes in an aqueous solution containing the desired dissolved materials to fill the tubes, and the capillary action of the tubes will pull the water and the solute into the nanotubes.

The major drawbacks for the large-scale production of nanotubes have been the fiscal difficulties. For the last seventeen years, the most efficient wide-scale production method for nanotubes has been the carbon arc method. Unfortunately, the carbon arc method requires substantial electricity to run the reaction. This means that carbon nanotubes, when they have been available to the commercial market, have costs upwards of two thousand dollars a gram. This price is prohibitive to all but the most lucrative of purchasers. Some new breakthroughs in technology however are promising to cause the price of carbon nanotubes to plummet. The method in development uses gaseous precursors that may form catalytic particuls. The catalyst is the molecule pentacarbonele, which is an iron atom encircled by five carbon monoxide groups. This gaseous catalyst, along with excess carbon monoxide, is released into a chamber that is heated to 1000°C. The intense heat pulls the carbon monoxide off the iron molecule leaving all the molecules with open electron orbitals. The carbon monoxide will then begin to form stable structures that leave single carbon atoms and the iron catalyst in the gaseous stage. This results in the carbon along with the catalyst to begin the growth mechanism described for SWNT earlier in this paper. This method of gas-phase synthesis is already in use today in the plastics industry so it is easily conceivable that it would work for nanotubes. Best of all this new method is easy to scale upwards. If the method is successful, carbon nanotube production could be rapidly brought up to the quantities and prices that would be viable in the marketplace.

CONCLUSION

Clearly, the carbon nanotube has a great potential to enrich the lives of mankind. However, skeptics have noted while new methods of manufacturing are being introduced at an amazing rate, none have yet lived up to what they claim they to do. However, this situation may change soon. The American government is now entering the fray in search of an inexpensive method of manufacturing nanotubes. The National Nanotechnology Innovative (NNI) program was funded in the last days of the Clinton presidency and is one of the few programs that is also supported heavily by the George Bush presidency. More then half a billion dollars has been funneled into the NNI program, to encourage research in the arena of nanotechnology, and nanotube manufacturing processes are high on the list for research funding. Schools are starting to look into nanotechnology degree programs for students interested in the field. Across the
world, many countries in Europe and Asia are starting their own nanotechnology drive. Japan has funded their nanotechnology program every bit as aggressively as America. The country that first develops an economical process for carbon nanotube production will have a massive advantage in creating cheap and strong materials for their industrial manufacturing companies. This makes the prize of carbon nanotubes all the sweeter.
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Epilepsy-A Seizure disorder and Its treatment
Using Anticonvulsant Drug Therapy

By Stephanie Capossere
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Written for Dr. Hank Mancini
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Abstract

This research paper will inform the reader of the seizure disorder called epilepsy. It will relate to the reader the types of seizures related to the disorder, the symptoms, the treatment using anticonvulsants, and the top three anticonvulsants most commonly prescribed. All medical, clinical, and drug information throughout the paper can be credited to the references listed in the bibliography.

Introduction

Epilepsy affects people of all ages, races and nationalities. According to the Epilepsy Foundation of America, about two and a half million people in the United States have a seizure disorder. It can develop at any time in life. Approximately two-thirds of the 125,000 persons who are newly diagnosed each year are adults. The symptoms, frequency, intensity and types of seizures vary greatly from person to person. Those whose condition is controlled by medication may not experience seizures at all. Diagnostic examinations vary according to the needs of each individual. Diagnosis usually involves a thorough physical and neurological examination, a detailed medical history, analysis of blood and other bodily fluids, an electroencephalogram (EEG), and a computerized tomography (CT) or magnetic resonance imaging (MRI) scan. The pattern of seizures must be measured, including types, frequency and duration to fully categorize the type of seizure an individual is experiencing. After the seizure type is identified, the process of medical attention will continue examining which medication can control the seizures that will enable the epileptic to live a comfortable life.

Epilepsy

The Epilepsy Foundation Web Page defines epilepsy as “a seizure disorder, that is a chronic medical condition produced by temporary changes in the electrical function of the brain, causing seizures, which affect awareness, movement, or sensation”. It is most important to understand that epilepsy “is not a specific disease, but rather a group of symptoms that are manifestations of any of a number of conditions that overstimulate nerve cells of the brain”. Since epilepsy is not labeled as one disease, but labeled as a group of symptoms, there are methods in classifying the types of seizures. The Miller-Keane Encyclopedia relates that the basis of origin of epilepsy can be idiopathic and symptomatic. This translates that if a person is labeled as an idiopathic epileptic the condition was self-originated, genetic, or no known cause. If a person is labeled as a symptomatic epileptic the condition was brought about after a physical cause, for example, brain tumor, head injury, or endocrine disorder.

There are four main types of epilepsy. The manifestations of epilepsy depend on the area of the brain where the abnormal discharge occurs. The types are as followed: Partial Seizures, generalized seizures, unilateral seizures, and the fourth group includes all other unclassified epileptic seizures. The most common types are Partial seizures, tonic-clonic seizures, and absence seizures.
Partial seizures can further be categorized into simple partial and complex partial seizures. When consciousness is not impaired, the seizure is classified as a simple partial seizure. When consciousness is impaired, the seizure is classified as a complex partial seizure. Either of these types of seizures can progress into a generalized motor seizure.\(^4\)

Simple partial seizures are focalized or local seizures. This means that they begin in one area of the brain and spread over the surrounding layer. The typical focal motor seizure is an onset of local tonic spasms followed by repetitive twitching, usually beginning in the mouth. When autonomic manifestations are included in the partial seizure, symptoms are described as abdominal pain, sweating, hair standing on end, loss of bowel and bladder control, and excessive salivation.\(^4\)

Complex partial seizures are psychomotor seizures, formally called temporal lobe epilepsy since that is where they are believed to originate. The psychomotor seizure was named because of their motor and behavior components. This type of seizure may produce a very complex pattern of motor-sensory behavior lasting several seconds to several minutes. Symptoms may include involuntary lip-chewing and smacking, swallowing, incoherent speech, staring into space, picking at or taking off clothing, rubbing of hands or legs, and odd, repetitive, and purposeless movements of the extremities. These unusual movements are called automatisms. The affected person may experience the same autonomic manifestations as simple partial along with headaches, constricted feeling, redness, spots before eyes, buzzing and ringing in ears, dizziness, anger or rage, fear, disturbances of intellect, complex visual and auditory hallucinations, and other bizarre phenomena. When the seizure is over the person may or may not be able to remember what happened. They will just want to lie down for a while.\(^4\)

Generalized tonic-clonic seizures are also known as grand mal seizures. Generalized means the entire body. Tonic means in a state of continuous, unremitting action, especially muscular contractions. Chonic means an alternating state of muscular contraction and relaxation (jerking with flexion and extension). GTC is the most common type of seizure. Some people may experience a warning, an aura before the generalized seizure, but the majority loses consciousness without any preceding symptom. Generalized seizures involve both hemispheres of the brain and are manifested in a muscular contraction of the entire body. A tonic seizure is a rigid, violent, muscular contraction that fixes the limbs in a strained position. There is usually a turning of the eyes and head toward one side. The features become distorted, the color of the face becomes pale and then flushed. In clonic seizures, muscle contractions and clonic spasms occur in the limbs, head, face, and trunk. When the spasm has ended, the person lies unconscious, sleeps heavily, and then drowsily awakens. Every person’s experience and reaction are unique. The entire attack generally lasts for a few minutes, followed by a period of several minutes of unarousable coma. Although the movements may appear to be painful, the person feels no pain during the seizure. The person may feel pain after because the severe muscle contraction and spasm.\(^4\)

The last type of seizure that will be discussed in this paper is called absence seizures or petit mal. Absence is a short type of seizure that may result in eye blinking, lip smacking, or sudden loss of awareness. Absence seizures are now included in the generalized category. Absence and GTC seizures are similar because they both start in the brain stem and involve the entire brain. The characteristic absence seizure may appear suddenly or abruptly, without warning, and include a “spell”, dizziness, a faint, a
flash, or a stillness during which time the individual is not aware of his surroundings. The person may stop talking for a few seconds, then go on talking. The eyes may become vacant with a glassy stare. When the seizure ends the person may look around, seem momentarily confused, and then carry on as if nothing has happened. This person may occasionally experience a headache afterwards. Some absence seizures will include a contraction of muscle tone or the complete opposite of decrease muscle tone. This person can also experience jerking movements and automatisms during the brief spell.  

**Anticonvulsants**

Anticonvulsants are used to reduce the number and the severity of seizures in patients with epilepsy. There are several types of anticonvulsants used in the management of epilepsy. They are derivatives of barbiturates, benzodiazepines, hydantoins, oxazolidinesdiones, or succinimides. However, many more anticonvulsants are now being prescribed that are in addition to the derivatives mentioned above. According to the AHFS Drug Information, “The precise mechanisms of action of anticonvulsants has not been confirmed at the molecular level. The basic mechanism is probably stabilization of the cell membrane secondary to modification of cation (sodium, potassium, calcium) transport either by increasing sodium efflux or inhibiting sodium influx.” The brain is a very complex organ that provides the body with all its functions. Research continues to try and explore all the complex phenomenon of the brain. Therefore, anticonvulsants and the precise mechanism can only be explained on a chemical level of the brain as a whole. “The principal pharmacologic actions of the anticonvulsants are elevation of the seizure threshold of the motor cortex to electrical or chemical stimuli and/or limitation of propagation of the seizure discharge from its origin to the effector organs.” This means that the anticonvulsants job is the change the chemical composition of what triggers a seizure to a higher level that the body should not reach, therefore prohibiting a seizure. The three most commonly prescribed anticonvulsants to manage the seizures due to epilepsy are Phenytoin (Dilantin®), Carbamazepine (Tegretol®), and Gabapentin (Neurontin®).  

**Clinical, Adverse Effects**

Adverse effects of anticonvulsants are numerous and range from those that are benign and completely reversible to benign but frequently irreversible to serious reactions which can be fatal. The most frequently occurring adverse effects common to nearly all chronically administered anticonvulsants are those related to the Central Nervous System and include drowsiness, ataxia, irritability, headache, restlessness, dizziness, and the list continues. Adverse CNS effects are usually dose related. Other adverse CNS effects related to Phenytoin were a few cases of ophthalmoplegia (paralysis of the eye muscles), mental dullness, and ataxia(irregularity and/or failure of muscular coordination). GI effects can be reduced in severity by administering the drugs with large quantities of water or food. Dermatologic reactions to nearly all the anticonvulsants have occurred. One widely common is gingival hyperplasia produced by phenytoin. This is the swelling of the gums. The use of certain anticonvulsants can also effect the blood. Some hematological effects are a high incidence of low erythrocyte and CSF folate
concentrations. Some clinicians recommend that all epileptic patients be treated prophylactically (ward off disease) with folic acid and cyanocobalamin when anticonvulsant therapy is begun to avoid folate deficiency or megaloblastic anemia.\textsuperscript{5} Other adverse effects for some patients taking anticonvulsants in high doses over long periods have developed hypocalcemia and very, very rarely rickets, or osteomalacia. To prevent this, a supplement of vitamin D and calcium will be recommended.

According to the Epilepsy Foundation, now manufacturers of some of the most widely used medicines are making them available in extended release dosages. These new drugs will release their seizure-preventing drugs more slowly, permitting them to be taken less often. The Epilepsy Foundation also reported that it has been suggested that extended release medicines may have fewer side effects because they produce a more even level of medication, with fewer highs and lows, when the active drug is released slowly.

**Phenytoin\textsuperscript{5}**

\[
\begin{align*}
\text{O} & \quad \text{C} \\
\text{N} & \quad \text{C - O} \\
\end{align*}
\]

Phenytoin is a derivative of the Hydantoins. The brand name that is manufactured by the company Pfizer is called Dilantin. Phenytoin is available in parenteral injectables, oral suspension, chewable tablets, capsules, and extended release capsules.\textsuperscript{6} The principal mechanism of action of the hydantoin anticonvulsants is limitation of seizure propagation by reduction of PTP (post-tetanic potentiation), by reducing the passive influx of sodium ions or by increasing the efficiency of the sodium pump so that excess accumulation of intracellular sodium does not occur during tetanic stimulation.\textsuperscript{5} This derivative is used mainly for control of tonic-clonic seizures (grand mal) and partial seizures with complex symptomatology (psychomotor seizures) and with autonomic symptoms. Phenytoin is not recommended for the treatment of pure absence (petit mal) seizures since the drug may increase the frequency of these seizures; however, phenytoin may be useful in conjunction with other anticonvulsants in the management of combined absence and tonic-clonic seizures.

**The Chemistry of Phenytoin**

The chemical name for phenytoin sodium is sodium 5,5-diphenyl-2,4-imidazolidinedione. The empirical formula is C\textsubscript{15}H\textsubscript{11}N\textsubscript{2}NaO\textsubscript{2} and the molecular weight of phenytoin is 274.25. Phenytoin is related to the barbiturates in chemical structure, but has a five-membered ring. Phenytoin is a white powder that is practically insoluble in water, soluble in hot alcohol, and slightly soluble in cold alcohol. Yet when the powder is converted to Phenytoin Sodium it is freely soluble in water, alcohol, and warm propylene glycol. Aqueous solutions of phenytoin sodium gradually absorb carbon.
dioxide, and the drug undergoes partial hydrolysis to phenytoin, resulting in turbid solutions. The drug is more stable in propylene glycol.

**Pharmacokinetics**

Studies using Dilantin® have shown that phenytoin and its sodium salt are usually completely absorbed from the GI tract. Prompt phenytoin capsules are rapidly absorbed and generally produce a peak serum concentrations in 1.5-3 hours, while extended release phenytoin sodium capsules are more slowly absorbed and generally produce a peak serum concentrations in 4-12 hours. When phenytoin sodium is administered IM, absorption may be erratic; this may result from crystallization of the drug as the injection site because of the change in pH.

**Carbamazepine**

Carbamazepine is an iminostilbene derivative that is used as both an anticonvulsant and for the relief of pain associated with trigeminal neuralgia. Trigeminal neuralgia is pain arising from irritation of the fifth cranial nerve. This disorder is characterized by brief attacks of severe pain in the face and forehead of the affected side. It also has uses in the symptomatic management of the acute phase of schizophrenia, as an adjunct to therapy with an antipsychotic agent in patients who fail to respond to an antipsychotic agent alone. However, for seizure disorders, carbamazepine is used in adults and children in the prophylactic management of partial seizures with complex symptomatology (psychomotor or temporal lobe seizures), generalized tonic-clonic (grand mal) seizures, and a mixture of seizure patterns. The drug is also ineffective in the management of absence (petit mal) seizures or myoclonic and akinetic seizures. Carbamazepine is available in chewable tablets, regular tablets, extended release tablets, extended release capsules, and oral suspension. The brand name that is commonly seen is called Tegretol®.

**The Chemistry of Carbamazepine**

The chemical name for carbamazepine is \(5H\text{-Dibenzo}[b,f]azepine-5\text{-carboxamide}\). The empirical formula is \(C_{15}H_{12}N_2O\) and the molecular weight of carbamazepine is 236.27. Carbamazepine is structurally related to the tricyclic antidepressants such as amitriptyline and imipramine. Carbamazepine is a white to off-white powder and is practically insoluble in water and soluble in alcohol and in acetone. Because dissolution characteristics and associated oral bioavailability of carbamazepine tablets may lose one-third or more of their oral bioavailability when exposed to excessive moisture.
Pharmacokinetics
The pharmacologic actions of carbamazepine appear to be qualitatively similar to those of the hydantoin-derivative anticonvulsants. The anticonvulsant activity of carbamazepine, like phenytoin, principally involves limitation of seizure propagation by reduction of post-tetanic potentiation of synaptic transmission. The drug has also demonstrated sedative, antidepressant, muscle relaxant, antidiuretic, and neuromuscular transmission-inhibitory actions. Carbamazepine, like phenytoin as well, is slowly absorbed in the GI tract. However, carbamazepine is widely distributed in the body.

Gabapentin

Gabapentin is an anticonvulsant agent structurally related to the inhibitory CNS neurotransmitter γ-aminobutyric acid (GABA). Although gabapentin was developed as a structural analog of GABA that would penetrate the blood-brain barrier (unlike GABA) and mimic the action of GABA at inhibitory neuronal synapses, the drug has no direct GABA-mimetic action and its precise mechanism has not been elucidated. Gabapentin is used in combination with other anticonvulsant agents in the management of partial seizures with or without secondary generalization. It is available in capsules, tablets, and oral solution. The brand name for gabapentin is called Neurontin®.

The Chemistry of Gabapentin
The chemical name for gabapentin is described as 1-(aminomethyl)cyclohexanecarboxylic acid. The empirical formula for the brand name Neurontin® is C₈H₁₇NO₂ with a molecular weight of 171.24. Gabapentin is a white to off-white crystalline solid. It is freely soluble in water and both basic and acidic aqueous solutions.

Pharmacokinetics
Unlike phenytoin and carbamazepine, gabapentin is a secondary drug treatment for the condition of epilepsy. This medication will rarely be seen as a single drug treatment. It will always be prescribed along with another anticonvulsant for proper treatment. The drug protects against seizures induced by electrical stimulation, suggesting that gabapentin may be effective in the management of tonic-clonic and partial seizures or absence seizures. Gabapentin does not bind to plasma proteins, is not appreciably metabolized, does not induce hepatic enzyme activity, and does not appear to alter the pharmacokinetics of commonly used anticonvulsant drugs. Therefore, making gabapentin an excellent secondary drug therapy. According to the package insert however, it clearly states that the mechanism by which gabapentin exerts its anticonvulsant action is unknown, however through tests, the drug does prevent seizures. It is important to note gabapentin is not metabolized in humans due to the activity of the
parent compound. The drug is therefore, eliminated from the systemic circulation by renal excretion as an unchanged drug.

Prediction

The Miller-Keane encyclopedia revealed that the basis of origin of epilepsy can be idiopathic and symptomatic. If the cause of the epilepsy is symptomatic, the cause of the condition is known. They know how it originated, why it originated, and have more insight as to how to treat that type of epilepsy. It becomes more difficult for the medical physicians and scientists to treat the idiopathic type of epilepsy since it cannot be traced to a single event or cause. It just occurred and now the goal is to find out why, how and what next. I feel that the scientists and their research teams will conduct more research on the idiopathic type of epilepsy and find a way that it can be predicted, yet even prevented. My mother suffers from idiopathic, complex partial seizures with a combination of GTC seizures and has for 16 years. There is no known cause for the epilepsy. All tests reveal it was self-originated. I feel that the research will continue as far as DNA testing to predict if epilepsy is genetic, preventable, and manageable. Patients suffering with the idiopathic epilepsy type are harder to treat with the anticonvulsants since tests sometime reveal little to nothing about the cause of the condition. With further research, there will be more advances for the population to treat the many complex symptoms of epilepsy.

Conclusion

In conclusion, epilepsy is a seizure disorder that affects over two and a half million Americans. This disorder does not have a single type, cause, or symptoms. It is a very complex disease that still needs further research in prediction and prevention. An epileptic can live a normal life through drug therapy using anticonvulsant drugs. However, the process of diagnosing an epileptic is a rigorous task. There are several medical tests, background medical history, and the important details of the seizure itself. How frequent do the seizures take place? What types of actions take place during and after the seizure? What does the epileptic feel like after? Does he or she remember? What took place before the seizure? All of these questions need to be addressed for the proper diagnosis. If the seizure cause is known, it is a good indication of how the doctor can treat the disorder. If the seizure condition is unknown, the medical team will have to take all available information into account and try to come up with a positive therapy for the patient. Each epileptic is different with cause and symptoms. That is why the research is still continuing today.
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Kidney Stones

Karole Davis
April 24, 2002
Organic Chemistry 236
Abstract

This paper will give a brief overview of kidney function and structure. It will discuss the formation of kidney stones and its mechanism. Then provide an explanation the types of stones; give their chemical structures, and methods of identification. Finally, it will list treatment and prevention options to decrease the risk of kidney stone recurrence.

Introduction

The kidneys are the master chemists of the body. They perform many complex and vital functions that keep a body in balance. The kidneys are responsible for: removing waste and excess fluid from the blood; retaining protein, glucose, minerals, and water; maintaining a balance of sodium, potassium, calcium, and phosphorus; producing renin (a substance that regulates water retention and influences blood pressure); and they are responsible for making erythropoetin (a hormone that produces red blood cells). [3] Urine production occurs constantly as blood flows into the kidneys. Millions of specialized tubes (called nephrons) filter wastes and allow a certain amount of fluid and dissolved solids to be removed from the blood. This results in the waste product known as urine, which flows out of the body through the ureters, bladder, and urethra. A breakdown in the balance of liquids and dissolved solids in the urine produced by the kidney results in the formation of a kidney stone (also called renal calculus or nephrolithiasis). A kidney stone is a hard mass made up of crystals that have settled out of urine while inside the kidney. [4]

Over one million Americans each year will have a kidney stone. [5] They are most common among caucasian males between 20 to 60 years old, those who have had stones before, and relatives of kidney stone patients. Although four out of five kidney stone sufferers are men, women also produce kidney stones. [4] Factors that contribute to stone formation in susceptible people include: too little fluid intake, chronic urinary tract infections, taking too much vitamin C or D, certain medications, urinary tract blockage, limited activity for several weeks, and certain genetic and metabolic diseases. [5]

Mechanism of Formation

Current understanding of the reasons why kidney stones form is attributed to many factors. The formation of kidney stones is a result of a complex biologic process that involves crystallization. Kidney stones result from carboxylic acids that combine with cations to form insoluble salts of the carboxylic acid which precipitate out of solution. This crystallization occurs as a result of supersaturation. A solution that contains any salt at a concentration above its solubility is said to be supersaturated. Supersaturation is often expressed as the ratio of a dissolved material to its solubility concentration; thus, a solution that contains a dissolved material at exactly its solubility concentration has a supersaturation of one. In tubular fluid and urine, the supersaturation may rise to between two and eight. Such a solution is called metastably supersaturated. When a solid phase is placed into metastable solution, crystalline growth of the particle occurs. At supersaturation values above the metastable upper limit, crystals will form
spontaneously, a process called nucleation. Once nucleation occurs, the kinetic phase, characterized by growth and aggregation proceeds, resulting in various crystal formations. The spectra of crystal formations include: individual crystals present in voided urine (crystalluria), tiny stones called gravel (termed “silent stones” because kidney function is normal and they pass without pain), larger stones that can cause obstructions and severe pain, and nephrocalcinosis (calcification of the nephron). [6] Loosely clustered crystals do not become a dense stone unless they are tightly glued together by some organic material. This process is called biomineralization, which requires an organic material on which the crystalline mineral is deposited. This matrix accounts for about 2% of the weight of a stone and is found in concentric layers throughout the stone. Chemical analysis of the matrix has proved to be unrewarding, because the dissolution of the stone for analysis requires aggressive procedures, such as acid hydrolysis. Thus, most of what is known about the composition is based on the substances found soluble in urine. Hence, the matrix is believed to be composed predominantly of protein, with small amounts of nonamino sugars, glucosamine, water and organic ash. [6]

Types of Stones

Most stones do not contain a single crystal type but rather a mixture of several different types with one or two that are predominant. To date over 200 components have been found in calculi, however, the most common constituent of kidney stones are: [1]

1. Calcium Oxalate Monohydrate (Whewellite) CaC2O4
2. Calcium Oxalate Dihydrate (Weddellite)CaC2O4·2H2O
3. Magnesium Ammonium Phosphate Hexahydrate (Struvite) MgNH4PO4·2H2O
4. Calcium Phosphate, Carbonate Form (Carbonate Apatite) Ca10(PO4-
   CO3)6(OH)2
5. Calcium Phosphate, Hydroxy Form (Hydroxylapatite) Ca10(PO4)6(OH)2
6. Calcium Hydrogen Phosphate Dihydrate (Brushite) CaHPO4·2H2O
7. Uric Acid C5H4N4O3
8. Cystine (SCH2CH(NH2)-COOH)2
9. Sodium Acid Urate NaH-C5H2O3N4-H2O
10. Tricalcium Phosphate (Whitlockite) Ca3(PO4)2
11. Ammonium Acid Urate NH4H-C5H2O3N4-H2O
12. Magnesium Hydrogen Phosphate Trihydrate (Newberyite) MgHPO4·3H2O

Calcium stones. About 80% of all kidney stones fall into this category. These stones are composed of either calcium oxalate (most common), or calcium phosphate. Whewellite is the mineral name for calcium oxalate monohydrate. Since it is possibly the best known of the crystalline organic minerals and the most common type of kidney stone, we will go into more detail about the chemistry of this component. Whewellite is the salt of oxalic acid (also known as ethanedoic acid). The formula for oxalic acid is H2C2O4. The calcium in whewellite has replaced the hydrogens in the oxalic acid by the following reaction with calcium hydroxide:

\[ \text{H}_2\text{C}_2\text{O}_4 + \text{Ca(OH)}_2 \rightarrow \text{CaC}_2\text{O}_4 + \text{H}_2\text{O} + \text{H}_2\text{O} \]
This reaction produces molecules of hydrated calcium oxalate (whewellite if in crystalline form) and water. Its structure is:

Another form of calcium oxalate is dihydrated calcium oxalate. The mineralogical name of the calcium oxalate 2(H2O) is Weddellite. Its reaction is the same as the monohydrate form.

The structure of calcium phosphate is:

**Struvite stones.** About 10% of all kidney stones fall into this category. This type of stone is composed of magnesium ammonium phosphate. These stones occur most often when patients have had repeated urinary tract infections with certain types of bacteria such as *proteus* or *pseudomonas*. These bacteria produce a substance called urease, which increases the urine pH and makes the urine more alkaline and less acidic. This chemical environment allows struvite to settle out of the urine, forming stones. [6] The structure of magnesium ammonium phosphate is:
Uric acid stones. About 5% of all kidney stones fall into this category. Uric acid stones occur when increased amounts of uric acid circulate in the bloodstream. When the uric acid content becomes very high, it can no longer remain dissolved and solid bits of uric acid settle out of the urine. A kidney stone is formed when these bits of uric acid begin to cling to each other within the kidney, slowly growing into a solid mass. About half of all patients with this type of stone also have deposits of uric acid elsewhere in their body, commonly in the joint of the big toe. This painful disorder is called gout. Other causes of uric acid stones include chemotherapy for cancer, certain bone marrow disorders where blood cells are over-produced, and an inherited disorder called Lesch-Nyhan syndrome. [6] The structure of uric acid is:

![](image1)

Cystine stones. About 2% of all kidney stones fall into this category. Cystine is a type of amino acid, and people with this type of kidney stone have an abnormality in the way their bodies process amino acids in the diet. [6]

![](image2)

Diagnosis

Diagnosing kidney stones is based on the patient's history of the very severe, distinctive pain associated with the stones. Diagnosis includes laboratory examination of a urine sample and an x-ray examination. During the passage of a stone, examination of the urine usually reveals blood and may or may not have individual crystals present. A number of x-ray tests are used to diagnose kidney stones. A plain x ray of the kidneys, ureters, and bladder may or may not reveal the stone. A series of x rays taken after injecting iodine dye into a vein is usually a more reliable way of seeing a stone. This procedure is called an intravenous pyelogram (IVP). The dye "lights up" the urinary system as it travels. In the case of an obstruction, the dye will be stopped by the stone or will only be able to get past the stone at a slow trickle. [6] When a patient is passing a kidney stone, it is important that all of his or her urine is strained through a special sieve. This is to make sure that the stone is caught. The stone can then be sent to a special laboratory for analysis so that the chemical composition of the stone can be determined.
Analytic techniques such as x-ray defraction, infrared spectroscopy, polarized microscopy, and wet chemical analysis are used to determine the chemical composition. After the kidney stone has been passed, other tests will also be required in order to understand the underlying condition that may have caused the stone to form. Serum concentrations of several chemical components are necessary to investigate the formation of a kidney stone. Collecting urine for 24 hours, followed by careful analysis of its chemical makeup, can also help determine a number of reasons for stone formation. [1]

Treatment

A patient with a kidney stone will say that the most important aspect of treatment is adequate pain relief. Because the pain of passing a kidney stone is so severe, narcotic pain medications (like morphine) are usually required. It is believed that stones may pass more quickly if the patient is encouraged to drink large amounts of water (2-3 quarts per day). If the patient is vomiting or unable to drink because of the pain, it may be necessary to provide fluids through a vein. If symptoms and urine tests indicate the presence of infection, antibiotics will be required. Although most kidney stones will pass on their own, some will not. Surgical removal of a stone may become necessary when a stone appears too large to pass. Surgery may also be required if the stone is causing serious obstructions, pain that cannot be treated, heavy bleeding, or infection. Several alternatives exist for removing stones. One method involves inserting a tube into the bladder and up into the ureter. A tiny basket is then passed through the tube, and an attempt is made to snare the stone and pull it out. Open surgery to remove an obstructing kidney stone was relatively common in the past, but current methods allow the stone to be crushed with shock waves (called lithotripsy). High energy shock waves are passed through the body and break the stone into pieces as small as grains of sand. [7] The stone fragments may then pass on their own. All of these methods reduce the patient's recovery time considerably when compared to the traditional open operation. [6]

Alternative treatment

Alternative treatments for kidney stones include the use of herbal medicine, homeopathy, acupuncture, acupressure, hypnosis, or guided imagery to relieve pain. Starfruit (Averrhoa carambola) is recommended to increase the amount of urine a patient passes and to relieve pain. Dietary changes can be made to reduce the risk of future stone formation and to facilitate the resorption of existing stones. Supplementation with magnesium, a smooth muscle relaxant, can help reduce pain and facilitate stone passing. Homeopathy and herbal medicine, both western and Chinese, recommend a number of remedies that may help prevent kidney stones. [6]

Prognosis

A patient's prognosis depends on the underlying disorder causing the development of kidney stones. In most cases, patients with uncomplicated calcium stones will recover very well. About 60% of these patients, however, will have other kidney stones. Struvite stones are particularly dangerous because they may grow extremely large, filling the tubes within the kidney. These are called staghorn stones and will not pass out in the
urine and require surgical removal. Uric acid stones may also become staghorn stones. [6]

**Prevention**

Prevention of kidney stones depends on the type of stone and the presence of an underlying disease. In almost all cases, increasing fluid intake so that a person consistently drinks several quarts of water a day is an important preventative measure to dilute the urine and help inhibit supersaturation. Oxalate salts are of great biological, medical, and industrial importance since calcium oxalate is the major component of more than 80% of kidney stones. People with calcium stones may have other diseases that cause them to have increased blood levels of calcium. These diseases include primary parathyroidism, sarcoidosis, hyperthyroidism, renal tubular acidosis, multiple myeloma, hyperoxaluria, and some types of cancer. [6] Although a diet high in calcium does not affect serum calcium levels because the excess is excreted in stool, high salt intake increases the amount of calcium in urine. Taking a medication called a diuretic also has the effect of decreasing the amount of calcium passed in the urine. Alternatively, a diet heavy in foods with a high content of oxalate acid will increase serum calcium levels since the oxalate acid binds with calcium. Foods with a high content of oxalate are spinach, rhubarb, beets, strawberries, wheat bran, nuts, nut butters, tea, and chocolate. Large amounts of these foods and dairy products (vitamin D), very large doses of vitamin C, excess salt, and heavy use of antacids should be avoided. [2] Uric acid stones may require treatment with a medication called allopurinol. Struvite stones will require removal and the patient should receive an antibiotic. When a disease is identified as the cause of stone formation, treatment specific to that disease may lessen the likelihood of repeated stones. [6]
References


The Effects of an Antioxidant, Lycopene, on Free Radical Mediated Oxidative Damage and Age-Related Diseases

By: Monica E. Dumitriu
April 26, 2002
Abstract

In recent years, the possible relationship between antioxidants and reactive oxygen species with age-related diseases has been expounded upon. Once a mere supposition, the free radical theory of aging, proposing that aging occurs from gradual deterioration of body cells and tissues caused by damaging reactions of free radical compounds, is currently being viewed as a significant factor in senescence.\(^1\) Factors that influence the progression of age-related degenerative pathologies include free radical mediated oxidative damage. The scope of this report will encompass the biological phenomenon of aging through the mechanism of free radical mediated oxidative damage; the detailed focus of the report will include reactive oxygen species and antioxidant defense mechanisms, specifically lycopene, and will review the current epidemiological data supporting lycopene as a key protective dietary antioxidant in aging through disease prevention. Furthermore, this proposal recommends future research in order to further elucidate the preventative effects of lycopene against tumor growth and certain cancers.
I. Introduction

Free radicals are unstable and highly reactive molecules that damage cells and may be a primary cause of tissue and organ senescence. In chemistry, a free radical is defined as an atom or molecule with an unpaired electron. Free radicals have long been thought to be a main component of aging. The free radical theory of aging proposes that aging is a result of the gradual deterioration of body cells and tissues caused by the damaging reactions of free radical compounds. While there are dozens of theories of aging, no one theory is universally accepted by biologists. However, recent studies of the antioxidant superoxide dismutase (SOD), an enzyme produced in human and other long-lived species tissue, suggest that free radicals may indeed be a significant factor in aging. These findings support that antioxidants prolong tissue function by reducing the damage caused by free radicals. Current antioxidant research has linked the dietary antioxidant lycopene with reduced risks of age related diseases. Therefore, it is suggested that lycopene may play a leading role as a protective dietary antioxidant in aging through disease prevention.

Free radical mediated oxidative damage has been implicated in aging and has been suggested to play critical roles in the pathogenesis of many biological conditions. Aging refers to the progressive deterioration of cells, tissues and organs. In aerobic organisms, such as humans, aging includes the various diseases and age-related disorders that often accompany an increase in calendar age. Calendar age refers to the consecutive accumulation of elapsed years an organism has lived. A major risk factor for neurodegenerative diseases such as Parkinson’s disease, Huntington’s disease and Alzheimer’s disease is aging.

Free radical mediated oxidative damage occurs when radical by-products, generated by aerobically active cells, react with biological macromolecules. These by-products are known as reactive oxygen species (ROS). Biological macromolecules include proteins, nucleic acids (DNA) and lipids. Although cells are protected by a series of defense systems, such as enzymatic and dietary antioxidants, recurring attack or inadequate protection against reactive oxygen species may damage the cells irreversibly. Oxidative damage is caused by an imbalance between reactive oxygen species exposure and oxidant protection. When damage to the structure or function of biological macromolecules occurs, a multitude of pathogeneses implicated in aging may arise (Table 1).
Table 1. A partial list of conditions that have been implicated in free radical mediated oxidative damage.

<table>
<thead>
<tr>
<th>Alzheimer Disease</th>
<th>Batten's Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arteriosclerosis</td>
<td>Myocardial Infarction</td>
</tr>
<tr>
<td>Autoimmune Diseases</td>
<td>Parkinson Disease</td>
</tr>
<tr>
<td>Cancer</td>
<td>Radiation Injury</td>
</tr>
<tr>
<td>Emphysema</td>
<td>Sunburn</td>
</tr>
</tbody>
</table>

Reactive oxygen species play a major role in oxidative stress, the unavoidable consequence of life in an oxygen-rich atmosphere. Reactive oxygen species are highly reactive oxidant molecules generated endogenously through regular metabolic activity, lifestyle and diet and are the culprits behind free radical mediated oxidative damage. Superoxide, singlet oxygen, and the hydroxyl radical are collectively known as reactive oxygen species (Figure 1).

Figure 1. The various forms of reactive oxygen species and their names.

<table>
<thead>
<tr>
<th>Molecular Oxygen</th>
<th>O-O</th>
</tr>
</thead>
<tbody>
<tr>
<td>Singlet Oxygen</td>
<td>O:O</td>
</tr>
<tr>
<td>Superoxide</td>
<td>O-O:</td>
</tr>
<tr>
<td>Hydroxyl Radical</td>
<td>H:O</td>
</tr>
</tbody>
</table>

O = oxygen atom, H = hydrogen atom, - = a single bond between two atoms; represents two bonding electrons, ' = 1 unpaired electron
Reactive oxygen species are also produced exogenously in the environment through such perturbations as x-rays and toxic chemicals (Table 2). Exogenous reactions are caused or produced by factors outside an organism. Thus they could be used to explain both normal aging and the accelerated aging sometimes exhibited under irradiation.

Table 2: A list of the multiple sources of reactive oxygen species and the damage reactive oxygen species are known to cause.

<table>
<thead>
<tr>
<th>Sources of ROS:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aerobic Metabolism,</td>
</tr>
<tr>
<td>Mitochondrial</td>
</tr>
<tr>
<td>Respiratory Chain,</td>
</tr>
<tr>
<td>Activated Leukocytes,</td>
</tr>
<tr>
<td>Air (cigarette smoke, radon, ozone), Drugs</td>
</tr>
<tr>
<td>Ultraviolet Light, etc.</td>
</tr>
</tbody>
</table>

May cause...

Oxidative Damage to:

| DNA          |
| Lipids       |
| Proteins     |

Antioxidants are protective agents that inactivate reactive oxygen species and therefore significantly delay or prevent oxidative damage. Antioxidants also prevent oxidative damage by reacting with oxidized products, thus interrupting radical chain reactions. The most effective antioxidants are dependant on the specific reactive oxygen species causing the damage. For example, the universal presence of superoxide dismutase in both cytoplasm and mitochondria insure that much of the superoxide radical generated by aerobically active cells is rapidly converted to hydrogen peroxide. Other antioxidant enzymes further reduce hydrogen peroxide into inert substances.
Antioxidants are significant participants in the mechanisms by which organisms protect themselves against the damaging effects of oxidants. Moreover, there are two major mechanisms by which specific antioxidants work. The first protection mechanisms against oxidative stress include endogenously produced and maintained antioxidant enzymes such as superoxide dismutase, catalase and glutathione peroxidase. These antioxidants are naturally present within human cells. The second protection mechanism is dependant on the intracellular levels of dietary antioxidants, such as vitamin C, vitamin E and the carotenoid family of compounds (Table 3). Foods such as fruits and vegetables are a rich source of antioxidants.

<table>
<thead>
<tr>
<th>Table 3. Some of the various types of antioxidants and antioxidant compounds that make up the two major mechanisms of protection against reactive oxygen species.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Enzymatic Antioxidants</strong></td>
</tr>
<tr>
<td>Superoxide dismutase</td>
</tr>
<tr>
<td>Catalase</td>
</tr>
<tr>
<td>Glutathione peroxidase</td>
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<td></td>
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<td></td>
</tr>
</tbody>
</table>

Aerobic organisms are constantly exposed to free radical and like antioxidant enzymes, a series of antioxidant compounds also react directly with oxidizing agents and disarm them. Compounds such as vitamin C and vitamin E, both dietary antioxidants, scavenge and bind themselves to the oxidizing agents. By binding directly to the radicals, these compounds neutralize their antagonists converting reactive oxygen species to harmless molecules, consequently preventing deleterious free radical mediated chain reactions from occurring. Such antioxidants are said to be “scavengers,” and their role is unavoidably suicidal. Antioxidant compounds are sacrificed to oxidation in order to protect more important cellular components. Antioxidant compounds such as these are primary defense mechanisms against oxidant damage and the fact that many of them are human vitamins underscores their biochemical significance in maintaining health.

The role of dietary antioxidants in aging and disease prevention has received much attention in recent years. Antioxidants such as carotenoids, the phytochemicals responsible for the natural pigment synthesized by red fruits and vegetables, have been shown to provide aerobic organisms with an array of defense against aging and disease and a diet rich in carotenoid-containing foods is associated with a number of health benefits. Carotenoids are biologically active substances found in plants that not only provide color but also protect against plant diseases. In humans, carotenoids act as antioxidants, immunoenhancers, inhibitors of mutagenesis and inhibitors of premalignant lesions and increased dietary intake of carotenoids is associated with decreased risk of macular degeneration and cataracts, some cancers and some
cardiovascular diseases. These findings are associated with endogenous maintenance of carotenoid plasma and tissue levels, however the mechanism of concentration within plasma and tissue is currently unknown.

Carotenoids include beta-carotenes, which give carrots their orange color and lycopenes, responsible for the red color of tomatoes, watermelon, pink grapefruit and guava. The nutraceutical activity of beta-carotene is related to its ability to form vitamin A within the body whereas the biological effect of lycopene has been attributed to mechanisms other than forming vitamin A.

II. Lycopene

Lycopene is one of the major carotenoids in Western diets and is found almost exclusively in tomatoes and tomato products. Lycopene is naturally present in human plasma in greater amounts than other dietary carotenoids, accounting for about 50% of the carotenoids in human serum. This carotenoid is also found to concentrate in the adrenal gland, testes, liver, and most prominently in the prostate gland. The predominance of lycopene within human serum perhaps indicates its greater biological significance in the human defense system when compared with alpha and beta carotenoids.

Lycopene is an open chain analog of beta-carotene (Figure 2), containing 14 carbon-carbon double bonds-more than any other carotenoid.

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Figure 2. The structural configuration of lycopene allows it to inactivate reactive oxygen species such as singlet oxygen and hydroxyl radicals

Lycopene

As an analog of beta-carotene, lycopene is similar in its antioxidant properties but different in its structure. The many conjugated bonds of carotenoids make them potentially powerful antioxidants, and lycopene is no exception. The double bonds in lycopene constitute a conjugated system in which the π-electrons are effectively delocalized over the entire length of the molecule’s chain. Moreover, this property allows lycopene to react easily with molecules willing to forfeit an electron. Each double bond contains four bound electrons that spin within their separate orbitals at close proximity to one another. Thus, the reason behind the reactivity of the bonds is due to the high amount of strain the double bonded electrons undergo due to their intrinsic requirement to form single bonds.
As an antioxidant, lycopene is capable of stabilizing and deactivating reactive oxygen species before they attack cells. One of the areas elucidating where lycopenes radical quenching abilities are most evident is in its ability to prevent oxidation of low-density lipoprotein (LDL) cholesterol. Lycopene has been shown to significantly prevent oxidation of LDL, thus reducing the risk of developing arteriosclerosis and coronary heart disease.\textsuperscript{12} The reactions between a lycopene molecule and hydroxyl radicals produce inert molecules and prevent the reactive oxygen species from attacking cholesterol macromolecules (Figure 3).

\textbf{Figure 3.} The product of a reaction between hydroxyl radicals and a molecule of lycopene is inert.

As an antioxidant, lycopene has a singlet oxygen quenching ability twice as high as that of beta-carotene (vitamin A relative) and ten times higher than that of alpha-tocopherol (vitamin E relative).\textsuperscript{13} The ability of lycopene to halt free radical mediated damage contributes to its antiproliferative properties against certain cancers. For example, lycopene strongly inhibits proliferation of endometrial, mammary and lung cancer cells.\textsuperscript{14} An analysis of 72 studies reviewing data that looked for a link between cancer risk and food made with tomatoes found that 57 studies linked tomato intake with reduced risk and in 35 of these the association was statistically significant.\textsuperscript{15} The statistical significance implies that the interpretation of data in 35 studies is backed by concrete mathematical support.

Epidemiological studies suggest that antioxidant capacity is improved by the consumption of tomato products, thereby decreasing the risk of developing diseases related to oxidative stress.\textsuperscript{16,17,18} For example, lycopene- or tomato-free diets resulted in loss of lycopene and increased lipid oxidation,\textsuperscript{19} whereas dietary supplementation of lycopene for 1 week increased serum lycopene levels and reduced endogenous levels of oxidation of lipids, proteins and DNA.\textsuperscript{17,19} DNA damage of lymphocytes by reactive oxygen species has been shown to significantly decrease after consumption of tomato puree. After subjects in one study consumed 25 grams of tomato puree for 14 consecutive days, DNA damage of lymphocytes challenged with hydrogen peroxide was reduced by ~50%, demonstrating an improvement in cell antioxidant property.\textsuperscript{20} Lycopene has also been shown to have significantly higher antiproliferative properties against endometrial, mammary and lung human cancer cells than alpha or beta-carotene.\textsuperscript{14} Epidemiological data supports lycopene as a significant antioxidant agent and this data should be considered as significant support providing evidence for the health benefits of lycopene (Table 4).
Table 4. Supporting evidence for the role of lycopene in aging and disease prevention.

<table>
<thead>
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<tr>
<td>Intake of 6.5 milligrams/day of lycopene for 28 consecutive days showed a 21% decreased risk of prostate cancer in men compared with those eating the least.\textsuperscript{19}</td>
</tr>
<tr>
<td>80% of 72 studies that analyzed tomato-based products and lycopene with respect to incidence of cancers showed that for the people studied, the higher the amount of lycopene in the blood stream, the less risk of suffering cancer.\textsuperscript{11}</td>
</tr>
<tr>
<td>Consumption of tomato products containing at 40 milligrams/day of lycopene for 7 consecutive days slowed progression of arteriosclerosis, due to its ability to inhibit oxidative damage of low-density lipoproteins.\textsuperscript{12}</td>
</tr>
<tr>
<td>Blood plasma levels of lycopene protected against cardiovascular disease when examining the relationship of adipose tissue antioxidant levels to heart attack.\textsuperscript{11}</td>
</tr>
<tr>
<td>Sample sizes of healthy people with the lowest level of lycopene in their blood plasma were twice as likely to get age-related macular degeneration (ARMD) as the other people who were studied.\textsuperscript{21}</td>
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<tr>
<td>Intake of 30 milligrams/day of lycopene for 21 consecutive days in men with localized prostate cancer showed signs of tumor regression and decreased malignancy as well as smaller tumor size.\textsuperscript{22}</td>
</tr>
<tr>
<td>Intake of 7 milligrams/day of lycopene for 14 consecutive days in the form of tomato puree increased blood plasma levels of lycopene and significantly reduced lymphocyte DNA damage in adult women.\textsuperscript{20}</td>
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<tr>
<td>In cell culture mediums, lycopene has been shown to be a more potent inhibitor of human cancer cell proliferation than either alpha- or beta-carotene and these effects were maintained 3 days after a 24-hour incubation period.\textsuperscript{14}</td>
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III. Conclusion

The production of oxidants is a constant process, which occurs as a consequence of the adaptation of organisms to aerobic conditions. Organisms are constantly exposed to specific oxidants collectively called reactive oxygen species. These reactive oxygen species include superoxide, singlet oxygen, and the hydroxyl radical and are generated from endogenous sources such as aerobic metabolism and the mitochondrial respiratory chain.

Reactive oxygen species react with the biological molecules that are of paramount importance for the existence of most aerobic organisms. These biological substrates include proteins, nucleic acids and lipids. The oxidative damage results in structural and functional damage, which is believed to accumulate with age and may causally contribute to a number of age-related diseases. Reactive oxygen species have been implicated in over 50 diseases. This large number suggests that radicals are not something esoteric, but that they participate as a fundamental component of tissue injury in many human diseases.

Antioxidants scavenge reactive oxygen species before they damage biological substrates, thus preventing the spread of oxidative damage through deleterious radical chain reactions. Antioxidant defense systems in humans include both enzymatic and dietary (non-enzymatic) protection against oxidative damage to biological molecules. The significance of these defense mechanisms is apparent from the consideration of the whole body and sub-cellular distribution of the different antioxidants. For example, enzymatic antioxidants such as superoxide dismutase and non-enzymatic dietary antioxidants such as vitamin E tend to be in higher concentrations in locations where oxidative damage is more likely and potentially more damaging. Oxidative damage is believed to be a major factor in aging and the significant presence of enzymatic as well as dietary antioxidants underscores free radical mediated damage as main component in aging and disease processes.

As discussed, lycopene has been shown to be the most efficient scavenger of singlet oxygen, where the efficiency of radical deactivation is directly correlated with the number of conjugated carbon-carbon double bonds. Thus, it is apparent that the unique structural features of lycopene contribute to specific biological properties. However, additional research is needed concerning lycopene bioavailability and associations between lycopene consumption and other dietary antioxidants. Numerous other potentially beneficial compounds are present in lycopene-rich tomatoes and conceivably, complex interactions among these multiple components may contribute to the beneficial properties of lycopene.

The role of the antioxidant lycopene in the process of aging and human disease is currently being investigated vigorously. Multiple epidemiological, animal and tissue culture studies suggest that the consumption of lycopene may protect humans against certain age-related degenerative diseases. Epidemiological studies indicate that lycopene sets itself apart from other carotenoids with its superior biological activities including antioxidant activity against singlet oxygen and protective effects against some types of cancer. Both in vitro and in vivo studies on growth of tumor cells support this conclusion. In vitro studies occur outside the living body, in artificial environments whereas in vivo studies occur within natural environments, such as the living body.

Research must also include secondary defense mechanisms, which may regulate endogenous activity of various antioxidants. Mounting evidence has confirmed that alongside the primary defense provided by antioxidant and enzymatic protective systems, aerobic organisms are also protected by secondary defense mechanisms. These mechanisms include direct repair,
damage removal and replacement repair as well as transient-growth arrest, in which damaged mitotic cells halt replication and minimize transcription and translation. These defense systems operate simultaneously, providing cells with a multidimensional array of specialized intracellular defenses and may share a symbiotic relationship with dietary antioxidants.

As promising as the epidemiological evidence gathered thus far may be, it is suggestive and the underlying mechanisms are not clearly understood. The full spectrum of cellular responses to oxidative stress must be considered when applying knowledge gained from empirical findings from studies of human diseases and aging. The lack of sufficient knowledge may be due to the inherent limitations of the epidemiological studies. These limitations include small sample sizes, incomplete dietary assessments and the lack of control for important confounding variables. Therefore, further research is critical to elucidate the dietary antioxidant lycopene as a significant mechanism of aging and disease prevention.

Evidence suggests that lycopene plays a leading role in protecting against cancer and other age-related diseases and although a link has been established between dietary practices that include extensive intake of fruits and vegetables to lower risks of nutritionally based cancers, the mechanism by which protection occurs requires considerable research. Although persuasive, the epidemiological evidence supporting lycopene as a preventative antioxidant against certain cancers should influence further research and studies demonstrating the anticancer activities of lycopene should be brought to the forefront of the medical arena for further analysis and testing via randomized clinical trials. The most promising studies have found that patients with existing small tumors who were treated with lycopene tomato extract showed signs of regression and decreased malignancy. Therefore, the mechanisms by which lycopene interacts with cancer cells by hindering tumor growth necessitates extensive research and should receive widespread interest within the expanding field of human health and disease prevention.
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Polymers

By:

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For:

CHE 236

Bishop
Polymers are a large class of materials consisting of many small molecules linked together to form long chains. A typical polymer may include tens of thousands of the small molecules, monomers. Because of their large size, polymers are classified as macromolecules. Humans have taken advantage of the versatility of polymers for centuries in the form of oils, tars, resins, and gums. However, it was not until the industrial revolution that the modern polymer industry began to develop. In the late 1830s, Charles Goodyear succeeded in producing a useful form of natural rubber through a process known as "vulcanization." Forty years later, Celluloid a hard plastic formed from nitrocellulose, was successfully commercialized. Despite these advances progress in polymer science was slow until the 1930s. When materials such as vinyl, neoprene, polystyrene, and nylon were developed (Fenichel). The introduction of these revolutionary materials began an explosion in polymer research that is still going on today. Unmatched in the diversity of their properties, polymers such as cotton, wool, rubber, Teflon, and all plastics are used in nearly every industry. Natural and synthetic polymers can be produced with a wide range of stiffness, strength, heat resistance, density, and even price.

Polymer synthesis is a complex procedure and can take place in a variety of ways. Addition polymerization is the method where monomers are added one by one to an active site on the growing chain. The most common type of addition polymerization is free radical polymerization (Odiyan). The tendency for the free radical to gain an additional electron in order to form a pair makes it highly reactive so that it breaks the bond on another molecule by stealing an electron, leaving that molecule with an unpaired electron. Free radicals are often created by the division of a molecule into two fragments along a single bond.

The stability of the radical determines it's own tendency to react with other compounds. An unstable radical will readily combine with many different molecules. However a stable radical will not easily interact with other chemical substances. The stability of free radicals can vary widely depending on the properties of the molecule. The active center is the location of the unpaired electron on the radical because this is where the reaction takes place. In free radical polymerization, the radical attacks one monomer, and the electron migrates to another part of the molecule. This newly formed radical attacks another monomer and the process is repeated. The active center moves down the chain as the polymerization occurs. There are three significant reactions that take place in addition polymerization: initiation, propagation, and termination steps (Odiyan).

This initiation step begins when an initiator decomposes into free radicals in the presence of monomers. The instability of carbon-carbon double bonds in the monomer makes them susceptible to reaction with the unpaired electrons in the radical. In this reaction, the active center of the radical "grabs" one of the electrons from the double bond of the monomer, leaving an unpaired electron to appear as a new active center at the end of the chain. In a typical synthesis, between 60% and 100% of the free radicals undergo an initiation reaction with a monomer (Odiyan). The remaining radicals may join with each other or with an impurity instead of with a monomer. "Self destruction" of free
radicals is a major hindrance to the initiation reaction. By controlling the monomer to radical ratio, this problem can be reduced.

In the propagation stage, the process of electron transfer and consequent movement of the active center down the chain proceeds. In free radical polymerization, the entire propagation reaction usually takes place within a fraction of a second. The propagation reaction should continue until the supply of monomers is exhausted. This outcome is very unlikely, however, most often the growth of a polymer chain is halted by the termination reaction.

Termination typically occurs in two ways combination and disproportionation. Combination occurs when the polymer growth is stopped by free electrons from two growing chains that join and form a single chain. Disproportionation halts the propagation reaction when a free radical strips a hydrogen atom from an active chain. A carbon-carbon double bond takes the place of the missing hydrogen. Disproportionation can also occur when the radical reacts with an impurity. This is why it is so important that polymerization be carried out under very clean conditions (Odian).

The physical structure of the chain is an important factor that determines the macroscopic properties. The configuration and conformation are used to describe the geometric structure of a polymer. Configuration refers to the order that is determined by chemical bonds. The configuration of a polymer cannot be altered unless chemical bonds are broken and reformed. Conformation refers to order that arises from the rotation of molecules about the single bonds. The two types of polymer configurations are cis and trans. The cis configuration arises when substituent groups are on the same side of a carbon-carbon double bond. Trans refers to the substituents are on opposite sides of the double bond. The configuration of polymer chains gives three distinct structures. Isotactic is an arrangement where all substituents are on the same side of the polymer chain. A syndiotactic polymer chain is composed of alternating groups and atactic is a random combination of the groups (Wade).

The geometric arrangement of the bonds is another way the structure of a polymer can vary. A branched polymer is formed when there are side chains attached to a main chain. One of these types, star branching, results when a polymerization starts with a single monomer and has branches radiating outward from that point. Another chain structure arises when more that one type of monomer is involved in the synthesis.
reaction. These polymers that incorporate more than one kind of monomer into their chain are copolymers. There are three important types of copolymers. A random copolymer contains a random arrangement of the multiple monomers. A block copolymer contains blocks of monomers of the same type, and a graft copolymer contains a main chain polymer consisting of one type of monomer with branches made up of other monomers (Brandrup).

In addition to the bonds that hold monomers together in a polymer chain, many polymers form bonds between neighboring chains. These bonds can be formed directly between the neighboring chains, or two chains may bond to a third common molecule. Though not as strong as the bonds within the chain, these cross-links have an important effect on the polymer. Polymers with a high enough degree of cross-linking have a "memory." When the polymer is stretched, the cross-links prevent the individual chains from sliding past one another. The chains may straighten out, but once the stress is removed they return to their original position.

The two major polymer classes are elastomers and plastics. Elastomers have a loose cross-linked structure. This type of chain structure causes elastomers to possess memory. Natural and synthetic rubbers are elastomers. Plastics can be molded or shaped under appropriate conditions of temperature and pressure. In contrast to elastomers, plastics have a greater stiffness and lack reversible elasticity. Polymers coexist in two forms crystalline materials and amorphous materials. A good comparison between the two forms is glass, an amorphous material, and ice, which is crystalline (Brandrup). Despite their appearance as hard, clear materials, capable of being melted, when viewed between crossed polarizers the highly ordered crystalline structure of ice changes the apparent properties of the polarized light, and the ice appears bright. Glass and water, lacking that highly ordered structure, both appear dark. Crystalline melting also leads to changes in optical properties during the melting process when observed through crossed polarizers. The reasons for the differing behaviors lie mainly in the structure of the solids.

Crystalline materials have their molecules arranged in repeating patterns. They are arranged in alternating rows and have the structure of a small cube. They all tend to have highly ordered and regular structures. Amorphous materials, by contrast, have their molecules arranged randomly and in long chains that twist and curve around one-another, making large regions of highly structured morphology unlikely. The morphology of most polymers is semi-crystalline. They form mixtures of small crystals and amorphous material and melt over a range of temperature instead of at a single melting point. The crystalline material shows a high degree of order formed by folding and stacking of the polymer chains. The amorphous or glass-like structure shows no long-range order, and the chains are tangled. There are some polymers that are completely amorphous, but most are a combination with the tangled and disordered regions surrounding the crystalline areas. An amorphous solid is formed when the chains have little orientation throughout the bulk polymer (Brandrup).

In the crystallization process the short chains organize themselves into crystalline structures more readily than longer molecules. Therefore, the degree of polymerization is
an important factor in determining the crystallinity of a polymer. Polymers with a high DP have difficulty organizing into layers because they tend to become tangled more. The cooling rate also influences the amount of crystallinity. Slow cooling provides time for greater amounts of crystallization to occur. Fast rates, on the other hand, yield highly amorphous materials. Subsequent heating and holding at an appropriate temperature below the crystalline melting point, followed by slow cooling would produce a significant increase in crystallinity in most polymers, as well as relieving stresses during formation. Low molecular weight polymers are generally weaker in strength. Although they are crystalline, only weak Van der Waals forces hold the lattice together. This allows the crystalline layers to slip past one another causing a break in the material. High DP, amorphous polymers, however, have greater strength because the molecules become tangled between layers. In the case of fibers, stretching to 3 or more times their original length when in a semi-crystalline state produces increased chain alignment, crystallinity and strength (Brandrup).

In most polymers, the combination of crystalline and amorphous structures forms a material with advantageous properties of strength and stiffness. Also influencing the polymer morphology is the size and shape of the monomers’ substituent groups. If the monomers are large and irregular, it is difficult for the polymer chains to arrange themselves in an ordered manner, resulting in a more amorphous solid.

The glass transition temperature of the glass transition state is important to the applications of the polymer, $T_g$. As the temperature of a polymer drops below $T_g$, it becomes increasingly brittle. As the temperature rises above the $T_g$, the polymer becomes more rubber-like. In general, values of $T_g$ well below room temperature define the domain of elastomers. The values above room temperature define rigid, structural polymers (Odian).

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A heat vs. temperature plot for an crystalline polymer, on the left; and a amorphous polymer on the right.

Another important property of polymers, also strongly dependent on their temperatures, is their response to the application of a force. Indicated by two main types of behavior: elastic and plastic. Elastic materials will return to their original shape once
the force is removed. Plastic materials will not regain their shape. In plastic materials, flow is occurring, much like a highly viscous liquid. Most materials demonstrate a combination of elastic and plastic behavior, showing plastic behavior after the elastic limit has been exceeded.

Glass is one of the few completely elastic materials while it is below its $T_g$. It will remain elastic until it reaches its breaking point. The $T_g$ of glass occurs between 510 and 560 degrees C, meaning that it will always be a brittle solid at room temperature. In comparison, polyvinyl chloride (PVC) has a $T_g$ of 83 degrees C, making it good, for example, for cold water pipes, but unsuitable for hot water. PVC also will always be a brittle solid at room temperature. Adding a small amount of plasticizer to PVC can lower the $T_g$ to −40 degrees C. This addition renders the PVC a soft, flexible material at room temperature, ideal for applications such as garden hoses. A plasticized PVC hose can become stiff and brittle in winter though. The relation of the $T_g$ to the ambient temperature is what determines the choice of a given material in a particular application (Odian).

Rubber is the most important of all elastomers. Natural rubber is a polymer whose repeating unit is isoprene. This material, obtained from the bark of the rubber tree, has been used for many centuries. It was not until 1823, however, that rubber became the valuable material we know today. In that year, Charles Goodyear succeeded in "vulcanizing" natural rubber by heating it with sulfur (Fenichell). In this process, sulfur chain fragments attack the polymer chains and lead to cross-linking. The term vulcanization is often used now to describe the cross-linking of all elastomers. Much of the rubber used in the United States today is a synthetic variety called styrene-butadiene rubber. Initial attempts to produce synthetic rubber revolved around isoprene because of its presence in natural rubber. Researchers eventually found success using butadiene and styrene with sodium metal as the initiator.

The two main types of plastics are thermoplastics and thermosets. Thermoplastics soften on heating and harden on cooling while thermosets, on heating, flow and cross-link to form rigid material that does not soften on future heating. Thermoplastics account for the majority of commercial usage. Among the most important and versatile of the hundreds of commercial plastics is polyethylene. Polyethylene is used in a wide variety of applications because, based on its structure, it can be produced in many different forms. The first type to be commercially exploited was called low-density polyethylene (LDPE) (Brandrup). This polymer is characterized by a large degree of branching, forcing the molecules to be packed rather loosely forming a low-density material.
The mechanism of "vulcanization".

LDPE is soft, pliable, and has applications ranging from plastic bags, containers, textiles, and electrical insulation, to coatings for packaging materials. Another form of polyethylene differing from LDPE only in structure is high-density polyethylene (HDPE) (Brandrup). This form demonstrates little or no branching, enabling the molecules to be tightly packed. HDPE is much more rigid than branched polyethylene and is used in applications where rigidity is important. Major uses of HDPE are plastic tubing, bottles, and bottle caps. Other forms of this material include high and ultra-high molecular weight polyethylenes, HMW and UHMW, as they are known. These are used in applications where extremely tough and resilient materials are needed.

Fibers represent a very important application of polymeric materials, including many examples from the categories of plastics and elastomers. Humans have used natural fibers such as cotton, wool, and silk for many centuries. In 1885, artificial silk was patented and launched the modern fiber industry. Man-made fibers include materials such as nylon, polyester, rayon, and acrylic. The combination of strength, weight, and durability has made these materials very important in modern industry (Fenichell). Fibers are at least 100 times longer than they are wide. Typical natural and artificial fibers can have axial ratio of 3000 or more. Synthetic polymers have been developed that possess desirable characteristics, such as a high softening point to allow for ironing, high tensile strength, adequate stiffness, and desirable fabric qualities. These
polymers are then formed into fibers with various characteristics. Nylon was developed in the 1930's and used for parachutes in World War II. This synthetic fiber, known for its strength, elasticity, toughness, and resistance to abrasion, has commercial applications including clothing and carpeting (Fenichel). Nylon has special properties that distinguish it from other materials. One such property is the elasticity. Nylon is very elastic, however after elastic limit has been exceeded the material will not return to its original shape. Like other synthetic fibers, Nylon has a large electrical resistance. From carpets to bulletproof vests, fibers have become very important in modern life. As the technology of fiber processing expands, new generations of strong and lightweight materials will be produced.

![Adipic Acid and Hexamethylene Diamine Reactions]

The mechanism for “nylon 6,6”

Once a polymer with the right properties is produced, it must be manipulated into some useful shape or object. Various methods are used in industry to do this. Injection molding and extrusion are widely used to process plastics while spinning is the process used to produce fibers.

One of the most widely used forms of plastic processing is injection molding. A plastic is heated above its glass transition temperature and then is forced under high pressure to fill the contents of a mold. The molten plastic in usually "squeezed" into the mold by a ram or a reciprocating screw. The plastic is allowed to cool and is then removed from the mold in its final form. The advantage of injection molding is speed; this process can be performed many times each second (Brandrup).

Extrusion is similar to injection molding except that the plastic is forced through a die rather than into a mold. However, the disadvantage of extrusion is that the objects made must have the same cross-sectional shape. Plastic tubing and hose is produced in this manner.

The process of producing fibers is called spinning. There are three main types of spinning: melt, dry, and wet. Melt spinning is used for polymers that can be melted
easily. Dry spinning involves dissolving the polymer into a solution that can be evaporated. Wet spinning is used when the solvent cannot be evaporated and must be removed by chemical means. All types of spinning use the same principle, so it is convenient to just describe just one. In melt spinning, a mass of polymer is heated until it will flow. The molten polymer is pumped to the face of a metal disk containing many small holes, called the spinneret. Tiny streams of polymer that emerge from these holes are wound together as they solidify, forming a long fiber. Speeds of up to 2500 feet/minute can be employed in spinning (Fenichell).

It is difficult to find an aspect of our lives that is not affected by polymers. Every industry is virtually dependant on polymers. In just 50 years, materials we now take for granted were non-existent. With further advances in the understanding of polymers, and with new applications being researched. There is no reason to believe that the polymer revolution in material chemistry and engineering will stop any time soon.
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Jacqueline Fischer

Risperdal®

Chemistry 236
Risperdal (risperdone) is a medication that is used mainly to treat schizophrenia. It is a new form of antipsychotic drug that is used because of its ability to lessen the affects of schizophrenia without having the same side affects, as did the old antipsychotic medications. To understand how Risperdal works, one must understand a few other things first. The things that will be covered in this paper are the description of neurons: what they are, how they work, and where they are located. We will also discuss what dopamine and serotonin are: their chemical structures, why they are important, and what they cause in the human body. We will then go into the specifics of Risperdal itself: the pharmacodynamics, pharmacokinetics, how it is derived, how it works, and its side-affects. Finally we will discuss schizophrenia itself and how Risperdal helps minimize the symptoms that schizophrenics endure.

Nerve cells are nerve cells that carry complex information rapidly. The neuron consists of four parts. The cell body, the dendrites, the axons, and the axon terminals. The cell body is the largest part of the neuron, in which it contains the nucleus. The dendrites are the fingers of the neuron. They are the "nerve endings" that carry information toward the cell body. The dendrites connect to skin, muscles, and other neurons. Axons are the long tail of the neuron that connects the cell body to the axon terminals. And finally, the axon terminals are located at the end of the neuron. It releases electrochemicals into other muscles, glands, and other neurons. The neurons that we want to focus on are in the central nervous system. These are the neurons that are completely located within the that brain and spinal column. Neurons send information to each other, muscles, and glands through synaptic transmission. In this process, tiny globules of electrochemicals called neurotransmitters skydive across the gap to complete the message. In order for the message to be received, they must land in their designated landing site.

Two of the neurotransmitters involved in synaptic transmission that we want to focus on are called dopamine and serotonin. Dopamine systems dominate the activity of diffuse systems, which couple the limbic system (controls emotion, also affects eating habits) to the neocortex. These systems modulate the activity of large areas of brain tissue, controlling mood, motivation and reward. Dopamine systems are a subset of adrenergic systems (which produce adrenalin). Dopamine affects brain processes that control movement, emotional response, and ability to experience pleasure and pain. Regulation of dopamine plays a crucial role in our mental and physical health. Neurons containing the neurotransmitter dopamine are clustered in the midbrain in an area called the substantia nigra. Serotonin also plays a crucial role in many of
our behaviors. For example, the serotonergic system is known to modulate mood, emotion, sleep and appetite and thus is implicated in the control of numerous behavioral and physiological functions. The concentration of synaptic serotonin is controlled directly by its reuptake into the pre-synaptic terminal. In addition, serotonin synapses are abundant in the cerebral cortex making it likely that they are involved in the processes of perception in some way.

Now that these basic bases are covered we can talk in depth about Risperdal. Risperdal is an antipsychotic agent belonging to a new chemical class, the benzisoxazole derivatives. The IUPAC name for Risperdal is 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-4H-pyridol-4-one. It has a molecular formula of C23H27FN4O2, and a molecular weight of 410.49g.

Risperdal®

Risperdone is a white to slightly beige powder, and is practically insoluble in water, but freely soluble in mehtylene chloride, and soluable in mehtanol and 0.1 N HCL.

Pharmacodynamics (http://www.rxlist.com/cgi/generic/risperid_cp.htm#CP)
The mechanism of action of risperidone, as with other antipsychotic drugs, is unknown. However, it has been proposed that this drug's antipsychotic activity is mediated through a combination of dopamine type 2 (D2) and serotonin type 2 (5HT2) antagonism (blocks the receptor sites of these neurotransmitters). Antagonism at receptors other than D2 and 5HT2 may explain some of the other effects of risperidone. Risperidone is a selective monoaminergic antagonist with high affinity (Ki of 0.12 to 7.3 nM) for the serotonin type 2 (5HT2), dopamine type 2 (D2), a1 and a2 adrenergic, and H1 histaminergic receptors. Risperidone antagonizes other receptors, but with lower potency. Risperidone has low to moderate affinity (Ki of 47 to 253 nM) for the serotonin 5HT1C, 5HT1D, and 5HT1A receptors, weak affinity (Ki of 620 to 800 nM) for the dopamine D1 and haloperidol-sensitive sigma site, and no affinity (when tested at concentrations >10^-5 M) for cholinergic muscarinic or b1 and b2 adrenergic receptors.

Pharmacokinetics (http://www.rxlist.com/cgi/generic/risperid_cp.htm#CP)
Risperidone is well absorbed, as illustrated by a mass balance study involving a single 1 mg oral dose of 14C-risperidone as a solution in 3 healthy male volunteers. Total recovery of radioactivity at 1 week was 85%, including 70% in the urine and 15% in the feces.
Risperidone is extensively metabolized in the liver by cytochrome P450IID6 to a major active metabolite, 9-hydroxyrisperidone, which is the predominant circulating specie, and appears approximately equi-effective with risperidone with respect to receptor binding activity and some effects in animals. (A second minor pathway is N-dealkylation). Consequently, the clinical effect of the drug likely results from the combined concentrations of risperidone plus 9-hydroxyrisperidone. Plasma concentrations of risperidone, 9-hydroxyrisperidone, and risperidone plus 9-hydroxyrisperidone are dose proportional over the dosing range of 1 to 16 mg daily (0.5 to 8 mg bid). The relative oral bioavailability of risperidone from a tablet was 94% (CV=10%) when compared to a solution (biavailibility for solution is 100%). Food does not affect either the rate or extent of absorption of risperidone. Thus, risperidone can be given with or without meals. The absolute oral bioavailability of risperidone was 70% (CV=25%).

The enzyme catalyzing hydroxylation of risperidone to 9-hydroxyrisperidone is cytochrome P450IID6, also called debrisoquin hydroxylase, the enzyme responsible for metabolism of many neuroleptics, antidepressants, antiarrhythmics, and other drugs. Cytochrome P450IID6 is subject to genetic polymorphism (about 6-8% of caucasiains, and a very low percent of Asians have little or no activity and are "poor metabolizers") and to inhibition by a variety of substrates and some non-substrates, notably quinidine. Extensive metabolizers convert risperidone rapidly into 9-hydroxyrisperidone, while poor metabolizers convert it much more slowly. Extensive metabolizers, therefore, have lower risperidone and higher 9-hydroxyrisperidone concentrations than poor metabolizers. Following oral administration of solution or tablet, mean peak plasma concentrations occurred at about 1 hour. Peak 9-hydroxyrisperidone occurred at about 3 hours in extensive metabolizers, and 17 hours in poor metabolizers. The apparent half-life of risperidone was 3 hours (CV=30%) in extensive metabolizers and 20 hours (CV=40%) in poor metabolizers. The apparent half-life of 9-hydroxyrisperidone was about 21 hours (CV=20%) in extensive metabolizers and 30 hours (CV=25%) in poor metabolizers. Steady-state concentrations of risperidone are reached in 1 day in extensive metabolizers and would be expected to reach steady state in about 5 days in poor metabolizers. Steady state concentrations of 9-hydroxyrisperidone are reached in 5-6 days (measured in extensive metabolizers).

Because risperidone and 9-hydroxyrisperidone are approximately equi-effective, the sum of their concentrations is pertinent. The pharmacokinetics of the sum of risperidone and 9-hydroxyrisperidone, after single and multiple doses, were similar in extensive and poor metabolizers, with an overall mean elimination half-life of about 20 hours. In analyses comparing adverse reaction rates in extensive and poor metabolizers in controlled and open studies, no important differences were seen.

Risperidone could be subject to 2 kinds of drug-drug interactions. First, inhibitors of cytochrome P450IID6 could interfere with conversion of risperidone to 9-hydroxyrisperidone. This in fact occurs with quinidine,
giving essentially all recipients a risperidone pharmacokinetic profile typical of poor metabolizers. The favorable and adverse effects of risperidone in patients receiving quinidine have not been evaluated, but observations in a modest number (n=70) of poor metabolizers given risperidone do not suggest important differences between poor and extensive metabolizers. It would also be possible for risperidone to interfere with metabolism of other drugs metabolized by cytochrome P450IID6. Relatively weak binding of risperidone to the enzyme suggests this is unlikely. The plasma protein binding of risperidone was about 90% over the in vitro concentration range of 0.5 to 200 ng/ml and increased with increasing concentrations of a1-acid glycoprotein. The plasma binding of 9-hydroxyrisperidone was 77%. Neither the parent nor the metabolite displaced each other from the plasma binding sites. High therapeutic concentrations of sulfamethazine (100 mcg/ml), warfarin (10 mcg/ml), and carbamazepine (10 mcg/ml) caused only a slight increase in the free fraction of risperidone at 10 ng/ml and 9-hydroxyrisperidone at 50 ng/ml, changes of unknown clinical significance.

**Adverse Reactions**

Approximately 9% of Risperdal-treated patients in phase 2-3 studies discontinued treatment due to an adverse event, compared with about 7% on placebo and 10% on active control drugs. Suicide attempt was associated with discontinuation in 1.2% of Risperdal-treated patients compared to .6% of placebo patients, but, given the almost 40-fold greater exposure time in Risperdal compared to placebo patients, it is unlikely that suicide attempt is a Risperdal related adverse event. (See Table III).

Now that we have explored the details about Risperdal, we can take a look in to how it actually works on the schizophrenic mind, but first lets describe what schizophrenia is. Schizophrenia is a psychiatric disorder in which previously normal cognitive abilities and behaviors become disturbed. The most common age of onset is just after reaching adulthood, typically the late-teens to the mid-thirties. It is manifested either by so-called positive symptoms (delusions, hallucinations, unusual or disorganized behavior) or by negative symptoms, including a marked lack of activity, loss of interest and unresponsiveness. Although the precise cause of schizophrenia remains unknown, an enormous amount of research has come up with a number of possibilities. Many early theories focused on behavioral or stress-induced events, but more recently, consensus holds that underlying biochemical abnormalities are more likely the cause. Lending great support to this idea is the fact that genetic predisposition may account for 50 percent of the risk of developing schizophrenia. Not surprisingly, these biochemical hypotheses center on dysfunction of the neurotransmitter systems in the brain, which provide for normal cognition and attention. The **Dopamine Hypothesis**: The notion that dopamine may be involved in schizophrenia derives from the therapeutic usefulness of drugs that block certain dopamine receptors in treating the disorder. Indeed, because dopamine blockers are so often effective, it has been proposed that an over activity of dopamine neurotransmission in cortical and limbic areas of the brain may cause
schizophrenia. Drugs with selectivity for the D4 dopamine receptor (such as clozapine or olanzapine) can be particularly effective, and so this receptor subtype may play a critical role; in fact, elevated levels of D4 receptor binding have been found post-autopsy in the brains of persons who had schizophrenia. Dopamine is further implicated by the fact that a schizophrenia-like psychosis can be induced by abusing amphetamines (cocaine), which act on dopamine pathways.

Risperdal is an antagonistic medication. As you can see from the pictures above, it partially blocks the receptor sites, by binding to them, therefore the amount of dopamine produced by the neuron is under control. On the other hand, as in the other picture, certain drugs act as an agonist (cocaine), which stimulates the production of dopamine, leaving a person with a schizophrenia-like psychosis.

**Schizophrenia in Identical Twins**

![MRI scans of 29-year-old male identical twins showing the enlarged brain ventricles in the twin with schizophrenia (right) compared to his well brother (left).](image)

Overall, to put the effects of Risperdal in a very basic statement, it is effective because it is an antagonist to the receptor sites of mainly dopamine and serotonin. By doing this it partially blocks the receptor sites for these neurotransmitters, in turn controlling (reducing) the amounts of dopamine and serotonin that they produce, which then relieves some of the symptoms seen in persons with schizophrenia.
<table>
<thead>
<tr>
<th>Body System/Preferred Term</th>
<th>Percentage of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Risperidone</td>
</tr>
<tr>
<td></td>
<td>&lt;= 10 mg/day (N=324)</td>
</tr>
<tr>
<td></td>
<td>16 mg/day (N=77)</td>
</tr>
<tr>
<td></td>
<td>Placebo (N=142)</td>
</tr>
<tr>
<td>Psychiatric</td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>26</td>
</tr>
<tr>
<td>Agitation</td>
<td>22</td>
</tr>
<tr>
<td>Anxiety</td>
<td>12</td>
</tr>
<tr>
<td>Somnolence</td>
<td>3</td>
</tr>
<tr>
<td>Aggressive Reaction</td>
<td>1</td>
</tr>
<tr>
<td>Neurological</td>
<td></td>
</tr>
<tr>
<td>Extrapyramidal symptoms(^b)</td>
<td>17</td>
</tr>
<tr>
<td>Headache</td>
<td>14</td>
</tr>
<tr>
<td>Dizziness</td>
<td>4</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>7</td>
</tr>
<tr>
<td>Nausea</td>
<td>6</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>5</td>
</tr>
<tr>
<td>Vomiting</td>
<td>5</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>4</td>
</tr>
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<td>Saliva increased</td>
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<tr>
<td>Toothache</td>
<td>2</td>
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<tr>
<td>Respiratory</td>
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</tr>
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<td>Rhinitis</td>
<td>10</td>
</tr>
<tr>
<td>Coughing</td>
<td>3</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>2</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>2</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>1</td>
</tr>
<tr>
<td>Body as a Whole</td>
<td></td>
</tr>
<tr>
<td>Back Pain</td>
<td>2</td>
</tr>
<tr>
<td>Chest Pain</td>
<td>2</td>
</tr>
<tr>
<td>Fever</td>
<td>2</td>
</tr>
<tr>
<td>Dermatological</td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>2</td>
</tr>
<tr>
<td>Dry skin</td>
<td>2</td>
</tr>
<tr>
<td>Seborrhea</td>
<td>1</td>
</tr>
<tr>
<td>Infections</td>
<td></td>
</tr>
<tr>
<td>Upper respiratory</td>
<td>3</td>
</tr>
<tr>
<td>Visual</td>
<td></td>
</tr>
<tr>
<td>Abnormal Vision</td>
<td>2</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>2</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td></td>
</tr>
<tr>
<td>Tachycardia</td>
<td>3</td>
</tr>
</tbody>
</table>
Resources

Deth, Richard C.

http://www.sciam.com/askexpert/medicine/medicine43/medicine43.html


E. Fuller, Torrey,


http://www.utexas.edu/research/asrec/dopamine.html


Chemistry of Wine

By Jamie Fishburn
Fall 2002
Chemistry 236
Winemaking is an art that has been passed down from generation to generation for centuries. Its difficulty has been compared to the science of alchemy. There is evidence that wine existed several thousands of years ago in Mesopotamia (1). In Roman Times a great bottle of wine was considered a gift from the gods. A rare bottle of wine was worth its weight in gold. What are the components that make a prestigious wine? There have been volumes of books written on this subject. There are two branches of science regarding wine, viticulture and oenology. Viticulture is the science of the cultivation of the vine, "grape farming". Oenology is the science of wine. There is a subdivision of oenology called vinification, which is the study of wine making. It is getting to be very common for large wineries to have chemist on staff in an effort to perfect their vintages. I will attempt to use the science of chemistry to examine the components of wine and the chemical reactions of wine fermentation.

Grape berries differ in size, shape, color, texture and chemical composition. Wine is made from the berry juice called must. The must is 90% water and 10% extract. It is the 10% extract that gives wine its character. The extract is composed mainly of sugar, acids, and phenols. It is vital when producing a great wine to start with the best grapes. A wine can never be better than the grapes from which it came (2). The chemistries of these compounds have an important effect on the quality of the wine.

Sugar is 95% of the dissolved solids in the must (3). Sugar makes up almost all of the must density. Sugar has the empirical formula C\textsubscript{n}H\textsubscript{2n}O\textsubscript{n} -iH\textsubscript{2} (I= 0, 1, 2, 3, 4, ...). The must contains glucose, fructose, rhamnose, arabinose, xylose, sucros, and pectin (4). Glucose and fructose are the main sugars in grape must. They are present in open chains as well as cyclic rings (5).

In mature grapes the contents of fructose and glucose are about equal. But depending on climate, grape variety and maturity the content ratio of glucose/fructose can range from 0.7-1.1 (5). The riper grapes, having high concentrations of sugar, will still have some sugar in the wine even after fermentation. The content of sugar is vital to the development of the wine since the sugar serves as the fuel for the fermentation process.

During the ripening process the sugar content will increase and the acid levels will decrease. Some acidity is desirable since the acid provides the freshness and lift to wine (2). Acid also effects the malolactic fermentation, color, aging rate, microbial stability,
tartrate stability, and protein stability (5). In the case of acid in wine, you can have too much of a good thing. Higher quantities of acid in the must will produce an undesirable sour taste. Striking the perfect balance between the sugar and acid content of the must is an important task of the winemaker. Not all winemakers agree on what is the ideal ratio of sugar and acids. The different sugar/acid ratios give the range of sweetness and dryness in wines.

Tartaric and Malic acid are the major acids in the must. These acids combines to make up 90% of the acid in wine (2). Table shows the development of acids during ripening levels in milliequivalents for 1000 berries. This example used a Cabernet Sauvignon (5). As the table shows, while the grape ripens the percentage of the tartaric acid and malic acid are changing. The amount of tartaric acid changes very little during the ripening of grapes where as the amount of malic acid drops continually. The reason for this is that malic acid is lost through respiration during the ripening process of the grape. The tartaric acid is unaffected by respiration. Tartaric acid content of must varies from about 0.2 to 0.8 % depending on grape type, region and temperature. The tartaric acid is only found in grapes not any other fruit. It gives wine an agreeable, soft taste. It also affects the wine’s pH, color, resistance to bacteria, and most importantly taste (4). Tartaric is a 4-carbon di-acid, which has four stereoisomers: RR, RS, SR, and SS. There structures are as follows (2).

<table>
<thead>
<tr>
<th>RR</th>
<th>SS</th>
<th>SR, SS</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-OOH</td>
<td>C-OOH</td>
<td>C-OOH</td>
</tr>
<tr>
<td>H-C-OH</td>
<td>H-C-OH</td>
<td>H-C-OH</td>
</tr>
<tr>
<td>HO-C-H</td>
<td>HO-C-H</td>
<td>HO-C-H</td>
</tr>
<tr>
<td>C-OOH</td>
<td>C-OOH</td>
<td>C-OOH</td>
</tr>
</tbody>
</table>

L(+) Tartaric Acid  D (-) Tartaric Acid  Meso-Tartaric Acid

It is the amount of malic acid that determines the quality of a wine vintage. Winemakers strive to have a total acid content around 0.7-0.9%. Table wines have acid levels of 0.6 – 0.85%. Dessert wines have acid levels of 0.4 to 0.65 % (4). Malic Acid gives wine a harsh taste. Only in very small amounts is malic acid acceptable in white wines. Malic acid is considered unacceptable in red wines. Because of the harsh flavor of the malic acid in red wine, the wine undergoes a second fermentation. The second fermentation is called malolactic fermentation. It is to remove the last traces of malic acid.

For thousands of years the simplest way to reduce the concentration of malic acid in the grape is by having the grape ripen until it is overripe. Almost all of the malic acid will be removed by respiration. The warmer the climate, then the quicker the respiration process
and the quicker the reduction of the unwanted acid. Like tartaric acid, Malic acid is a 4-carbon di-acid with only one asymmetric carbon (8). It has two optical isomers of D and L (5). Only the L malic acid is found in grapes.

<table>
<thead>
<tr>
<th>C-OOH</th>
<th>C-OOH</th>
</tr>
</thead>
<tbody>
<tr>
<td>H-C-H</td>
<td>H-C-H</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>HO-C-H</td>
<td>HO-C-H</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>C-OOH</td>
<td>C-OH</td>
</tr>
</tbody>
</table>

L(+)-Malic Acid  D(-)-Malic Acid

The other major components of the must are the phenolic compounds. They provide the must and wine with some of its color, bitterness, antioxidants, and some of its flavors. Phenols are present in the grape’s seeds, skins, stem and juice. Additional phenols can be gained from the oak barrels used in aging. 65% of the grape’s phenols are present in the seeds and stem, 30% of the phenols are present in the skins. Only 4-5% of the phenols are found in the juice. The skin of the wine contains the polyphenols, which include the pigment and tannin. The tannins are odorless and have an unripe flavor. They produce the deep color and contribute to the flavor of red wine. The tannins also help red wine age properly. In contrast, white wine should have very little tannin. The tannin gives white wine an unwanted harsh flavor.

The phenols content in the must depend on the grape variety, climate during ripening period, as well as, the amount of contact the must had with the seeds, stem and skins. On average, white varieties have a phenolic content of 4g/kg of must, and red varieties have a phenolic content of 5.5g/kg of must. Given the limited amount of phenols in the juice, the phenol content has to be increased by allowing the pressed berries to stay in contact with the skins and seeds. Depending on the vintage and desired flavor the stems may be completely, partially or not at all removed from the grape before fermentation. The stems can give a young wine a harsh flavor and will give the wine a longer aging period. Some winemakers believe that after the longer aging period the wine will have a more mature and fuller flavor because of the wine’s contact with the stem.

There are two common phenolic compounds present in must and wine. They are gallic acid and vanillin. Their structures are as follows.

Gallic Acid

Vanillin
(9). Phenols are present as monophenols, meta, ortho and para-diphenols. 3-isobutyl-2-methoxypyrazine has also been identified in Cabernet Sauvignon grapes but only in trace amounts (9)

Since the phenol compounds have such an impact on the flavor of the wine, its reactions are closely monitored during the winemaking process. The effects of phenol compounds are still being studied. As is stated by Yair Margalit “many of the changes of the phenols (in the wine making process) are not yet understood” (9). It is known that the phenols can be easily affected during the processing of the wine by the fermentation temperature, the movement of the juice during fermentation, and the type of pressing of the grapes. Phenols react very quickly in the presence of oxygen. One of the effects of the oxidation of phenols is the change in color of the wine. For red wine, the color will change from a rich dark red color to a more purple or garnet color. White wine will change from a straw color to a golden yellow color (3). Chardonnay and Sauvignon Blanc when periodically exposed to air have a decreased fruity flavor and an increased oxidation flavor. The overall quality of the wine was noticeably compromised when tested by a tasting panel. (3)

Only certain phenols are directly affected by oxidation. Only the ortho and para-diphenols are directly affected. Where as the mono- and meta-diphenols are only indirectly affected by oxidation? In the presence of the enzyme, polyphenoloxidases, the phenol is oxidized. The polyphenoloxidases is hindered by the presence of sulfur dioxide. Many winemakers use sulfur dioxide to reduce the oxidation process. The enzyme lassase is present in mold and can also be a catalyst for oxidation. Unfortunately lassase is not affected by sulfur dioxide. Winemakers attempt to only include the healthiest berries into the prestigious wines. The phenolate free radical reacts with oxygen or ionic free radical oxygen to form the quinone. In the ortho and para-postion the phenolate free radical will resonates to stabilize. Gallic acid oxidizes in a similar manner.

As mentioned earlier the phenols provide the must with the color. This brings us the major difference between making red and white wines. The red wines are fermented with their skins to allow more of the phenols, the color producer, to be absorbed into the must. The grapes are pressed only after the fermentation process. The white wines are pressed to remove the seeds and the skins before fermentation. Some winemakers may leave the skins in the white must for up to 24 hours but the skins are removed before the fermentation process is begun.

The must can also contain many different aldehydes, which provide some of the flavor to the wine. The aldehyde content is increased as the contact with the contact of the must with the skins of the grapes. They are then reduced during fermentation to their corresponding alcohol. The aldehydes have distinct flavors and they are as follows. Flavor characteristics of volatile, short chain aldehydes (9).
<table>
<thead>
<tr>
<th>Substance</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formaldehyde</td>
<td>Sharp, pungent odor</td>
</tr>
<tr>
<td>Acetaldehyde</td>
<td>Overripe bruised apples, nutty, sherry-like</td>
</tr>
<tr>
<td>Propanal</td>
<td>Similar to acetaldehyde</td>
</tr>
<tr>
<td>Butanal</td>
<td>Pungent</td>
</tr>
<tr>
<td>2-Methyl-1-propanal (isobutanal)</td>
<td>Characteristic, slightly apple-like</td>
</tr>
<tr>
<td>Pentanal</td>
<td>Warm, slightly fruity, nut-like, pungent at high concentrations</td>
</tr>
<tr>
<td>3-methyl-1-butanal (isovaleraldehyde)</td>
<td>Warm, herbaceous, slightly fruity, nut-like, penetrating, acrid at high levels</td>
</tr>
<tr>
<td>2-methyl-1-butanal</td>
<td>Cocoa, coffee-like, sweet, slightly fruity, powerful, choking at high levels</td>
</tr>
<tr>
<td>Hexanal</td>
<td>Green, grassy, fruity</td>
</tr>
<tr>
<td>Heptanal</td>
<td>Fatty, unpleasant</td>
</tr>
<tr>
<td>Octanal</td>
<td>Sharp, fatty, fruity</td>
</tr>
<tr>
<td>Nonanal</td>
<td>Fatty, orange-rose-like, citrus-like</td>
</tr>
</tbody>
</table>

The second ingredient necessary to produce a prestigious wine is yeast. In actuality yeast is needed to make even table wine. If you ask 12 different winemaker what the best yeast is you will most likely get 12 different answers. The majority of the yeast used by winemakers is derivatives from Saccharomyces.

What is yeast? It is a single-celled fungus. It is one of the simplest microorganisms. The botanical name of wine yeast is Saccharomyces ellipsoideus or Saccharomyces cerevisiae. Yeast multiplies by cell division that releases energy in the form of heat. The fuel of the division is sugar. The sugar is present in the must of the grapes. This process is called fermentation and its product is alcohol. The yeasts’ enzymes break down the sugar of the grape then form alcohol and carbon dioxide.

Yeast is found in nature. They are present wherever grapes grow. When they are found in nature they are referred to as “ambient” yeast cultures. The vineyards of Europe have been there for generations. The yeast there has evolved into relatively pure strains. Yet the relatively young vineyards in California have not been established long enough to have developed a pure strain of yeast. Their ambient yeast are not of similar quality to those of Europe. Therefore, many of the California vineyards use yeast, which have been refined in the laboratories. These yeasts are referred to as cultured yeast. Each strain of yeast is very specialized. For example the saccharomyces chevalieri is used mostly in red wine fermentation (3). It forms the fruity acetates (6) Produces 2-hydroxyglutaric acid ester. The property of the ester is weak, fatty, lactone-like. The saccharomyces oviformis strain is resistant to higher alcohol levels. The torulopsis stellata has adapted to the mold botrytis cinerea (dehydrates the grapes forming noble rot). It is used in creating the noble sweet wines. When a winemaker selects the variety of yeast to be used in a wine, necessary alcohol tolerance and the sensitivity to heat is considered.

Each strain of yeast has a certain tolerance to the alcohol content. If the alcohol raises above the tolerance then the yeast becomes inactive. Knowing this, the winemakers will
utilize many different yeasts when creating a wine. Each of the yeast strains will react differently to the chemical components of the wine. For example a winemaker may use one strain which is able to live in 3 or 4 percent alcohol in the beginning of fermentation. Then use a 2\textsuperscript{nd} strain, which can sustain cell division in alcohol contents of 12 percent. Two such yeasts would be necessary when creating dry white wines. If the winemaker is using noble sweet grapes which have extremely high levels of sugar in the must of the grapes then a 3\textsuperscript{rd} strain of yeast would be needed (1). The 3\textsuperscript{rd} strain would be able to withstand alcohol levels as high as 17 percent.

The winemaker’s next challenge is controlling the fermentation process. It is very easy to ruin a vat of perfect grape must. There is an art to the fermentation process. It happens time and time again that winemakers take good grapes and manage to make bad wine out of them” (2). Fermentation is controlled by several conditions that include temperature, and as mentioned earlier alcohol content.

Controlling the temperature is vital to the fermentation process. As mentioned earlier, heat is released during the cell division of the sugar. There is a fine line between what is considered the perfect temperature. As the temperature increases the yeast will multiply quicker. A quick fermentation can take away some of the volatile flavors in a wine. If the heat rises too quickly during the early stages of fermentation then the final flavor of the wine can be seriously damaged (10). To complicate matters, if the temperature is allowed to fall below 54 degrees F, then fermentation will stop. This would be the demise of the wine. The premature stopping of the fermentation process is the winemaker’s nightmare. The winemaker wants the yeast to multiply until the last trace of sugar has been consumed. This is the only way to produce the maximum amount of alcohol.

The fermentation process is a complicated series of chemical reactions. French Scientist Gay-Lussac in 1810 was the first to document that each sugar molecule was converted into 2 molecules of ethanol and 2 molecules of carbon dioxide. His general formula for turning sugar into alcohol is as follows:
\[ \text{C}_6\text{H}_{12}\text{O}_6 \text{ (sugar)} \rightarrow 2\text{C}_2\text{H}_5\text{OH} \text{ (alcohol)} + 2\text{CO}_2 \text{ (carbon dioxide)} + \text{heat} \ (6). \]
\[ \text{MW=180} \quad \text{MW=46} \]
Gay-Lussac provided the foundation for enology. From the equation, theoretically 180 grams of sugar will produce 92 grams of alcohol (10). But in actuality, traces of the sugar are used to produce several other by products such as glycerol, succini acid, lactic acid, 2,3-butandiol, acetic acid and others (5). This formula is the backbone of the chemistry of wine fermentation.
Following the fermentation process, all that is needed is time. The vintage will be aged to perfection. The components needed to create a great bottle of wine include grapes selected with the perfect combination of sugar/acid, yeast that provide the ideal tolerance to alcohol, pH and temperature, and controlling of fermentation. The wine industry is continually trying to improve the wine process. To accomplish this, a thorough understanding of the chemistry of wine is necessary. Scientists are currently working on refining yeast strains. In the future there will be yeast designed to produce the desired flavor and will be more tolerant to a wider range of alcohol contents.

The science of winemaking is an ongoing vibrant learning process that has been evolving for thousands of years. While the chemistry involved in winemaking continues to be understood more as time goes by, what remains something of a mystery is, what are the characteristics of the perfect winemaker. It is the mystery of the human element. Thus the often quoted statement that "the perfect wine is part art and part science" (3). I’ve attempted to cover the science of winemaking with this paper but the other important (some say the more important -human element) is outside the scope of this paper, as well as, the skill of its author. So cheer's and good luck to the psychologists. May all their wines be fine wines.
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Erectile Dysfunction and a Brief Introduction to Viagra.

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4-25-02

Prepared for: Chm236
Abstract

Erectile Dysfunction (ED) has plagued man since the dawn of time. ED can cause undue stress and sexual frustration between couples in a relationship.

This paper will give an introduction to erectile dysfunction. It will also cover the major causes of ED, as well as the most advanced treatment currently being used which is a chemical compound known as Viagra.

The origin of Viagra, its side effects and special precautions will also be covered in depth.

The problem with Erectile Dysfunction

Erectile dysfunction is the inability of the male to have a fully erect penis. This problem causes sexual un-fulfilment, which in turn can cause tension and strife within the relationship.

Contrary to popular belief, erectile dysfunction is a rather old problem and according to written history, dates back to as early as ancient Greece. Today it is well known that erectile dysfunction is a growing problem. ED usually effects men of age 45 and up, but men as young as 17 years of age have reported problems associated with ED.

The causes of Erectile Dysfunction

There are many causes of Erectile Dysfunction, and researchers are discovering more causes of E.D. every year. The following list is a short explanation of various ailments, which are known to cause erectile dysfunction.

Hypertension
Hypertension is a silent, but wide spread disease mainly involving high blood pressure. There are almost no other symptoms, which make this disease hard to diagnose. Experts believe that 15% of men who are hyper-tensive experience complete erectile dysfunction.

Arteriosclerosis
Arteriosclerosis, also termed hardening of the arteries, can cause blockage of the veins and arteries, which can reduce blood flow to the penis. This deficiency of blood flow to the penis can be a serious culprit of ED. According to a study published in 1985, it is found that 53% of the 440 impotent men participating in the study had narrowing of the veins/arteries due to arteriosclerosis.

Diabetes
Diabetes is a disorder in which the body does not produce enough insulin. Insulin is a transport hormone responsible for transporting glucose across the cell membrane. Sadly, this is a growing epidemic and is the largest cause of erectile dysfunction. It is proven that the older a diabetic patient gets, the more likely it is that he will develop erectile dysfunction. Men with diabetes over the duration of 35 years are seven times more likely to develop ED \((^1\) .

Alcoholism
Alcoholism is often associated with erectile dysfunction because 3-4 drinks a day over a lengthy period of time can cause neuropathy. Neuropathy is a form of nerve damage, which can hinder the normal function of nerves in the pelvic region, and can lead to ED \((^1\) .
The Psychological Relation
Abnormal psychological problems are a serious cause of ED. Problems such as depression in male patients have led to ED. Other psychological problems, which may cause ED, are Bipolar disorder, manic depressive tendencies, anorexia nervosa, narcolepsy, and problems with low self-esteem. However, through time, these psychological problems tend to pass or subside, and a normal ability for erection can return.

Age and ED
Aging certainly has a profound effect on the ability to develop a fully erect penis. As one gets older it is harder to maintain a healthy sex life due to the increasing physical limitations which come with aging. Even if there are none of the precursors, age still remains a major factor in relation to ED. For example moderate ED increased from 17% in 40 year old men to 34% in 70-year old men [1].

Neurological Damage
Neurological damage such as spinal cord injuries and strokes contribute to the problem of ED. Certain chemicals in medications, as well as illegal drugs, can lead to ED. Hormonal imbalances have also been proven to lead to some degree of ED.

Erectile Dysfunction seems to be plaguing the male population, but this does not effect only men. The problems lead to friction and dissatisfaction between couples. One might ask, is there a cure for ED? Can people suffering from a lack of an adequate sex life take control and return to a healthy level of sexual fulfillment? There is an answer to these questions, and it takes the form of Viagra.

Viagra, What is it?
Viagra is the common trade name for a chemical compound known as Sildenafil Citrate. Sildenafil Citrate is a highly selective enzyme inhibitor. The particular function for Viagra is to inhibit concentrations of phosphodiesterase #5 (PDE5) from forming. Viagra's chemical structure can be seen in the diagram below:
The lupac name for Viagra is designated to be 1-[[3-(6,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3-d]pyrimidine-5-yl)-4-ethoxyphenyl]sulfonyl]-4-methyl-piperazine citrate.

Sildenafil Citrate is a white to off white crystalline powder with a solubility of 3.5 mg/ml in water and a molecular weight of 666.7 grams/mol. Viagra (Sildenafil Citrate) is formulated as a blue, film coated round-diamond-shaped tablets equivalent to 25mg, 50mg and 100mg of sildenafil for oral administration.

Viagra, How it came to be.

As of this writing, Viagra is the latest drug in the treatment of ED, however, it did not start its existence as a drug intended to treat ED, as we will soon see.

In 1986, scientists in the Pfizer laboratories created a chemical called Sildenafil Citrate, which they had considered as a candidate for the treatment of angina. Rigorous drug testing began in order to prove sildenafil’s potential as a leading replacement for the older angina medications.

After many field tests and double blind placebo tests, it was realized that sildenafil citrate was a failure in the treatment of angina. There were two interesting side effects which were observed in patients. The first was temporary impairment of color vision (mainly blue/green hues), and the other side effect, which was only observed in male patients whom were involved in the studies, was restored erectile function.

This astonishing side effect left the researchers baffled. The Pfizer researchers discontinued the angina testing and concentrated on the side effect which sildenafil had on male patients. The researchers began by posing the question: Is sexual health linked to the vascularity in a manner that can be treated with a single pill? With that question, and the recent discovery, a team of Pfizer researchers lead by Dr Ian Osterlich began testing sildenafil, this time as a possible treatment of ED.

Shortly after the new research began, Pfizer began clinical testing with more than three thousand men worldwide. Those tested had ED due to various issues such as hypertension, diabetes, arteriosclerosis, and other miscellaneous physiological problems. In the experimental group 82% of the patients included in the study experienced return of a fully functional erection, while a control group taking placebos experienced a 20% increase in erections. The studies have shown sildenafil to be effective in a wide range of patients: diabetics, patients treated for hypertension, patients with spinal cord injury, prostatectomies, depression, and/or ED due to psychogenic origins.

After thousands of tests, countless man-hours of research, and 500 million dollars, sildenafil was approved by the Food and Drug Administration, and it was given the trade name of Viagra.

How Viagra Works

During the time that sildenafil went through its initial angina testing, a group of scientists unrelated to Pfizer discovered that nerves in the penis release nitric oxide (NO) which then increases cyclic guanosine monophosphate (CGMP). CGMP is a chemical responsible for smooth muscle relaxation, which is imperative to achieve an erection. An enzyme called PDE5 is produced; PDE5 is responsible for converting CGMP to
guanosine monophosphate (GMP) this causes the smooth muscle to constrict. The following chart displays the relationship between the function of each enzyme, and the role Viagra plays.

**How Viagra works to help you achieve and maintain an erection**

- **Endothelial cells**
- **NANC** → NO
- **NO** is released from neurons and endothelial cells (lining the arteries), increasing the amount of smooth muscle cGMP; increased levels of cGMP are involved in smooth muscle relaxation; this, in turn, leads to penile erection. Next, cGMP is converted back to GMP by PDE5. Viagra is a highly selective inhibitor of PDE5 and prevents the breakdown of cGMP; thus, premature loss of erection does not occur.

| NO | Nitric oxide |
| NANC | Nonadrenergic-noncholinergic neurons |
| GTP | Guanosine triphosphate |
| GMP | Guanosine monophosphate |
| cGMP | Cyclic guanosine monophosphate |
| PDE5 | Phosphodiesterase type 5 |

Since sildenafil is a highly selective PDE5 inhibitor, it prevents cGMP from being broken down, allowing the patient to maintain an erection for the duration in which the drug exists in the body.

Once the patient ingests Viagra, he must be aroused in order to achieve an erection. Viagra will not give the patient an instant erection, Viagra is not an aphrodisiac. The patient can achieve an erection through self-stimulation, or stimulation by a partner.

Pfizer states that the average duration of Viagra is usually one hour after the chemical enters the blood stream, however, duration depends on factors such as metabolism and cardiovascular fitness.

**Side Effects of Viagra**

Now that Viagra has been released to the public, one might ask, are there any risks involved with taking this new wonder drug? The answer is yes. There are indeed risks associated with taking Viagra. Any time a patient begins taking a new medication, he might experience a change in homeostasis, Viagra is no exception.

In one study, 734 men received Viagra. The most common side effects were headaches. A very interesting side effect, first observed in the initial test studies was a visual disturbance, mainly with difficulties in distinguishing blue/green hues. Though the side effect usually cleared up within 2 to 6 hours. In placebo controlled clinical studies, the discontinuation rate due to adverse side effects for Viagra (2.5%) was not significantly different from placebo test (2.3%) [9]. The most common side effects for Viagra can be found in the following table.
### Adverse Events Reported by

≥2% of Patients Treated with Viagra and More Frequent on Drug Than Placebo

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Percentage of Patients Reporting Event</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>VIAGRA (N=734)</td>
</tr>
<tr>
<td>Headache</td>
<td>16%</td>
</tr>
<tr>
<td>Flushing</td>
<td>10%</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>7%</td>
</tr>
<tr>
<td>Nasal Congestion</td>
<td>4%</td>
</tr>
<tr>
<td>Urinary Tract Infection</td>
<td>3%</td>
</tr>
<tr>
<td>Abnormal Vision†</td>
<td>3%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>2%</td>
</tr>
<tr>
<td>Rash</td>
<td>2%</td>
</tr>
</tbody>
</table>

†Abnormal Vision: Mild and transient, predominantly color tinge to vision, but also increased sensitivity to light or blurred vision. In these studies, only one patient discontinued due to abnormal vision.

The most serious side effect with any medication can be death. Since Viagra’s release onto the healthcare market, there have been some deaths which have been directly related to Viagra. First 6 deaths were reported with Viagra, then 69, then by November 1998, just seven and a half months after Viagra was introduced, the FDA reported 130 deaths in men taking Viagra (actually 242 deaths were reported, but the FDA excluded 112 deaths as unverifiable [3]). “Researchers from Cedars-Sinai Medical center in Los Angeles analyzed post-marketing surveillance data and found 522 deaths and 517 MIS associated with sildenafil use among American men from April 1998 to May 1999. Two thirds of the deaths occurred within 4 to 5 hours of sildenafil administration [6].

Since deaths have been reported from the use of Viagra, researchers and doctors have attempted to explain this phenomenon. The first possible explanation for the cause of death is pre-existing heart conditions or hypertension, which had gone undiagnosed before the administration of Viagra. Another explanation for the deaths might be due to patients whom take well over the recommended dose in the hopes of better performance. Pfizer is alarmed about the misuse of its drug, Viagra, and the company is reiterating its guidelines for the safe prescription of sildenafil [3]. Though these theories have not been proven beyond a doubt, they do indeed offer some insight to the tragic deaths, which have resulted from the use of Viagra.

There are deaths, which can be related to almost every medicine since the dawn of time. Though there have indeed been deaths related to Viagra, doctors believe that if the recommended doses are followed strictly, Viagra can improve one’s life rather safely.

**Warnings**

Pfizer warns that patients whom are taking nitrates such as nitroglycerine, absolutely can not take Viagra. Although data is lacking, ingesting sildenafil and nitrates within a 24-hour span appears to significantly increase the risk of life-threatening hypertension, which can precipitate heart attack or death [6]. Patients with heart disease should avoid taking Viagra due to possible complications.
Future Drugs To Combat ED

Viagra currently leads the way in treatment of ED, however, other treatment options will be available shortly. Two promising challengers for center stage are Vardenafil, a product from Bayer, and Cialis, which comes from a company called Icos-Lilly. Vardenafil appears the most promising: It works faster and longer than Viagra and has a better side-effect profile. Cialis has been touted as the “weekend drug” for its potential 24-hour effectiveness, as opposed to four hours of effectiveness for Viagra.

Another drug which may prove to be a for-runner to the success of Viagra, is a drug called Vasomax. Vasomax is a product from the pharmaceutical company known as Zonagen. Men taking the 40mg Vasomax pill had a 40 percent success rate versus the 17 percent improvement achieved by men taking the placebo. While these initial figures do not appear as astounding as the Viagra success data, it does offer people an alternative choice in treatment of their problem.

These drugs as well as others are being developed to help people combat the misery of ED. Only time will tell the story of how effective these medications are, and what side effects can be expected from extended use. Viagra is the only effective drug for treatment of ED to which all others will be measured against.

Theories

ED is mainly caused by such ailments as hypertension, heart disease, and diabetes. These ailments can mainly be associated with poor diet, lack of exercise, or undue stress. From my experiences in life, human beings are creatures of habit, usually poor habits, and are mostly unwilling or unable to change. Therefore, it is my belief that we will never see the end of ED. It will be a problem that will continuously plague men, and trouble couples for the rest of our existence.

Viagra is a step in the right direction. It has proven itself to be very capable in combating ED, and improving the lives and sexual relations of many couples. This is the “wonder drug,” the most advanced treatment of ED in current use. Many patients are very grateful to have Viagra enter their lives, and turn frowns upside down so to speak. But there are many more patients who are afraid to take Viagra due to heart disease, or hypertension. There are many more patients who cannot afford Viagra, at $22 dollars a pill, some people are still left frustrated, and feel cheated, but there is still hope.

New drugs are on the way to combat ED. The competition has begun for Viagra, and it will only be a little while before more deaths associated with Viagra are reported to the FDA. It is my belief that Viagra has a good chance of being pulled from the market, due to the amount of deaths which have been associated with it. This is indeed is sad news for those that have become reliant on Viagra, but with the new discoveries and advances in medicine new treatment for ED is sure to be available shortly.
BIBLIOGRAPHY


Positron Emission Tomography: The future of brain imaging

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By: Dan R. Gilbert
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Positron Emission Tomography (PET): The future of brain imaging

I. Abstract
Positron emission tomography (PET) is one of the most powerful imaging techniques for modern medicine. The following selection will elucidate many characteristics and key components of this modality. In addition, a few experimental illustrations are included to highlight the importance of PET. The paper will discuss the success and limitations of PET for identifying neurological diseases and other physiological functions.

II. Introduction
Imagine for a moment that you have just opened your eyes. You are disoriented and your head is radiating pain from the right side. You slowly realize that you are in your bathroom. You scan the bathroom from your back and notice that everything seems to be normal minus the blood on your shirt. As you turn your head to the left you recoil in horror at the site before you. You make your way to your feet and frantically race to the nearest phone. Your journey to the phone is a difficult one. Keeping your balance is extremely challenging and as you continually stumble into the wall on your left. With trembling fingers you dial 9-1-1. As soon as the emergency operator answers you tell them to send the police. With great confusion and fear you explain that someone has broken into your house, struck you in the head and placed a severed arm and leg beside you. A few days later you find yourself in a hospital with a neuropathologist trying to explain what has happened. The doctor explains that you slipped in the bathroom and hit your head on the counter. He claims that you lost consciousness and obtained a serious lesion to the posterior parietal lobe of your brain. In addition, he tells you that no one actually broke into your house and in fact, it was your own arm and leg lying beside you in the bathroom.

In very rare circumstances, individuals with lesions of the nondominant (usually right) posterior parietal lobe develop agnosia. Agnosia is essentially a “deficit in body image and in the perception of spatial relations (1).” Somatic sensations remain intact despite the patient failing to recognize one side of their body. They fail to dress, undress, wash or even recognize the afflicted side. In severe instances the individual may even ask “who put this arm and leg in bed with me?” This is just one frightening example of a brain abnormality that scientists and doctors fail to understand completely. Many of these impairments are degenerative diseases that take decades to manifest. Our knowledge of the human brain is shockingly limited, which can seem surprising considering some of the accomplishments humans have made. After all we’ve landed on the moon, broke the speed of sound, created an artificial heart and (to the chagrin of many) cloned several different organisms. So how is it we know so little of the human mind. Well, consider this. It has over 100 billion discrete nerve cells, interconnected in systems that provide us with many different abilities (1). Into this mathematical nightmare, include the incredible variability that each mind possesses, and the task seems daunting. Enter Nuclear Medicine.
The basis for nuclear medicine and positron emission tomography (PET) began in the 1920’s when Dr. Hevesy first used radio-indicator techniques in living organisms (2). In the 1950’s W. Sweet and G. Brownell experimented with positron emitting tracers and in 1975 Ter-Pogossian, Phelps and Hoffman built the first PET scanner (3). That apparatus shared many of the same components (albeit much more primitive) as the ones used today in hospitals and research facilities. PET has since developed into one of the most powerful tools available to the medical community. PET’s successful ability to image neurological dysfunction is just one example of its power.

Although the images this modality produces lack the precise resolution that computerized tomography (CT) or magnetic resonance imaging (MRI) does, it gives feedback on the functionality of the organ in question. Furthermore, the resolution is rapidly improving with better instrumentation and techniques. With this possibility and our expanding knowledge of brain function, there is an exciting future for PET. With PET a radiologist will likely be able to diagnose a brain disorder years before the effects take place, virtually eliminating the need for investigational surgery. As Michael Kuchar, a specialist in radiopharmacology states, “PET scanning in neuroscience and clinical medicine is providing a window into the human body that was never dreamt possible just 15 or 20 years ago (4).

III. What is PET?

PET is a technique that uses positron-emitting radiopharmaceuticals with an advanced tomographic apparatus to take cross-sectional images of an organ’s physiological processes. This is built on the nuclear fundamentals of physics and chemistry. PET relies on an unstable atom with an excess of protons in the nucleus, relative to the number of neutrons. As the proton decays in the nucleus it gives off a positron (an antimatter electron). As soon as the positron comes to rest it undergoes annihilation with an oppositely spinning electron. This collision causes the release of a large amount of energy in the form of gamma radiation. Two gamma photons (\(\gamma\)) are emitted from this location at an angle of 180° (5). It is with this phenomena (which obeys the law of conservation) that the gamma camera, which detects the radiation, can locate where the radiopharmaceutical was absorbed in the body (5). Unfortunately, because the gamma camera detects the energy of annihilation after the positron travels a certain distance in tissue the resolution of the image is compromised (2). Examples of these positron-emitting isotopes are Carbon-11 (half-life 20 minutes), nitrogen-13 (half-life 10 minutes), fluorine-18 (half-life 110 minutes) and oxygen-15 (half-life 2 minutes) (2). The advantages of using molecules such as these, lay in their organic characteristics. Each of these radionuclides exists in a stable form within our bodies. Because of this, the isotopes don’t perturbate the organic pharmaceutical that binds with the particular neuroreceptor or other body structure.

The hardware of a PET scanner essentially consists of a ring of detectors that surround the patient. Attached to each detector is a collimator. The collimator facilitates localization of the signal by only allowing single-plane gamma rays to pass through. The detectors are crystal plates (often made from bismuth germinate) that absorb the gamma photons (3). The origin of annihilation is traced when opposing detectors absorb the same gamma photon. When these photons are absorbed the detectors emit small bursts of light (a process called scintillation). A polymer (or alloy coating) directs the light into
Photo Multiplier Tubes (PMT). PMT’s essentially amplify and analyze the signals from the crystals. Immediately following, a series of circuits and amplifiers refine the signals and send them on to a computer. The computer can then process the information and reconstruct an image (3). In addition, a PET facility must house or have immediate access to a cyclotron. A cyclotron, which will be discussed later, is an apparatus that produces the short-lived isotopes.

The general procedure of a PET scan is relatively quick and painless. The patient is initially injected with a radiopharmaceutical: A solution that contains a mixture of an isotope bonded to an organic molecule, such as a sugar. The patient is asked to rest for 35 to 45 minutes while the pharmaceutical is acquired by the organ(s) of interest. After this time, the patient sits on the examination table, which passes through the PET scanner. The PET computer records signals and an image of the patient’s metabolic functions is reconstructed. Once the image is processed onto film or a computer system a radiologist can decipher the data (2).

IV. What are the advantages and disadvantages of PET?

One of the primary advantages of PET is its ability to image metabolic and physiological functions in the body. Other modalities, such as MRI and CT are designed to image gross anatomy. These static images are very useful in certain instances. However, it is common for physiologic changes to develop long before structural changes. Mental disorders are a glaring example of this fact. Alzheimer’s Disease (AD) presents itself in the patient many years before definite symptoms actualize. In addition, positron tomography has an acute ability to identify cancer, coronary artery disease, Parkinson’s disease, epilepsy, and Huntington’s Disease (HD) (6). The resolution and acuity of PET scans has dramatically improved over the last decade and shows no signs of slowing. The last 20 years have demonstrated PET as the most prosperous discipline for imaging brain abnormalities. This speaks volumes, considering it is an area of the body that is, arguably the least understood. Another huge advantage to PET is the use of organic isotopes (i.e. 15O and 18C). This characteristic allows the body to integrate the isotope in a normal biological fashion (3). This is in opposition to general nuclear medicine imaging, which relies on bulky isotopes like technetium-99m. Finally, PET’s infinite power relies heavily on its ability to non-invasively examine pathophysiology. Post mortem examination of patients with neurological disorders (i.e. Alzheimer’s, Parkinson’s) complicates data with more variability (7). Many secondary alterations occur in the human brain following initial symptoms (i.e. lesions). Therefore PET affords us the opportunity to examine more cause than effect for a particular disease (8).

Like all modalities PET has problems as well. Although the quality of the image has improved exponentially there are still acuity issues. Blurring is a large drawback to this discipline as it prevents small regions of the brain and the edges of larger structures from being visualized. As Jonathan Links in Quantitative Imaging states, “By definition, the structures visible with (PET) can only represent those portions of anatomical structures that are functionally active (6). However, PET, when used with other modalities (MRI and CT), can delineate specific structures better. This is invaluable to “determine the position(s) of the slice(s) of interest prior to actual acquisition of PET data (6).” This eliminates the need for PET to depict the structure in question by itself. Another issue with PET is certain illnesses can cause changes in regional blood flow,
which alters the delivery of a radiopharmaceutical to the targeted structure. Thus significant variability between patients can be a problem (7). Patients might also be sensitive to certain radiopharmaceuticals. As Dannals et al state, “...idiopathic or allergic reactions to drugs administered to humans in vivo are possible (7).” However, this is exceedingly rare. Another complaint with PET is the inability to precisely locate the origin of a specific gamma photon (a.k.a. resolution). Occasionally the positrons will “scatter” when contacting a nucleus in the tissue. The photon and electron depart from the site of annihilation at an unknown angle. The photon detected by the PET crystals is unpaired and thus does not show up on the image. This means that the amount of radiation emitted from a patient is always underestimated. However, this complication can be corrected by using a calibration device to ascertain the amount of positron “scattering” and tissue attenuation that each individual exhibits. In addition, the cost of PET is still too high for very practical use. It is estimated that a PET facility will spend upwards of 3.5-4.0 million dollars on equipment alone, while one clinical PET study remains at approximately $1,000-1,500 (3). However, many more institutions are making this investment and driving the cost down. Regardless of these drawbacks to PET scanning, the positives far outweigh the negatives. When used in concert with other imaging modalities PET scanning can dramatically accelerate our understanding of brain abnormalities. In vivo experiments will continue developing more receptor-selective radiopharmaceuticals creating limitless possibilities for PET.

V. The Radiopharmaceutical

It goes without saying that the success of PET hinges largely on the radiopharmaceuticals used. The quality of the radiotracer can make the difference between an accurate image and useless one. The research that goes into developing these substances is intensive and requires vast amounts of knowledge and time. The art of radioligand production demands a mastery of physics and nuclear chemistry along with precision that is unequaled.

The first useful isotope discovered was iodine-131 (half-life 8 days) by Livingood and Seaborg (3). Intense research began in 1939 when Ernest Lawrence developed the first “medical cyclotron” for “quick” production of isotopes. Nuclear fission followed closely on that discovery's heels. This practice flourished following World War II leading to major production sites in Oak Ridge, TN and Hanford, WA. In 1951, a radioisotope generator was designed, which was similar to the units used in today’s medical community (3).

There are many important components to consider when designing radiopharmaceuticals. The gamma photons that the isotope emits must be within a particular range of energy. If the energy is too low the gamma camera will not detect the radiation, while higher radiation will not be collected accurately by the crystals and collimators on the apparatus. In addition, it is very important to have a relatively stable isotope that will not shed electrons or alpha protons, which increases tissue damage in the body (3). Furthermore, the half-life of the isotope must be long enough to allow for proper acquisition and uptake in the body. Suitable half-lives can range from a few minutes (oxygen-15) to a few hours (Fluorine-18)(7). Radioisotopes must also be relatively easy to produce and moderately inexpensive. There are three major ways that isotopes can be produced. Nuclear fission of plutonium or uranium is one example.
Another way is with the use of a cyclotron (A primary source for PET). This process involves the bombardment of nuclei with alpha protons or deuterons in the cyclotron apparatus. This practice is the most impractical of the three but, because it can be done on-site, is vital for the production of shorter-lived isotopes. An example of an equation that describes isotopic production might look something like the following:

\[ ^{99}\text{Mo} (n,\gamma) ^{100}\text{Mo} \]

Fig. 1

The parent element is written on the left and the product on the right. The ‘n’ represents the particles used to bombard the target (in this case it is neutrons) and the ‘γ’ indicates type of radiation emitted (3) (Fig. 1). The third method employs the use of radiotracer generator. This technique separates a parent nuclide into a shorter-lived daughter radionuclide. This is the most practical and popular technique used for nuclear medicine because it creates longer-lived isotopes.

The second component of the radiopharmaceutical is the pharmaceutical. Because of the expense of producing an isotope, it is imperative that the pharmaceutical be easy to produce and inexpensive. In addition, it is important that the pharmaceutical combine easily with the isotope (called isotopic substitution). Any perturbation to the pharmaceutical by the added isotope can cause the compound to react somewhat unexpectedly in the human body. Again, this demonstrates why the organic isotopes produced for emission tomography are so biologically interesting. They lead to an easy addition reaction with the pharmaceutical allowing it to behave predictably. Furthermore, when producing a radiotracer, sufficient purification is essential (usually with high-performance liquid chromatography (HPLC) to remove any of the stable starting material (called carrier contamination)(2). Otherwise the radioactivity can be severely limited. Finally, the pharmaceutical must be highly selective (before and after it is labeled) for the neuroreceptor in question. For example, rather than targeting mu, kappa, and delta-type opiate receptors the ligand should be specific for just one of the three receptors (2).

Countless hours of exhausting research have been dedicated to composing viable radiotracers for scientific and medicinal applications. The following are some simple isotopic substitution reactions to illustrate a few procedures. One such example is the addition of carbon-11 to IMB (a benzamide) (Fig. 2).
This substituted benzamide is called $^{11}$Craclopride and is a very successful radiotracer of D2 dopamine receptors for PET scans (fig. 2). In this organic reaction a hydrogen molecule is replaced, by means of alklylation, by $^{11}$Cmethylidoxide. Dimethylformamide (DMF) and HPLC are a catalyst and purifier respectively (2). An even less-complex example might be the combination of a Grignard reagent with $^{11}$Ccarbon dioxide and acid (fig. 3).

Fig. 3

This reaction is an oversimplified illustration of radiopharmaceutical production. An organic chemist would not likely use this reaction for a number of reasons. In particular, $^{11}$Cacetic acid would be harmful to the human body and the radioactivity would probably be insufficient. Grignard Reagents are very sensitive to carrier carbon (12C) contamination, which as previously stated, exponentially reduces the specific activity of the isotope. Nevertheless, it serves as an easy illustration of radiopharmaceutical production. A more likely molecule, which is relatively easy to produce and very effective, is atipamezole. In Quantitative Imaging D. Roeda et al demonstrate this by taking an 11-Carbon isotope of carbon dioxide from a cyclotron and reducing it with lithium aluminum hydride in THF (9). This reduced product is then reacted with a silver containing catalyst to give $^{11}$Cformaldehyde (fig. 4). 2-ethyl-2-oxoacetylindane is then combined with the formaldehyde isotope in aqueous THF, zinc oxide and ammonium hydroxide to yield the product (9).

Fig. 4

The labors that have produced radiopharmaceuticals (such as those listed above) are invaluable to modern medicine. They give PET and nuclear medicine in general, the uniquely powerful ability to non-invasively image functional physiology. Furthermore, the extent of this “power” is far from realized. As medicine uncovers more about the human brain and its function from nuclear medicine, the diagnostic ability of PET will increase without limit.

VI. Experimental Illustrations of PET

Now that the fundamentals of PET are presented, what clinical data supports its success? The research community is saturated with literature describing the clinical success of PET. However, the true test is to separate out the “quality” research. Much of the research that exists presently is still far from scientifically sound and is only
theoretical in nature. One positive to this is that most of the theoretical research and initial data strongly support PET’s clinical necessity.

Researchers at the University of Pittsburgh School of Medicine recently carried out an experiment using PET imaging on Bulimia Nervosa patients. Their data showed significant support for the theory that people whom are recovering from this eating disorder show a neurophysiological abnormality (10). PET images visualized a decreased binding of the radiopharmaceutical ([18F]altanserin) to the 5-HT2A receptor, which contributes to altered feeding, mood or impulse control (10). This implies that people recovering from eating disorders may need special neurological therapy in order to prevent remission. Once this implication is further evaluated there may be a need to develop therapeutic drugs which combat this abnormality.

In another study, Feigin, Leenders, Moeller, Missimer, Kuenig, Spetsieris, Antonini and Eidelberg used PET to examine Huntington’s Disease (HD). The radiotracer [18F]FDG (fluorodeoxyglucose) was injected into a group of preclinical HD patients and gene-negative relatives and contiguous PET images were taken. They demonstrated that discrete patterns of metabolic abnormality existed in the preclinical HD carriers. Feigin et al concluded that this could provide a useful means of quantifying the rate of disease progression during the earliest stages of the disease (11).

Perhaps, the most energy has been expended trying to unravel the mystery of Alzheimer’s Disease (AD). It is arguably the most devastating and least understood common neurodegenerative disease that exists today. PET has been heavily relied on for untangling the web and so far has had relative success. Thomas Chase, an authority on AD detection states that PET solidifies the “...possibility that a linkage can be established between a particular set of neurological signs and dysfunction in a particular transmitter system (8).” Much of the current literature presented by PET imaging supports the argument that AD is characteristically selective in neuronal degeneration. In this study Chase et al show that the PET-FDG exam indicates the identification of particular transmitter system alterations responsible for the dementia of AD (8). Two of these systems they identified were the cholinergic system and the GABA system. These profound results indicate success in treating an isolated transmitter system in an AD patient.

VII. Conclusion

Even with all of the promising experiments, such as those listed above, there is a long way to go before understanding the causes and treatments for these devastating neurological diseases. Nevertheless, PET has allowed the opportunity to come much closer to unraveling the mysteries. PET is still a modality in its infant stages (especially when imaging brain function). The spatial resolution and sensitivity of PET apparatuses are still major obstacles preventing the discipline from realizing its potential. Undoubtedly, as medicine progresses PET will be heavily emphasized as a premier imaging tool. As this occurs, more money will be dedicated to its refinement and the cost of this clinical procedure will fall dramatically. Ideally the exam will become as routine as a physical and countless numbers of people will avoid the horrific effects of neurological diseases like AD and HD. The development of new radiotracers for imaging is just one example of future possibilities. Many in vitro radiopharmaceuticals have been discovered for the imaging of countless receptor and binding sites. However, the in vivo
imaging ligand area is still grossly limited (4). In addition, the range of radiopharmaceuticals must be expanded. Rather than just receptor sites, uptake sites, “false” neurotransmitters, and neurotransmitter metabolism should be closely examined (2). Likewise, instrumentation and mathematical modeling should be an area of future focus. Integration of modalities such as MRI and CT with PET is also a relatively unexplored technique. Combining detailed images of gross anatomy with pathophysiological images is undoubtedly the future of medical imaging. This will result in a significant decrease in examination time and cost. Regardless of current limitations the present success of PET indicates a very promising future for diagnostic imaging.

VIII. References


RITALIN
(Methylphenidate hydrochloride)

Submitted to Dr. Mancini, Paradise Valley

By
Josh Gilliland
04-20-02
Abstract

The drug Ritalin and Ritalin-SR have been used for years to treat narcolepsy and attention-deficit disorders. Ritalin is a stimulant. It is effective on reducing the hyperactivity, distractibility, and impulsiveness of school children and adults alike. It has been used for years, but not without controversy. This paper will discuss the chemistry, structure, synthesis, benefits and side effects of Ritalin.

Ritalin hydrochloride, methylphenidate hydrochloride, chemical name methyl α-phenyl-2-piperidineacetate hydrochloride is a mild central nervous system stimulant used to treat narcolepsy (sudden and uncontrollable attacks of drowsiness and sleep) and attention-deficit disorders. The molecular formula of methylphenidate is C_{14}H_{24}N_{0.5}, and it has the molecular weight of 269.77 g. Its structural formula is

\[
\text{COOCH}_3 \quad \text{CH} \quad \text{CH} \quad \text{HN} \quad \text{HCl}
\]

Methylphenidate hydrochloride is a white, odorless, fine crystalline powder. On litmus paper the solutions are acidic. It is freely soluble in water and methanol, soluble in alcohol, and slightly soluble in chloroform and acetone. One way to synthesize the racemic chiral methylphenidate is using Doyle’s Rh\textsubscript{2} (S-MEPY)\textsubscript{4} catalyst as follows.

![Synthesis Reaction Diagram](attachment:image)

This process involves an asymmetric C-H insertion reaction at the position of the
N-Boc piperidine with methylphenyl diazoacetate, in the presence of a Rh catalyst, followed by the deprotection of the Boc. Doyle's Rh$_2$(S-MEPY)$_4$ catalyst gave a 69% ee for the $d$-threo-isomer with very good selectivity ($de = 95$), he was able to improve the ee to 95% by two recrystallizations.

Methylphenidate hydrochloride is mainly used to treat attention-deficit disorders, which were previously known as Minimal Brain Dysfunction in Children. Other terms describing the behaviors include Hyperkinetic Child Syndrome, Minimal Brain Damage, Minimal Cerebral Dysfunction, and Minor Cerebral Dysfunction. Although we know that methylphenidate is a mild central nervous system stimulant the mode of action in man is not completely understood, but it presumably activates the brain stem arousal system and cortex to produce its stimulant effect. There is no evidence which clearly establishes the mechanism whereby Ritalin produces its mental and behavioral effects on children, there is also no evidence regarding how these effects relate to the condition of the central nervous system.

Ritalin is to be used as only part of a whole treatment program which usually includes other remedial measures (psychological, educational, social) for stabilizing effect in children with a behavioral syndrome characterized by the following group of developmentally inappropriate symptoms: moderate to severe distractibility, short attention span, hyperactivity, emotional liability, and impulsivity. The diagnosis of this syndrome should not be made with finality when these symptoms are only of comparatively recent origin. Nonlocalizing (soft) neurological signs, learning disability and abnormal EEG may or may not be present, and a diagnosis of central nervous system dysfunction may or may not be warranted.

Be aware that specific etiology of this syndrome is unknown, and there is no single diagnostic test. Adequate diagnosis requires the use not only of medication but of special psychological, educational and social resources as well.

Some of the characteristics commonly repeated include: chronic history of short attention span, distractibility, emotional liability, impulsivity and, moderate to severe hyperactivity; minor neurological signs and abnormal EEG. Learning may or may not be impaired. The diagnosis must be based upon history and evaluation of the child and not solely on the presence of one or more of these characteristics.

Drug treatment is not indicated for all children with this syndrome. Stimulants are not intended for use in the child who display symptoms secondary to environmental factors and/or primary psychiatric disorders, including psychosis. Appropriate educational placement is essential and psychosocial intervention is generally necessary. When remedial measures alone are insufficient, the decision to prescribe stimulant medication will depend upon the physician's assessment of the chronicity and severity of the child's symptoms.

Ritalin is available tablets of 5, 10, and 20 mg for oral administration. The come
in bottles of 100 tablets. 5 mg tablets are round yellow pills with the imprint CIBA 7. 10 mg tablets are round, pale green pills with the imprint CIBA 3. Energy: 1.88 kJ (0.45 Kcal). 20 mg tablets are round, pale yellow pills with the imprint CIBA 34. Energy 2.4 kJ (0.58 Kcal). Ritalin-SR is available as sustained-release tablets of 20 mg for oral administration they also come in bottles of 100 tablets. They are round, white pills with the imprint CIBA 16. Energy 1.55kJ (0.37 Kcal).

The recommended amount of Ritalin to be taken by adults is in doses 2-3 times daily, preferably 30-45 minutes before meals. Average dosage is 20 to 30 mg daily. Some patients may require 40 to 60 mg daily. In others, 10-15 mg daily will be sufficient. Patients who are unable to sleep if medication is taken late in the day should take the last dose before 6 pm. Ritalin-SR tablets have a duration of action of approximately 8 hours. Therefore, Ritalin-SR tablets may be used in place of Ritalin tablets when the 8 hour dosage of Ritalin-SR corresponds to the titrated 8 hour dosage of Ritalin. Ritalin-SR tablets must be swallowed whole and never crushed or chewed.

The recommended amount of Ritalin to be taken by children 6 years or older is to start with small doses, and slowly work up in weekly increments. Daily dosage above 60 mg is not recommended. If improvement is not observed after appropriate dosage adjustment over a one-month period, the drug should be discontinued. For tablets start with a 5 mg twice daily (before breakfast and lunch) with gradual increments of 5 to 10 mg weekly.

As in adults, Ritalin-SR tablets have a duration of action of approximately 8 hours. Ritalin-SR tablets may be used in place of Ritalin tablets when the 8-hour dosage of Ritalin-SR corresponds to the titrated 8-hour dosage of Ritalin. Ritalin-SR tablets must be swallowed whole and never crushed or chewed. If paradoxical aggravation of symptoms or other adverse effects occur, reduce dosage, or, if necessary, discontinue the drug. Ritalin should be periodically discontinued to assess the child's condition. Improvement may be sustained when the drug is either temporarily or permanently discontinued. Drug treatment should not and need not be indefinite and usually may be discontinued after puberty.

Signs and symptoms of acute over dosage, resulting principally from over stimulation of the central nervous system and from excessive sympathomimetic effects, may include the following: Vomiting, agitation, tremors, hyperreflexia, muscle twitching, convulsions, euphoria, confusion, hallucinations, delirium, sweating, flushing, headache, hyperpnea, tachycardia, palpitations, cardiac arrhythmias, hypertension, mydriasis, and dryness of mucous membranes. Consult with a Certified poison Control Center regarding treatment for up-to-date guidance and advise.

Methylphenidate is rapidly and extensively absorbed from the tablets following oral administration, however owing to extensive first-pass metabolism, bioavailability is low (approx. 30%) and large individual differences exists (11 to 52%). In one study, the administration of methylphenidate with food accelerated absorption, but had no effect on
the amount absorbed.

Peak Plasma concentrations of 10.8 and 7.8 ng/mL were observed, on average, two hours after administration of 0.30 mg/kg in children and adults, respectively. However, peak plasma concentrations showed marked variability between subjects. Both the area under the plasma concentration curve (AUC), and the peak plasma concentrations (C(max)) showed dose-proportionality.

Methylphenidate is eliminated from the plasma with a mean half-life of 2.4 hours in children and 2.1 hours in adults. The apparent mean systemic clearance is 10.2 and 10.5 L/hr/kg in children and adults, respectively for a 0.3 mg/kg dose. This data indicates that the pharmacokinetic behavior of methylphenidate in hyperactive children is similar to that in normal adults. The apparent distribution volume of methylphenidate in children was approximately 20 L/kg, with substantial variability (11 to 33 L/kg).

Following oral administration of methylphenidate, 78 to 97% of the dose is excreted in the urine and 1 to 3% in the feces in the form of metabolites within 48 to 96 hours. The main urinary metabolite is ritalinic acid (alpha-phenyl-2-piperidine acetic acid, PPAA); unchanged methylphenidate is excreted in the urine in small amounts (<1%). Peak PPAA plasma concentrations occurred approximately the same time as peak methylphenidate concentrations, however, levels were several-fold greater than those of the unchanged drugs. The half-life of PPAA was approximately 20L/kg, with substantial variability (11 to 33 L/kg).

In blood, methylphenidate and its metabolites are distributed between plasma (57%) and erythrocytes (43%). Methylphenidate and its metabolites exhibit low plasma protein binding (approx. 15%).

Methylphenidate in the extended-release tablets are more slowly, but as extensively absorbed as regular tablets. Relatively bioavailability of the Ritalin SR tablet, compared to the Ritalin tablet, measured by the urinary excretion of methylphenidate major metabolite (PPAA), was 105% (49-168%) in children and 101% (85-152%) in adults. The time peak rate in children was 4.7 hours (1.3 to 8.2 hours) for the extended-release tablets and 1.9 (0.3 to 4.4 hours) for the regular tablets. The elimination half-life and the cumulative urinary excretion of PPAA are not significantly different between the two dosage forms. An average of 67% of the extended-release tablet dose was excreted in children as compared 86% in adults.

Ritalin should not be taken by children under the age of six, since safety and efficacy in this age group have not been established.

Although a casual relationship has not been established, suppression of growth (i.e. weight gain and/or height) has been reported with the long term use of stimulants in children. Anyone using Ritalin for long term therapy should be carefully monitored. It is
also recommended to withhold the drug on weekends and during school holidays as much as possible.

Methylphenidate should not be used for severe depression of either exogenous or endogenous origin. Clinical experience has shown that in psychotic children, methylphenidate may exacerbate symptoms of behavior disturbance and thought disorder 8. Ritalin should not be used to prevent or treatment of normal fatigue states.

Sufficient reproductive studies to establish safe use of methylphenidate have not yet been conducted. However, in a recent study, methylphenidate has been shown to have teratogenic effects in rabbits when given in doses of 200 mg/kg/day, which is about 167 times and 78 times the maximum recommended human dose on a mg/kg and a mg/m² basis. In rats, teratogenic effects were not seen when the drug was given in doses of 75 mg/kg/day, which is about 62.5 to 13.5 times the maximum dosage recommended for a human on a mg/kg and mg/m² basis 9. Therefore until more information is available, Ritalin should not be used by older women, unless in the opinion of the physician, the potential benefits outweigh the possible risks.

Ritalin should be given cautiously to emotionally unstable patients, like people who have a history of drug dependency or alcoholism, because they might increase the dosage on their own. Repeated abusive use of methylphenidate can lead to marked tolerance and psychic dependence with varying degrees of abnormal behavior. Abrupt psychotic episodes can occur, especially with parenteral abuse. Careful supervision is required during drug withdrawal, since severe depression as well as the effects of chronic overactivity can be unmasked. Long-term follow up may be required because of patient’s basic personality disturbances.

Ritalin has been used as a recreational drug and has had drug addiction problems. One drawback to Ritalin is its popularity as an illicit drug. From 1993 - 1994 the number of high school seniors admitting to have abused Ritalin doubled, representing about 350,000 students nationwide 6. Kids refer to the drug as “Vitamin-R” “R-Ball” or “the smart drug”. Some use it to study better and others use it to just get high. One student took Ritalin in order to help focus his attention in his studies and soon he was snorting twice daily, needing more and more for the same results. They describe the feeling as hyperactive. The side effects of Ritalin addiction include strokes, hyperthermia, hypertension, and seizures. Several deaths have been attributed to the abuse of Ritalin, including one case where a high school student from Roanoke, Virginia died from snorting Ritalin after drinking a beer 7.

Although the drug is good at treating certain behaviors, it can also add some unwanted effects. Nervousness and insomnia are the most frequently seen adverse reaction, but can normally be controlled by reducing dosage and omitting the drug in the afternoon or evening. Other reactions include hypersensitivity (including skin rash, urticaria, fever, arthralgia, exfoliative dermatitis, erythema multiforme with histopathological findings of necrotizing vasculitis, and thrombocytopenic); anorexia,
nausea, dizziness, palpitations, headache, dyskinesia, drowsiness, blood pressure and pulse change both up and down, tachycardia, angina; cardiac arrhythmia, abdominal pain, weight loss during prolong usage.

There has been rare reports of Tourette’s Syndrome. Toxic psychosis has been reported. Although a definite relationship has not been established the following have been reported while taking the drug: instances in of abnormal liver function, ranging from transaminase, evaluation of hepatic coma; isolated cases of cerebral arteritis and/or occlusion; leukopenia and/or anemia; transient depressed mood; a few instances of scalp hair loss. Very rare reports of neuroleptic malignant syndrome (NMS) have been received and in most of these, patients were concurrently receiving therapies associated with NMS. In a single report a boy who had been taking Ritalin for about 18 months experience a NMS-like event within 45 minutes after taking venlafaxine. It is uncertain whether or not this case was a drug-drug interaction, a response to one alone, or some other case.

Another thing that people need to be aware of is the interactions the drug may have. Ritalin may decrease the hypotensive effect of guanethidine. Use cautiously with pressor agents. Human pharmacologic studies have shown that Ritalin may inhibit the metabolism of coumarin anticoagulants (phenobarbital, diphenylhydantoin, primidone) phenylbutazone, and tricyclic drugs (imipramine, clomipramine, desipramine). Downward dosage adjustments of these drugs may be required when given concomitantly with Ritalin.

Serious adverse effects have been observed in concomitant use with clonidine, although no causality for the combination has been established. The safety of using methylphenidate in combinations with clonidine or other centrally acting alpha-2 agonist has not been systematically evaluated.

It has been seen that the use of Ritalin can be used to treat attention-deficit disorders and narcolepsy, but not without some pretty severe side effects. In my opinion I think other means of treatment will prevail and that slowly Ritalin will stop being used. Perhaps with further research the drug will be taken off the market because of all of its side effects. Only time will tell.
Bibliography


6) www.healthsource.com/ritalin.html

A Study of Birth Control: Ortho Tri-Cyclen

Prepared for
Dr. Mancini
Paradise Valley Community College

By
Samantha Gimbel

April 26, 2002
Abstract

This report gives an overview on the oral contraceptive, Ortho Tri-Cyclen. The history and background behind the drug is discussed. Also, this paper explains the ways in which the drug is administered, the mechanism of action to synthesis of the drug, and the effects, both good and bad, of Ortho Tri-Cyclen.
Introduction

Contraception, more widely termed birth control, is a method used to reduce fertility. The phrase birth control is used more commonly because of the implications of controlling the time at which one decides to begin a family or avoid unplanned pregnancies. Here in the 21st century birth control has been deemed a socially acceptable custom. However that was not always the case.

In Canada in the 1960's, Pope Paul VI issued an encyclical condemning the birth control pill. This was revoked after Pierre Elliot Trudeau became Prime Minister in 1969. When the pill was first released in America it could only be prescribed to regulate the menstrual cycle. \(^1\) Now times have changed. The newer form of birth control, oral contraceptives, is used by 84% of American women ages 20 to 35. \(^1\) However before the release of “the pill” in the 1960’s, people found other ways to control pregnancy.

Condoms became available in 1838, but were unreliable and expensive. In the early 1900’s the intrauterine device became available. Diaphragms with spermicides became available in the 1920’s. And the unpopular method of abstinence has been used since the beginning of time. In 1937 scientists Makepeace, Weinstein, and Friedman had tested the concept of a contraceptive pill on animals. \(^2\) However, it was not until 1950 that the oral contraceptive pill was born. The man who is credited for the breakthrough is Gregory Pincus. It was Margaret Sanger, a women’s activist, who came to Pincus in 1950 and helped launch his research with a $150,000 donation that she had raised. It was then that the successful pill had become known and 10 years later in 1960, the birth control pill was released in America. \(^1\)

The first pill that was used was called Envoid. It was discovered that Envoid had 10 times the amount of hormones that were required for contraception after millions who had taken the pill had died. \(^3\) More research was done on the pill and 40 years later oral contraceptives are safe and effective. Two kinds of pills are used. Progestin only pills and combination pills containing estrogen and progestin. Some examples include such brands as Alesse (progestin only), Levora (combination of progestin and estrogen), Desogen (progestin only), and one of the newest oral contraceptives that also helps cure acne, is Ortho Tri-Cyclen (combination of estrogen and progestin).

Background

Ortho Tri-Cyclen is an oral tablet used in the prevention of pregnancies and occurrence of acne. It is the first clinically proven drug to prevent both of these phenomena. It was invented in 1989 and released in 1996 by Ortho-McNeil.\(^4\) Ortho Tri-Cyclen is a combination drug containing both the progestational compound norgestimate and the estrogenic compound ethinyl estradiol. The different chemical make-ups of the synthetic versus natural occurring hormones are outlined in figure 1.
The IUPAC name for norgestimate is (18, 19-Dinor-17-pregn-4-en-20-yn-3-one, 17-(acetyloxy)-13-ethyl-oxime. The IUPAC name for ethinyl estradiol is (19-nor-17alpha-pregna, 1,3,5(10)-trien-20-yne-3, 17-diol).

Ethinyl estradiol and norgestimate are steroid hormones. The typical molecular structure of steroids is made of 17 carbon atoms bonded to 28 hydrogen atoms. The parent structure of these molecules is a steroid nucleus or a gonane. There are many isomers of a steroid nucleus. This is what makes each one unique. With the addition of rings to the steroid nucleus provides different functional groups to each molecule.

A technique used to determine the properties of steroid chemistry is chromatography. Chromatography is used to determine the behavior of a steroid. The tests available for steroid chemistry include thin-layer chromatography, paper chromatography, and liquid chromatography.

**Administering Ortho Tri-Cyclen**

This drug is available only by prescription and is administered to women who have moderate acne vulgaris to help the breakout of blemishes along with the prevention of pregnancy. The 28-day regimen is designed in a four-week cycle, with each 7-day period containing tablets with different amounts of the synthetic hormones, norgestimate and ethinyl estadiol. The start of the cycle is a white tablet containing 0.180 mg of norgestimate and ethinyl estadiol compound. The second week is a light blue tablet.
containing 0.215 mg of the norgestimate and ethinyl estradiol compound. The third 7-day cycle is the dark blue tablet containing 0.250 mg of the combination compound. The last week of the cycle is a green tablet that has only inert ingredients.4

The tablets are to be administered at the same time each day as to aid in the effectiveness of the drug.5 Combination pills such as Ortho Tri-Cyclen are said to have a 0.1% chance of pregnancy as opposed to the progestin only pills that have a 0.5% chance of pregnancy.6 This is outlined in figure 2 along with the effectiveness of other birth control.

The Effectiveness of Contraceptives

<table>
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<tr>
<th>Method</th>
<th>% of Women Experiencing an Unintended Pregnancy within the First Year of Use</th>
<th>% of Women Continuing Use at One Year</th>
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<tr>
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<td>Perfect Use²</td>
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<td></td>
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<tr>
<td>Corticosteroid binding globulin (CBG)</td>
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</table>

Mechanism of Action:

The combination of the synthetic hormones ethinyl estradiol and norgestimate act together to prevent pregnancy. The primary action of the two hormones is to stop the hypothalamic-pituitary system and decrease the secretion of the gonadotropin releasing hormone (GnRH). Ethinyl estradiol inhibits the maturation and release of the dominant ovule by suppressing the follicle-stimulating hormone (FSH) from the anterior pituitary gland. Norgestimate thickens the mucus membrane in the uterus so that sperm are unable to penetrate an egg if it was released. This is done by stopping the luteinizing hormone (LH).5

At the cellular level, ethinyl estradiol and norgestimate diffuse into target cells and interact with a protein receptor. The receptor that ethinyl estradiol and other estrogens bind to is albumin. Norgestimate binds to the protein receptor albumin, but also binds to the sex hormone binding globulin (SHBG). The binding to the receptor causes a DNA and hormone receptor complex. Ethinyl estradiol increases the concentrations of the serum including sex hormone binding globulin (SHBG) and corticosteroid binding globulin (CBG). There, hormones are then metabolized in the GI mucus and in the liver.7 The metabolism of the two drugs is outlined in figures 4 and 5.
Figure 4

Metabolic Pathway For Estrogens

Major metabolic pathways for estrogens.
Metabolic Pathways For Progestins

Major metabolic pathways for 19-nortestosterones.
The major first pass path of ethinyl estradiol is its sulfate conjugation. It is metabolized in the liver by cytochrome P450 enzymes (CYP3A4). This causes the 2-hydroxylation which is the major oxidative reaction. The resulting 2-hydroxyethinylestradiol metabolite is transformed further by methylation and glucuronidation before being excreted as wastes. The estrogen conjugates can be hydrolyzed back to the active drug in the GI tract and then undergo entero-hepatic recycling. The difference in ethinyl estradiol and testosterone is that ethinyl estadiol lacks a C19 group. Ethinyl estradiol is has an A ring that is aromatic and is planar. Norgestimate is different in that it is considered a pro-drug. It is metabolized by hydrolysis, reduction, and hydroxylation to 17-deacetyl norgestimate, 3-ketonoergestate, and levonorgestrel. The three metabolites all undergo glucuronide and sulfate conjugation. It is thought that the 17-deacetyl-norgestimate is the only metabolite that contributes to the activity of the drug. After oral administration in the 3rd cycle, about 60% of the norgestimate survives absorption and passes through to the liver. There is about 83% of the ethinyl estradiol that passes through to the liver. The elimination half life of norgestimate is about 12 to 30 hours and about 26 hours for the ethinyl estradiol. The excretion of the inactive metabolites occurs via urine and feces. It is the prolonged effects of the drugs, lasting hours, that allows for the daily administration of the drug.

The promising effects of helping acne with Ortho Tri-Cyclen is due to the norgestimate. More androgenic progestins can alter the carbohydrate metabolism causing an aggravation of the sebaceous gland hence causing acne. Norgestimate is low in the androgens so it actually reduces the effects of acne.

Benefits:
Oral contraceptives such as Ortho Tri-Cyclen have many benefits that are not so obvious. Some of the more common benefits seen by most women that take “the pill” include their menstrual cycles being more regular and also their menstrual cycles being shorter and lighter. Birth control pills have also been proven to decrease the risk of some cancers including breast, ovarian, and cancer in the lining of the uterus. The pill helps to prevent ectopic or tubal pregnancies. It has been documented to prevent pelvic inflammatory disease, which commonly leads to infertility. Anemia due to heavy menstrual flow has also been decreased due to oral contraceptives. Another benefit is that birth control can help rheumatoid arthritis. One of the new benefits to the pill is one exclusive to Ortho Tri –Cyclen, previously mentioned, to clear up skin blemishes due to acne.

Possible Side Effects
Birth control pills may have many benefits, but some possible side effects can occur too. The most common side effects that women experience are weight gain or loss, bleeding in-between menstrual cycles, and breast tenderness. The pill can cause nausea that leads to vomiting or headaches. Some women report a loss of sexual desire or depression. Some severe side effects that may occur are blood clots. It has been reported that some women have experienced blood clots in their lungs, legs, brain, or heart. Rarely high blood pressure may occur in women who take the pill. Sometimes even
more rare is the chance of liver tumors, gallstones, and jaundice. People who are
pregnant or plan on becoming pregnant should not take the pill. Women who smoke
develop a higher risk to the effects listed above. Also women who have high cholesterol
or high blood pressure should not take oral contraceptives. In the figure 6 is a table of
deaths related to oral contraceptives.\(^4\)

Figure 6

<table>
<thead>
<tr>
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<td>1.4</td>
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<tr>
<td>Condom*</td>
<td>1.1</td>
<td>1.6</td>
<td>0.7</td>
<td>0.2</td>
<td>0.3</td>
<td>0.4</td>
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<tr>
<td>Diaphragm/spermicide*</td>
<td>1.9</td>
<td>1.2</td>
<td>1.2</td>
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<tr>
<td>Fenoic abstinence*</td>
<td>2.5</td>
<td>1.6</td>
<td>1.6</td>
<td>1.7</td>
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<tr>
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<tr>
<td>Deaths are method-related</td>
<td></td>
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</tbody>
</table>

Adapted from H.W. Ory. ref. #35.

Clinical Studies

In a clinical trial of 1,651 subjects using Ortho Tri-Cyclen, who had completed
24,272 cycles, a total of 18 pregnancies were reported. This represents a pregnancy rate
of 0.96 per 100 women. The study did not include those women who did not take the pill
correctly. In four other clinical trials using Ortho Tri-Cyclen the pregnancy rate ranged
from 0.68 to 1.47 per 100 women. In two blind, placebo controlled, clinical trials over a
six-month period, Ortho Tri-Cyclen showed a significantly lower decrease in
inflammatory lesion count. In another clinical trial with the drug, 2,312 patients who
used Ortho Tri-Cyclen reported only 8 pregnancies. This is a pregnancy rate of 0.94 per
100 women.\(^4\)

Conclusion

Ortho Tri-Cyclen is an oral contraceptive used in the prevention of pregnancy. It
is a combination birth control pill with ethinyl estradiol and norgestimate. Ortho Tri-
Cyclen is a fairly new drug with many benefits and little side effects. Clinical studies
show that the pregnancy rate with correct use of the drug is less than 1%.\(^7\) Ortho Tri-
Cyclen is becoming increasingly popular because it is one of the only oral contraceptives
that also fights acne, possibly the most beneficial side effect out there.
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Levodopa: its uses, derivatives, and syntheses.

Kari Guinn
O-Chem 236
April 2002
Dr. Bishop
SMCC
Levodopa, also known as 3,4-dihydroxy-L-phenylalanine, has become increasingly more recognized for its importance, not only as a major amino acid derivative, but also for its own derivatives and uses as well, within the human neurological system.

Brain and neural activity all depend on a very delicately balanced system of chemicals and ion concentrations to run properly. At the same time, the nervous system does not depend on only one method to function properly, but has incorporated numerous pathways to achieve the same goal. For example, the production of tyrosine can either be made from the body's own phenylalanine, or it can be absorbed from various high protein foods (<http://www.tnp.com>). This in itself is of extreme importance to neural activity, because it is from tyrosine that the body produces some of its major neurotransmitters (Briggs, Clark A., Holliday, Mark W., Kerwin, James F., Sullivan, James P., Williams, Michael, 2000).

Every neural signal that is sent or not sent through the body is the direct result of one or more neurotransmitters, precursors and enzymes present or not present in the presynaptic nerve terminal (Briggs, Clark A., et al.). Minor fluctuations and changes within the system are monitored and regulated to maintain homeostasis, but any sudden or major changes in the system could be detrimental. Improper drug use or neurological disease seriously affects the system, which impairs the individual.

Dopamine (3,4-dihydroxyphenethylamine) is one of the major neurotransmitters of the brain. It controls motor function, emotional response, and the ability to experience pleasure and pain (<http://www.utexas.edu>). Dopamine is the basis for the syntheses of other neurotransmitters, namely norepinephrine and epinephrine. When dopamine levels are affected, major problems can occur. Too much dopamine leads to schizophrenic symptoms (<http://www.utexas.edu>), but on the other hand, too little dopamine leads to Parkinsonian symptoms (Briggs, Clark A., et al.). To better understand the symptoms related to neurological problems surrounding the various transmitters, it is necessary to understand the syntheses involving those transmitters.

Even though tyrosine is the basis for many neurotransmitters, this amino acid is involved in many more syntheses than just in transmitter production. Tyrosine helps the body to fight off fatigue and it increases mental alertness. Tyrosine levels in the body also greatly impact dopamine levels as it is converted into levodopa which is the basis for dopamine. Typically, the body is not in short supply of tyrosine. As aforementioned, the body can either make its own from phenylalanine, or it can be absorbed from meat, dairy, fish and beans which are all high in tyrosine levels by nature (<http://www.tnp.com>).

Levodopa is the most closely related compound to dopamine and its derivatives and it is directly synthesized from tyrosine in the presence of tyrosine hydroxylase.
The mechanism for this synthesis, like many other enzyme based reactions, is not known, but it appears to be a substitution reaction.

Levodopa is converted to dopamine in the brain by the substantia nigra in the presence of dopa decarboxylase, which pulls off a CO2 molecule. Amino acids are actually ionic in structure and is subject to change according to pH levels. The carboxyl group loses a proton, giving a carboxylate ion and the amino group is protonated to an ammonium ion. This is called a dipolor ion or a zwitterion (Wade, 1999). From here it becomes a little easier to see the removal of the COO- ion and the repositioning of the amino group.

Dopamine is produced in the aforementioned midbrain structure as it is needed, but if that structure is impaired or damaged in any way, then the entire body suffers, as seen in Parkinson's patients. Unlike dopamine, levodopa has the ability to cross the blood brain barrier where the basal ganglia and other structures are able to produce dopamine and alleviate the disease's symptoms. This is the basis for treatment of the disease.

As indicated by its name, L-dopa has its mirror image in D-dopa. Studies have demonstrated short term, beneficial results in the use of L-dopa with Parkinson's symptoms, but eventually, its effectiveness wears off and L-dopa can become toxic. The effects of D-dopa have also been compared with L-dopa and dopamine in the treatment of Parkinsonian symptoms from induced lesions around the substantia nigra. One study by by Alexander, Sortwell, Sladek, Roth, and Steeoe-Collier (1997) found that in two different strains of mice, both dopamine and L-dopa became toxic at levels around 1 nm, causing cell death, whereas D-dopa did not become toxic until after 100 µm were administered, \( p < 0.01 \). On the other hand, they also found that D-dopa was of no significant benefit to reducing the symptoms produced by the lesions. This, they found, was due to the fact that the enzyme responsible for converting dopa to dopamine is highly stereoselective, and D-dopa had no impact on brain dopamine levels (1997). Dopamine was found to be the most toxic, and L-dopa had the greatest impact on
alleviating Parkinsonian symptoms in the mice, both to a significant level of $p < 0.01$ (1997).

Again, the mechanism is not known for the synthesis of dopamine from L-dopa, or even why the enzyme is stereoselective, nor is the exact cause of neural cell death in Parkinson’s patients known. However, the importance of L-dopa in reducing symptoms is known.

At the same time that the brain is using L-dopa, the rest of the body is also using L-dopa for conversion to norepinephrine and epinephrine. As a result, levodopa prescription levels must be high enough, that the brain receives the dosage it needs to function properly. Unfortunately, the side effects of such large doses are detrimental to nerve cells and its beneficial affects are short lived. Carbidopa became the answer to this particular problem.

\[
\text{Carbidopa}
\]

Carbidopa in conjunction with levodopa can effectively reduce levodopa dosages and still provide the amount needed by the brain. Carbidopa, like d-dopa, cannot be synthesized to produce dopamine, and like dopamine, it cannot cross the blood-brain barrier. Carbidopa has no direct effect on the body, other than the important fact that it does not allow the body to use the levodopa, until it passes into the brain where carbidopa does not follow. The rest of the neural system can still produce site specific neurotransmitters, but free L-dopa in the system, is less work than constantly remaking it. Levodopa-carbidopa is still not without its side effects. Prolonged usage may lead to “chewing, gnawing, twisting, tongue or mouth movements, head bobbing, or movements of the feet, hands or shoulder. Muscle twitching, dizziness, muscle jerks during sleep, and hand tremor also may occur (http://www.focusonmedications.com)." According to a study by Kashihara, K., Manabe, Y., Murakami, T., Abe, Koji (2002), “the severity of the disease (Parkinson’s) and the dose and duration of levodopa therapy are considered to be associated with the development of the dyskinesia.” Dyskinesia is defined as hyperkinetic, involuntary movement (Kahn, Shaharyar M., Smith, Trisha S., Bennett, James P. Jr., 1999). This may be caused by an increase in sensitivity at dopaminergic sites. As levels of dopamine drop within the brain, the dopamine active sites become more sensitive to what dopamine is left, the body then over reacts to an increase of L-dopa and subsequent dopamine levels brought in by oral medication. Eventually, the body quits responding even to increasingly larger doses of L-dopa.
The dopamine derivatives norepinephrine (NE) and epinephrine (E) are both used by the body to control heart rate and blood pressure (<http://www.pascaldental.com/dealer/tissue_management.html>) and are the main neurotransmitters of the sympathetic nervous system. Norepinephrine is directly synthesized from dopamine in the presence of dopamine-beta-oxidase in the adrenal medulla, brain and peripheral nerves (Pugsley, Thomas A., 2000). NE is also responsible for immediate utilization of energy by stimulating the liver to convert glycogen into glucose and the adipose tissue to convert fats into fatty acids. This energy is used by the body in brief moments of greatly increased stress, and the sympathetic nervous system is responsible for what is commonly referred to as the “fight or flight” mechanism.

Epinephrine, sometimes called adrenalin, is a vasoconstrictor, which in itself increases blood pressure, but it also restricts blood flow to sites of injury on the body (<http://www.pascaldental.com/dealer/tissue_management.html>). Medically, it is the primary treatment for anaphylactic shock and asthma victims (Pugsley, Thomas A., 2000). For those suffering from asthma, epinephrine relaxes the bronchial smooth muscles, which reduces bronchospasms (2000).

As previously mentioned, levodopa is the primary drug in alleviating the effects of Parkinson’s disease. The exact cause for the deterioration of the dopaminergic neurons in the substantia nigra (Zeng, B.-Y., Dass, B., Owen, A., Rose, S., Cannizzaro, C., Tel, B.C., Jenner, P., 2002) is unknown, but according to a study by Stokes, Alan H., Hastings, Teresa G., Vrana, Kent E. (1999), cell death of these dopaminergic neurons may be due to normal metabolism of dopamine. The normal catabolism of dopamine by monoamine oxidase is hydrogen peroxide (1999), a free radical that can cause tremendous amount of cellular damage, resulting in cell death. If the hydrogen peroxide is not eliminated by surrounding enzymes, it may react with near by transition metals to become the “reactive hydroxyl radical through the Fenton reaction” (1999). Another possible toxin is quinone, produced from the oxidation of the unstable catechol ring, which is an aromatic ring with vicinal hydroxyl groups. This reaction is spontaneous and is accelerated by the presence of transition metal ions, or any number of other enzymes (1999). These reactions may explain the continual deterioration of the dopaminergic neurons within the brain and subsequent on set of motor dysfunction, due to the lack of dopamine. Until further research is done, the only known alleviation is through drug interaction of levodopa to aid in elevating dopamine levels in the brain.
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PYRUVATE

By
Michele Gumenik
April 21, 2002
Abstract

The purpose of this paper is to inform individuals, especially those interested in enhanced training supplements, what type of an effect of ingesting pyruvate has on the performance of aerobically well trained individuals. The paper contains background history of what pyruvate actually is and its function in the body, and how it is produced and broken down. The paper also contains a recent study done in August of 2000 with 9 subjects given different doses of pyruvate, to actually test the effect if any on active individuals.

History of Pyruvate

Pyruvate is created by the body during the metabolism of carbohydrates and proteins. It is formed by the body during digestion, and can also be found in several foods, such as apples (red only), cheese, dark beers, and red wine. Pyruvate also supplies the body with pyruvic acid, a natural compound that plays an important role in the manufacture and use of energy. Pyruvate is not an essential nutrient, since your body makes all it needs. An average diet supplies anywhere from 100 mg to 2 g daily. Natural sources of pyruvate are; apples (red only), cheese, dark beers, and red wine.

ATP is responsible for us being able to do work and plays a role in the breakdown of pyruvate. The circulation of protons across the cell membrane is the driving force that generates ATP. The protons are generated catabolically in three stages. The second stage is what will be focused on. In the second stage almost everything is broken down to pyruvate, the key metabolic intermediate. The metabolic direction taken by pyruvate depends on whether the organism is an aerobe or an anaerobe. If it is aerobe, further breakdown takes place via the Krebs cycle (Herzberg. 1).
If anaerobe, pyruvate is further metabolized by fermentation.

**Fermentation Reactions**
Electrons from NADH must be passed on
Homolactic fermentation (muscles; most lactic-acid bacteria)
- Simplest fermentation
- pyruvate is reduced to lactate
- Pyruvate + NADH → *acetaldehyde + CO2 + NADH → ethanol + CO2
In any fermentation, products must balance reactants (C, H, O); C6H12O6 → 2 x C3H6O3

**Glycolytic Pathway**
The process to get from glucose to pyruvate is the glycolytic pathway. The glycolytic pathway can be broken down into two parts. In the first, glucose is converted to fructose-1,6-diphosphate, preparatory to being split into two three-carbon compounds. In the second, the phosphorylated fructose is split and converted to two molecules of pyruvate.

Two Glycolysis reactions are bypassed by simple hydrolysis reactions:

Hexokinase (Glycolysis) catalyzes:

\[
glucose + ATP = glucose-6-P + ADP
\]

Glucose-6-Phosphatase (Gluconeogenesis) catalyzes:

\[
glucose-6-P + H2O = glucose + Pi
\]
Some amino acids are catabolized to pyruvate, oxaloacetate, or precursors of these. The source of pyruvate and oxaloacetate for gluconeogenesis, during fasting or carbohydrate starvation, is mainly amino acid catabolism. Muscles proteins may break down to supply amino acids that are deaminated, and catabolized to form inputs to gluconeogenesis. If both pathways were simultaneously active in a cell, it would constitute a “futile cycle” that would waste energy.

Glycolysis:

Glucose + 2NAD$^+$ + 2ADP + 2 Pi = 2 pyruvate + 2NADH + 2ATP

Gluconeogenesis:

2 pyruvate + 2NADH + 4ATP + 2GTP = glucose + 2NAD$^+$ + 4ADP + 2GDP + 6 Pi

**Phosphoroclastic Reaction**

- Pyruvate + NADH -> acetyl-CoA + HCOOH + NADH -> acetate + CO2 + H2 + NADH (phosphoroclastic reaction)
- Must be coupled with another, NADH-consuming, reaction
- Acetyl-CoA is transferred to phosphate (acetyl phosphate), and the phosphate is then transferred to ADP, making ATP and acetate
- This reaction provides an extra ATP, but doesn’t dispose of extra electrons (NADH) from early oxidation reactions

**Reduction of Pyruvate**

Reduction reactions must balance phosphoroclastic reactions

Ethanol production (4-electron reduction [or 2NADH] of acetate)

- Pyruvate + 2NADH -> acetate + HCOOH + 2NADH -> ethanol + HCOOH + NAD$^+$
- 2 pyruvate + 2NADH -> acetate + ethanol + 2HCOOH + 2NAD$^+$ + ATP
- This is a dominant reaction of the mixed acid fermentation (enteric bacteria such as Escherichia coli)

**Aerobic and Anaerobic Conditions**

During aerobic conditions, aerobic performance permits the extraction of additional usable energy from pyruvate by funneling this three-carbon compound into the mitochondria for use as substrate in the Citric Acid Cycle. This process requires molecular oxygen as the terminal electron acceptor (Umich 3, lecture 12). The three carbons from pyruvate enter the cycle as acetyl CoA. The production of Acetyl CoA is catalyzed by pyruvate dehydrogenase complex, a multi-enzyme complex. This is a protein complex containing multiple copies of three different enzymes which A channel at substrate form one subunit to the next making the overall reaction rate faster than could occur by diffusion alone (Umich 1, lecture 14). The three subunits are, pyruvate,
dehydrogenase (E1), dihydrolipoyl transacetylase (E2), and dihydrolipoyl dehydrogenase (E3).

E1 requires a prosthetic group, thiamine pyrophosphate (TPP, vitamin B derivative). This group accepts 2 of the 3 carbons of pyruvate by a nucleophytic attack of the TPP carbanion on electron deficient C₂ of pyruvate (Umich 1, lecture 14).

E2 requires a prosthetic group, lipoate. This group is bound to the R group of a lysine and forms a flexible Aarm at which binds the acetyl group and accepts two electrons in the process resulting in the reduction of the disulfide bond on lipoate and the oxidation of the acetyl group. The thioester bond with lipoate is analogous to the phosphate bond in ATP molecules, they have a high transfer potential. The phosthetic group then transfers the ecetyl group to CoA-SH forming Acetyl – CoA (Umich 1, lecture14).

The remainder of the reactions catalyzed by E3 serves to regenerate the disulfide bond and restore the original oxidized state the PD complex. Oxidation of lipoate is achieved by reducing the prosthetic group on E3, FAD to FADH₂. FADH₂ is then reduced to NAD⁺ generating NADH and the original enzyme complex. NADH’s produced in this reaction, in glycolysis and in the citric acid cycle will be oxidized in the electron transport chain to produce ATP.

Under anaerobic conditions where oxygen is not present or cannot be supplied quickly enough for the Citric Acid Cycle to proceed require that pyruvate be the terminal electron donor. An example of anaerobic activity would be sprinting or heavy intense weight training. This happens because glycolisis would grind to a halt once all the NAD⁺ was converted to NADH.

In muscle cells, pyruvate accepts an electron form the reduced NADH to generate lactate and NAD⁺. In some cases, pyruvate is first converted to acetaldehyde with the liberation of one carbon in the form of CO₂. The acetaldehyde then becomes the terminal electron acceptor, again accepting an electron from NADH to form NAD⁺ and ethanol (Umich 3, lecture 12).

**Anaerobic fermentation of pyruvate + NADH → lactate + NAD⁺**

**Fermentation of pyruvate→ acetaldehyde + NADH + H⁺ → ethanol + CO₂ + NAD⁺**
Recent Study: Pyruvate ingestion for 7 days does not improve aerobic performance in well-trained individuals.

The purpose of these studies was to test the hypotheses that lower dosages of oral pyruvate ingestion would increase blood pyruvate concentration and that the ingestion of a commonly recommended dosage of pyruvate (7g) for 7 days would enhance performance during intense aerobic exercise in well-trained individuals. Nine individuals (8 women, 1 man) consumed 7, 15, or 25g of pyruvate and were monitored for a four-hour period to determine whether blood metabolites were altered, as well as 7 well-trained male cyclists to determine if there was any kind of enhanced performance in the individuals. Pyruvate consumption failed to significantly elevated blood pyruvate, and there was no difference in performance in the cyclists.

Recent reports indicate that a combination of pyruvate and dihydroxyacetone are reported to enhance weight loss and improve endurance during aerobic exercise. Pyruvate supplements have become popular with bodybuilders and other athletes, based on claims that it can reduce body fat and enhances energy. On the basis of these reports, pyruvate is being marketed as a weight-loss and ergogenic supplement. The amount that is being marketed is a considerably lower dosage than those in the studies, and yet is still advertised as a "scientifically proven" ergogenic aid (Morrison, 550).
BIBLIOGRAPHY


Imitrex
Toni Hughes
042302
Abstract:

In this paper I will give an understanding of the effects of a migraine. I will explain it biologically and illustrate how it has haunted the world for years. This will be followed by a timeline of past methods used. Lastly I will explain what Imitrex is and, how it is understood to relieve migraines.

Over the years there has been a growing concern for people suffering from various disabilities. One sickness that has been underrated for years has been the headache. A brief description of a headache is a narrowing of the blood vessels in the brain. Within the headache area of study there is the phenomenon known as the migraine. Migraines are one of the ailments recognized by man. One can find migraine-like symptoms described in writing as old as 3000 BC. A migraine occurs when two structures deep in the brain called the thalamus (TH), which is the processing center for most of the senses, and the hypothalamus (HyT), which regulates body temperature, sleep-wake patterns, and many hormonal and glandular activities. The most widely held theory is that outside or internal trigger causes an over-excitation. This over-excitation in the case of the hypothalamus signals will get sent to trigger sensations of nausea. Whereas, signals from the thalamus sends triggers to arteries in the face to increase blood flow (dilatation), causing flushing in the face and a throbbing sensation. (See diagram 1 & 2)

Since its exact triggers and causes remain a mystery the research to find a cure or even semi/permanent relief is a huge industry. In the past the Egyptians in about 1200 BC used idols, magic and herbs, where as in Arabia, in 10AD doctors used hot iron or garlic to a temple incision. In the mid-1600's AD blood letting, leeches and natural products (rosemary or vinegar) were widely used. By 1868, with a paper published by the British Medical Journal, ergot of rye was used to treat one-sided headaches. Since ergotamine
Ergotamine tartrate has many side effects there have been efforts made to find better forms and, from this we have dihydroergotamine and methysergide (developed in the 1960’s)

Then there was preventive group, which includes beta- blockers and clonidine. The first of this group was propranolol or 1- (Isopropylamino)-3-(1-naphthyloxy)-2-propanol hydrochloride. Now, there is the last group called the triptans. They were developed in the early 1980’s to treat acute migraine attacks. Triptans can be divided into 2 groups: fast onset or slow onset. In the fast group, there is high headache response so; the drugs used are sumatripan, zolmitriptan, rizatriptan, almotriptan, and eletriptan. For the slow group the onset is not as fast and there is a lower efficacy rate and, the drugs used for this are naratriptan and frovatriptan.

The medicines that are used today can be grouped according to their uses in relieving specific symptoms:

* relieve pain – e.g. non-steroidal anti-inflammatory agents (NSAIDs) and analgesics such as ibuprofen or tolfenamic acid, and products containing aspirin, paracetamol or codeine alone, or in various combinations,

* control other symptoms such as nausea – e.g. prochlorperazine, metoclopramide, buclizine, domperidone, sometimes in combination with analgesics,

* they are preventive and have long-term use – e.g. some beta-blockers such as metoprolol, nadolol and timolol, as well as clonidine, pizotifen – a serotonin antagonist, and some anti-epileptics,

* offer acute relief of an attack already started, e.g. ergotamine, isometheptine, and the triptans, and

* other agents – e.g. antihistamines and minor tranquillisers, which seem to benefit a few, people whose migraine is food-related or who are anxious.
The triptans are the most selective and the most useful medicines used to treat acute migraine pain. In 1988, scientists at Glaxo Wellcome discovered a compound known as sumatripan; it was the first of the new class of anti-migraine medicines.

![Structure of sumatripan and succinate](image)

The pharmaceutical manufacturer GlaxoSmithKline developed injectable shots (in 1993), pill (in 1995) and nasal spray form of sumatripan commercially called Imetrex. Imitrex, which has the IUPAC name 3-[2-(dimethylamino) ethyl]-N-methyl-indole-5-methanesulfonamide succinate (5-hydroxytryptamine) became, the newest and most used drug for the treatment of migraine headaches.

Diagram 3

- Peptide release e.g. CGRP, neurokinins triggered by nerve signals
- Activation of 5-HT1D receptors reduces the release of peptides
- Blockade of peptides released in blood vessel wall
- Inhibition of inflammatory factors by NSAIDs
- Vasoconstriction of blood vessels by elimination of 5-HT1D receptors
- Fluid leakage and sterile inflammation
- Inhibition of pain centres in brain and brain stem
- Decreased excitation of trigeminal nerves
- Inhibition of nausea centres in brain and gut
- Blockade of pain centres in brain and brain stem
- Nerve
- Brain
- Blood vessel in cross section
- Brain stem
- Pain centre
- Cerebellum
- Brain
- Meninges
- Blood vessels
[In diagram 3, you can see the part of the brain that is described in the paper as being the place where the Imitrex will target the 5-HT1 receptors. This is why it is believed to be one of the best medications. Since it will only target this these particular receptors it is very effective.]

Diagram 2

{In this diagram you can see where the thalamus and the hypothalamus are located deep within the brain, and how they are understood to be involved in the pain associated with a migraine.}
Unlike other migraine medications, Imitrex selectively activates (as an agonist) the receptors that constrict blood vessels in the head, which are thought to be dilated and distended during a migraine attack. Because Imitrex is highly selective to a particular receptor (5-HT1) (see diagram 3), it is able to achieve greater favorable advantages. Imitrex is thought mimics certain actions of serotonin, a naturally occurring neurotransmitter that plays a role in several biological functions in the body, including some in the brain. Serotonin affects nerve cells by stimulating and interacting with various types of receptors, which in turn trigger certain responses in the cells.

I was unable to locate the exact mechanism of this compound but, this explanation for the mechanism for was found throughout my research. It seemed to mirror at every location.

Mechanism of action
Sumatriptan is a selective agonist (A drug or other chemical that can combine with a receptor on a cell to produce a physiologic reaction typical of a naturally occurring substance,) at only the 5-HT1 families of receptors. It is most potent at 5-HT1B and 5-HT1D receptors, which are currently thought to mediate the anti-migraine effect of ergotamine and sumatriptan. There are 2 hypotheses concerning the anti-migraine effects of 5-HT1B and 5-HT1D agonists. Migraine headache is theorized to result in abnormal vasodilation. Diversion of blood from capillary beds results in cerebral ischemia and hypoxia. Both ergotamine and sumatriptan close these shunts (via vasoconstriction), restoring blood flow to brain parenchyma. In the second hypothesis, agonists effects at 5-HT1B and 5-HT1D receptors (which also function as "autoreceptors") block the release of proinflammatory neurotransmitters at the level of the nerve terminal in the perivascular space.

Formula: C14H21N3O5S•C4H6O4
Molecular Weight: 413.5
Molecular Weight of the nasal spray (which doesn’t contain succinate): 295.4
Solubility in Water: yes and saline
PH: 4.2- 5.3
PH for the nasal spray: 5.5
Stability: yes, under normal conditions
Physical State: white to off white powder
In Pill form has 71.43% sumatriptan to mg dosage i.e. 35mg for the 25mg tablet.

Side effects/ warnings
Due to the fact that Imitrex can increase the blood pressure, this drug should not be given to people with hypotension. It has been know to cause birth defects and deaths.
Sumatriptan will be excreted through breast milk. It was studied that Imitrex decrease the fertility levels of lab rats during mating periods, and this was with them receiving an adult dose daily.

The affects felt after taking the medication:
Atypical sensation =burning or numbness, tight feeling in the head
Cardiovascular = palpatations, decreased blood pressure, increased blood pressure
Endocrine and Metabolic = thirst ie dry mouth
Eye = visual disturbances, eye irritation, itching
Gastrointestinal = diarrhea, constipation, gastroesophageal reflux, salivary glands
Swelling
Musculoskeletal = muscle cramps
Skin = sweating
And others not as major
The table below shows some of these events during a study of placebo vs Imitrex tablets
The results are as follows:

<table>
<thead>
<tr>
<th>Adverse Event Type</th>
<th>Placebo (n = 309)</th>
<th>IMITREX 25 mg (n = 417)</th>
<th>IMITREX 50 mg (n = 771)</th>
<th>IMITREX 100 mg (n = 437)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atypical sensations</td>
<td>4%</td>
<td>5%</td>
<td>6%</td>
<td>6%</td>
</tr>
<tr>
<td>Paresthesia (all types)</td>
<td>2%</td>
<td>3%</td>
<td>5%</td>
<td>3%</td>
</tr>
<tr>
<td>Sensation warm/cold</td>
<td>2%</td>
<td>3%</td>
<td>2%</td>
<td>3%</td>
</tr>
<tr>
<td>Pain and other pressure sensations</td>
<td>4%</td>
<td>6%</td>
<td>6%</td>
<td>8%</td>
</tr>
<tr>
<td>Chest - pain/tightness/pressure and/or heaviness</td>
<td>1%</td>
<td>1%</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>Neck/throat/jaw - pain/tightness/pressure</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>2%</td>
<td>3%</td>
</tr>
<tr>
<td>Pain - location specified</td>
<td>1%</td>
<td>2%</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>Other - pressure/tightness/heaviness</td>
<td>2%</td>
<td>1%</td>
<td>1%</td>
<td>3%</td>
</tr>
<tr>
<td>Neurological</td>
<td></td>
<td></td>
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*Events that occurred at a frequency of 2% or more in the group treated with IMITREX Tablets and that occurred more frequently in that group than the placebo group.
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TAXOL

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Abstract

In the venture to treat, and hopefully one day cure, the devastating disease of cancer, anticancer agents are constantly being developed and investigated. Taxol is one of those agents that have shown reputable activity against a wide variety of tumors, including those associated with ovarian and breast cancer. While at this time, taxol will not cure most patients, it may allow them to live longer and fuller lives because of this significant activity in several cancers. In looking closer at Taxol, it is valuable to take into account its origin, its chemical structure, possible synthesis of the drug, mechanisms of action, and the side effects involved.

Introduction

Cancer is a disease of cells characterized by the loss of the normal controlling mechanisms that maintain tissue organization. These cells multiply without control, destroy healthy tissue, and endanger life. There are about one hundred kinds of cancer attacking humans and is a leading cause of death in many countries. (1) Developing novel anticancer drugs with unique mechanisms of action and broad clinical activity is the constant challenge of cancer researchers. New treatments for cancer must not only be effective, but also have a favorable therapeutic index.

Taxol, also generically known as paclitaxel, belongs to a group of drugs called the taxane diterpenoids, which currently has over three hundred members. (2) However, at the time of the discovery of taxol, the group was small and was a relatively unexplored class of natural products. These anticancer taxanes, including taxol, are now one of the more promising new chemotherapeutic agents.

Taxol is one of the most broadly active compounds available to treat human malignancy with activity demonstrated in cancer of ovary, breast, lung, head and neck, esophagus, bladder, and testis. Taxol is obtained from the slow growing Pacific yew tree found predominantly in the Pacific Northwest. The yew tree itself is very interesting, and greatly attributes to the history and interest concerning taxol, as well as its obstacles it has had to face.

History and Origin

Before the spark of taxol research began, the yew tree was observed with wonder and great caution. The poisonous effects caused by yew trees were known as early as two thousand years ago. Many people believed sitting or sleeping beneath a yew tree would cause death and for several years, the Native Americans told tales of poison related to the yew tree. (3) The yew was also more currently known as the cause of sheep and cow poisoning. The name taxus may have a connection to the word toxic, which originally meant ‘used for poisoning arrows’ or toxic, meaning poison. (4) These historical beliefs as well as more current incidents brought the yew into the spotlight, inspiring clinical trials, which lead to a paramount event in cancer research.

The building history of the anticancer drug taxol continued in 1963–1964 with the discovery that extracts of the bark of the Pacific yew, Taxus brevifolia, showed significant cytotoxic and antileukemic activity. (2) The National Cancer Institute in the United States initiated a program of biological screening of extracts isolated from the yew bark. One of these extracts was found to exhibit marked antitumor activity against a broad range of rodent tumors. Although this discovery was made in 1962, it was not until
five years later that two researchers, Dr. Monroe Wall and Dr. Mansukh Wani, of the Research Triangle Institute isolated the active compound. In 1971, they published the structure of this promising new anticancer lead compound. (5)

Despite taxol's well-documented biological activity, the science community was not completely convinced and showed little interest, until researchers reported its unique mode of action in 1980. It was believed that the cytotoxic properties of taxol were due to its ability to destabilize microtubules. This novel mechanism renewed interest in taxol, but simultaneously leads to some significant problems. (5)

Groups interested in taxol greatly increased, many who wanted to conduct clinical trials, but large quantities of this material were required. Its source, the Pacific yew tree, is an environmentally protected species, and also one of the slowest growing trees in the world. Isolation of the compound involves killing the tree due to its source in the bark and the quantities obtained by this method are terribly slim. It would take six one hundred-year old trees to provide enough taxol to treat just one patient. (5)

Luckily, additional testing was conducted yielding the discovery that in the addition to the isolation of taxol from the bark, it can also be acquired from the needles. The use of needles has an obvious advantage in that they are a renewable resource. The extraction of taxol is more complicated due to the large amounts of lipid material, but methods have been developed to remedy this problem. (6) Despite the laborious extraction of the new needle source, it was renewable and sufficient quantities were attained to carry out clinical trials. (5)

Clinical trials conducted in the late 1980's and early 1990's demonstrated impressive activity against advanced ovarian and breast cancer, and these results were published in 1989. In 1992, the United States Food and Drug Administration approved taxol for the treatment of ovarian cancer, followed by approval for breast cancer in 1994. (5)

The relatively non-toxic properties of taxol have made it a leading light in the treatment of cancer in the 1990's, providing an alternative to the more radical techniques of radiotherapy and surgery. However, the cost and labor of this new wonder drug do put it at a disadvantage. These limiting factors have inspired researchers to investigate deeper, specifically at its structure. This examination of its skeleton has lead to synthetic organic chemistry, which may provide a solution to its original obstacles.

Structure

As soon as taxol was isolated in pure form, the structure of the compound was investigated using available spectroscopic methods. At first, the structural characterization was extremely slow. Although methods for ultraviolet, infrared, and mass spectrometry were at a reasonably advanced stage in the late 1960's, Nuclear Magnetic Resonance (NMR) was relatively primitive compared to the sophisticated instrumentation now available. (7)

By comparing taxol with a number of taxane derivatives, it was evident that it contained the taxane skeleton. Taxol was found to be more complex since its molecular weight from high-resolution mass spectrometry was C47H51NO14, corresponding to a molecular weight of 853. Taxol, and its groups’ derivatives, share the common C-20 carbon skeleton, but taxol differs from most other taxoids in two key respects. First, its taxane skeleton is esterified at C-13 with a complex N-benzoylphenylaloserine ester group.
Secondly, it has an unusual fourth ring in the form of an oxetane ring attached at the C-4,5 positions. Both features attribute to its unique biological activity.

![Chemical structure of Taxol](image)

Fig. 1 (5)

The conventional chemical representations of taxol make it appear to be a planar molecule, but in fact it has the shape of an inverted cup. The C-13 ester side chain is free to position itself under the mouth of the cup. The A-ring (twisted boat) and the C-ring (twisted chair) are almost perpendicular to the central B-ring, which assumes the boat-chair conformation. The taxol molecule’s shape can be better understood by examining its structure in two parts, the side chain and taxol skeleton.

Using the powerful technique of NMR, the conformation of taxol has been revealed. In examining the side chain, it was found it is critical for maintaining activity, specifically by interacting with tubulin residues to give a stable drug-receptor complex. There are three free hydroxyl groups, all distinguished by their chemical nature. The 1-OH group is tertiary and is thus unreactive to all but the most vigorous acylation conditions. The 7-OH group is secondary but is sterically hindered by the adjacent 8-CH₃ group. This leaves the secondary and unhindered 2'-OH group, which is the most reactive. (4)

Studies have shown the protection of the C2' hydroxyl group as an ester results in loss of activity in terms of microtubulin stabilization but not in cytotoxicity. The C3' bound nitrogen can be replaced by an oxygen atom without loss of activity. The C3' aryl group is needed and replacement by a methyl group reduces the activity 19-fold. (9) Along with the side chain features, the skeleton provides more interesting insights into taxol and its activity.

Taxol consists of several rings: a four-membered, a six-membered, and a eight-membered ring, as well as peripheral functionalities. The oxetane ring is a unique feature of the structure and is crucial for maintaining the activity. Researchers believe it could serve at least two functions. One it is a hydrogen-bond acceptor and also serves as a rigid “lock” on the taxoid skeleton. The lock function is illustrated by the fact that ring opened analogues adopt a different conformation. (9)

Contraction of the eight-membered ring to a seven-membered ring still provides the molecule with tubulin depolymerization properties. It was also found that removal of the C-10 acetyl group does not have any effect on the activity. (9) The structure activity relationships are important to the study of taxol, especially in the endeavor to synthetically produce this anticancer product.

**Synthesis**

Taxol represents an enormous challenge to the ingenuity and creativity of the synthetic organic chemist. Over the years, there have been many approaches to the total synthesis of taxol. The semi-synthesis approach involves the conversion of
10-Deacetylbaectatin III (10-DAB) to taxol. 10-DAB is isolated from the needles of the widely distributed Taxus baccata and is available in large quantities. Research groups have focused their efforts on the development of practical asymmetric syntheses of the side-chain and its attachment to the baccatin core. These strategies have allowed the synthesis of a variety of side-chain analogs of taxol, aiding the further search of more effective anti-tumor drugs. Research groups have also achieved total synthesis of taxol. Three approaches have been accomplished to date.

The Holton route uses (-)-borneol as the starting material, which is converted to an unsaturated ketone over thirteen chemical steps. This ketone is converted into β-patchouline oxide and then epoxidised and treated with a Lewis acid. A skeletal rearrangement is induced and provides a tertiary alcohol. This alcohol is again epoxidised and undergoes a fragmentation reaction to create the A and B-rings of taxol. (5)

Another approach is the Nicolaou route. This method is convergent rather than linear, where the A and C-rings are constructed separately and then linked together using a Shapiro reaction to connect the southern part. The B-ring is completed by a McMurray coupling reaction, and finally all three rings are fused together. (5)
The third method, known as the Danishefsky route, begins with the Wieland-Miescher ketone. It is then elaborated to a complex enol triflate, bearing an olefin on the C-ring for development of taxol via an intramolecular Heck reaction. (5)

![Chemical structure](image)

**Fig. 4 (5)**

The major impact of both forms of syntheses is they open doors to the preparation of additional analogs of taxol. It is very possible an active analog of taxol will be developed, either through total synthesis or by structure modification of taxol itself. (10) Understanding the chemistry behind taxol clarifies its composition and concentrates attention on its distinctive mechanism of action and its methodology in cancer treatment.

**Uses and Mechanisms of Action**

Taxol is a drug of considerable current interest because of its activity in a number of human malignancies, and its unusual chemical structure and system of action. Taxol acts as a unique mitotic spindle poison. It promotes assembly of microtubules and stabilizes them against depolymerization. (11) Most other antimitotic agents act by preventing the assembly of tubulin. At the time of the discovery of taxol, it was the first compound to act as a promoter of microtubule assembly. (2)

When cells are incubated with taxol, discrete bundles of stable microtubules are formed in the cell. These bundles result from a reorganization of the microtubule skeleton. It is believed that taxol acts by altering the normal equilibrium and shifting in favor of the formation of the microtubule polymer from its subunits. This results in an inability of cells to replicate. Microtubules are required for normal cell replication and function. They are a major component for normal cell division, maintaining cell shape and motility, and transport between organelles. (6) A drug such as taxol that alters the normal dynamic behavior of the inner workings will dramatically influence normal cell behavior and replication. The evaluation and comprehension of the methods of taxol bring us to how it is employed and the cancer towards which it is effective.

Taxol is administered by intravenous infusion, typically for a 24-hour period. Shorter infusion times of three to six hours are associated with patients experiencing severe side effects. (11) At present there are no hard and fast dosages schedules that can be recommended for routine use. Dosages often depend on the individual patient and the cancer involved.

Taxol may be one of the most broadly active compounds available to treat human malignancy. Thirty years after its original identification, taxol was approved for treatment of refractory ovarian cancer, and more recently for refractory breast cancer. It has also shown activity with a wide range of other cancers, including lung, bladder, head and neck, testis, esophagus, and possibly some hematological and pediatric malignancies. (11)

Ovarian carcinoma is one of the leading gynecologic cancers and a major cause of death worldwide. (1) Approximately one woman in seventy will develop ovarian cancer.
The cause is unknown, but is associated with consumption of animal fat, and is more common in patients with a history of breast cancer. (7) The two most important features of the disease which determine outcome are the extent of the disease and the aggressiveness of the tumor. Unfortunately, 75-85 percent of patients are diagnosed with advanced disease, which has metastasized from the ovaries in the pelvic cavity to the abdominal cavity. Treatment with chemotherapy may reduce symptoms and prolong life. (1)

Taxol enters the treatment when other types of therapies have failed, and tumors have displayed partial to complete resistance. During the initial trials of taxol, several responses were reported in patients with ovarian cancer. In one study, a 30 percent response rate was noted in heavily pretreated patients. Chemotherapy begins one to two weeks after surgery and taxol is administered intravenously every three to four weeks as tolerated for six cycles. In general, the expected response rate is 40-80 percent. (1)

Taxol is also active in the treatment of patients with metastatic breast cancer, the most common malignancy affecting women. Exposure to pesticides at a young age has been implicated in breast cancer because of the estrogen-like effect of DDT. The current trend for delayed or deferred childbearing may also be a cause, increasing the incidence of breast cancer. (12) Taxol is used for tumors that have metastasized beyond the loco regional area. Recurrent breast cancer often indicates more widespread metastatic disease will occur in the future. It commonly reoccurs in the area of the breast surgery or chest wall. (McGuire). Although taxol does not cure unresponsive breast cancer, several early studies found it to be effective in shrinking tumors. In a trial of 471 patients in Canada and Europe, taxol decreased tumor size by one half in 26 percent of the patients. (9)

Lung cancer, the leading cause of death in the United States in both men and women, has been treated with taxol in some clinical trials. More than 170,000 cases are diagnosed each year, and more than 140,000 people die of the disease in the same period. Lung cancer is divided into two major biological and clinical subtypes: non-small cell lung cancer, which is relatively insensitive to chemotherapy, and small lung cancer, which is very sensitive to chemotherapy. Patients with non-small cell lung cancer are the usual candidates for taxol. This area is still in the testing stage, but is important, for this type of lung cancer accounts for more than three quarters of all lung cancer cases. (12) Investigational approaches are currently being tested, and in some group trials, taxol had a major impact on the survival for those patients with stage III non-small cell lung cancer. Large randomized trials have shown that chemotherapy may prolong survival in patients with this cancer, but the benefit in overall survival duration is measured only in months. Therefore, it is obvious that new agents, like taxol, are needed for treatment of non-small cell lung cancer.

A less talked about, but just as devastating, form of cancer is that of the head and neck. This comprises a broad range of tumors of the oral cavity, pharynx, and larynx, and accounts for more than 40,000 cases of cancer in the United States each year. (12) The vast majority of these cancers are squamous cell histologic type, and early stage lesions can be cured with surgery and/or radiotherapy. Unfortunately, patients frequently suffering from this disease have had it either invade adjacent local structures or metastasize to local lymph nodes. (12) Either of these markedly shortens survival to a median of six months; death is usually due to local-regional or distant metastasis. This
area is also still in trial stage, but studies have revealed that taxol may be most effective when combined with other single chemotherapeutic agents like cisplatin.

After surmounting multiple preclinical and clinical problems, taxol has demonstrated potent anti-tumor activity in a variety of cancers. Many issues regarding the optimal duration of infusion, understanding of how tumors develop resistance, and development of agent combinations are still being investigated. Taxol may be one of the leading and most promising anti-tumor drugs on the table, but unfortunately, many times the higher the potency and effectiveness, the higher the consequences. Like most cancer drugs, taxol has various side effects, some which can be rather serious. The sequence and infusion duration of taxol, as well as in combination with other drugs, affects the type and severity of these side effects.

Toxicity and Side Effects

Taxol is beneficial in treating various types of cancer. Each person’s reaction to chemotherapy and the agents involved is unique. Some people have very few side effects, while others experience more. The more common side effects can often be lessened with altering dosage, or administering taxol-containing combinations. Taxol has provided a great deal of hope for cancer patients and inspired research in the science community, but many times great breakthroughs are accompanied by risks.

A common side effect is hypersensitivity reactions to taxol, which typically occur within ten minutes of starting a drug infusion. Reactions are neither dose related nor dependent on prior taxol exposure. These reactions probably relate to histamine release and may include flushing of the face, skin rash, or shortness of breath. Other signs of allergic reaction are shivering, dizziness, headache, and anxiety. Patients often receive medication to prevent such reactions before taking taxol. (5)

Taxol can also cause temporary damage to bone marrow. The bone marrow produces blood cells, fights infections, carries oxygen, and helps prevent bleeding by causing blood clots. (9) This temporary reduction of bone marrow function can result in anemia and risk of bruising, bleeding or infection. This effect can begin about seven days after the treatment has been given and usually reaches its lowest point at ten to fourteen days after the chemotherapy. The blood count will then increase steadily and will usually return to normal. (9)

Like many chemotherapy drugs, taxol can cause hair loss. This usually starts two to three weeks after the first dose, and may be complete loss or just thinning. Thinning or loss of eyelashes, eyebrows, and other body hair may also occur. These effects are temporary and hair returns to normal once treatment is finished. (5)

Another common side effect is numbness or tingling in hands and feet, which is due to the effect of taxol on the nervous system. This usually improves slowly a few months after the treatment is finished. Aching or pain in the joints and muscles may also occur, but may be controlled by prescribed painkillers or anti-inflammatory drugs. Taxol can cause flu-like symptoms as well, including fever, fatigue, and diarrhea. Mouth sores and ulcers may form, but these too can be treated with a doctor’s prescription. (2)

Cardiac side effects have been occasionally associated with brief infusions of taxol in patients without prior cardiac risk factors. One study showed taxol induced slowing of the heart rhythm in 30 percent of the patients. If closely monitored, it does not usually cause any harm. (5)
Less common side effects due to taxol include low blood pressure, abdominal pain and temporary taste alterations. Taxol may also cause changes in liver function, but will return to normal when the treatment has ended. (9) Nevertheless, for many patients with cancer, the benefits outweigh the risks. Prescribed medication and agent combinations containing taxol can often reduce all side effects. Current studies show taxol in combination with agents such as filgrastim, doxorubicin, and cisplatin, the doses can usually be higher. Cytotoxic effects were enhanced either when tumor cells were exposed initially to taxol, followed sometime thereafter by the introduction of the other drug in the combination. (1) The blending of different anti-cancer drugs also provides a solution to cancer cell resistance, an area that is of significant concern in cancer research.

Conclusion

Despite extensive drug research efforts over the past twenty years, cancer remains the second cause of death in the industrialized countries. (1) Fortunately, research continues as better equipment is available, and discoveries lead to new prospects. Recently, there has been commercialization of the once “investigational” drugs and an explosive growth of biotechnology agents for cancer treatment and support.

Chemotherapeutic agents are instrumental in the fight against this dreaded disease, and effective anticancer agents, like taxol, are critical objectives in western medicine. Taxol had a slow start in convincing the science community but achieved its well deserved appreciation once more of its dynamics were revealed.

Thirty years after its original identification, the FDA approved taxol for the treatment of refractory ovarian and breast cancer, and it continues to be successful in clinical trials for a number of other forms of cancer. The hurdles scientists are trying to overcome involve the limited resource of the yew tree and the growing drug resistance of cancer cells. There are several approaches to both, all in hopes of better treating this disease or possibly one day finding a cure.

The pharmaceutical potential of taxol elevated the status of the yew tree from a nuisance weed to a precious commodity and natural resource. The discovery of taxol in the needles of the tree was a great improvement, but did not prove substantial for all patients and trials that needed it. A single course of clinical treatment is 125-300mg of taxol, and typical treatments extend for ten or more courses. With current isolation methodologies, one kilogram of taxol is isolated from 25,000 pounds of dried yew bark and needles. Therefore, treating one form of cancer for over one year period would consume 90,000 mature yew trees. (1)

Several workers have investigated plant tissue culture methods for producing taxol. The first published report relating to this idea was in 1989, and since then many more have appeared. (1) From these reports it appears that tissue culture will certainly become a viable method for the production of taxol.

An exciting recent development has been the report that taxol is produced by the fungus *Taxomyces andreanae*. This fungus was found growing on the yew tree and produced taxol in small amounts. However, since strain improvement and genetic engineering techniques can be applied much more readily to fungi than to higher plants, it is very likely this fungus could be developed as a taxol producer. (1) If this were to transpire, it would raise the attractive option of a fermentation route to taxol, with production by well-developed techniques in large fermenters. Synthetic methods of
making taxol are also being researched and this provides another promising route to solving the limited resource of the yew tree.

Although there are nearly fifty different antineoplastic drugs in use, only a dozen are effective in the treatment of each specific tumor type because of intrinsic or primary resistance. (12) The emergence of drug resistance is a significant problem that develops during the treatment of human malignancies with cancer chemotherapeutic agents. The problem is not that useful antitumor drugs are unavailable, but rather that tumor cells can, by a variety of methods, develop resistance and replicate in the presence of cytotoxic agents. Malignant cells are clever and are determined to survive, by one method or another.

For more than two decades, it has been recognized that the heterogeneous nature of cancer and its ability to develop drug resistance provides a strong rationale for combination chemotherapy. (1) Because of its natural product origin and hydrophobic nature, taxol is an excellent compound to use for the selection of cells that have the multidrug resistance phenotype. Investigators indicate that is their intention to evaluate taxol in combination settings with most of the known marketed anticancer drugs and several others being developed. These future studies will often include sequence analyses and a range of concentrations of each drug. Taxol’s unique mechanism of action and its demonstrable ability against many tumor models when used alone, makes it an obvious candidate for inclusion in such combination regimens.

The research efforts involving alternate supply methods are significant for both practical and philosophical reasons. First, they could have a profound effect on the supply issues concerning the important anticancer compound taxol. A fungus or plant tissue culture methods represent an inexhaustible source of the drug. From both an ecological and an economic viewpoint, a microbial or synthetic source would supplant reliance on the yew tree. We would no longer be confronted with the choice of saving lives or saving yew trees. If any of the new sources yielded reasonable and reliable quantities of taxol, more drug would be available for both studies and treatment procedures at a lower cost to patients and no cost to the environment.

As studies continue and new discoveries are made, the future of taxol is very bright. It is quite miraculous that the yew tree, once known as the tree of death, now provides the gift of life. A breakthrough of such stature opens many doors, and provides a blank slate for improvements, modifications, and novel inspirations. With any discovery, obstacles often appear, but it is from trying to maneuver and overcome these obstacles, that more beneficial and innovative methods are born. From taxol’s struggle with resource demand and cancer cell resistance, helpful methods like plant tissue culture, fungal fermentation, synthetic formation, and combination with other agents may lead to potentially more powerful forms of the drug, as well as an opportunity for a diverse new assortment of anticancer agents.
References


Leukotriene Antagonists: Are They the Answer for Asthma Sufferers?

Prepared for
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By
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Abstract

Asthma is a serious condition that causes many Americans to have trouble breathing. Scientists have identified one of the main problems that cause asthma attacks as leukotrienes. Leukotrienes induce asthma attacks by causing the constriction of the bronchioles. This closes the airway and restricts the amount of air that enters and exits the body. The new drugs that have been created to stop this action are called leukotriene antagonists. They block the creation of leukotrienes preventing asthma attacks from occurring.
Introduction

Asthma

Asthma is a lung disorder. The disease causes the constriction of a person’s bronchial tubes lowering the volume of air allowed into the lungs. “Asthma consists mostly of allergens, and some nonspecific stimuli, such as cold air, exercise and irritants”1. An asthma attack can be one or several problems occurring in the respiratory system. Some of these problems are bronchoconstriction, inflammation, mucus hypersecretion, neuronal stimulation, bronchial smooth-muscle constriction and proliferation. This condition is not thought to be life threatening but over 5,000 Americans become one of its victims each year3.

Asthma Prevention

Asthma is controllable and preventable. In the past asthma has been controllable most effectively with the use of Corticosteroids. Corticosteroids can be taken orally or inhaled. “Prednisone, prednisolone, cortisone, triamcinolone, hydrocortisone” are all examples of oral Corticosteroids. Oral Corticosteroids have been proven to have many side effects if taken over long periods of time. Inhaled Corticosteroids are much safer and include “beclomethasone, fluticasone, budesonide, and flunisolide”3. These drugs usually provide instant relief and are currently the best line of defense against asthma attacks today.

Most asthma attacks can be prevented. In many cases, certain foods or activities induce the attack. Not eating these foods or not participating in these activities, can reduce the chance of having an asthma attack will reduce. Other preventative measures include watching out for warning signs of an attack coming on, or the use of a peak flow meter. Warning signs can be different between adult and child. “Warning signs for adults may include: increased shortness of breath or wheezing, disturbed sleep caused by shortness of breath, coughing or wheezing, chest tightness or pain, and increased use of bronchodilators medications that open up airways by relaxing the surrounding muscles3. Warning signs for children may include: an audible whistling or wheezing when the child exhales, coughing (especially if the cough is frequent and occurs in spasms), waking at night with coughing or wheezing, shortness of breath (which may or may not occur when the child exercises), and a tight feeling in the child’s chest3.

Peak flow meters are used by thousands of asthma sufferers. A peak flow meter enables patients to see the size of their lung capacity for any given day. Peak flows are based on a daily average. This means the patient must find an average range of everyday good health, and when a bad day occurs with a low peak flow reading, a patient knows that he/she is vulnerable for an asthma attack.

New Treatment

New drugs are being developed for the treatment of asthma all the time. The newest released drugs are leukotriene antagonists. These drugs work on the basis of stopping the bodily production of cysteinyl leukotrienes. By reducing the production of cysteinyl leukotrienes, scientists reduce the probability of an asthma attack occurring.
Leukotrienes

Leukotrienes are one of the main focuses in asthma today. They have been recognized to trigger acute asthma attacks. Leukotrienes have been found to be much stronger and potent than that of histamines. "Leukotrienes are one of several substances which are released by mast cells during an asthma attack and it is leukotrienes which are primarily responsible for the bronchoconstriction". There are two types of leukotrienes, neutrophil dependant and cysteinyl leukotrienes. The neutrophil leukotrienes deal with conditions such as cystic fibrosis and psoriasis. Cysteinyl leukotrienes are produced and concentrated on the disruption and constriction of the bronchioles. "Leukotrienes increase microvascular permeability, modulate the afferent nervous system, stimulate mucus release, slow mucus transport and decrease the activity of human respiratory cilia".

Cysteinyl Leukotriene Synthesis

Cysteinyl leukotrienes are generated inside the body. The process is very similar to making a fifteen-cent bag of noodles from the local grocery store. Leukotrienes are synthesized from arachidonic acid. The arachidonic acid is like the solid block of noodles strait from the bag. "Leukotriene synthesis results from the action of 5-lipoxygenase on arachidonic acid. 5-lipoxygenase is unable to react with arachidonic acid on its own. The assistance of 5-lipoxygenase activating protein (FLAP) is necessary for the reaction to proceed". Together 5-lipoxygenase and FLAP act as one. The combination of the two are like the two cups of water that is added to the noodles, this way the noodles will react and change. Once the three components unite and begin to respond to each other, the result is 5-hydroxyperoxy-eicosatetraenoic acid (5-HPETE). The 5-HPETE is then transformed with a second attack of 5-lipoxygenase and FLAP into leukotriene A4. The production of leukotriene A4 is like the stage in which the flavoring is added to the noodles. Next, leukotriene A4 reacts either with hydrolase to form leukotriene B4, or synthase to form leukotriene C4. Leukotriene B4 is produced by neutrophil. As seen in Fig 1, leukotrienes D4 and E4 are derived through the addition of transpeptidase and dipeptidase. Different flavors create different products. Leukotrienes D4 and E4 are like a combination of spices and goods to enhance the noodles. Making a bag of noodles does not take very long and Leukotriene synthesis being similar occurs very quickly as well.
Leukotriene Synthesis

Arachidonic Acid

5-Lipoxygenase
Plus FLAP

5-HPETE

5-Lipoxygenase
Plus FLAP

Leukotriene
biosynthesis
inhibitors

Leukotriene A4

LT A4 hydrolase

Leukotriene B4

LT C4 synthase

Leukotriene C4

Transpeptidase

Leukotriene D4

Dipeptidase

Leukotriene E4

Inflammation
Bronchoconstriction
Hyperresponsiveness

[1]
Leukotriene Antagonists

Antileukotriene agents are responsible for stopping Cysteinyl Leukotriene Synthesis. The leukotriene antagonist accomplishes this by attaching the reaction of 5-HPETE 5-lipoxygenase and FLAP. By attacking this area in the reaction, it blocks the binding of LTD4 and leukotriene A4 is unable to formulate. If leukotriene A4 is unable to form, so are all of its derivatives (B4, C4, D4, E4). By lowering the production of leukotriene A4, a scientist lowers the risk for an asthma attack.

Leukotriene antagonists were first introduced in 1996. The two main leukotriene antagonists include (in order of newest released to oldest) montelukast (Singular), zafirlukast (Accolate). Montelukast and zafirlukast are taken orally. Montelukast is rapidly absorbed, reaching peak plasma concentrations in 3 to 4 hours. These drugs are a “non-steroid anti-inflammatory treatment for asthma”\(^7\). The two-leukotriene antagonists have very few drug interactions.

Fig. 2

[Chemical structures of Zafirlukast and Montelukast are shown.]
Studies in Leukotriene Antagonists

Several case studies have been performed on both montelukast and zafirlukast. Scientists started testing with short periods, such as two – four weeks. These periods revealed inconclusive evidence. The optimal testing period for these drugs is about twelve weeks. Scientists have been running double blind tests with a placebo. The main two questions that scientists wanted answered about montelukast and zafirlukast related to side effects and leukotriene antagonists being used as a monotherapy drug.

The side effects of the drug are very low. Examples of side effects with these drugs are headache, nausea, diarrhea and abdominal pain. In the United States the FDA has approved the drugs for monotherapy with persistent asthma. The drugs have not been proven to completely recess the signs and symptoms of asthma.

In a twelve-week double blind test with montelukast and placebo, montelukast was tested for the effects upon asthma sufferers. The test measured how often signs and symptoms of asthma occurred, what they were and average lung capacity while taking the drug at a rate of 10mg once daily. Signs and symptoms of the patients on montelukast seemed to decrease, their expiration rate (PEFR) increased with a low amount of side effects. As seen in Fig 3 montelukast was very effective with the increase in PEFR in this clinical trial.

Fig 3

Exercise induced asthma studies with montelukast have shown little improvement. The drugs main purpose is to prevent and protect the body from asthma attacks, but does not usually prevent asthma after exercise. “In a two day, placebo-controlled crossover trial in 27 children 6 to 14 years old with exercise induced asthma 5mg of montelukast taken on 2 consecutive nights attenuated the decrease in FEV1 after a standardized exercise challenge 20-24 hours after the last dose”.

8
Several studies with montelukast and have shown the same results. The drug is very effective and the limitations to asthma sufferers are low. Still there are patients who believe that montelukast is less effective than that of inhaled Corticosteroids. “One study has shown that the introduction of montelukast allows a reduction in the dose of inhaled corticosteroid without loss of asthma control”.

Problems with Leukotriene Antagonists

There are not many problems with montelukast (Singulair), and zafirlukast (Accolate). These drugs are very safe with similar side effects as to sugar pill. The problem that has been the focus with these two drugs is the development of a Chorg-Strauss like syndrome. Chorg-Strauss disease is a connective tissue disorder. Often occurs in patients with pulmonary history and is not easily detected. The signs and symptoms are like the flu but the results are not. The disease attacks the lungs and nervous system causing a build up of white blood cells in the lungs. This creates cavities in the lungs and sometimes organ failure. The Food and Drug Administration says the drugs positive effect outweigh the negative ones.

Conclusion

Leukotriene antagonists are great for the right case. I am an asthmatic and I have used both drugs described above. The drugs have helped me considerably in exercised and allergen-induced asthma. These drugs work but only over a large period; they do not activate right away. I believe the drugs must travel throughout the body where other leukotrienes may be present and blocking their formation. If this is the case, the lungs are only getting a small portion of the drug to reduce asthma attacks.

In the future, I believe scientists will find that leukotrienes are not only in the lungs but also in other areas of the body causing similar problems. Soon scientists will realize that leukotriene antagonists have more than just one function in the body.
References


Catalytic Converters and Pollutants

Prepared for
Dr. Hank Mancini
Paradise Valley Community College
Prepared by Justin Kartler
April 26, 2002
Abstract

The purpose of this report is to give information on catalytic converters to a general audience. The aspects of this report include a background of emissions standards, examples of emission tests, and the reactions that take place inside a vehicle’s catalytic converter. A non-bias approach was taken and information both positive and negative to the use of catalytic converters is provided.
I. Introduction

All vehicles that are produced in the United States and around the world have one aspect in common, they are all equipped with catalytic converters. These catalytic converters are aimed at reducing the amount of pollutants emitted from any given vehicle. In recent studies it has been found that not only do catalytic converters reduce some exhaust emissions, but also leave traces of pollutants behind. This paper will explain what catalytic converters are, how they work, and the problems that they cause.

Catalytic converters are aimed at reducing three main pollutants: hydrocarbons (HC), carbon monoxide (CO), and nitrogen oxides (NOx). Hydrocarbons are products of unburned fuel that evaporate into the atmosphere. Sunlight will break down hydrocarbons to form oxidants, which will react with nitrogen oxides to form what is known as smog. Carbon monoxide is a poisonous gas that has no odor or color. Nitrogen oxides are a combination of both NO and NO₂, but are collectively referred to as NOₓ. Oxides of nitrogen aid in the production of smog, acid rain, and can even cause irritation to human skin.

Hydrocarbons are molecules in which are only made up of hydrogens and carbons. Hydrocarbons can have different types of bonding and shapes within the molecule. These types of bonds include alkanes, alkenes, alkynes, and aromatic. Alkanes are molecules that do not contain any multiple bonds. Alkenes are molecules that have carbon to carbon double bonds. Alkynes are carbon to carbon triple bonds. Aromatic hydrocarbons are molecules that have at least one multiple bond within a cyclic structure. See figure #1 for an example of a hydrocarbon.

![Kekulé structure for benzene](image)

Exposure to carbon monoxide, even at low levels, has shown to have adverse effects on the human body. Carbon monoxide can enter the blood stream through the lungs. Once in the lungs, carbon monoxide inhibits the blood's ability to carry oxygen to the organs of the body. This inhibiting compound is called carboxyhemoglobin. The individuals that are at highest risk are infants, elderly, and those with respiratory diseases. The effects of carbon monoxide include impaired exercise capacity, impaired visual perception, impaired learning functions, and manual dexterity. To help in the control of this pollutant many cities in the United States are participating in Wintertime Oxygenated Fuels Program. Phoenix, Arizona is one of the cities that is participating in this program.
Oxides of nitrogen are very dangerous to humans. While high levels of nitrogen oxides can be fatal, lower levels can cause damage to lung tissue or lung irritation. In humans, short term exposure at concentrations greater than 3 parts per million can cause recognizable decrease in lung function. Concentrations of nitrogen oxides less than 3 parts per million can irritate lungs. Oxides of nitrogen in concentrations of as low as 0.1 parts per million cause lung irritation and measurable decreases in lung function in those individuals with asthma. Long term low-level exposure can destroy lung tissue, leading to emphysema. ⁹

II. Background material on catalytic converters

It was in the early 1970s that catalytic converters were introduced on cars to decrease emissions, which was of growing concern in the United States. ⁷ In 1976, California was the first state to introduce legislation for the use of three-way catalytic converters on gasoline vehicles. ³ Soon after this legislation, most new cars were equipped with catalytic converters.

The catalytic converters that are used today have evolved through the process of technology and with the increase of emission standards. There have been four generations of catalytic converters from the 1970s through the 1990s. From 1976 to 1979, cars were equipped with two-way catalysts. These catalysts contained Pt (Platinum) and Pd (Palladium) which helped in the reduction of hydrocarbons and carbon monoxide. The next generation of catalytic converters lasted from 1979 to 1986. These second generation catalysts contained Pt, Pd, and Rh (Rhodium), but were only effective in reducing the emission of NOₓ. The third generation of catalysts was the same three-way catalyst as generation two, but was better adjusted to higher temperatures. From 1992 to present day, automotive companies are using the fourth generation catalytic converter. This catalyst contains Pt, Pd, and Rh, but is enriched with Pd. The fourth generation catalytic converter has evolved to meet the legislation that has progressively gotten more strict. ¹

When a vehicle is running, it produces two types of emissions, those regulated by law and those unregulated by law. Unregulated pollutants include benzene, toluene, ethylbenzene, xylene, propylbenzene, and ethyltoluene. This paper will focus on the reactions involving regulated compounds. These constituents consist of hydrocarbons (HC), carbon monoxide (CO), and nitrogen oxides (NOₓ). ³

Catalytic converters are located in the exhaust system of a car between the engine and the muffler(s). The placement of the catalytic converter is important because if it is placed too close to the engine, the temperature of the converter increases and its life span decreases. When catalytic converters are placed too far from the engine, then the time that it takes the converter to reach proper operating temperature is increased. The proper operating temperature for catalytic converters is about 350°C, which takes the average car one to two minutes to reach. ² This "cold start," when a gas powered engine first begins running is when the most pollutants are emitted. In an experiment performed by Westerholm, Christensen, and Rosen, it was shown that it is in this cold start phase that the most HC, CO, and NOₓ are produced. In this experiment, the test vehicle produced 0.49 g km⁻¹ HC, 6.01 CO, and 4.40 NOₓ before it had reached the proper running
temperature. This same vehicle, once it had reached a proper running temperature, produced the following pollutants: 0.04 HC, 0.38 CO and 0.03 NOx. As the numbers show, temperature is an important factor for catalytic converter use.

III. Example emission tests

Two vehicles are compared by their emissions inspection results. In order to make this comparison one vehicle was equipped with a catalytic converter, while the other vehicle was not. The first vehicle is a 1967 Ford car. This car has eight cylinders, no catalytic converters, and uses on average one gallon of gasoline for every 12 miles driven. Table #1 is the vehicle inspection report for this car. The emission test gives a reading for loaded and idle for both hydrocarbons and carbon monoxide and the standards that are allowed. A loaded reading is the reading when the vehicle is under acceleration and therefore working harder. An idle reading is when the vehicle is running, but not under load. This vehicle is polluting the most under idle conditions.

**EMISSIONS INSPECTION RESULTS**

<table>
<thead>
<tr>
<th>Pollutant</th>
<th>Loaded Reading</th>
<th>Loaded Standard</th>
<th>Loaded Result</th>
<th>Idle Reading</th>
<th>Idle Standard</th>
<th>Idle Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrocarbons (HC) in ppm</td>
<td>182</td>
<td>450</td>
<td>PASS</td>
<td>203</td>
<td>450</td>
<td>PASS</td>
</tr>
<tr>
<td>Carbon Monoxide (CO) in %</td>
<td>0.70</td>
<td>3.75</td>
<td>PASS</td>
<td>2.35</td>
<td>5.00</td>
<td>PASS</td>
</tr>
</tbody>
</table>

This is an initial inspection of this vehicle. This vehicle has passed the equipment inspection and the emissions test. Congratulations! Thank you for helping clean our air. Use the tear-out section below for registering your vehicle. Keep the upper portion of this VIR until you receive your new registration. It is your proof of compliance with VIP requirements!

The second vehicle that was chosen for the comparison is a 1996 Chevy truck. This truck is equipped with a four cylinder, one catalytic converter, and gets about 22 miles per gallon of gasoline. Table #2 is the emission test results for this vehicle in 1996 when the truck had 4 thousand miles, and table #3 is the same truck in 2002 with 66 thousand miles on the engine. When this trucks' emission standards are compared with itself, it can be seen that after the vehicle has driven over 60 thousand miles, the catalytic converter is working at a less productive rate. The emission of hydrocarbons had increased over 25%. Carbon monoxide emissions had increased over 30%. Nitrogen oxides had also increased from 0.0 to 0.41 grams/mile. It is also important to note that as
this vehicle aged and began to pollute more, the emission standards for it became more stringent. The applicable standards for both HC and CO emissions decreased significantly.

Table #2

<table>
<thead>
<tr>
<th>Pollutant</th>
<th>This Vehicle's Emissions</th>
<th>Applicable Standard</th>
<th>Result for This Pollutant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrocarbons (HC) in grams/mile</td>
<td>0.01</td>
<td>2.40</td>
<td>Pass</td>
</tr>
<tr>
<td>Carbon monoxide (CO) in grams/mile</td>
<td>0.3</td>
<td>60.0</td>
<td>Pass</td>
</tr>
<tr>
<td>Oxides of Nitrogen (NOx) in grams/mile</td>
<td>0.0</td>
<td>3.0</td>
<td>Pass</td>
</tr>
</tbody>
</table>

This is an initial inspection of this vehicle. This vehicle has passed the equipment inspection and the emissions test. Congratulations! Thank you for helping clean our air. Use the tear-out section below for registering your vehicle. Keep the upper portion of this VIP until you receive your new registration. It is your proof of compliance with VIP requirements.

Table #3

<table>
<thead>
<tr>
<th>Pollutant</th>
<th>This Vehicle's Emissions</th>
<th>Applicable Standard</th>
<th>Result for This Pollutant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrocarbons (HC) in grams/mile</td>
<td>0.28</td>
<td>1.60</td>
<td>Pass</td>
</tr>
<tr>
<td>Carbon monoxide (CO) in grams/mile</td>
<td>10.09</td>
<td>20.00</td>
<td>Pass</td>
</tr>
<tr>
<td>Oxides of Nitrogen (NOx) in grams/mile</td>
<td>0.41</td>
<td>3.00</td>
<td>Pass</td>
</tr>
</tbody>
</table>

This is an initial inspection of this vehicle. This vehicle has passed the equipment inspection and the emissions test. Congratulations! Thank you for helping clean our air. Use the tear-out section below for registering your vehicle. Keep the upper portion of this VIP until you receive your new registration. It is your proof of compliance with car care requirements.

The comparison of these two vehicles poses one problem, with older vehicles the EPA has standards in parts per million and newer vehicles have standards in grams per mile. The 1967 Ford had a rebuilt engine with about four thousand miles so a comparison can be made between tables #1 and #2. It is important to note that with older vehicles not only are the standards higher, but the oxides of nitrogen are not tested. The
best comparison is between tables #2 and #3. Since the only variable between the two tables is age of the vehicle, direct evidence of catalytic converters losing effectiveness over time is seen.

IV. Reactions

Three-way catalytic converters are involved in three main reactions. First, they reduce NO\textsubscript{x} to nitrogen and water. Catalytic converters also oxidize carbon monoxide into carbon dioxide. Lastly, they oxidize hydrocarbons. The reduction catalyst, either platinum or rhodium, which is located in the first stage of the catalytic converter reduce NO\textsubscript{x} emissions. As a NO or NO\textsubscript{2} molecules enter into the converter, the catalyst, either platinum or rhodium removes the nitrogen from the oxygen. The free oxygen is then available to attach to another oxygen, if it is not O\textsubscript{2} already, and exit the exhaust system. The nitrogens that are attached to the catalyst then bond with each other and exit as N\textsubscript{2}.

\[2\text{NO} \rightarrow \text{N}_2 + \text{O}_2\]

or

\[2\text{NO}_2 \rightarrow \text{N}_2 + 2\text{O}_2\]

The second stage of the catalytic converter uses palladium as the oxidizing catalyst. Hydrocarbons and carbon monoxide from the unburned fuel are oxidized to form unharful molecules.

\[2\text{C}0 + \text{O}_2 \rightarrow 2\text{CO}_2\]

The oxygen for the reaction comes from oxygen that is pumped into the exhaust system and is monitored by an oxygen sensor that is in front of the catalytic converter.\textsuperscript{5}

Although the reactions that take place inside the catalytic converter are simple, they are not only very important, but have an extremely important impact on our environment because of the volume of vehicles that are performing these reactions on a daily basis.

V. Pollutants given off from catalytic converters

The use of palladium, platinum, and rhodium are not only very expensive, but in recent studies have been shown to cause pollutants themselves. It is believed that catalytic converters are responsible for increased amounts of Pt and Pd found along roadsides in soil, grass, river sediment, and even sewage.\textsuperscript{7} In a study performed in the Boston Harbor, it was found that Pt and Pd concentrations in sediments had increased about 5 times the amount found in background concentrations.\textsuperscript{7}

Catalytic converters are responsible for scattering platinum-group elements (PGEs). These PGEs are dispersed at a rate that is higher when the vehicle is moving at a
faster rate of speed and when the catalytic converter is at a higher temperature. The environmental hazard that can be caused from this roadside polluting is the possibility that these PGEs will enter into the food chain through the uptake by plants.

The amount of PGEs being dispersed into the environment is of a great concern. Although it is estimated that a car equipped with a catalytic converter disperses Pt at a rate of only 65 to 180 ng km\(^{-1}\), it is the amount of km per year driven and the the amount of cars on the road that make the numbers staggering. With an estimated 500 million cars world wide that are equipped with catalytic converters and each car driving about 15,000 km per year, the estimated Pt emission is 0.5 - 1.4 tons per year.\(^5\) Catalytic converters seem to be trading one problem for another. Automotive catalytic converters are replacing one pollutant for another.

VI. Conclusion

Since the 1970s, cars have been required to be equipped with catalytic converters. These converters have evolved over time into what is now referred to as three-way catalysts. The three-way catalysts have expensive elements which include Platinum, Palladium, and Rhodium. The pollutants that catalytic converters are responsible for reducing or oxidizing are hydrocarbons, carbon monoxide, and oxides of nitrogen. Catalytic converters have proven to decrease the emissions of these law regulated pollutants. Over time, mainly because of heat damage, catalytic converters will decrease in efficiency. Catalytic converters are also the main source for increased Platinum-Group element accumulation along roadsides and in the atmosphere. To solve the problem of increasing pollution due to car emissions many car manufactures have built cleaner burning vehicles. This would include trucks and cars that use propane or natural gas as an alternative to gasoline. Propane and natural gas burn more completely and have less emissions out of the tailpipe. Most cars that are sold today are more fuel economy based in design with lightweight plastics being used and aerodynamics playing a major role in body design.

Catalytic converters play a major role in reducing the amount of pollutants that are emitted from cars and trucks. Although catalytic converters leave pollutants along roadsides, they seem to be the best way to lower vehicle emissions. The reactions that take place inside of catalytic converters are simple, but effective in the outcome. With technology leading the way better performing and longer lasting converters will help in the fight against the polluting of the planet.
References


The History and Effects of Polychlorinated Biphenyls in the Environment

By Melanie S. Korman

Prepared for

William Mancini
Paradise Valley Community College
Abstract

This report is about the effect of polychlorinated biphenyls on humans and, in particular, marine mammals. The history of polychlorinated biphenyls, and the uses of these toxins, is discussed. Finally, this paper explains the environmental properties of polychlorinated biphenyls.
Introduction

Industry often uses chemicals that are toxic and often have a hard time discarding them. Another problem ensues when the company is not aware chemicals they are using are harmful, or if they know and just do not acknowledge that the chemical is harmful. Many companies use an "I just didn't know," excuse for not pre-examining the chemicals they choose to use for harmful side affects. This is the case when it comes to polychlorinated biphenyls for they were used by companies and nations all over the world, and only now is there evidence of their environmental effects. Polychlorinated biphenyls have been shown to have adverse effects on the environment, have been leading to developmental and health problems in humans, and to the diminishing population of killer whales, among other things.

Polychlorinated biphenyl, also known as PCB, is a stable compound with an oily texture. This liquid was used in industry as a coolant for electrical transformers and capacitors. It was also an additive in many products, such as lubricants, paints, insecticides, and varnishes. The reason it is so harsh on the environment is because it is such a stable compound. PCBs are slow to break down and travel through air and water, and concentrate in sediments. The concentrations of this toxin in the sediment of rivers and the ocean are becoming noticeably significant in the animals, such as humans, who feed off of organisms that dwell in these ecosystems. PCBs have the ability to travel long distances and can deposit in the atmosphere and redistribute back into the environment anywhere. This makes it difficult to locate and clean up this contaminant.

Monsanto, a company that used PCBs, has been found guilty of six counts of failure to notify the public of the hazards of this chemical. While they are paying a settlement, the environment and animals are paying the price for their mistake.

When consumed, PCBs deposit and accumulate in the body fat of an animal. In fish, it deposits in the oils of its scales, as well. When an animal is high on the food chain, and lives longer, it accumulates higher concentrations of contaminants. This is because concentrations continue to build with continuous exposure to the chemical. This is long lasting and damaging to the organism that consumes it.

Affect on Humans

People consume a variety of organisms from the ocean. They eat crab, which forage on the bottom of the ocean, salmon which eat many bottom dwellers and other contaminated organisms. Humans on average have concentration levels of less than 1 part per million of PCBs in their bloodstream. This quantity is more than sufficient to cause abnormalities in infants having prenatal exposure to PCBs. The toxin is transmitted over the placenta and has been linked to neurological and behavioral abnormalities.
The lasting effects are evident in the cognitive abilities of children with prenatal exposure to even small quantities of PCBs. These children can develop learning disabilities, IQ deficits, and other complications that go on through teenage years.3

PCBs can also interfere with sexual maturity in adolescents. There have been many limited correlations between PCB levels and testosterone levels in maturing males. Conversely, there are significant correlations between slower breast development in maturing females and concentrations of PCBs.7 These complications arise from fetal, neonatal, or prepubescent exposure to contaminants.7 People are susceptible at many times in their growth and contamination from PCBs is virtually inevitable.

Moreover, this toxin has been shown to have an effect on memory in adults. Studies have shown that people with high concentrations of PCBs are more inclined to score poorly on memorization tests than people with low levels.3 People often remember items in groups, for example a grocery list is broken up into categories of meats, sweets, fruits, and so forth. While most participants with low concentrations of PCBs were able to recall items from a categorized list, most participants with high levels could not.3 This shows risk to toxins as the individual ages.

How these problems occur has yet to be determined, and PCBs are currently being researched along with other organic chemical toxins. Some research suggests that PCBs may cause imbalances of the thyroid hormone in the bloodstream.8 The thyroid hormone is important to the development of the nervous system.8 In laboratory studies, doses of PCBs have shown a decreased production of the thyroid hormone thyroxine (T4), the primary hormone circulating in the blood. These toxic effects may be explained by the structural similarity between the compounds PCB and T4. The structural formula for these compounds is in Figure 1.

Figure 1:
PCB metabolites bind to a protein called transthryetin, which is the protein that normally binds to T4 and carries it through the blood stream. Charlotte Shubert proposed that PCBs mimic T4, causing adverse affects on the body’s ability to function.\(^8\)

PCBs clearly appear to be harmful even doses less than 1 part per million, to human beings. In general, before chemicals are produced in massive quantities, and used in industry, health risks should first be analyzed. If industry cannot learn from its mistakes, there may eventually be no environment for industry to thrive in.

**Affect on Killer Whales**

The state of the oceans and the animals within it are good indicators of the state of the overall environment. The killer whale is most likely the best indicator, for it is at the top of the food chain. The Southern Resident killer whales are located in Puget Sound, Washington.\(^9\) This community, comprised of three pods or matrilineal families, is diminishing in size. The Southern Residents have maintained a population size of about 100 whales.\(^9\) This was until the early 60s, when infants from these pods were captured for aquariums and entertainment.\(^9\) After the capture of killer whales was banned in the early 80s, the population grew in size and returned to 98 whales in about 1996\(^9\) (Figure 2 shows the population from 1960-1999).\(^10\) Since then, there has been a rapid decline in the amount of calves able to live past five years old, the number of male adults able to live to the life expectancy (which is between 30-60 years), and the number of females able to reproduce.\(^9\) The reasons for this are unknown. The problem could even reverse itself and the population could flourish again.\(^1\) The following is just one hypothesis.

Human tissue contains, on average, less than 1 part per million of PCBs in the blood stream. Harbor seals have exhibited immune system failure with 17
parts per million (ppm). Northern Resident killer whales which have an average of 37 ppm, and finally the Southern Residents averaging about 146 ppm of PCBs in their blood stream.\(^1\) Given the afflictions that humans encounter at low PCB concentrations, one might be able to better understand the plight of the killer whales at these high concentrations. Since whales maintain a layer of blubber or fat, whales have ample room to collect high concentrations of PCBs. Since the Southern Residents each eat between 300-500 pounds of contaminated salmon every day, the Orcas are unable to escape this toxin and probably others.\(^1\)

A whale from the Southern Resident community was found dead March 2000, and had washed up onshore. This female was about 22 years old, and was completely emaciated. When she was tested in 1994, about 63 ppm of PCBs were found in her blubber. However, no comparative follow-up tests for PCBs were conducted because she had metabolized much of her blubber and an accurate sample could not be obtained.\(^1\) Upon an autopsy, her reproductive organs were found underdeveloped. However, she had been killed by a normally harmless bacterial infection in an abscess on her stomach.\(^1\) This shows a deficiency in the immune system, and lack of development in the reproductive system. PCBs could be the reason that these seemingly reproductive females are having trouble procreating.

If a female exposed to PCBs has a successful birth, she may pass those PCBs on to her offspring via the milk-fat.\(^9\) Since calves are constantly growing, and their cells are differentiating, PCBs, by way of thyroid imbalances, can significantly harm the immune system and other developmental aspects of the calf.\(^9\) This could be the explanation of the increased infant mortality among the Southern Residents.\(^9\) On the other hand, passing PCBs to her offspring helps the reproductive female, because it can actually lower the concentration of the toxin in her blood stream, and may stabilize her health while nursing and raising her calf, if she is not too ill already.

The problem becomes more complex with males in the Southern Resident population. Males cannot rid themselves of the toxin, thus they end up accumulating it over time. Since males become much larger than females, they eat more and therefore have more exposure to contaminants.\(^10\) With no way to free themselves, males are subject to the toxins' effects. This could explain the deaths of post-reproductive adult males.

Most likely, there are a series of events that has led to the downward spiral of the population of killer whales. Other explanations include the diminishing population of a food source, namely salmon, and an increased amount of boat traffic around the whales at any given time.\(^10\)

**Conclusion**

PCBs have been widely used in industry. When Monsanto learned of their harmful effects, they did not admit it to the public. While Monsanto is paying retributions, PCBs are taking their toll on the environment. This chemical is a highly stable compound which is slow to
break down. PCBs tend to get into the atmosphere and redeposit in other areas. This toxin stays in the air, in the water, and deposits in sediments. Animals that are exposed to PCBs have the chemical deposited in their fat. The higher on the food chain and the longer the animals live, the higher concentrations they accumulate in their fat and even in their blood stream.

People accumulate less than 1 ppm in their body. This chemical can cause developmental problems in children with prenatal exposure, can slow the development of reproductive organs with pre-adolescent exposure, and can cause memory problems in adults. With this small quantity, many problems still occur within the body.

In comparison, the killer whales that traverse Puget Sound have an average of 146 ppm of PCBs in their system. This may show why this community is having trouble sustaining its population. Adult females are not having as many calves, infant mortality has increased greatly, and adult males are not surviving, as well. While other situations may have aided in the diminishing population of the Southern Resident killer whales such as smaller food source and increased boat traffic, the probability that they are most affected by the toxins polluting their ecosystem cannot be ignored.

The environment is at the will of industry and other decisions all determined by people. When the environment starts affecting the health of humans is when it is time to take action to reverse the problems they created in the first place. If more precautionary terms were set for the uses of products and new chemicals, people could begin to prevent potential hazards. Moreover, if industry realizes that the problems it creates extend to more that just humans, but to animals and the environment as well, and if it takes responsibility for those problems imposed in a timely manner, then a solution may develop before the problem is beyond repair. Rendon asks, "What does it take to bring down a killer whale?" Unfortunately, the question that should be asked is, "What will bring up the population of killer whales?" The solution only appears when one is looking, and if people deny responsibility for their actions, the consequence could be the extinction of one of the most amazing species on the planet and in the ocean, the *Orcinus Orca*, or the killer whale.
Figure 2:

Southern Resident Population (1960-99)

Number

Year
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OxyContin

By: Jennifer M. Kostus
April 26, 2002
Dr. Mancini
I. Abstract

Chronic pain is a terrible condition of which thousands suffer. In the past people had to take several pills with frequent dosages. Controlled release OxyContin decreases the frequency of dosages to two, while providing maximum strength pain relief over a 24-hour period. This drug has been deemed a miracle to many, but some feel it has done more harm than good due to the fact that it has the reputation of a popular street drug. This paper will explore the properties, synthesis, uses, abuses, delivery, and absorption of OxyContin.

II. Properties

OxyContin is a schedule II controlled substance. This drug is classified as a pure, strong opioid agonist, which refers to the fact that it is derived from an opiate working against the antagonist, in this case pain. Also included in this class are morphine, hydromorphone, fentanyl, codeine, and hydrocodone. These drugs are primarily used as analgesics or pain relievers.

While OxyContin contains several ingredients, the main active ingredient is oxycodone hydrochloride. This substance occurs as a white, odorless crystal or powder. Oxycodone hydrochloride has a molecular weight of 351.83 and melts between 274–278° C. This substance is soluble in water and slightly soluble in alcohol. The chemical formula is C_{18}H_{21}NO_{4} • HCl or (5α)-4,5-Epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one hydrochloride. The structure is as follows:

\[
\text{CH}_3\text{O} \\
\text{O} \\
\text{O} \\
\text{N}^{+} \text{Cl}^{-} \\
\text{CH}_3
\]

\[
\text{C}_{18}\text{H}_{21}\text{NO}_4 \cdot \text{HCl} \quad \text{MW 351.83}
\]
III. Synthesis

Oxycodone Hydrochloride exists as a tautomeric salt of oxycodone, which is derived from an opium alkaloid (C<sub>19</sub>H<sub>21</sub>NO<sub>3</sub>) named (5α)-6,7,8,14-Tetrahydro-4,5-epoxy-3,6-dimethoxy-17-methylmorphinan or Thebaine. This molecule comes from a strain of the poppy plant known as *Papaver bracteum*<sup>2</sup>. Thebaine itself has no analgesic properties, even though after reacting an analgesic property is obtained. The structure of oxycodone was first introduced in 1950, and approved by the FDA in 1976. The patented controlled release salt of this form was not released for medicinal use until December of 1995.

The synthesis<sup>2</sup> is as follows: First, thebaine reacts with hydrogen peroxide. This involves a 1,4-addition of two hydroxyl groups across the diene, forming a hydroxyl group at position 14β and a hemiacetal at position 6. Then, acid is added and hydrolysis occurs to produce an enone. Next, hydrogenation occurs to form oxycodone. Finally, hydrochloric acid is added to improve solubility.
III. Function

When taken correctly, OxyContin is useful in patients who need relief 24 hours a day for a long period of time due to chronic pain. Chronic pain is defined as moderate to severe pain lasting over a long period of time. Such pain can be from postoperative, postpartum, degeneration of the spine or disks, Tourette syndrome, or even cancer. Due to the controlled release formula, OxyContin needs to be taken just twice daily. Due to the strong nature of this drug, other pain relief options may be explored prior to starting treatment with OxyContin.

IV. Mechanism of Action

One of the main effects of opioid agonists is experienced by the central nervous system. Opioid agonists work by binding at specific opiate receptor sites. The receptors include OP1 or Δ receptor, OP2 or κ receptor, and OP3 or μ receptor (the most used of the three). The majority of these receptors are in the limbic system, thalamus, striatum, hypothalamus, midbrain, and spinal cord. The pain threshold and pain impulses are not changed. However, the perception and emotional responses to pain are greatly changed in the spinal cord and central nervous system.

The Δ, κ, and μ receptors pair with guanine-nucleotide-binding protein receptors (G-protein receptors) and transmit synapses to trigger proteins such as adenylyl cyclase-cyclic adenosine monophosphate (cAMP) and phospholipase C-inositol 1,4,5 triphosphate (PLC Ins(1,4,5)P3)-Ca²⁺.

The κ receptor works to close the Nitrogen channels while the μ and Δ receptors work to open the potassium channels in the body. This opening of one channel and closing the other results in hyperpolarization and reduces the state of excitement of the neurons. Next, the opiate binds causing the exchange of guanosine triphosphate (GTP) for guanosine diphosphate (GDP) on the G-protein. When GTP binds, a portion of the G-protein is released affecting the levels of adenylate cyclase and cAMP inside the plasma membrane.

The opioid decreases the cAMP levels by blocking adenylate cyclase. The outcome is less release of nociceptive receptors like dopamine and
norepinephrine. Inhibiting the release of nociceptive receptors stimulates the $\mu$ and $\kappa$ receptors. The $\mu$ receptor produces analgesia, euphoria, respiratory depression, miosis, decreased gastrointestinal motility, and physical dependence. Stimulation of the $\kappa$ receptor produces analgesia, miosis, respiratory depression, dysphoria, and sometimes disorientation$^3$. The receptor sites are shown in the next two pictures$^4$: 
V. Delivery

OxyContin uses the patented AcroContin delivery system in the body. This delivery involves dual control of two hydrophobic retarding polymers. An acrylic polymer as well as another hydrophobic macromolecule allows the drug to be delivered regardless of the pH in the body.

The OxyContin tablet must be swallowed whole with a substantial amount of water. The outer film coating dissolves first then the body begins the breakdown and diffusion of the drug. The acrylic polymer matrix allows for two phases of absorption. This produces two half-lives. As the body begins the initial breakdown, some of the drug is absorbed immediately and effects should be noticed within an hour. The next phase occurs when the oxycodone concentration in the blood begins to decrease. At this time, more oxycodone is released in the bloodstream and the level is kept constant by subsequent releases over a 12-hour period. High fat diets may actually alter the concentrations by increasing the levels of oxycodone in the blood, but more tests and studies need to be performed in order to support this possibility.
VII. Contraindications

OxyContin is not recommended for anyone who cannot tolerate oxycodone or other drugs derived from opiates. Patients already experiencing respiratory depression, bronchial asthma, or hypercarbia (excess carbon dioxide in the lungs), prior to drug use are advised not to use this drug. People who have a history of opiate dependence or abuse should not use OxyContin. This drug is only recommended for those patients who take medicine as prescribed in which pain is constant and persists.

VIII. Side Effects

Certain people will experience some side effects with OxyContin. Side effects are most common in those patients who are not used to opiate drugs or those with a high strength of the drug resulting in a larger oxycodone plasma concentration. The most common side effects include: dizziness, lightheadedness, nausea or vomiting, drowsiness, constipation, and itching. Less common side effects include: swelling in the feet, sweating, euphoria, and urinary retention. Serious side effects are common in those who overdose. These side effects include: confusion, excessive sleepiness, slurred speech, unconsciousness, small pupils, clammy skin, slow breathing, seizures, excessive weakness, and excessive dizziness.

IX. Abuses

One of the concerns with OxyContin includes improper use. OxyContin “is sometimes called ‘hillbilly heroin in Kentucky, Ohio, Virginia, and West Virginia.’” The extended time-release property of the drug is diminished if the drug is chewed, broken, or crushed. Drug abusers know they can achieve a euphoric high if they chew, snort, or inject the medication. Since the medication is addicting when taken improperly, a dangerous and illegal habit is formed.

In fact, the euphoric experience is so pleasurable in some that they resort to waiting in drug store pharmacies hoping someone will pick up OxyContin. Once the drug is picked up, the addict waits for the patient to leave in their car. The addict follows in a car driven by an accomplice and the home address of the patient is found. Then the addicts watch the victim for a period until the patient leaves and no one is home. At this time, the home is broken into and the drug is stolen. People are amazed that their expensive televisions, stereos, and jewelry go untouched, yet their prescription pain medication is gone.

Because of the abuse epidemic the company responsible for producing the drug, Purdue Pharma has developed a ten-point plan “to reduce prescription drug abuse and diversion without compromising patient access to proper pain control.” They have also begun testing a new formula of the drug combining oxycodone with an antagonist. So far, the company has developed two new formulas with naloxone and naltrexone working as antagonists. These drugs would not interfere
with proper use; however, if the drug was chewed or crushed these drugs would work against the effects of the oxycodone high and instead induce withdrawal symptoms. Tests and studies for the new formulations will be introduced to the FDA by next year.

X. Conclusion

OxyContin has been an excellent medication for those in great pain. It has given new hope for some, allowing for improved quality of life. The problem lies with those who abuse the drug and take it for purposes other than pain. Something needs to be done to prevent improper use and reduce the number of addicts. I think the new formulations with the agonist and antagonist combination is just the key.
Works Cited

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How Safe Is Ephedrine?

Daniel LaFontaine

April 26, 2002
ABSTRACT: The use of Ephedrine is as widespread and diverse as it is controversial. As a result of uncertainty regarding safety, many people refrain from using products containing ephedrine. The purpose of this report is to shed some light on exactly what ephedrine is, where it comes from, and how it can be used safely.

Ephedrine is a drug derived from the plant Ephedra equisetina. Used for centuries as both a stimulant and bronchodilator (often under its traditional Chinese name, Ma huang), ephedrine is chemically similar to the amphetamines. A main ingredient in legally-available energizers, nutritional supplements, and dietary teas, ephedrine is also found in herbal substitutes for the hallucinogenic amphetamine MDMA, or "ecstasy." A synthetic form of the drug, known as pseudoephedrine, is a common ingredient in over-the-counter and prescription cold and allergy products. In its pure form, ephedrine is a white powder, but more often, it's sold in tablet or capsule form or as loose plant material. Ephedrine triggers a mild burst of energy, due to its similarities to the body hormone epinephrine (or adrenaline) and the street drug methamphetamine. In addition to its stimulant effects (which can include feelings of alertness and reduced appetite), ephedrine also relaxes bronchial muscles and dilates airways, and can cause sharp increases in both blood pressure and heart rate. Ephedrine is approved as a drug by the FDA for human consumption, but because it is a precursor for several scheduled drugs (methamphetamine & methcathinone), it is highly regulated. Sales of large quantities are monitored and many states heavily regulate the forms and methods in which it is sold.1

As a sympathomimetic, ephedrine acts to stimulate the sympathetic nervous system. It does this by causing pre-synaptic nerve terminals to release norepinephrine, or what is commonly called noradrenaline (NA), into the synaptic space. It also has the effect of increasing circulating adrenaline (Adr), the body's chief beta-2 agonist. Noradrenaline, once released into the synaptic space, interacts with adrenergic receptors on the surface of adipocytes (also known as plain old fat cells). This initiates a sequence of events within the adipocyte that increases lipolysis.

Lipolysis is the process of breaking down triglycerides into glycerol and fatty acids. This process is dependent on an enzyme called hormone sensitive lipase (HSL). Activating HSL is the last step of a chain of intracellular reactions that make up the second messenger system. It is called a second messenger system because NA acts as the first messenger and Cyclic Adenosine Monophosphate (cAMP) acts as the second.

The entire chain of events that occurs after administration of ephedrine goes as follows: 1) Ephedrine stimulates the release of NA from sympathetic nerve endings. 2) NA then binds to adrenergic receptors on the surface of all tissues that contain these receptors. Adipose tissue and skeletal muscle have abundant adrenoreceptors on their surface. 3) As NA binds to beta-adrenergic receptors, stimulatory guanine nucleotide regulatory proteins(Gs-proteins) within
the cell membrane activate the enzyme adenylate cyclase. 4) Adenylate cyclase then converts ATP into 3'-5' cAMP. 5) cAMP then binds to the regulatory subunit of protein kinase A. 6) Once bound by cAMP, protein kinase A releases its catalytic subunit. 7) The catalytic subunit phosphorylates HSL, thus transforming it into the active form, HSL-P. 8) HSL-P then catalyzes a three step hydrolysis reaction to reduce triglycerides into glycerol and fatty acids. (2)

**Step One**

In step one it is important to realize that ephedrine does not interact directly with adrenergic receptors. It is through its effects on the release of NA that ephedrine increases adrenergic activity. This was determined by examining the effects of ephedrine on adipose tissue with intact sympathetic nerves or without. Once the nerves had been removed, the ephedrine had little, if any, effect at concentrations typical of oral administration. This has a number of disadvantages as well as some advantages. First the disadvantages. Ephedrine is called a non-specific adrenergic agonist because through the release of NA, it has an effect on more than one class of adrenergic receptor. NA can bind with alpha and beta receptors alike. This produces a generalized effect because alpha receptors, particularly alpha-2 receptors, decrease lipolysis and beta receptors increase lipolysis. The overall lipolytic effect of ephedrine is determined by the ratio of alpha and beta receptors on each particular adipocyte. Another disadvantage is potency. Non-specific agonists have a far weaker effect on beta-receptors than specific beta agonists such as epinephrine, Albuterol or Clenbuterol. Ephedrine is dependent on the release of noradrenaline to do the job and is only dose dependent up to a point.

The assertion that beta-agonists such as clenbuterol and ephedrine have no anabolic effects in humans is premature. There is a large difference in the dosages normally given to animals (4 mg/kg) as compared to humans (up to 40 μg/day). Research showing preservation of lean tissue and significantly improved protein deposition in response to treatment with ephedrine during caloric restriction indicates that beta-agonists are exerting an anabolic effect in humans. More research is needed to determine the extent and most efficacious way to administer these compounds to elicit an anabolic effect in man.

Concerning beta-2 receptor desensitization, the fact that ephedrine is less potent than specific beta-2 agonists decreases the amount of beta receptor down regulation subsequent to chronic treatment. Chronic stimulation of beta2-adrenergic receptors causes a decrease in the sensitivity of tissues to beta agonists. This decrease in sensitivity involves either homologous desensitization, where the receptor’s active site is translocated within the cell membrane so that the binding site is no longer positioned extra
cellularly, or it involves heterologous desensitization, where the receptor is phosphorylated rendering it incapable of participating in the second messenger system. Receptor desensitization is a complex process with several different mechanisms. This complexity allows for more control of hormone signaling. As a general rule, the more potent the stimulus, the greater and more rapid the desensitization.

In summary, the advantages of using a non-selective beta agonist such as ephedrine are, it has beneficial effects on thyroxin deiodinase activity thereby increasing the T3/T4 ratio, it’s effect on beta-3 receptors, and it’s tendency not to cause extreme desensitization of beta-2 receptors. All of this lends to the fact that the thermogenic affects of ephedrine are enhanced after chronic treatment. (2)

**Step Two**

Going back to the steps of ephedrine stimulated lipolysis, in step two we see that NA binds to the adrenergic receptors on the surface of tissues that contain them. By looking at all of ephedrine’s side effects you get an idea of what tissues contain adrenergic receptors. In the beginning you get an increase in heart rate. This is because beta adrenergic stimulation of the heart increases it’s rate, force and frequency of contraction. It also causes vasoconstriction which leads to a decrease in blood flow to most organs including skin, eyes, kidney and gastrointestinal tract. In most all of these tissues, the sympathetic response is designed to help the body respond to perceived emergencies. You may have heard of the "flight or flight" response. By reducing blood flow to the viscera, more blood is available to be diverted to working muscles. The heart pumps more blood, the eyes dilate, the GI tract slows motility (no time for potty breaks), and attention, or alertness, is enhanced allowing the animal (or person) to be focused on escape or capture and less focused or perceptive of pain.

Muscle and fat tissue also contain adrenergic receptors. In fat tissue there are gender specific ratios of beta to alpha receptors on various parts of the body. This gives rise to the familiar male (android) and female (gynoid) fat patterning. Females tend to resist lipolysis on their hips, buttocks and thighs, whereas men tend to resist lipolysis on their abdomen and oblique region. This is due to a preponderance of antilipolytic alpha receptors on the cells in these regions. Our goal in using beta agonists is to increase lipolysis in fat tissue. The effect of both alpha and beta receptors being located on fat tissue allows for more control of lipolysis. In essence it gives the body both an accelerator and a brake.

In muscle tissue, beta adrenergic activation seems to stimulate protein synthesis rates through the same second messenger system that stimulates lipolysis in fat tissue. In studies measuring body composition as well as
weight loss, ephedrine has shown the ability to prevent lean tissue loss. In a small double blind study lasting only eight weeks, two groups of obese women were given either 20 mg ephedrine with 200 mg caffeine (E+C) or placebo (P). After eight weeks weight-loss was not significantly different between the groups, but the E+C group lost 4.5 kg more body fat and 2.8 kg less fat-free mass (FFM). That is a difference of more than six pounds in eight weeks. The expected decrease in 24-hour energy expenditure (EE) seen in the P group was 10% at day 1 and 13% at day 56, but was only 7% and 8% in the treated group. The higher EE in the E+C group was entirely covered by fat oxidation. People have speculated that beta-agonists were catabolic. This is disproved somewhat by the fact that 3-methylhistidine, which is used as an index for skeletal muscle breakdown, was not altered by ephedrine administration yet nitrogen balance was significantly improved during very low calorie dieting. So although muscle tissue was being broken down at the same rate, more lean tissue was being produced. (2)

**Step Three**

In step three we see that G proteins play a key role in regulating fat metabolism in adipocytes. In this step NA binds to the adrenergic beta-receptor activating stimulatory G proteins (Gs). These G proteins then go on to activate adenylate cyclase. When alpha receptors are activated, inhibitory G proteins (Gi) are activated and adenylate cyclase is not activated. This puts a halt to cAMP formation and hence a halt to lipolysis. G proteins are also involved, at least in part, in receptor desensitization. If you recall it was briefly mentioned that one of the ways beta-receptors are desensitized is called heterologous desensitization. This involves uncoupling of the receptor from stimulatory G proteins. This has the effect of stopping the message from getting any further than the receptor itself. Other mechanisms are also involved in heterologous desensitization but we will not go into it any further in this article. (2)

**Step Four**

In step four, ATP is converted into cAMP and inorganic phosphate (PPi) by the enzyme adenylate cyclase. cAMP contains a single phosphate group that is attached both to the 3' carbon and the 5' carbon of the sugar ribose. This is why it is called "cyclic" AMP. Neither PPi nor cAMP is allowed to exist in these forms for very long. The PPi that is formed when ATP is converted to cAMP is hydrolyzed by inorganic pyrophosphatase to form two Pi. 3'-5'-cAMP is also quickly rendered inactive by the enzyme known as cyclic AMP phosphodiesterase (PDE). PDE breaks the bond between the 3' carbon of ribose and the phosphate group thus making 5'-cAMP. 5'-cAMP is inactive and does not bind to protein kinase A and does not lead to the activation of HSL. This is the first feedback inhibition
mechanism we've discussed so far but there are others that act to shut off the original signal and slow lipolysis. As we will see later, feed back inhibition is one area we can target to increase the effectiveness of ephedrine. (2)

Steps 5-8

In steps five, six, seven and eight cAMP binds to the regulatory subunit of protein kinase A. This binding releases the catalytic subunit of protein kinase A which then phosphorylates HSL. Once HSL is phosphorylated it can then participate in the actual process of lipolysis. This brings us to the final step. HSL-P catalyzes the breakdown of triglycerides in three steps. Each of the three steps removes one fatty acid until all that is left is glycerol and three fatty acids. Now, just because you have disassembled your stored fat does not mean it is gone for good. If you do not burn this fat it will simply be re-esterified and turned back into triacylglycerol (storable triglycerides). This process of lipolysis and lipogenesis using the same fatty acids is called a "futile cycle" for obvious reasons. (2)
# RAW EPHEDRINE

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**U.S. FEDERAL LEGAL STATUS (8)**

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<td>SCHEDULE</td>
<td>DEA List I Chemical</td>
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## EPHEDRINE IN PRODUCT FORM

**Description**

Colourless crystals or white orthorhombic needles or powder, odourless with a bitter taste; freely soluble in water.

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**Structure**

![Structure diagram](image)

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<td>Melting Range</td>
<td>Between 217°C and 220°C</td>
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<tr>
<td>Specific Optical Rotation (50 mg/ml in water)</td>
<td>Between -33° and -35.5° calculated on dry weight basis</td>
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<td>Acidity / Alkalinity (1.0 gm/20ml in water)</td>
<td>Not more than 0.1 ml of 0.02 N Hcl or 0.2 ml of 0.02 N NaCl</td>
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<tr>
<td>pH (0.5% W/V solution)</td>
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The appropriate use of ephedrine has been a matter of much debate in recent years. There have been a number of reported cases wherein the use of ephedrine for one reason or another has produced adverse affects. These reported affects range from relatively minor side effects such as dizziness to more serious problems including heart attack. For example, more than 60 adverse events -- suicide, psychotic episodes, seizure, stroke and cardiovascular events ranging from hypertension to myocardial infarction have been reported in Canada. Other recognized adverse effects include anxiety, tremors, headaches, insomnia and flushing. Health Canada warns that some over-the-counter supplements used to increase energy and promote weight loss and bodybuilding pose a serious risk to health. The warning applies to supplements containing the herb ephedra or its alkaloid derivative, ephedrine; in Canada, ephedrine is authorized for use only as a nasal decongestant. (3)

An independent analysis of 140 adverse events reported to the US Food and Drug Administration (FDA) between June 1997 and March 1999 found that 47% involved the cardiovascular system and 18% the central nervous system (CNS). Health Canada has recalled unapproved herbal preparations containing more than the recommended dose of ephedrine. In addition, the manufacturers of approved commercial higher-dose preparations are being asked to submit data demonstrating their safety and efficacy. The recall includes all ephedra/ephedrine products having a dose unit of more than 8 mg of ephedrine or a label recommending more than 8 mg/dose or 32 mg/day and/or are labeled for use exceeding seven days. This involves products used for appetite suppression, weight loss promotion, metabolic enhancement, increased exercise tolerance, body-building effects, euphoria, increased energy or wakefulness, or other stimulant effects products containing Ephedra which are marketed for traditional medicine will continue to be available in decongestant form, provided they do not contain caffeine and that the ephedrine content does not exceed 8 mg/dose to a maximum of 32 mg/day. (4)

Cantox Health Science International, an internationally recognized scientific research organization, prepared a report for the Council for Responsible Nutrition on December 20, 2000. Referred to as the "Cantox Report," this report is the only formal risk assessment that has been done to date for dietary supplements containing Ephedra. The method of analysis used was developed by the Food and Nutrition Board, Institute of Medicine, National Academies, for application to nutrients. This risk assessment establishes that Ephedra is safe when consumed according to the industry recommendations, which has been adopted as state law in several states. These recommendations are as follows:

- Do not take more than 25 mg ephedrine alkaloids per serving and not more than 100 mg per day.
- Consult a health care professional before consuming an Ephedra-containing dietary supplement if you have heart disease, thyroid disease, diabetes, high blood pressure, depression or other psychiatric condition, glaucoma, difficulty in urinating, prostate enlargement, or seizure disorder, if you are using a monoamine oxidase inhibitor (MAOI) or any other prescription drug, or you are using an over-the-counter drug containing ephedrine, pseudoephedrine or
phenylpropanolamine (ingredients found in certain allergy, asthma, cough/cold and weight control products).
- Do not use Ephedra products if you are under the age of 18. Do not use Ephedra products if you are pregnant or nursing.
- Discontinue use and call a health care professional immediately if you experience rapid heartbeat, dizziness, severe headache, shortness of breath, or other similar symptoms.
- Exceeding recommended serving will not improve results and may result in serious adverse health effects.

The battle over whether ephedrine should be either more strictly controlled or outright banned by the U. S. government (F.D.A.) has some interesting and perhaps shady political links. Not long after Governor George W. Bush named him Texas health commissioner in September 1997, William Archer decided to restrict sales of dietary supplements containing ephedrine. It was a bold but logical move for the head of a nationally applauded state agency. Products with ephedrine had in the previous five years been linked to eight deaths and more than 1,400 health problems in Texas.

A few months after Archer's decision to crack down on ephedrine, something curious happened. Archer abruptly changed course. He called in large manufacturers and let them negotiate looser rules for marketing their ephedrine products. A physician and son of powerful House Ways and Means Committee chairman Bill Archer, William Archer had seemingly become an industry ally.

Why the flip? Archer reversed himself because of the ephedrine industry's strong opposition and its threats of litigation, according to his spokesman. But records and interviews obtained by TIME suggest another plausible reason: the office of Governor Bush encouraged, if not inspired, Archer's about-face after lawyers close to Bush began work for a leading manufacturer. Those same lawyers funneled $40,000 to Bush's reelection drive about the time of a key industry meeting with Archer. The rise and fall of ephedrine regulation offers a case study of politics, policy and money in George W. Bush's Texas. (6)

Despite the many reports indicating the safety of ephedrine and ephedrine containing products when used appropriately and in moderation, two of the most major athletics organizations in the world, the NFL and the Olympic Committee have completely banned their use. (7) Considering the extreme level of intensity with which these types of athletes already train, banning ephedrine for them was probably a prudent step. However, for the average workout enthusiast or just someone looking to shed a few pounds, ephedrine can be quite helpful if used with care.
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(4) Natural Life, Mar/Apr 2002, Issue 84, p6


(8) www.erowid.org