11th Annual
Science Symposium
Volume II
May 11, 2005
Paradise Valley College
Foreword

The 11th Annual Science Symposium was held on May 11, 2005. Students enrolled in General Organic Chemistry II, CHM 236 from Paradise Valley Community College (PVCC) participated in the event.

Each contributor was responsible for selecting and researching their topic and preparing a paper. A few orally presented 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 Dr. Rick Vaughn, PVCC math faculty. Through his hard work and leadership, this college was able to receive reaccreditation from the Higher Learning Commission (HLC) for another 10 years. Over the two plus years of this project Dr. Vaughn never lost sight of his mission and purpose. His leadership and direction allowed a diverse group of faculty and staff to achieve this success. As educators and students we acknowledge his efforts.

William L. “Hank” Mancini, PhD
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Varivax:
~The end to Chickenpox~
What is known and what is unknown about this new immunization.

Prepared by
Stephanie Harris

4/11/05
Abstract

One of the most recent vaccines now available is Varivax. Varivax is the varicella virus vaccine, commonly known in the United States as the chicken pox vaccination. This paper will discuss how and why this vaccine works, as well as, looking into the more recent research on the future of this vaccine.

History

A 3-year-old Japanese boy with varicella has skin lesions that the virus was isolated from. Takahashi et al. then developed a live attenuated VZV (varicella zoster virus) vaccine in 1974. Merck and Co, Inc. manufactured the US licensed Varivax, a similar varicella vaccine in 1995. The virus obtained by the boy was introduced to human embryonic lung cells, embryo guinea pig cells and human diploid cells (WI-38). At the Merck Research Laboratories further passage of the virus for varicella vaccine was performed in human diploid cells (MRC-5). Thus the live attenuated varicella vaccine is a lyophilized preparation. Vaccines made this way are often the most successful vaccines, mainly because they multiply in the body therefore causing a large immune response. Unfortunately these live, attenuated vaccines also carry the greatest risk because they can mutate back to the virulent form at anytime. Mutation such as this could result in induction of the disease rather than protection against it. [1]

Introduction

Viruses are reactive biochemical forms capable of replication through the division of living life form cell components. Excess viral structures can be excrated through any fluid including saliva, respiratory air, urine, sexual fluids, sweat, or fleeces. One of the greatest impacts on the world's health has been the discovery of vaccines. Vaccines are the reason why many infectious diseases are under control in the United States. Before any vaccines were available for chicken pox, there were approximately 4 million cases a year in the United States and 100 deaths a year were caused by this
disease. [2] In 1995 the United Stated Food and Drug Administration approved Merck & Company's Varivax. Varivax is a preparation of the Oka/Merck strain of live attenuated varicella virus. Varicella is a virus belonging to the herpes family. This disease is highly contagious by coughing and sneezing. Symptoms of chicken pox include moderate fever, mild headache, loss of appetite, and general discomfort. A rash of itchy, small red spots usually first appear on the chest, stomach or back. However they can develop anywhere on or in the body within three to five days. These spots will eventually change into clear blisters that will become cloudy, break open, dry, scab and heal within 5 to 20 days. Although the varicella virus is generally harmless it can be associated with serious complications and/or rarely death. Chicken pox can have dangerous complications in newborns, adults, and those with compromised immune systems, such as HIV.

Clinical Trials

The majority of subjects who received Varivax and were exposed to wild-type virus, in combined trials, were either completely protected from chicken pox or experienced a milder form of the disease. By comparing chicken pox rates in vaccines versus historical controls, by assessment of protection from disease following household exposure and by a placebo-controlled clinical trial, Varivax was evaluated. [3] The duration of protection of Varivax is still unknown at the present time. There also may not be protection in all healthy susceptible children, adolescents, and adults from the Varivax vaccine. Studies are continuously ongoing to evaluate the need and timing for booster vaccinations.

Indications and Usage

Merck & Co., Inc. and the Center for Disease Control (CDC) both indicate, Varivax given to children between 12 and 18 months of age should have one dose of chickenpox vaccine, although children who have had chickenpox do not need the vaccine. [4] Those children who are between 19 months and their 13th birthday who have not had chickenpox should be vaccinated with a single dose, but those who are 13 and older that have not yet had chickenpox also should have the vaccine, but should be administered two doses that are 4-8 weeks apart.

Administration and Dosage

This vaccine should only be administered subcutaneously and never injected intravenously. The lyophilized vaccine must be stored frozen at an average temperature 15 degrees Celsius. This vaccine should be administered immediately after reconstitution and should be discarded within 30 minutes after reconstitution if it is not used. Children that are 12 months to 12-13 years should be given a single 0.5ml dose. Each 0.5ml dose after reconstitution contains a minimum of 1350 plaque forming units of Oka/Merk
varicella virus, 25mg sucrose, 12.5mg hydrolyzed gelatin, 3.2mg sodium chloride, 0.5mg monosodium L-glutamate, 0.45mg sodium phosphate dibasic, 0.08mg potassium phosphate monobasic, 0.08mg potassium chloride, residual components of MRC-5 cells including protein and DNA, and trace quantities of sodium phosphate monobasic, EDTA, neomycin, and fetal bovine serum. [5]

Precautions

Those people who have ever had an allergy to varicella virus vaccine or neomycin should not be given this vaccination, or those who are moderately to severely ill at the time of administration of Varivax. Pregnant women should not be given Varivax and it is recommended that women should not get pregnant within one months time of receiving the vaccination. Anyone that has a disease that affects their immune system or are taking drugs that affect their immune system, such as steroids, should not be given the vaccination. Although modern vaccines are extremely safe and effective, there are not 100% so. Adverse reactions have been reported with all vaccines. The National Vaccine Injury Compensation Program requires that all physicians and other health care providers who administer vaccines to maintain permanent vaccination records. They must also report certain occurrences of adverse events to the US Department of Health and Human Services. [6]

Statistics

According to the National Advisory Committee on Immunization (NACI), “In actual use, it is estimated that the vaccine will offer 70% to 90% protection against varicella of any severity and 95% protection against severe varicella for at least 7 to 10 years after vaccination…” [7] Those who have had the Varivax vaccine and later got chickenpox reported having milder forms of discomfort, lesions, and fever. The symptoms typically seemed to have only lasted 3-5 days. Shortening the number of days spent that children are missing school and/or parents missing work. Varivax has helped cut down the number of hospitalizations due to this virus and is projected to decrease the number of deaths associated with varicella virus.

Concerns

There is some concern if an individual gets the varicella virus vaccine they can actually give chickenpox to other, unprotected, persons. This appears to happen extremely rarely, and only when that individual who was vaccinated develops a rash. To be safe, anyone with a suppressed immune system should consider avoiding contact with an individual who develops a rash after getting the chickenpox vaccination -- just as they should avoid anyone who has a case of chickenpox. Most research that was done early on indicated that after one dose of Varivax an individual would be completely immune to the varicella virus, however, like many vaccines, it will probably take more than one dose.
Due to the recent documented breakthrough illness in up to 56% of vaccinated individuals, the question is how effective is Varivax? A case controlled study from March 1997 thru June 2003 was conducted in Connecticut consisting of children that were 13 months or older, that had been given the vaccine. This study was to determine the effectiveness of the vaccine, especially the effects of time since vaccination and age at the time of vaccination. There was a substantial difference in the vaccine's effectiveness in the first year after vaccination (97%) and in years 2 to 8 after vaccination (84%). The vaccine's effectiveness in year 1 was substantially lower if the vaccine was administered at younger than 15 months (73%) than if it was administered at 15 months or older (99%), although the difference in effectiveness overall for children immunized at younger than 15 months was not statistically significantly different than for those immunized at 15 months or older. [9]

Conclusion

Diseases are the result of chemical changes disrupting the life process of organisms. Different drugs act in many different ways to fight diseases. Vaccines are a type of drug that are obtained from the natural sources. They prevent illness by stimulating the body's immune system to make antibodies that attack and fight off disease causing organisms. Vaccines are responsible for saving many lives, they protect against infectious diseases and they play a crucial role in disease prevention to the public health. As all vaccines have done, varicella vaccine will affect the epidemiology of the disease. As transmission continues to decline, decreasing circulation of wild virus will increase the likelihood that unexposed and unvaccinated children will enter adolescence and adulthood without immunity. [10] Thus, it is increasingly important to offer vaccine to all susceptible adolescents and adults as well as children in line with current recommendations.

Only with time will it be better understood if varicella virus vaccines will have to be given as booster shots, and the true efficiency of Varivax. Too many chickenpox is just a minor childhood disease that many will go through and be fine. But to those who are looking ahead and aware of other diseases that growing at rapid paces, such as HIV/AIDS, this vaccine could be crucial to their survival. Many can argue that the total number of deaths reported in the past that were related to the varicella virus was a small number of less significance. But others will say one death is too many, especially if it is a death of a child, in which it could have been prevented.
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Metformin

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April 18, 2005
Abstract

Diabetes mellitus is a chronic disease that is growing worldwide; therefore, an increasing number of pharmaceutical therapies are being synthesized. Metformin is an oral antidiabetic agent used to control glucose tolerance in patients with type 2 diabetes mellitus. This paper discusses the drugs’ controversial history, and the effects it has on the human body in order to successfully do its job. The various risk factors associated with the drug will also be explained, including its association with lactic acidosis.

Introduction

Diabetes mellitus affects 17 million people in the United States and about a third of them are undiagnosed. It is a metabolic disorder that is characterized by a decrease in insulin release from the pancreas and a resistance to insulin by the muscles, liver, and fat tissues. The major causes of insulin resistance are genetics, age, and obesity (Figure 1). Hyperglycemia is also associated with the diseases because as diabetes progresses, the pancreas begins to decrease its production and secretion of insulin. A critical component to the treatment of the disease is diet, exercise, and weight loss; however, to reach a target glucose level pharmaceutical therapy is an option.

![Figure 1 Factors that cause the chronic disease called type 2 diabetes mellitus](image)

Insulin resistance is a metabolic defect and the target for the class of oral antidiabetic agents, called biguanides. They are characterized as insulin sensitizing drugs and include phenformin, buformin, and metformin. In 1977, phenformin was banned from the United States due to the increased possibility of patients developing lactic acidosis. Buformin is only used in a few countries, which makes metformin the only biguanide used worldwide. Metformin was introduced in Europe in 1957, but it was not until 1995 that the FDA approved for its use in the United States after safety concerns were satisfied. Since then a metformin oral solution, called Riomet, was approved in September 2003, and a generic extended-release formulation, called Fortamet, was approved in April 2004.
Description and Synthesis

The chemical name for metformin is N,N-dimethylimidodicarbonimidic diamide hydrochloride, and its chemical structure is shown in Figure 2. The molecular formula is C₄H₁₁N₇HCl and the molecular weight is 165.63 g/mol. Complex 1 of the compound is called cis-monochloro(dimethyl-sulfoxide)metformin platinum (II) chloride, while complex 2 is named tetrachloro(metformin)platinum (IV). Metformin is soluble in water; however, it is insoluble in acetone, ether, and chloroform. A 1% aqueous solution of metformin has a pH of 6.68.

\[
\begin{align*}
\text{CH}_3 & \quad \text{NH} \\
| & \quad | \\
\text{CH}_3 & - \text{N} - \text{C} - \text{NH} & - \text{C} - \text{NH}_2 \\
\quad & \quad \cdot \text{HCl}
\end{align*}
\]

Figure 2: Structural Formula

Metformin is a white to off-white crystalline compound that contains 500mg, 850mg, or 1000mg of metformin hydrochloride (Figure 3). The tablet includes the inactive ingredients magnesium stearate, microcrystalline cellulose and povidone. The coating also contains hypromellose 2910, polyethylene glycol 400 and titanium dioxide.

![Figure 3: Metformin 500mg Manufactured by Teva](image)

Metformin is capable of binding to many transition metals due its two imine groups in the *cis* position that act as a chelating agent. Some of the metals include copper (II), nickel (II), cobalt (II), and platinum (II), all of which give a highly colored chelate complex.

Besides its imine groups, metformin is characterized by its non polar –CH₃ group on the side chain, and the carbon to nitrogen bonds. The C-N bonds have characteristics of both single and double bonds. Normally a single bond has a length of 1.47 Å and the double bond has a length of 1.265 Å. However, the C1-N2 bond shown in Figure 4 has a length of 1.33 Å, and the C2-N4 bond has a length of 1.29 Å. Both of these bonds are
single, but their lengths are similar to a double bond. The reason for this may be because of the electron withdrawal from the nitrogen, which is due to metal coordination.  

![Chemical structure diagram](image)

**Figure 4** Tetrachloro(metformin)platinum (IV) dimethylsulfoxide solvate

Complex 2 has two planar halves that make a dihedral angle of 15°, and complex 1 has an angle of 7°. However, the crystal structure of metformin hydrochloride has an angle of 67.9°. The two halves include the C1 out of the N1, N2, and N3 plane, and the C2 out of the N3, N4, and N5 plane (Figure 4). All of the nitrogens have electrons in their p-orbitals, therefore, a “considerable delocalization of the π-system” occurs.  

The compound has torsion angles at N4-C2-N3-C1 and C2-N3-C1-N2 (Figure 4). In the complex 2 compound the angles are 15° and 14°, “respectively, corresponding to a Z,Z stereochemistry.” On the other hand, “in metformin hydrochloride, the homologous torsion angle values of 130.9° and 159.7°, respectively, imply a change in the N4-C2-N3-C1-N2 stereochemistry.”

The synthesis of complex 2 begins with the starting material of K₂PtCl₆ and metformin hydrochloride. Four milli-mol or 1.94 g of K₂PtCl₆ was dissolved in 100 milliliters of hot water. Eight milli-mol or 1.32 g of metformin hydrochloride was dissolved in 10 milliliters of water, and this solution was stirred into the first. The complete mixture was stirred and kept at 70°C for 36 hours, which formed a yellow solid. The solid was washed with water, methanol, and ethyl ether to separate it by filtration. The final product was dried to get a percent yield of about 27%.
Mechanism of Action

Metformin has a variety of metabolic effects (Table 1 and Figure 5); however, its molecular mechanisms have not been completely identified yet. It is different than any other oral antidiabetic agent because it uses other mechanisms to lower plasma glucose in order to stabilize the glucose tolerance of the patient. The main glucose lowering action of metformin is to reduce the rate of hepatic glucose production by increasing the hepatic sensitivity to insulin. The drug is characterized as an anti-hyperglycemic because, unlike other oral agents, it is able to lower the blood glucose without causing hyperglycemia. This is because it does not increase insulin production, but decreases fasting insulin concentrations by 25 to 30%.

<table>
<thead>
<tr>
<th>Table 1 Summary of the Metabolic and Vascular Effect of Metformin</th>
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<tbody>
<tr>
<td>* Anti-hyperglycemic action</td>
</tr>
<tr>
<td>• suppresses hepatic glucose output</td>
</tr>
<tr>
<td>• increases insulin-mediated glucose utilization</td>
</tr>
<tr>
<td>• decreases fatty acid oxidation</td>
</tr>
<tr>
<td>• increases splanchnic glucose turnover</td>
</tr>
<tr>
<td>* Weight stabilization or reduction</td>
</tr>
<tr>
<td>* Improves lipid profile</td>
</tr>
<tr>
<td>• reduced hypertriglyceridemia</td>
</tr>
<tr>
<td>• lowers plasma fatty acids and LDL-cholesterol</td>
</tr>
<tr>
<td>• raises HDL-cholesterol in some patients</td>
</tr>
<tr>
<td>* No risk of serious hypoglycemia</td>
</tr>
<tr>
<td>* Counters insulin resistance</td>
</tr>
<tr>
<td>• decreases endogenous or exogenous insulin requirements</td>
</tr>
<tr>
<td>• reduces basal insulin concentrations</td>
</tr>
<tr>
<td>* Vascular effects</td>
</tr>
<tr>
<td>• increased fibrinolysis</td>
</tr>
<tr>
<td>• decreases Pal-1 levels</td>
</tr>
<tr>
<td>• improved endothelial function</td>
</tr>
</tbody>
</table>

On the cellular level, metformin increases insulin sensitivity, and reduces the effects of hyperglycemia and oxidation of fatty acids. In 2001, it was discovered that metformin activates adenosine 5'-monophosphate-activated protein kinase (AMPK). AMPK regulates glucose, metabolism of lipids, and cellular energy. This is what allows the drug to only decrease fasting insulin concentrations. Another importance of AMPK is that it decreases the presence of sterol-regulatory-element-binding-protein-1 (SREBP-1), which is a key factor in the pathogenesis of insulin resistance in patients. The process of AMPK activation is shown in Figure 6.

AMPK is an important factor in reducing hepatic glucose production and increasing glucose absorption of skeletal muscles. The drug increases the glucose absorption of skeletal muscles and fat tissues by increasing the movement of insulin-sensitive glucose transporter molecules to the cell membrane. This increase in activity encourages glycogen synthesis. The effect is due to “improved binding of insulin to
insulin receptors since metformin is not effective in diabetics without some residual functioning pancreatic islet cells. Through insulin-independent mechanisms, metformin raises the glucose metabolism in the splanchnic bed of the muscles. This helps with the glucose-lowering abilities of the drug and the benefit of preventing weight gains.

**Figure 5:** Actions of metformin

**Figure 6:** Metformin activates AMPK
Metformin reduces the oxidation of fatty acids and triglyceride levels, which decreases the energy supply of hepatic gluconeogenesis. Studies show that metformin causes a 10% to 20% decrease in fatty acid oxidation. “Unlike phenformin, metformin does not inhibit the mitochondrial oxidation of lactate unless plasma concentrations of metformin become excessive.” This occurs in patients with renal failure, which means the drug can accumulate and lead to the development of lactic acidosis. Metformin also slightly increases glucose oxidation.

**Pharmacokinetics**

Metformin is quickly absorbed and eliminated unchanged by the kidneys. It is not metabolized by the liver, which may be the reason for its low risk of lactic acidosis compared to phenformin. However, patients need good renal function in order to avoid any accumulation of the drug. About 90% of the drug is absorbed, while the unabsorbed metformin is excreted in the feces. It is widely distributed by binding to plasma proteins, but most is retained in the walls of the gastrointestinal tract, which maintains the plasma concentrations. Tubular secretion eliminates the drug, so metformin encounters cimetidine and increases the drugs concentration in the plasma. These concentrations have a half life of 6.2 hours and 90% of the absorbed drug is gone within 24 hours.

The bioavailability of metformin is about 50% to 60% and the plasma levels peak after about 2.5 hours. The absorption rate is greatly affected by food. When taken with food, there is a 40% decrease in peak plasma concentrations, and it takes 35 minutes longer to reach this concentration. However, the absorption of the extended-release version of metformin increases by 50% when taken with food.

**Therapy and Dosage**

Metformin is the recommended therapy for overweight and obese patients with type 2 diabetes and can be used in combination with other oral antidiabetic agents and insulin. In a study performed by the United States Diabetes Prevention Program, metformin reduced the onset of diabetes in overweight patients with impaired glucose tolerance by 33%. However, that is compared to the 58% delay in patients who were treated with diet and exercise. Lifestyle changes should always be considered first before any pharmaceutical therapy is implemented.

Patients should start with the lowest dosage required so that any increase needed can be easily satisfied. They are usually started with 500mg or 850mg once daily or 500mg twice daily. The dosage should be increased slowly by one tablet every two weeks until the target level is obtained. The maximum daily dose of metformin is about 2000mg. If an increase in dosage shows no effect, then combination therapy should be considered. Glucovance is a combination tablet between metformin and glyburide, and has shown to improve glycaemic control and to simplify treatment for patients. This combination therapy had a significantly greater decrease in hyperglycemia and fasting plasma glucose compared to the tablets during monotherapy. However, the risk of hypoglycemia associated with glyburide may increase. Other optional combination therapies are listed in Table 2.
Metformin plus:
- Sulfonylurea
- Non-sulfonylurea insulin secretagogue
- Thiazolidinedione
- α-Glucosidase inhibitor

Table 2 Potential Therapy Combinations with Metformin

Contraindications and Adverse Reactions

Contraindications of metformin include cardiac or respiratory insufficiency, liver disease, alcohol abuse, metabolic acidosis, and renal disease. Patients with these health problems are at an increased risk of developing lactic acidosis. For long term use, checks should be performed annually for elevated serum creating concentration, decrease in B12 absorption, and hemoglobin measurements for possible nutritional deficiencies. It is also necessary for patients to discontinue use of metformin and use insulin when using intravenous radiographic contrast media. Elderly patients are at an increased risk of having the above contraindications, so close monitoring is crucial, especially for sufficient renal function.

Metformin is the only oral antidiabetic agent known to “demonstrate significant cardiovascular benefit over and above its glucose lowering effect in diabetes.” The United Kingdom Prospective Diabetes Study (UKPDS) suggested that “overweight patients who started oral antidiabetic therapy with metformin showed a statistically significant 39% reduced risk of myocardial infarction compared with conventional treatment.”

It is recommended that the drug be taken with food in order to decrease the possibility of gastrointestinal problems, such as diarrhea, bloating, and discomfort. It is estimated that 10% to 15% of patients experience gastrointestinal problems, and the only explanation is the fact that metformin decreases intestinal glucose absorption. This problem improves during continued use and less likely to occur if the patient is started at a low dose. A list of other possible adverse reactions is featured in Table 3.

Table 3 Most Common Adverse Effects in a Placebo vs. Controlled Clinical Study

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Metformin Monotherapy</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>53.2</td>
<td>11.7</td>
</tr>
<tr>
<td>Nausea/Vomiting</td>
<td>25.5</td>
<td>8.3</td>
</tr>
<tr>
<td>Flatulence</td>
<td>12.1</td>
<td>5.5</td>
</tr>
<tr>
<td>Asthenia</td>
<td>9.2</td>
<td>5.5</td>
</tr>
<tr>
<td>Indigestion</td>
<td>7.1</td>
<td>4.1</td>
</tr>
<tr>
<td>Abdominal Discomfort</td>
<td>6.4</td>
<td>4.8</td>
</tr>
<tr>
<td>Headache</td>
<td>5.7</td>
<td>4.8</td>
</tr>
</tbody>
</table>

Lactic acidosis is a metabolic complication that is rare, but very serious, for patients taking metformin. It is “defined as an accumulation of lactate that usually occurs in patients with insufficient cardiac, pulmonary, hepatic and/or renal function.” It is
"characterized by raised blood lactate concentration, decreased blood pH and/or bicarbonate concentration." The main causes of lactic acidosis are inappropriate dosage of metformin and insufficient renal function.\textsuperscript{3} The symptoms of lactic acidosis include respiratory and abdominal distress, sleepiness, and depression.\textsuperscript{4}

The development of lactic acidosis in patients taking metformin is very rare. It occurs in about 0.03 cases per 1000 patients taking the drug;\textsuperscript{3} however, the mortality rate is about 50\%.\textsuperscript{6} Metformin is different from other biguanides because it “is rapidly excreted, unchanged by the kidneys” making it less likely to accumulate, “whereas phenformin elimination requires conjugation and deactivation by the liver.”\textsuperscript{2} Therefore, the FDA found that the benefits of metformin outweigh the rare possibility of this complication. The renal function of patients should be regularly checked, and they should be kept on the lowest effective dose to avoid any complications.\textsuperscript{6}

A case study in Europe was conducted in 2003 to determine if metformin actually caused lactic acidosis or if it was a coincidence. A total of 37 articles written between 1957 and 1999 were chosen because of sufficient data, and all had 26 variables in common. The article reported 80 cases of lactic acidosis development during metformin use. The study suggested that there is no relationship between the two, and any association is purely coincidental. After the study was over, the researchers speculated that the only reason metformin was thought to have caused lactic acidosis is because of its connection to phenformin and buformin.\textsuperscript{5}

Other Known Uses

Metformin is also proven to help in the treatment of patients with polycystic ovarian syndrome (PCOS). The primary cause of this disease is insulin resistance; therefore, metformin reduces insulin resistance and lowers insulin levels. By doing this, serum androgen concentrations are lowered, and normal menstrual cycles and ovulation are restored. The infertility associated with the syndrome may also be corrected. Metformin has shown to “significantly reduce serum leuteinizing hormone (LH), and increase follicle stimulating hormone (FSH) and sex hormone binding globulin (SHBG)” in women with PCOS. Also, serum testosterone concentrations are decreased by half.\textsuperscript{4}

Conclusion

The number of Americans with diabetes mellitus is estimated to reach 22 million by the year 2025. The disease already costs the United States over $130 billion for treatment and complications.\textsuperscript{1} This chronic disease will continue to grow along with the overweight and elderly populations of America. Although metformin has shown to control glucose levels in diabetic patients, it should always be accompanied by a treatment of diet and exercise.

Pharmaceutical options are continually becoming more expensive for diabetics. It is a maintenance drug, so patients have to purchase the drug each month. This can become difficult for elderly patients on a fixed income. Metformin has the extra benefit of being one of the least expensive oral antidiabetic agents available on the market.\textsuperscript{3} It is also on most formulary lists and covered by many insurance plans. Metformin is a new
drug but has already proven to be an important drug for diabetics and continues to improve their quality of life.
References


The Discovery and Uses of Fluoride in the Prevention of Dental Caries

Prepared for
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Prepared by
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April 22, 2005
Abstract:

This report will provide an overview of how fluoride helps to prevent dental caries. It will review the properties of fluorine as well as the history concerning the discovery of fluoride. This includes fluoride's toxicity as well as its benefits at lower levels.

Introduction:

For many Americans, Fluoride is a part of their everyday lives, whether one realizes it or not. Fluoride can be incorporated into toothpaste, drinking water, and now even chewing gum. Discovery of Fluorine began in the late 1800's and resulted in the discovery of its effect on bone structure and dental decay during the early to mid 1900's. Its effectiveness on the prevention of tooth decay was discovered through an epidemic of fluorosis, which flourished due to excessive Fluoride in the water from industrial pollutants. It was later shown that although large exposure to Fluoride can have a toxic outcome and lead to severe dental fluorosis, small amounts could in fact help prevent dental decay through remineralization of the tooth's enamel. Following is an overview of the properties of Fluorine, the discovery and possible toxicity of Fluoride, and the uses of Fluoride in dental care.

Properties of Fluorine:

Fluorine is known today as one of the most electronegative elements on the Periodic Table and was discovered in France by Henri Moissan in 1886. Fluorine is a yellowish gas at room temperature, but is usually found in nature as a salt compound, never in its elemental form. It can be found in the form of minerals such as fluorspar (CaF2), fluorite (CaF2), and cryolite (Na2AlF6). These compounds can be found in the soil and rocks either naturally or deposited there by means of factory pollution. Fluorine is highly reactive as a member of the Halogen family of the Periodic Table and reacts readily with most compounds. The oxidation state of Fluorine is -1 and only has to gain one electron to have a complete electron shell. Fig 1.0 is a picture of the electron shell model of Fluorine.
The electron configuration of Fluorine is 1s\(^2\) 2s\(^2\) p\(^5\), and its valance electron configuration is 2s\(^2\)p\(^5\).\(^2\)

**Toxicity:**

"Both elemental Fluorine and the fluoride ion are highly toxic."\(^3\) Fluorine’s uses in industry has lead to a large release of this element into the atmosphere as hydrofluoric acid (HF) due to its uses in combustion reactions and can then become part of the soil and water supply.\(^4\) “Fluoride substances show toxicity in both animals and plants when encountered in the form of fumes and dust emitted from industrial facilities. These levels can also be obtained through natural emissions from the eruption of volcanoes.\(^4\)

Abnormally high levels of fluoride in water also have caused fluorine toxicity in animals and mottled teeth in humans.\(^5\) Factory workers handling fluorine are required to wear a wide range of protective equipment such as special gloves, chemical goggles, and even gas masks. Today when Fluorine levels reach a very high concentration level, areas of the factory must be evacuated. Fluorine can cause both chemical and thermal burns and may not be detected immediately. Due to the fact that it reacts readily with water to form HCL, it can dissolve protein easily.\(^5\) "The recommended maximum allowable concentration for a daily 8-hour time-weighted exposure is 0.1 ppm."\(^3\) This safety level was determined after studies done by scientists in the 1930’s and 1940’s.

**Discovery of effect of Fluoride on the skeleton:**

During the early 1900’s, a series of events caught scientist’s eye. Bouts of fluorosis were occurring throughout the United States. Cases of severe fluorine toxicity showed up in states such as Utah, Wisconsin and Arizona. Levels of Fluorine were as much as 18ppm and ranged anywhere from notable safe quantities of <1.0 ppm to 4.8 ppm. In one case near Phoenix, a farmer’s herd began experiencing symptoms of fluorosis such as lameness, stiffness,
emaciation and in some cases anemia. Following years showed mottled and worn incisors.\textsuperscript{6}

Around the same time in Scotland around 1949, the atmosphere around an aluminum factory in Inverness-shire showed winds containing as much as 1,104 ppm to 35 and 7 depending on the distance from the factory.\textsuperscript{6} These examples of excessive fluorine produced by industrial factories into nature lead to studies on the symptoms caused by the pollution. It is stated that in most cases, there occurred lameness, but most importantly was the pronounced skeletal changes.\textsuperscript{6}

In Denmark as early as 1932, factory workers who produced the mineral cryolite in their factory established symptoms with varying degrees of changes to their bone structure. It was here that Dr. Kaj Roholm and P. Flemming Moller hypothesized the effects of small amounts of cryolite or sodium fluoride administered to those with bone diseases to help restore them to a healthy state after seeing what a wide range of fluorine doses did to the skeletal system. While working with the factory workers, Roholm wrote: “The most important effect of fluorine is on the osseous and dental system. Fluorine disturbs the normal balance between apposition and absorption in the bone, so that the result is a relative preponderance of the bone-forming processes.” He goes on to state that the effect of fluorine indeed affects the entire skeleton and does so by making them more dense and thick.\textsuperscript{6}

In 1939-1942, Dr. T. Ockerse studied Endemic Fluorosis in South Africa where he examined 46,547 school children’s teeth. The drinking water contained from 2.4 to 40.66 ppm depending on the source of water. However, a different city with traces as low as 0.22 ppm of fluoride experienced no mottled teeth as in the former cities. It was also seen that although these children had mottled teeth, they also showed less signs of dental caries.\textsuperscript{6} Research was continued throughout the 1900’s and refocused on the prevention of dental caries with the aid of topical and systemic fluoride.

How Fluoride works to prevent Dental Caries:

Cavities originally form when bacteria in the mouth called the “natural flora” of the mouth stick to the teeth. They do this by sticking to the plaque formed on the teeth by the bacteria. “Plaque is made up of microorganisms that are able to attach to the surfaces of teeth because the bacteria secrete a sticky slime called zooelge (living glue).”\textsuperscript{6} These bacteria feed on the glucose from foods. “When sugar or carbohydrates contact the plaque, acids are produced within a few minutes.”\textsuperscript{6} As the concentration grows over several hours, it can become so strong that it can dissolve the tooth enamel. Fluorine prevents this by taking the bacteria that normally release a plaque enzyme, and “ after entry into the bacteria, the HF ionizes releasing H+ which inhibits plaque enzymes by lowering the pH away from their optimum.” This interferes with the glucose uptake of the bacteria and therefore slows down acid production.\textsuperscript{7}
In an article written in 1987, research shows that “bacteria can be inhibited by Fluorine” and that this “indicates an internal binding to enzymes.” This means that the fluoride prevents the bacteria from sticking to the plaque by becoming an enzyme inhibitor. This prevention is due to the fact that Fluoride is also present in the saliva in one’s mouth due to systemic fluoride. In experiments on dogs, fluoride was injected and found to enter saliva and gingival fluid.” Below is a figure from this article, which contains a diagram and an explanation of this inhibition.

![Diagram](image)

**Fig 1.** Simplified scheme for the uptake of glucose by bacteria and the sites of inhibition by F. Fluoride inhibits enolase reducing the formation of PEP and consequently (a) reducing the uptake of glucose by the PEP phosphotransferase system (PEP PT), thus (b) reducing lactic acid production and (c) reducing ATP synthesis required by the proton motive force system (PMF). F also inhibits the ATPase required for (d), the uptake of the PMF system.

This prevention of plaque is not the only way that fluoride prevents dental caries. Another study done is on the remineralization of the tooth’s enamel. As acids produced by Streptococcus mutan (the main acid producing bacteria in the mouth) begin to create soft spots in the enamel of the tooth, fluoride can come in to stop the acids from burrowing into the tooth further by remineralizing the base of the cavity. Since the fluoridation of water in the 1940’s, “even trace concentrations of fluoride ions are effective in promoting calcium hydroxyapatite formation from supersaturated solutions of calcium and phosphate.” However,
it is stated that remineralization is “limited by the presence of calcium in saliva” because of the equilibrium that must be brought about between demineralization and remineralization to stop the further process of one or the other.\textsuperscript{9}

The process of remineralization forms hydroxyapatite and fluoroapatite (Ca$_5$(PO$_4$)$_3$F) and are involved in making the enamel of the tooth less soluble than carbonated calcium hydroxyapatite which is the original compound of the tooth’s enamel.\textsuperscript{9,10} Below is a diagram of remineralization.

Fig 3. “Some Chemical reactions relevant to the caries process involving fluoride”\textsuperscript{9}

\textbf{Amounts of Fluoride in Products:}

Today ADA accepted amounts of Fluoride used in rinses and toothpaste are less than 1 percent. A product called Omnii Gel \textsuperscript{TM} uses as little as 0.4 percent for their “Stannous Fluoride Brush-On Gel” and another brand name Ortho Wash \textsuperscript{1} uses as little as 0.044 % for their APF Daily Rinse. These are actually considered high for regular use, but depending on the severity of the dental decay or the period of application, a different strength may be used. Toothpaste may contain as little as 0.243% sodium fluoride whereas mouthwashes such as Listerine do not carry any fluoride. Instead they help to kill the bacteria that aid in dental decay, rather than work on remineralization. \textsuperscript{11}
Conclusion:

Scientists are still researching how fluoride is metabolized and by what method it enters the tooth. They are also trying to put together a better compound for more effective remineralization. However, what scientists have found are the properties of fluorine and the discovery of fluoride’s benefits to dental health. This report provides a brief summary of these findings along with a discussion on the toxicity of fluoride as well as safe levels for today’s fluoride users.
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Geodon: Metabolism, Catalysts and Outcomes

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I. Abstract

This report discusses the novel or unusual, antipsychotic drug Geodon (generic name ziprasidone). Positive and negative schizophrenic symptoms are reduced by ziprasidone. Ziprasidone does not exhibit the typical weight gain side effect of other second-generation antipsychotic drugs. Ziprasidone’s metabolism within the human body and chemistry are discussed. The document investigates the significance of various catalysts used by the body and possible outcomes.

II. Introduction

Geodon is an atypical antipsychotic drug used to treat schizophrenia.\(^1\) Mosby’s Medical, Nursing, & Allied Health Dictionary\(^2\) defines Schizophrenia as a disorder in which a person has an altered view of reality, withdraws from social interaction, and whose thought patterns, perceptions and emotional reactions are disorganized and fragmented. This person may exhibit hallucinations, rambling speech, incoherence, evasiveness and rapidly shifting emotions (sometimes called bipolar). Schizophrenic symptoms are described as having positive and negative symptoms.

Positive symptoms include hallucinations, both auditory and visual, and paranoid thoughts.\(^3\) Negative symptoms include lethargy and an inability to experience happiness in things that ordinarily would be pleasurable, otherwise known as episodes of depression.\(^3\) There are two types of antipsychotic drugs currently on the market. First-generation antipsychotic drugs (FGDs) are dopamine receptor antagonists. This means they block dopamine receptors and hence diminish the positive symptoms. Second-generation (atypical) antipsychotic drugs (SGDs) are dopamine and serotonin antagonists in the central nervous system (CNS). By blocking both of these receptors, positive and negative symptoms are reduced.

Geodon is a “new” second-generation antipsychotic that does not induce the typical weight gain associated with other SGDs. Geodon will be referred to by the generic name of ziprasidone throughout this document. Ziprasidone is considered atypical or novel because its metabolism and receptor affinity indicate that it is effective in treating both positive and negative symptoms. In this document, the human metabolism of ziprasidone is discussed including the catalysts used by the body. Side affects are discussed which are now being documented in journal articles and by emergency room personnel.

III. Metabolism

Ziprasidone has a molecular weight of 412.92 (free base). "Free base" means that it is the molecular weight of the ziprasidone molecule itself with no stabilizing salt. Its empirical formula of C\(_{21}\)H\(_{21}\)ClN\(_4\)OS (free base) is represented by the following structural formula:\(^4\)
The journal article “Ziprasidone Metabolism, Aldehyde Oxidase, and Clinical Implications” was used to determine the organic chemistry of ziprasidone (Christine Beedham PhD). This article discusses the metabolism of Ziprasidone in humans and is summarized in this section of the document. Two different metabolic pathways lead to the production of four metabolites in the human body. These are ziprasidone sulfoxide, benzisothiazole piperazine (BITP) sulfoxide, BITP-sulfone, and S-methylidihydroziprasidone. Figure 1, located at the bottom of this page, illustrates these pathways and was obtained from Beedham’s article. Throughout the discussion of ziprasidone’s breakdown in the human body, Figure 1 is referenced.

One pathway is a reduction cleavage of the N-S bond. This reaction is catalyzed by aldehyde oxidase. This pathway accounts for 66% of ziprasidone metabolism. The intermediate dihydroziprasidone is S-methylated, meaning a methyl group is added to the S atom, producing S-Methylidihydroziprasidone, which is predominately eliminated in the feces. What is not removed from the body is S-oxidized using CYP3A4 creating S-Methylidihydroziprasidone sulfoxide.

Two oxidative pathways that use the catalyst CYP3A4 process the remaining ziprasidone in the body. In one case, ziprasidone is S-oxidized. This means that oxidation occurs at the sulfur atom to produce Ziprasidone Sulfoxide. Ziprasidone Sulfoxide then undergoes oxidative cleavage to yield benzisothiazole piperazine (BITP). This intermediate then undergoes further S-oxidation to result in the product BITP-Sulfoxide (the shaded molecule on the far left of Figure 1). Ziprasidone Sulfoxide, the shaded box in the middle of Figure 1, undergoes a second S-oxidation to create ziprasidone sulfone. Ziprasidone sulfone undergoes oxidative cleavage to create BITP-Sulfone.

Figure 1. Summary of the metabolic pathways of ziprasidone in humans. Shaded boxes indicate metabolites present in circulation.\(^4\)
The way the primary metabolites of ziprasidone were determined is interesting and worth discussing. The metabolites were determined by creating ziprasidone with a radioactive isotope. Figure 2, taken from an article by Dr. C. Prakash dealing with the formation of the primary metabolites of ziprasidone, shows how the ziprasidone was labeled with the radioactive isotopes $^{14}\text{C}$ or $^3\text{H}$. To test if and how the liver metabolizes ziprasidone, human liver samples from organ donors were used. The liver sample is then centrifuged which lyses the cells releasing the cytoplasm and organelles. Ribosomes of the endoplasmic reticulum, which are part of the resulting homogenate, are known to play a part in the metabolism of many drugs. Five different CYP isoforms including CYP3A4 were used to prepare the liver microsomes used in this experiment. Ziprasidone and other basic chemicals were added which allowed the organelles to perform their normal biological reactions. After specific incubation periods have passed, the resultant mixture is “analyzed by high pressure liquid chromatography (h.p.l.c.) using a radioactivity monitor.” In this way, the scientist can determine if the metabolite he or she is studying came from the radioactively marked ziprasidone. This is how the metabolites of the oxidative pathway of ziprasidone were determined. Similar experiments were performed with the addition of ketoconazole, a selective inhibitor of CYP3A4. When ketoconazole was added, the N-dealkylation pathway, which forms the BITP intermediate, was blocked 100 percent. Ziprasidone sulfone and ziprasidone sulfoxide were inhibited 79 percent. This data was used to confirm metabolism by an oxidative pathway using CYP3A4 as a catalyst. Note that these are in vitro studies, meaning they occurred in a laboratory setting.

Figure 2. Major in vitro metabolic pathways of ziprasidone by human liver microsomes.

IV. Catalysts

As indicated in the section on metabolism, ziprasidone is metabolized using two enzymes. These are cytochrome P4503A4 (CYP3A4) and aldehyde oxidase. The CYP3A4 catalyst can cause various drug-drug interactions. The presence of CYP3A4 in the gastrointestinal tract is responsible for the poor oral availability of many drugs” as noted in NIH
drug metabolism training documentation. Ziprasidone is metabolized in the liver and “Exposure to CYP3A4 inhibitors cause increases in exposure to drugs metabolized by this enzyme. Inducers of CYP3A4 actually decrease the exposure to drugs metabolized by this enzyme.” Two clinical interaction inhibition studies were undertaken to determine if there would be any drug-drug interactions in schizophrenics taking ziprasidone. A drug called ketoconazole, which is an inhibitor of CYP3A4 catalyst was concomitantly administered to patients taking ziprasidone. The study indicated a 35-40% increase in exposure to ziprasidone. A 35-40% increase in exposure to any drug appears significant. However, this in vivo study showed little or no clinical side effect differences in patients receiving the placebo versus those receiving ketoconazole. The most common adverse effects were mild to moderate dizziness, lack of energy and drowsiness. These symptoms were seen in both those receiving the placebo and ketoconazole.

In another study, a CYP3A4 inducer, carbamazepine was administered with ziprasidone. “Carbamazepine was originally approved to control certain types of seizures associated with epilepsy. Carbamazepine has been found to be effective as an antipsychotic and antimanic.” Therefore, it is likely to be used in conjunction with ziprasidone in a real world setting. The results of this study indicated a decreased ziprasidone exposure of 36 percent. The reason this is considered insignificant is because a clinically effective dose of ziprasidone is 1500-fold lower than the dose of ziprasidone required to inhibit CYP3A4. Therefore, taking ziprasidone is unlikely to influence the metabolism of carbamazepine.

Aldehyde oxidase is another catalyst involved in the metabolism of ziprasidone. Aldehyde oxidase can have oxidation and reduction occurring at different sites on the enzyme. This means that both reactions can happen at the same time. This enzyme can be inhibited by Menadione, which is a relative of vitamin K. Theoretically taking vitamin K could increase exposure to ziprasidone. These studies indicate an induction in rat liver aldehyde oxidase, which has not been shown to happen in human liver metabolism. Many studies are performed on other animal tissues, and it is not necessarily true that the same outcome will happen within the human body. A study involving a proven weak inhibitor of aldehyde oxidase, Cimetidine, was coadministered to patients taking ziprasidone. This showed only a 6% increase in exposure to ziprasidone and was determined not to be clinically significant.

These studies and others indicate that ziprasidone is not clinically affected by drugs that alter the effectiveness of enzymes used to metabolize ziprasidone. This is also thought to be why this new second-generation antipsychotic drug does not have the side effects seen in previous SGDs. This will be discussed in the following section on side effects.

V. Possible Side Effects

Even though the section on catalysts indicates that there should be no side effects from ziprasidone use, of course, they are starting to turn up with long-term use. On the positive side, ziprasidone does not appear to carry the risk of diabetes and obesity, which is a usual side effect of second-generation antipsychotic use. Most second-generation antipsychotics cause metabolic abnormalities that result in weight gain, an increased risk of diabetes and poor cholesterol readings. These are indicated by elevated low-density lipoprotein cholesterol (LDL-C) levels. For example, risperidone is known to have an average weight gain of 4.63 pounds after 10 weeks of treatment. Risperidone also has a 0.3% annual incidence of tardive dyskinesia. Clozapine and olanzapine have been associated with an increased risk of new-onset diabetes. Ziprasidone has
demonstrated a reduced relapse rate of psychotic positive and negative symptoms. The positive symptoms are hallucinations, both auditory and visual, and paranoid thoughts. Negative symptoms include lethargy and an inability to experience happiness in things that ordinarily would be pleasurable, otherwise known as episodes of depression. One undesirable side effect of ziprasidone is mild sedation. This can be very disturbing to patients who do not want to feel drugged. Ziprasidone also has the advantage of being available in an intramuscular injection, which is often used in emergency room situations.

Negative side effects are possible with ziprasidone also. One example is the prolongation of QT interval, which can be seen in electrocardiogram (ECG) readings, found in some patients. Prolongation of this interval can cause fatal proarrhythmias (heart attack). Because ziprasidone has the potential to prolong the Q-T interval, there is an increased risk of torsades de pointes or cardiac arrhythmias. The number of drugs taken that prolong the Q-T interval compounds the chance of heart problems. Many schizophrenics take several medications. They may take more than one type of antipsychotic, several antidepressants, sleeping pills, and others. Each medication added increases the risk of a drug interaction. When depressed many schizophrenics will overdose on whatever medications they have on hand. One documented example is an intentional ziprasidone (Geodon) and bupropion (Wellburtin) overdose. In this case, a seventeen year old with a history of severe depression took 120 tablets of 20 mg. ziprasidone, 15-20 tablets of bupropion SR 150 mg, 15 tablets of clonazepam 0.5 mg, and 4 tablets of lorazepam 0.5 mg tablets. This led to cardiac distress due to a prolonged Q-T interval. As mentioned previously, tardive dyskinesia (TD) is another typical side effect of antipsychotics. "Tardive dyskinesia is an involuntary movement of the muscles in the face, limbs and trunk." This symptom is just starting to be reported. For example, two patients taking ziprasidone monotherapeutically for 34 months and 23 months reported to the emergency room exhibiting TD.

The second-generation antipsychotic drugs are being used to treat more than just schizophrenia. According to an article by Ralph J. Leo, M.D. and Paula Del Regno, M.D. in the Primary Care Companion Journal of Clinical Psychiatry, primary care physicians are treating patients with psychotic disorders and prescribing antipsychotic drugs. With the wide array of choices, first-generation versus second-generation antipsychotic drugs, it has become more and more important that these primary care physicians are familiar with the symptoms treated by a particular drug. It is easy for a physician not focused on these illnesses to misinterpret symptoms in their patients and prescribe the wrong medication. The positive symptoms of psychosis such as hallucinations and delusions are fairly easy for anyone to recognize. The negative symptoms such as loss of vitality, lessening in communication skills or attempts to socialize, and absence of motivation can be much harder to recognize. These negative symptoms lead to the patient being emotionally restricted, lonely, withdrawn, lacking a social drive, and becoming isolated. "These symptoms are characteristic of many psychiatric disorders. Diagnosis of a particular condition can only be made based on a presence and pattern of psychotic symptoms, the relationship between mood disturbances and triggers. These triggers may be substance abuse, alcohol withdrawal, central nervous system disorders, and metabolic abnormalities. Because the positive symptoms are easy to identify, a physician may tend to initially place patients on first-generation antipsychotics. These medications have been the primary method of treating psychosis for many years. These drugs include chlorpromazine and haloperidol. Forty-fifty percent of the people treated with these first-generation antipsychotics develop side effects which can be inconvenient, debilitative, and potentially dangerous. These side effects include
akathisia or restlessness, pacing, and fidgeting. Other side effects include dystonia or involuntary muscle spasms and parkinsonia. These side effects can be anxiety-provoking and may be worse than the original psychotic symptoms which the drugs are meant to prevent. This leads to discontinued use of the drug in many cases. Despite these facts and a standard treatment guideline which advocates second-generation antipsychotics as the first choice of medication for patients with schizophrenia, FGDs are still being prescribed. This may be due to the fact that older physicians are five times more likely to prescribe FGDs than younger doctors. This tends to indicate that many physicians are likely to prescribe medications they are familiar with or exposed to during their medical school training. This is unfortunate as antipsychotic medications should be prescribed based on the symptoms the patient is experiencing.

Atypical or second-generation antipsychotic drugs produce fewer of these "extrapyramidal side effects." For this reason, SGDs are now recommended as the first choice in treating psychotic symptoms. The cost of the new SGDs, like ziprasidone, is higher than other SGDs and FGDs. Reduced psychotic symptoms, reduced suicide threats associated with psychosis, reduced hospitalization rate, and increased quality of life for those suffering from schizophrenia may be worth this higher prescription cost over the long term. Many formularies are now starting to cover this expense because of these stated benefits. Hopefully, these combined effects will move all doctors to prescribing SGDs as a first attempt to relieve schizophrenic symptoms and provide a better quality of life for patients. It should be noted that for some patients, first-generation drugs are the only treatment needed. However, the lower risk of harmful side effects makes trying SGDs a safer course of action. If the second-generation medications are not effective, patients can be switched to a typical, first-generation drug.

VI. Conclusion

While side effects are possible with all medications, ziprasidone exhibits few detrimental symptoms. I have a sister who is a diagnosed schizophrenic. She used to talk to a head, my father, on her bookshelf. She heard voices that told her to cut herself. With the use of various antipsychotics and antidepressants, she has been able to hold a job, most of the time. She is periodically hospitalized for depression. It can take several weeks to readjust her medications and find the right combination to relieve her symptoms. Schizophrenics can be manipulative, and my sister has managed to obtain prescriptions for every imaginable symptom. She was actually taking ten different drugs at one point. This can lead to a high risk of drug-drug interactions. I am relieved that she has finally found a doctor who is willing to analyze what she really needs. Thanks to this person, she is now only taking three different medications, one of which is Geodon, the brand name for ziprasidone.
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Methadone

Prepared for
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Spring 2005
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Abstract

Methadone, a synthetic opioid, has been used clinically since post-World-War II. It’s pharmacological activity is similar to that of morphine. The relationships between the different opioid agonists will be discussed as well as the history of the uses and misuses of this family of drugs. A brief overview of methadone’s development, chemical properties, mechanism of action and it’s modern use as a heroin cessation tool will be outlined. There are risks and benefits to physician supervised methadone use and data collected in studies supporting both the pros and cons are noted. A brief overview of future trends and what I believe should be considered in regards to this drug concludes the paper.

History of Naturally Occurring Opiates

Opioid analgesics are a group of natural and synthetic drugs having similar actions on the central nervous system. The name “opioid” refers to the actual receptors in the cells that are activated by the presence of this type of drug. Morphine is the most recognizable opioid and several synthetics such as methadone were synthesized to mimic its effects on the body. Morphine is the main pain-relieving agent isolated from crude opium. Opium has been used for thousands of years to aid in sleep, produce euphoria and even relieve diarrhea. The earliest descriptions of the effects of opium have been found dating to about 3000 B.C. Opium was used in early Egyptian, Greek and Arabic cultures mainly for the treatment of diarrhea, but later its variety of other properties were recognized and it became a cure for all sorts of ailments including cough, epilepsy and headaches. In the early nineteenth century morphine was isolated from crude opium, which is the extract of the exudate from the opium poppy, *Papaver somniferum*. This purification revolutionized the use of opioids, and since then morphine has been used throughout the world as the primary agent for treating severe pain.

During the nineteenth century in the United States, morphine and opium were freely available from doctors, drugstores, general stores and through mail order. These drugs were added to syrups and sold as remedies for ailments of every kind. Opium was even given to babies in dilute amounts as soothers! Concerns began to mount about the dangers of opioids and their addictive qualities after the Civil War and the advent of the hypodermic needle, addiction was more visible and prevalent. Uncontrolled and free use of morphine and opium was banned in 1914 with the passage of the Harrison Narcotic Act.

![Methadone and Morphine Structures](image)

Figure 1. Chemical structures: synthetic methadone and naturally occurring morphine
Development of Methadone

Although never completely synthesized by them, the chemical structure of methadone was first discovered by a team of German scientists in the 1930's. These scientists were motivated to create a pain-killing drug due to the most prevalent and adverse affect of morphine: its addictiveness. It wasn't until World War II that another team of German scientists synthesized methadone. The bulk of their research had been done for them 10 years earlier. Methadone was created to replace the dwindling war supplies of morphine and other pain relieving drugs. After the end of WWII, the United States obtained the rights to the drug, and in 1947 methadone, (named by the U.S.), was introduced as a pain reliever. Unfortunately, the original motivation for the synthesis of methadone has never been realized: Methadone is physically and mentally addictive.

The continued increase in heroin usage during the 1960's motivated researchers to search for a substance that could reduce or eliminate drug craving and minimize withdrawal symptoms for recovering heroin addicts. During this time, doctors Nyswander and Dole, of the National Institutes of Health in Bethesda, Maryland, promoted methadone as a therapeutic tool to rehabilitate narcotic addicts. These doctors discovered, through research with cultured nerve cells, that methadone could be used as a substitute for heroin. Presently, methadone is the most frequently used agent in medically supervised opiate withdrawal and maintenance programs. Federal, state and local guidelines strictly regulate methadone treatment of opiate dependance.

As seen in figure 2., heroin is very similar structurally to morphine, with the exception the 2 carboxyl groups.

![Heroin Chemical Structure](image)

Figure 2. Chemical structure of heroin
CONDITIONS FOR DISTRIBUTION AND USE OF METHADONE PRODUCTS:

*Code of Federal Regulations, Title 21, sec. 291.505*

METHADONE PRODUCTS, WHEN USED FOR THE TREATMENT OF NARCOTIC ADDICTION IN DETOXIFICATION OR MAINTENANCE PROGRAMS SHALL BE DISPENSED ONLY BY APPROVED HOSPITAL PHARMACIES, APPROVED COMMUNITY PHARMACIES, AND MAINTENANCE PROGRAMS APPROVED BY THE FOOD AND DRUG ADMINISTRATION AND THE DESIGNATED STATE AUTHORITY.

APPROVED MAINTENANCE PROGRAMS SHALL DISPENSE AND USE METHADONE IN ORAL FORM ONLY AND ACCORDING TO THE TREATMENT REQUIREMENTS STIPULATED IN THE FEDERAL METHADONE REGULATIONS (21 CFR 291.505)

FAILURE TO ABIDE BY THE REQUIREMENTS IN THESE REGULATIONS MAY RESULT IN CRIMINAL PROSECUTION, SEIZURE OF THE DRUG SUPPLY AND REVOCATION OF THE PROGRAM APPROVAL.  

Figure 3. Federal Code of Regulation of Methadone

Methadone works as a substitute for heroin, in supervised treatment programs, because it greatly reduces the craving for the illicit drug, and because of its long half-life, the extreme highs and lows of the heroin rush aren’t experienced. Methadone relieves the severe withdrawal symptoms of heroin cessation to an extent. It’s actions on the receptors in the nerve cells block the “high” an addict would get on heroin, thus reducing the motivation for the addict to go back on the illegal drug. This simplistic explanation will be expanded upon.

**Some Basics About Methadone**

Methadone hydrochloride: 6-(dimethylamino)-4, 4-diphenyl-3-hexanone hydrochloride is a white crystalline substance that is water soluble. It’s molecular weight is 345.91 gr/mole. It is classified as a synthetic narcotic analgesic with actions similar to morphine that affect the central nervous system and smooth muscle tissue. It is available in tablet, liquid and injectable forms, although only specially formulated dispensable tablets and unit dosed oral liquid are allowed for methadone maintenance treatment. Methadone is a racemic mixture, meaning it exists as 2 isomers. One isomer is responsible for the drug’s analgesic affects and the other exhibits significantly less analgesic action and isn’t responsible for the addictive nature of the drug. Even though methadone is an effective analgesic, it is considered a second-line agent in the treatment of severe pain. Methadone may be useful in patients who have built up a tolerance for other opioid agonists, such as codeine or morphine, or have experienced unusually severe side affects.

As stated before, methadone is primarily used for treatment of heroin addiction. Heroin is about three times as potent as morphine. It’s increased lipid solubility leads to faster penetration of the blood-brain barrier, producing an intense “rush” when it is either smoked or
injected. Methadone, on the other hand, has a blunted euphoric effect due to its long duration of action and slow onset of action. The decreased euphoric effects of methadone make it unattractive as a drug of abuse and an appropriate agent for the management of opiate dependance. Methadone suppresses opiate “craving” and produces a blockade of the euphoria induced by opiates such as heroin and morphine.

**Mechanism of Action and the “Addicted Cell”**

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<thead>
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<th>General depressants</th>
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<td>alcohol</td>
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<td>dexamphetamine</td>
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<tr>
<td>chlorpromazine</td>
<td>methylene-dioxymethamphetamine</td>
</tr>
<tr>
<td>benzodiazepines</td>
<td>(ecstasy)</td>
</tr>
<tr>
<td>Opioids</td>
<td>Hallucinogens</td>
</tr>
<tr>
<td>heroin (diamorphine)</td>
<td>LSD</td>
</tr>
<tr>
<td>morphine</td>
<td>psilocin</td>
</tr>
<tr>
<td>pethidine</td>
<td>mescaline</td>
</tr>
<tr>
<td>others</td>
<td>dimethyltryptamine</td>
</tr>
<tr>
<td></td>
<td>(DMT)</td>
</tr>
</tbody>
</table>

![Diagram](image)

Figure 4. The neuroadaptive changes following chronic drug use. Opioids like morphine and methadone affect *mu* receptor activation and “second-messengers”

Methadone is a potent *mu* - opiate receptor agonist. Opiate receptors include *mu*, *kappa* and *delta*, referred to presently as OP3, OP2 and OP1 respectively. Agonist drugs bind with the receptors to activate and produce the maximum response of the individual receptor. Opiate receptors mediate slow modulatory neurotransmission. This involves the activation of a receptor-linked enzyme on the inner face of the nerve cell membrane, which in turn regulates the opening or closing of ion channels from inside the cell. Opiates such as morphine and heroin activate their receptor, resulting in reduced enzyme activity and inhibition of nerve cell firing. These receptors are coupled with G-protein receptors and function as modulators, both positive and negative of synaptic transmission via G-proteins that activate effector proteins. Stimulation of the *mu*-receptor, the main receptor affected with opiates, produces analgesia, euphoria, respiratory depression, decreased gastrointestinal motility and physical dependance. With continued exposure to an opiate such as heroin, the nerve cell compensates by “manufacturing” increased amounts of the enzyme. The cell “learns” to operate in the continued presence of the drug and becomes physically dependant on it. Therefore when the drug is withdrawn, the activity of the enzyme remains excessively high until it regains equilibrium again. This time frame,
which can last days or weeks, is the period in which the addict goes through withdrawal. Methadone use as a transition off of heroin eases the withdrawal symptoms and reduces the cravings of the illicit drug by blocking the receptors that activate euphoric responses.

Figure 5. Receptor interactions of opioids

Figure 6. Pathways of drugs
Methadone Maintenance Treatment Goals and Outcomes

It is true that heroin dependent individuals have better outcomes when they are maintained on methadone than when they are not treated at all, acutely detoxified and released, expelled from treatment programs or when a program ends. According to a study by the National Institute on Drug Abuse, the Drug Treatment Outcome Study found that in those patients treated by outpatient methadone centers, weekly heroin use decreased by 69%, cocaine use decreased by 48%, illegal activity by 52% and full time work increased by 24%. There is also evidence that methadone treatment is effective in reducing transmission of HIV and hepatitis B and C infections by reducing intravenous drug use and needle sharing.

According to the U.S. Department of Health and Human Services, continuous MMT is associated with several other benefits:

* MMT costs about $13 per day and is considered a cost-effective alternative to incarceration.
* MMT has significant effects on the spread of HIV/AIDS infection, hepatitis B and C, tuberculosis and sexually transmitted diseases.

The objectives of methadone maintenance treatment is clear, but unfortunately the statistics show a dimmer picture. According to Decastro and Sabate of the World Health Organization, “adherence is a primary determinant of treatment effectiveness: thus, poor adherence attenuates optimum clinical benefit. Data suggests that patients who adhere continuously to methadone treatment are less likely to continue injecting illicit drugs and sharing contaminated injection equipment...but other factors dilute the lower HIV infection rate. Although methadone programs reduce the risk of injecting drugs, sexual risk behaviors causing HIV transmission still continued at high levels.” Many also argue that the high rate of overdose with methadone use outweighs its benefits. In a study conducted by the National Addiction Centre, London, 135 opiate users currently in treatment were studied historically and statistics were gathered regarding their history of overdosing. The results over the course of 7 months are as follows:

Results

Seventy-six patients (56%) had overdosed (lifetime), on a mean of 3.9 (SD = 6.9) occasions. The last overdose occurred 5.8 years (SD = 6.2) previously, with 11 (16%) reporting at least one overdose in the previous year (missing data for 5 clients). Forty of these (53%) reported immediately going into overdose. Those who took longer to show signs of overdose (n = 36), estimated that it took a mean of 17.7 min (SD = 18.3 min) between use and entering an overdose state. Sixty-eight (89%) stated their last overdose was accidental and 8 (11%) deliberate.

Figure 7. Results of overdose study
Conclusion

Methadone is a powerful drug used in the fight against chronic pain, but more so in the treatment of heroin addiction. Despite the longevity of federally regulated methadone maintenance treatment programs, only about 20% of heroin addicts currently are in treatment. I believe that unless treatment includes comprehensive psychological therapy and the medical personnel involved look at all the aspects of the individual’s life, MMT will fail most addicts. Methadone itself is highly addictive, and aside from its small use as a pain reliever, it's generally used as a “damage controller”. I am not convinced that its use is the only way out of opiate addiction. Serious counseling has to be a part of the picture. Follow up is critical and behavior modification is a must. These things take determination, and methadone can only be relied on as a crutch, not a life-sustainer.
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Anti Cancer Drugs: Camptotheca, Camptothecin and its derivatives

Submitted by Solomon Idowu

To: Dr. Mancini, Organic Chemistry

22 April 2005
Abstract

Topoisomerase I inhibitors are known to be very effective on cancer and cancer growth. Aminocamptothecin, Nitrocamptothecin, Irinotecan, Topotecan, Phenylacetate and Phenylbutrate Camptothecin are just some Topoisomerase I inhibitors which belong in the same family of compounds all derivatives of Camptothecin. In order to be ingested by the human body they are often either administered orally or through i.v. or injected. Tests have been done with some of these derivatives to prove their effectiveness on certain cancer patients in strict environments and in specific conditions as will be further elaborated on in this paper. Some of these derivatives have even achieved FDA approval such as Irinotecan and Topotecan, which are currently used for people with breast cancer and colon cancer. Although mild, side effects from Irinotecan and Topotecan varies from each patient, usually mild to severe diarrhea. Each patient is closely monitored and is checked off a checklist of certain concerns before taking the drugs.

Introduction

Camptotheca Acuminata is a tree in which Camptothecin is extracted from. Camptothecin is an alkaloid quinoline chemical compound that has been known for its treatments of certain ailments and illnesses. Recently, doctors have found that it has an affect on cancer Topoisomerase I. Topoisomerase enzymes are responsible for the rearrangement of DNA in a cell like cell growth and replication(6). Camptothecin inhibits these enzymes which kill cancer and stops their growth. Unfortunately Camptothecin has been known to be very cytotoxic and non-water soluble, doctors have since made certain derivatives of Camptothecin in order to make it easier to absorb by the human body and attack the cancerous cells.

Camptotheca

Camptotheca acuminata, the full name of Camptotheca, is a Chinese deciduous tree locally found only in South China and Tibet. This tree can grow up to 80 feet tall sprouting reddish-brown colored barks that branch near the top. Locally it is known as “Xi Shu” (“Happy tree”), a reputation that was awarded it after it’s discovered affects on illnesses and the cold(4a.). For many years the Chinese have used the leaves of this tree to treat sicknesses such as Psoriasis; and diseases in the Liver, Stomach, Gallbladder and Spleen(3.). In 1958, Dr. Monroe E. Wall and Jonathan Hartwell, of the National Cancer Institution, were the first researchers to discover that Camptotheca had anti-cancer properties(4a). Unfortunately Camptotheca was found to be poisonous and highly cytotoxic with its most active ingredient being naturally water-insoluble. Scientist have thus far found
Topoisomerase I poison mechanism:

**FDA-approved drugs - Topoisomerase I Poisons.**

**Topotecan**  
(NSC-609699)

**Irinotecan**  
(NSC-616348)

**Camptothecin**  
(NSC-94600)  
*NOT FDA-approved*

Topoisomerase I poisons stabilize a covalent complex between the enzyme and DNA in which one DNA strand has been broken effectively blocking the "religation" reaction carried out by Topoisomerase I. Both FDA-approved Topoisomerase I poisons are derivatives of the natural product Camptothecin.

**Metalation of Pyridines - Synthesis of Camptothecin**

patients. 16% of those tested experienced either early death or aplastic death in the leukemia cells while the leukemia in the majority of those tested had a secondary resistance, primary resistance with a minority of the patients leukemia being either invaluable or were totally resistant to the DX-8514F. This shows that the derivative of Camptothecin was effective against the leukemia being helpful in stopping the spread of the disease, sadly the cytotoxicity of the compound also yielded undesired side-effects which were harmful to those who were studied(5).

In a similar test, Phenylacetate and Phenylbutrate Camptothecin was tested with SW620 and SW480 colon carcinoma cells that were cultured and obtained from the American Type Culture Collection and grown to confluent monolayers in RPMI-1640 bicarbonate medium, the medium was supplemented with 10% heat inactive fetal bovine serum and 4mM glutamine. The cells were then sub cultured by trypsination and seeded onto 9x55 mm rectangular plastic slides of Leighton tubes to allow for attachment and growth to subconfluency(7).

PA and PB Camptothecin was added from 100-fold stock solutions to buffers so it can be calibrated to the right pH by being titrated with NaOH with a pH of 7.4. As a result PA Camptothecin caused a SW620 reduction by 14.3±2.8% for 5 mM, 20.2±2.1% for 10mM 36.7±0.5% for 20mM, 74.7±1.5% for 30mM, and 85.8±2.4% for 40mM PA Camptothecin. The Camptothecin significantly reduced the amount of cancerous cells in the patients and in most cases stopped the spread and growth of the malignancies(7).

Other Camptothecin compounds were tested for their affects on breast cancer. 9-Aminocamptothecin and 9-Nitrocamptothecin were obtained from SuperGen (in Dublin, CA) and were prepared in 10mm stock of DMSO. Breast cancer cells were cultured and exposed to 9-AC and 9-NC at 37 degrees Celsius for 35 minutes, the cells were then washed twice in ice cold calcium and magnesium-free Cultecce's PBS and harvested by scraping. After being centrifuged, cell lysates were studies for protein content and then stored at -80 degrees Celsius for further and later analysis. As a result the breast cancer cells protein linkage were drastically reduced from 100% to less then 10% as
Fig 2(8a).

Ph 3SnH, AIBN  
Z = CN and CO2Me

Bu3SnH, AIBN  
Z = CN and CO2Me

R = H, OMe  
Rings A/D of camptothecin

R = H, OMe  
Rings A/D of camptothecin

Fig 3(10a). Irinotecan mechanism
more 9-AC was added, the 9-NC was found to be more effective(4).

The results of all these experiments all appear very promising; unfortunately these versions of Camptothecin and Camptothecin itself are very cytotoxic and were never cleared for widespread medical use. Many scientists have tried to figure out ways to make Camptothecin more water soluble and thus easier and human ingestion and absorption, 2 such drugs have been synthesized and approved by the FDA; Irinotecan and Topotecan.

**Irinotecan:**

Inirinotecan, Irinotecan hydrochloride trihydrate a.k.a. Camptosar®, is a semi-synthetic derivative of Camptothecin. Peak plasma concentrations occur at the end of intravenous infusion and increase in a dose dependent manner. Irinotecan is metabolized in its active form of SN38 in the presence of hepatic or gastrointestinal carboxylesterase, both Irinotecan and its active form, SN38, undergo a pH dependent irreversible hydrolysis from the active closed-ring lactone to an open inactive carboxylate form. After it is done in the body SN38 undergoes conjugation by UDP glucuronyl transferase to form a glucuronide metabolite then excreted as bile.(9)

Irinotecan is mainly used as part of chemotherapy for patients suffering from Metastatic Colorectal cancer. The only toxicities with Irinotecan are diarrhea and neutropenia, with the most severe of these side effects being diarrhea, all side effect severity are related to dosing.

In order for dosing for Irinotecan to be effective anti-emetic therapy and prophylactic loperamide need to be provided. Premedication with 10mg dexamethasone in conjunction with another anti-emetic agent should be administered 30 min prior to Irinotecan therapy. In adults, as a single agent, Irinotecan is given as dosages of 125mg/m^2 weekly for 4 weeks and a 2 week rest period, if no toxicity is present then the dosage maybe increased to 150mg(9).

Some concerns with Irinotecan are with patients with known hypersensitivity to the product and cannot have it coadministered with azole antifungals. Elderly patients with Gilbert’s syndrome may become more susceptible to the effects of Irinotecan. Increased risk of severe myelosuppresion may follow concurrent Irinotecan therapy with abdominal irradiation(9).

**Topotecan:**

Topotecan Hydrochloride and NSC-609699 are just some common names for this drug. “Topotecan is a
semisynthetic, water-soluble derivative of camptothecin, which is a cytotoxic alkaloid extracted from plants such as Camptotheca acuminata. Topotecan has the same mechanism of action as irinotecan. It inhibits the action of topoisomerase I, an enzyme that produces reversible single-strand breaks in DNA during DNA replication. These single-strand breaks relieve torsional strain and allow DNA replication to proceed. Topotecan binds to the topoisomerase I-DNA complex and prevents religation of the DNA strand, resulting in double strand DNA breakage and cell death. Unlike irinotecan, topotecan is found predominantly in the inactive carboxylate form at neutral pH and it is not a prodrug. As a result, topotecan has different antitumour activities and toxicities from irinotecan. Topotecan is a radiation-sensitizing agent. It is cell cycle phase-specific (S-phase).”

Oral absorption of Topotecan ranges between 30 and 40 percent but it is still being tested in clinical trials. It is evenly distributed in cells and intensively distributed in muscle tissue. This derivative is mainly used against ovarian cancer and is and is also used against lung cancer and Leukemia.

Concerns with Topotecan stem from many factors as high lighted from the BC Cancer Agency.

- **Topotecan** (toe-poc-TEE-kan) is a drug that is used to treat some kinds of cancers. It is a clear liquid that is injected into a vein.

- **A blood test** may be taken before each treatment. The dose and timing of your chemotherapy may be changed based on the test results and/or other side effects.

- Other drugs such as phenytoin (Dilantin®) may interact with topotecan. Tell your doctor if you are taking this or any other drugs as you may need extra blood tests or your dose may need to be changed. Check with your doctor or pharmacist before you start taking any new drugs.

- The **drinking of alcohol** (in small amounts) does not appear to affect the safety or usefulness of topotecan.

- Topotecan may damage sperm and may harm the baby if used during pregnancy. It is best to use **birth control** while being treated with topotecan. Tell your doctor right away if you or your partner becomes pregnant. Do not breast feed during treatment.

- **Tell** doctors or dentists that you are being treated with topotecan before you receive any treatment from them.

Known side effects are Nausea, sore mouth, hair loss, pain and tenderness where injected, diarrhea and constipation.
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LIDOCAINE HYDROCHLORIDE

Prepared by
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Prepared for
Renee Cornell
Scientific Technical Writing
April 18, 2005
Abstract

Lidocaine Hydrochloride is an amide-type local anesthetic and is the preferred local anesthetic for doctors today. Not only is this drug used as a numbing agent for surgical procedures, it is also used as an aide in cardiac arrest patients and/or patients who have allergic reactions to certain medications and venomous bites from animals. This paper will show how Lidocaine Hydrochloride is used for two separate purposes and how it benefits everyone if used correctly.

Structure with Hypothesized Intermediates:

I extrapolate the above structures to be correct based on my current knowledge and with the help of Dr. Santinder Bains an Organic Chemistry professor at Paradise Valley Community College. I was unable to find the intermediate steps of Lidocaine hydrochloride due to its patent.
The need for the Chlorine to leave is imperative because of its toxicity in human beings (shown in steps 3 and 4). After the Chlorine leaves the basic Nitrogen group is left (step 5). This nitro group resonates back and forth, with the help of the Hydrogen Chloride that was converted to a salt, to assure its ability to remain in the polar environment of human beings (steps 5 and 6).

Synthesis:

\[ R_{1}AcONa, S_{2}AcOEt \]
\[ ClCH_{2}(=O)Cl \]
\[ Et_{2}NH, S_{2}H_{2}O \]
\[ Me_{2}CO \]
\[ HCl \]

Note: 1) Schotten-Baumann acylation,

Reagents: 3, Solvents: 2, Steps: 2, Stages: 6, Most stages in any one step: 4

"This invention is related to a process for preparation of the well known anesthetic Lidocaine Hydrochloride (I) and its related salts in 2 steps by Schotten-Baumann acylation of 2,6-dimethylaniline with chloroacetyl chloride and alkylation of DEA with the chloroacetamide intermediate (II). The advantages include minimization of steps, and simple purification of the intermediate and products. Specifically, (II) was prepared by Schotten-Baumann acylation of 2,6-dimethylaniline with chloroacetyl chloride in the presence of sodium acetate as buffer in Et acetate at a temperature less than 20 degrees. Lbul.HCL was prepared by alkylation of DEA (in excess) with (II) in water for 30 minutes, followed by acidulation with concentrated HCL in acetone."
patient then epinephrine should not be used due to the effects of the epinephrine being a vasoconstrictor and causing the blood vessels to not carry enough blood supply to the body. Lidocaine hydrochloride is one of the most common local anesthetic and ephedrine type medication used by doctors and clinicians alike, because of its few adverse effects, versatility, and continued success.

**Lidocaine Hydrochloride used as an Anesthetic.**

**Why “caine” drugs? Understanding why the “caine” in cocaine works:**

In the late nineteenth century, cocaine was found to have anesthetic properties and was easily obtained through the coca shrub (Erythroxylon coca). Albert Niemann was the first chemist to isolate this new found drug and studied it in great detail. Many of today’s local anesthetics came from the study of cocaine including but not limited to Lidocaine Hydrochloride (trade name Xylocaine). Cocaine was desired clinically because of its effectiveness to block nerve impulses, but it had an increased toxicity danger. This toxicity occurred because cocaine would block catecholamine uptake in the central and peripheral nervous systems in the body. Lidocaine hydrochloride and other “caine” drugs do not block the uptake of vasoconstrictors or cause sensitivity to catecholamines which makes them better in the clinical world.¹³

**Mechanism of action:**

Local anesthetics prevent the generation and conduction of nerve impulses. Conduction is blocked by decreasing or preventing the large transient increase in the permeability of excitable membranes to Na⁺ that normally is produced by a slight depolarization of the membrane.³ "Lidocaine hydrochloride stabilizes the neuronal membrane by inhibiting the ionic fluxes required for the initiation and conduction on impulses, thereby effecting the local anesthetic actions."⁵

**Duration of Anesthesia:**

When used for dental procedures by infiltration, lidocaine hydrochloride with epinephrine has an onset of less than two minutes and has an average pulp anesthesia that lasts approximately sixty minutes with a duration of soft tissue anesthesia that lasts approximately 2.5 hours. When used for nerve blocks in dental procedures, the onset of lidocaine hydrochloride with epinephrine is approximately
two to four minutes with anesthesia lasting at least ninety minutes with the
numbness in the tissue lasting roughly 3.25 hours. When used for obstetrics, the
duration of anesthesia is dependent upon the amount, locale, and individual
patients.

Pharmacokinetics

Absorption:

Information derived from diverse formulations, concentrations, and usages
revealed that Lidocaine hydrochloride is completely and rapidly absorbed after
parenteral (introducing a chemical into the body by either intravenous,
subcutaneous, intramuscular, or intramedullary injection) administration and from
the gastrointestinal and respiratory tracts. Although Lidocaine hydrochloride is
effective when used without a vasoconstrictor, (a drug that constricts the blood
vessels), it is more effective when used with epinephrine because the toxicity and
the rate of absorption is decreased with prolonged numbing effects. The rate of
absorption is dependent upon various factors such as the injection site locale and
whether it is used with epinephrine (a vasoconstrictor) or not. Researchers believe
that lidocaine hydrochloride crosses the blood-brain and placental barriers, in all
probability by passive diffusion. With this in mind, the doctor should inject only at
the rate of which the body can equally absorb and eliminate safely.

Elimination:

Lidocaine is dealkylated in the liver by mixed-function oxidase to
monoethylglycine xylylde and glycine xylylde. Both of these metabolites retain
some local anesthetic activity and in human beings, 75% of the xylylde is excreted
in the urine as the final product 4-hydroxy-2,6-dimethylaniline. Lidocaine is
metabolized rapidly by the liver and metabolites, and the unchanged drugs are
excreted by the kidneys. Biotransformation includes oxidative N-dealkylation, ring
hydroxylation, cleavage of the amide linkage and conjugation. N-dealkylation, a
major pathway of biotransformation yields the metabolites
monoethylglycinexylidide and glycineenylide. Approximately ninety percent of
lidocaine administered is excreted in the form of various metabolites, and less than
ten percent is excreted unchanged.
Adverse Effects:

Toxicity:

The side effects of lidocaine hydrochloride seen with an increasing dose include drowsiness, tinnitus, dysgeusia, dizziness, and twitching of which all are central nervous system related. Some believe that during the elimination process the metabolites formed, monoethylglycine xylidide and glycine xylidide may cause some of the above adverse effects.\textsuperscript{1,3,5,6}

Precautions:

The effectiveness and safety of lidocaine are dependent on the proper dosages, sufficient precautions, and use of the correct techniques. Effective low dosages should be used to avoid high levels of plasma and undesired side effects. Accumulation of metabolites and lidocaine hydrochloride can increase blood levels if the drug is repeatedly administered. Due to lidocaine hydrochloride being metabolized by the liver, extreme caution should be used when administering the drug to hepatic diseased patients, because of their inefficiency to break down the drug normally causing them to develop toxic plasma concentrations.\textsuperscript{4,5,6}

Cautions:

Some commercially available formulations of lidocaine hydrochloride contain sodium metabisulfite, a sulfite that may cause allergic-type reactions, including anaphylaxis and life threatening or less severe asthmatic episodes, in certain susceptible individuals.\textsuperscript{4,6}

Lidocaine Hydrochloride used for Ventricular Arrhythmias.\textsuperscript{1,5}

Amiodarone is an antiarrhythmic drug, but lidocaine hydrochloride is considered to be the best on the market, says the American Heart Association with others, for the “advanced cardiovascular life support in the treatment of ventricular ectopy and ventricular wide-QRS-complex tachyarrhythmias associated with acute myocardial ischemia or infarction.”\textsuperscript{1} Lidocaine is membrane-stabilizing and is believed to control ventricular arrhythmias by suppressing automaticity in the His-Purkinje system and by suppressing spontaneous depolarization of the ventricles.
during diastole. Lidocaine does not produce any noticeable changes in blood pressure or heart contractions in normal dosages, but if used in larger quantities (more than the recommended dosage per body mass and/or individual patient) the drug could increase coronary blood flow in previous myocardial infarction patients.\textsuperscript{1,5}

Pharmacokinetics

Absorption:

Lidocaine hydrochloride is absorbed in the gastrointestinal tract, but in each oral dose only 35% of the drug reaches the systemic circulation unchanged. This drug begins working within 45 to 90 seconds after admission and can last up to 10-20 minutes. One absorption factor no longer used in the United States is the intradeltoid method due to its higher blood concentrations after injection. It also caused a rapid increase in peak blood concentrations that can lead to toxicity problems.\textsuperscript{1,3} Lidocaine is distributed throughout the body tissue including kidneys, lungs, and heart, causing concern for toxicity and/or adverse effects. The effects are the same as when this drug is used as an anesthetic.\textsuperscript{1,3}

Elimination:

The elimination procedure follows that of the anesthetic form of lidocaine hydrochloride, which is through the liver and is excreted as the metabolites monoethylglycine xylidide and glycine xylidide. The only problem to this excretion is if the patient has a history of heart trouble the half-life of the aforementioned metabolites will be prolonged, and the excretion of the 4-hydroxyxylidine would decrease causing more toxicity.\textsuperscript{1,3,4,5}

Chemistry:

"Lidocaine Hydrochloride is known as: Acetamide, 2-(diethylamino)-N-(2,6-dimethylphenyl)-monohydrochloride, monohydrate; Lignocaine (in the UK). It has a slightly bitter taste, white, odorless, crystalline powder and melts at approximately 76 degrees Celsius. The pK\textsubscript{a} factor associated with this drug is 7.86 (base). It is soluble in water with a ratio of 1 gram of product to 0.7 ml of water, and in alcohol with a ratio of 1 gram of product to 1.5 ml of water to give a 0.5% solution in the pH range of 5.0 to 7.0. Although local anesthetics are only somewhat soluble as unprotonated amines, they are marketed as water-soluble salts typically mild acidic hydrochlorides allowing the drug to be more stable. Lidocaine Hydrochloride has a molecular weight of 270.80 and a molecular structure C\textsubscript{14}H\textsubscript{22}N\textsubscript{2}O + HCL."\textsuperscript{4,1}
Conclusion:

Lidocaine Hydrochloride has several purposes in the medical field. Many doctors and clinicians consider it the most versatile and usable drug on the market today. If used correctly, it can either allow a patient the relief of pain or save another patient from anaphylactic shock or cardiac arrest. Doctors should remember that if using the drug intravenously (in the blood vessels), epinephrine should not be used, and if using lidocaine hydrochloride for local anesthesia, not intravenously, using it with epinephrine can allow the drug to anesthetize the area longer with lesser side effects.
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Diabetes-Type I vs. Type II:
Symptoms, Diagnosis and Treatment Options

Kenett Kelly
April 22, 2005
Abstract
Diabetes is a harmful disease that is on the rise due to changing eating habits and more sedentary lifestyles. This is particularly true of Type II diabetes which is now attacking younger people than ever before. The symptoms are often ignored considering roughly 30% of those with diabetes are unaware that they are stricken. Diagnosis is conducted via a simple blood test that determines the level of glucose in the blood. Treatment options for managing the symptoms brought on by the disease are plentiful but as of yet there is no safe, reliable cure.

Introduction
Diabetes is a growing disease in which the afflicted person’s body either does not produce enough insulin or fails to use it effectively. It is the seventh leading cause of death in the U.S. with upwards of 80,000 dead every year.\(^{10}\) There exist two major types, now referred to as Type I and Type II (in addition to gestational diabetes and prediabetes).\(^{1}\) Type I diabetes was formerly called “juvenile” diabetes due to the fact that it showed up primarily in the young. It involves the destruction of the beta cells of the pancreas such that they cease to produce insulin. Insulin is critical for allowing the body’s cells to use sugar for fuel. Without insulin, the blood sugar of patients will rise as there is no available mechanism for it to be used up. Type II diabetes, on the other hand, was previously referred to as “adult-onset” diabetes as it used to be found almost exclusively in adult patients. Unfortunately, this naming system has been altered as Type II diabetes has now been frequently discovered in children as well as young adults. Type II diabetes involves either insufficient insulin production or insulin but does not function properly. In many cases, the pancreas produces a sufficient amount of insulin, but due to constantly high production of insulin (due to continually elevated blood glucose levels) the cells have become resistant to the insulin and fail to use it efficiently to bring the sugar out of the blood and into the cells. In either Type I or Type II diabetes, there are two fundamental problems that may arise: first, the cells may begin to become severely energy-deficient due to a lack of available “fuel” and secondly, the constant condition of high blood sugar levels can lead to extensive damage to the eyes, nerves, kidneys or heart. This damage can eventually lead to death.\(^{10}\)

Prevalence of Diagnosed Diabetes by Age, United States, 1980-2002 \(^{6}\)
Symptoms
Type 1 diabetes consists of 5-10% of all diabetes cases. The symptoms of Type I diabetes are wide-ranging, generally occur in children and depend a great deal on any complications within the person. If the patient is experiencing hypoglycemia (low-blood sugar, below 90 mg/dl) some symptoms include: shakiness, dizziness, sweating, hunger, headache, moodiness, clumsy or jerky movements, and confusion. On the other hand, if one is afflicted with hyperglycemia (high-blood sugar, above 240 mg/dl) the symptoms may include: a large amount of sugar in the urine, frequent urination and increased thirst. Hyperglycemia is the ailment that most often leads to serious problems and causes most of the damage to critical organs. It may lead to a condition called ketoacidosis, which is found when the body fails to breakdown sugar for use as fuel by the cells, so instead the body breaks down fats for energy. This leads to the creation of a waste product called ketones. The body will attempt to eliminate these acids via the urine, but if it is unable to do so sufficiently, the following symptoms may be found: shortness of breath, “fruity”-smelling breath, nausea and/or vomiting, confusion, persistent tiredness and a very dry mouth. This condition is serious and can lead to a diabetic coma.

The symptoms of Type II diabetes are similar to those of Type I diabetes. While it may occur in children (a fairly recent development), adults over 40 are at the highest risk for the disease. Type II diabetes is the most common type of diabetes, affecting about 90-95% of diagnosed patients. The symptoms when patients develop hypo- or hyperglycemia as a result of Type II diabetes are the same as with Type I. However, with Type II diabetics, ketoacidosis is a rare occurrence. Instead, Type II patients are more likely to develop Hyperosmolar Hyperglycemic Nonketotic Syndrome (HHNS). It is primarily found in older Type II patients, but can occur with younger Type II patients or even Type I diabetics. The affliction occurs when the blood glucose levels soar to extreme heights and may lead to seizure, coma or even death of the patient. The symptoms of HHNS include: blood sugar greater than 600 mg/dl, dry mouth, incredible thirst (which may go away), high fever, confusion, blindness, hallucinations, and weakness.

Both forms of diabetes can lead to some devastating, potentially lethal complications. These complications may include: heart disease, blindness, nerve damage and damage to the kidneys. Due to poor circulation brought on by the disease, patients are at an elevated risk for heart attack or stroke. Eyesight is impacted primarily through acquiring diseases such as glaucoma, cataracts, or retinopathy. Glaucoma happens when extreme pressure build-up occurs within the eye. This pressure can lead to restriction of the blood flow to the retina and optic nerve leading to damage and loss of eyesight. Cataracts, meanwhile, occurs when the lens of the eye becomes cloudy limiting vision. Retinopathy exists in two types and is a non-specific term for all retina disorders caused by diabetes. The two primary types include nonproliferative and proliferative. Nonproliferative is more common and not as serious. This occurs when the capillaries of the eye swell without actually causing vision loss. If this problem progresses, however, it can evolve into proliferative retinopathy which is far more serious and happens when the damaged blood vessels close shut. New blood vessels grown in the retina but are usually not strong enough and can leak impairing vision quality. Retinal detachment can also become a
problem if the scar tissue of these new blood vessels distorts the retina or pulls it out of position. The symptoms of these eye disorders may be minimal until the problem has become severe and the likelihood of these problems developing increases as the length of time as a diabetic increases. Nerve damage, or neuropathy includes numerous nerve diseases. It is the most common complication of diabetes, affecting about 62% of diabetic Americans. Diabetic neuropathy disorders affect the peripheral nerves and may include damage to the motor, sensory or autonomic nervous systems. It is still unclear why elevated glucose levels lead to damage of the nerves of the body, but it is probably a secondary relationship. Symptoms indicating the possibility of diabetic neuropathy may include: numbness, tingling, weakness or pain in the extremities. Finally, kidney damage (as well as heart disease) is one of the most dangerous possible complications from diabetes. The kidneys have millions of blood vessels that serve as blood filters removing wastes for elimination via the urine. When the blood sugar levels are elevated for long periods of time, the kidneys must filter out too much blood. This leads to damage and leaking of the filters allowing protein to escape and be eliminated via the urine. If the disease progresses, the kidneys can cease to function and dialysis or a kidney transplant may be needed. Symptoms of kidney disorder include fluid buildup, diminished appetite, stomach ailments, weakness and confusion.\(^{(1)}\)

A newly discovered complication for patients with diabetes is a problem with bone health, also known as osteoporosis. There is strong existing evidence showing that Type I diabetics are at high risk for developing some forms of osteoporosis. In addition, there is mounting evidence that the same can be said for those patients that have Type II diabetes. It is believed that Type I diabetes may have particularly diminished bone growth and repair through negative effects on the osteoblasts (the cells relied upon for bone formation). Osteoporosis can become very dangerous particularly late in life when falls and other accidents can result in bone fractures that may lead to fatal complications. Therefore, bone health is something that should be looked at closely in addition to the more known complications of the nerves, eyes, heart and kidneys.\(^{(5)}\)

**Diagnosis**

In order to diagnose Type I or Type II diabetes, a physician will most likely perform one of two tests: Fasting Glucose Test (FPG) or the Oral Glucose Tolerance Test (OGTT). The FPG tests measures blood glucose levels after a period of fasting. The FPG defines a person with diabetes as anyone with a fasting blood glucose level over 126 mg/dl. The normal fasting blood sugar should be below 100 mg/dl, while those in between are considered "pre-diabetes.” The OGTT test, on the other hand measures the blood glucose level of a patient 2 hours after consuming a glucose-laden beverage, following a fast. Its standard is that anyone with blood sugar of 200 mg/dl or more is diabetic. A healthy individual would have a level below 140 mg/dl with anyone in between considered pre-diabetic. Both tests are considered appropriate although the FPG test tends to be quicker and cheaper.\(^{(1)}\)
Treatment Options
The basic treatment options for the diseases themselves are diet, exercise, blood glucose monitoring and insulin injection (for Type I or Type II) and/or oral diabetic pills (Type II only). Type I diabetics, as they have no insulin production of their own, must obviously obtain insulin from an outside source. Insulin must be administered via injection into the bloodstream (via the fat under the skin). It cannot be administered via a pill form because the body would digest it just like any protein. There are, however, a few options regarding the delivery device as well as over 20 types of insulin currently being sold in this country alone. The types of delivery devices include the traditional syringe, the insulin pen, and the insulin pump. The syringe is the most basic method, and the most cost effective. The insulin required (which is often a combination of different types) is pulled into the syringe and then injected into the body. Insulin pens, on the other hand, come with a small container of insulin to be inserted into the pen, with the dosage dialed on the pen and injection occurring much like a syringe. The negative of the pen is that if multiple types of insulin are to be injected, the patient must inject himself/herself more than once as each pen contains only one type. Finally, there is the insulin pump which connects to a catheter inserted into the patient’s skin. The pump delivers periodic doses of insulin throughout the day based on the needs of the patient. They are convenient because there is no need for multiple injections and they also allow for a more flexible eating schedule, as continuous dosage adjustments can be made as needed. The downsides of the pump include possible weight gain, greater cost, inconvenience of continuous attachment and potential for ketoacidosis if the pump became disengaged accidentally. \(^{(1)}\)

Insulin
Insulin itself is divided into four primary categories. They are organized based upon three criteria: \textit{onset}-amount of time following injection before blood glucose begins to be lowered, \textit{peak}-time at which the insulin functions at the greatest strength, and \textit{duration}-how long the insulin keeps lowering glucose levels. First, there is “rapidacting” insulin which begins working within five minutes of injection, peaks at one hour and keeps working for two to four hours. This includes brands such as Humalog (lispro)
or NovoLog (aspart). Secondly, there is a variety dubbed “regular or short-acting” which includes Humulin R and Novolin R. This type starts functioning within thirty minutes, peaking after two to three hours and lasting for about three to six hours total. Also, there is “intermediate-acting” insulin that takes effect in about two to four hours, peaks at four to twelve hours and lasts for approximately twelve to eighteen hours. This category includes Humulin N, Novolin N, Humulin L and Novolin L. Finally, there is “long-acting” insulin that begins working six to ten hours following the injection. Some of the insulin brands included in this category are Ultralente and Lantus (glargine). It reaches its peak function after six to ten hours and continues to work for about twenty to twenty-four hours. It is common for these insulin types to be combined, with two being a frequent number to allow sustained effect. Those with Type I diabetes generally take from two to four injections per day to sustain a constant blood glucose level based on individual food intake and exercise. Type II patients, however, usually require only one or two injections per day. Type II patients also have the option of diabetes pills that may be used with or without insulin injections.

NovoLog (insulin aspart) is made by Novo Nordisk and is synthesized using recombinant DNA technology with Saccharomyces cerevisiae serving as the producing organism. It is practically the same as standard human insulin with the exception of a substitution of proline by aspartic acid. It has the formula C_{256}H_{381}N_{65}O_{79}S_{6} and a weight of 5825.8. It functions by binding to insulin receptors on fat and muscle cells and causing the use of glucose by cells and prevents the liver from releasing additional glucose. It works much like regular human insulin but has been found to be faster acting and shorter lasting. It is considered to be “rapid-acting” insulin so it begins to take effect within fifteen minutes and lasts up to three to five hours.

**NovoLog (insulin aspart)**

Humalog (insulin lispro) is produced by Eli Lilly and is essentially the same in function as NovoLog. It is also rapid-acting insulin produced synthetically using DNA recombinant technology with Escherichia coli bacteria serving to create the substance. It is identical to human insulin except for the swapping of the amino acids at positions 28 and 29 on the insulin B chain. It has an empirical formula of C_{257}H_{383}N_{65}O_{77}S_{6} and a weight of 5808, both of which are exactly the same as non-synthetic human insulin.
Again, like NovoLog, Humalog is quicker to take effect and functions for a shorter time period than regular human insulin. (8)

**Humalog (insulin lispro)**

Lantus (insulin glargine) is produced by Aventis and is also produced via recombinant DNA technology. It is intended to serve as a "long-acting" insulin with onset of action within one hour but lasting effects as long as twenty-four hours. As in Humalog, a non-disease forming version of Escherichia coli serves as the producing organism. It has the empirical formula of C_{667}H_{804}N_{72}O_{78}S_{6} with a molecular weight of 6063. The fundamental difference from the structure of standard human insulin is that the amino acid asparagine is replaced by glycine and two arginines are added. It functions in the same manner as NovoLog or Humalog in that it serves to increase the glucose absorption of fat and muscle cells while inhibiting glucose release by the liver. However, as this synthetic insulin is slower acting and longer lasting than NovoLog and Humalog, it is closer in function to real human insulin. In fact it actually appears to work slower and steadier at blood glucose reduction than normal human insulin. (2)
Oral Diabetic Pills
Type II patients have numerous diabetes pills (oral) to choose from, which work only for
those patients that still have some level of insulin production by their pancreas. (This is
why the pills are ineffective for Type I patients who show no natural insulin production).
These medications work in one of three manners: they may stimulate greater insulin
production by the pancreas, they may increase the cells’ responsiveness to existing
insulin or they may delay food breakdown into glucose. There are six different varieties
of diabetes pills: sulfonylureas, meglitinides, nateglinides, biguanides, thiazolidiones and
alpha-glucose inhibitors. Sulfonylurea drugs act to cause beta cells of the pancreas to up
its insulin production and include the drugs Diabinese (generic name=chlorpropamide),
Glucotrol (glipizide), DiaBeta/Micronase/Glynase (glyburide) and Amaryl (glimepiride).
The Meglitinide category also works to increase insulin production and includes Prandin
(repaglinide). The Nateglinide variety works similarly to the sulfonylurea type and
include Starlix (nateglinide). Biguanide, on the other hand works to sensitize the body’s
cells to the existing insulin present in the bloodstream. It includes the medications
Glucophage (metformin), Glucophage XR (metformin, long lasting), Glucovance
(metformin with glyburide). The Thiazolidinedione category attempts to make insulin
work better in muscle and fat by reducing resistance to insulin and includes Avandia
(rosiglitazone) and Actos (pioglitazone). Finally, there are Alpha-Glucose Inhibitors that
slow down the body’s breakdown of food into glucose, thus slowing down the increase of
blood glucose levels following eating. Included in this group are Precose (acarbose) and
Glyset (miglitol). All of these pills serve to improve the body’s ability to make glucose
usable by the cells and keep blood glucose levels from becoming too high. While there
were once dramatic increases in the creation of new pill options, the number of new drugs
has leveled off somewhat over the last five years. (18)

Actos (pioglitazone hydrochloride tablets), a member of the thiazolidinedione group is
produced by Eli Lilly and Company and acts mainly to minimize the body’s resistance to
insulin. The molecule of the drug has one asymmetric carbon and is used in its racemic
mixture. There has been no difference found in the relative effectiveness of either
enantiomer of the drug. It has a molecular formula of C$_{19}$H$_{20}$N$_{2}$O$_{5}$S$^*$HCl and a molecular
weight of 392.90. It is available in 3 possible dosages: 15 mg, 30 mg, and 45 mg. In
order for the drug to function properly, insulin must be present. It is metabolized by
hydroxylation and oxidation. (7)

Actos (pioglitazone hydrochloride)

Avandia (rosiglitazone maleate tablets), a drug also in the thiazolidinedione category is
made by SmithKline Beecham Pharmaceuticals and also functions to increase sensitivity
to insulin. It also has one chiral carbon with both enantiomers suitable for use medically.
The molecular formula for this drug is C$_{18}$H$_{19}$N$_{2}$O$_{5}$S$^*$C$_{4}$H$_{4}$O$_{4}$ with a molecular weight of
473.52. Its metabolic routes are N-demethylation and hydroxylation. The drug is made
available in 2 mg, 4 mg or 8 mg tablets. (15)
Glucophage (metformin hydrochloride tablets) is often taken in conjunction with Actos or Avandia with no ill effects. It is a member of the Biguanide group which is intended to improve glucose tolerance in Type II diabetics. The molecular formula of this compound is $C_{6}H_{11}N_{2}$HCl with a molecular weight of 165.63. Unlike Actos and Avandia, Glucophage is soluble in water, removing the need for it to metabolize into another substance. It is excreted unchanged in the urine via the kidneys. It is available in 500 mg, 850 mg, or 1000 mg tablets from Bristol Myers Squibb.\(^{(3)}\)

Glucovance (glyburide and metformin HCl tablets) is considered a biguanide similar to Glucophage. It is manufactured by Bristol Myers Squibb. Glucovance contains two drugs for oral treatment of Type II diabetes. Unlike those previously mentioned, these drugs work together to both stimulate the release of insulin from the pancreas via the glyburide present and also improve glucose tolerance via the metformin hydrochloride. Glyburide has a molecular formula of $C_{22}H_{28}ClN_{3}O_{5}S$ and a molecular weight of 494.01. The metformin HCl used in Glucovance is the same as that shown above for Glucophage so both the molecular formula and weight are identical to that shown above. Glyburide is metabolized into 4-trans-hydroxy and 3-cis-hydroxy derivatives. These are subsequently excreted via the bile and urine (50% each). Again, the metformin HCl acts identically to that of the Glucaphage with regards to metabolism. That is, that it is unchanged and excreted via the urine. There are three possible dosage combinations available: 1.25 mg glyburide/250 mg metformin HCl, 2.5 mg/500 mg, and 5mg/500 mg respectively.\(^{(4)}\)
Glucovance (glyburide and metformin hydrochloride)

Prandin (repaglinide) is another oral tablet used to fight Type II diabetes. It is produced by Novo Nordisk Pharmaceuticals, Inc. and is found in the meglitinide group and functions by increasing insulin release by the beta cells of the pancreas. It has a formula of C_{27}H_{36}N_{2}O_{4} and a weight of 452.6. The medication serves to close potassium producers in the beta cells, causing an increase in calcium production. This calcium increase creates greater insulin production by the beta cells. The increased release of insulin occurs only so long as glucose levels are still high within the system. It is metabolized by oxidative biotransformation and glucuronic acid into oxidized dicarboxylic acid, aromatic amine and acyl glucuronide which are excreted via the feces and urine. This drug is prescribed via dosages of 0.5mg, 1 mg, or 2 mg. \(^{(14)}\)

Prandin (repaglinide)

Starlix (nateglinide tablets) is an oral medication produced by Novartis that is included in the nateglinide group. It works by stimulating the beta cells to produce more insulin in a method similar to that of Prandin. It is insoluble in water with a formula of C_{19}H_{27}NO_{3} and a molecular weight of 317.43. Starlix is metabolized by hydroxylation. It is available in 60 mg or 120 mg tablets. \(^{(12)}\)

Starlix (nateglinide)
Additionally, there has recently been FDA approval of a new injectable drug for use by both Type I and Type II patients. It is called Symlin and is intended to serve as a supplemental medication for use with traditional insulin therapy. It is particularly designed to help patients during the time immediately following meals. Symlin is primarily intended for those currently unable to keep their blood glucose levels in check with insulin alone. The drug, produced by Amylin Pharmaceuticals, INC. is the first alternative to insulin to be made available to Type I patients. The primary risks of this medication include hypoglycemia, and side effects including: nausea, vomiting, headache, fatigue and dizziness. (19)

Another new drug approved by the FDA recently is intended for treatment of pain caused by diabetic neuropathy. It is called Cymbalta ( duloxetine hydrochloride), is made by Eli Lilly and Company and comes in capsule form. It is the first such drug produced to be specifically used for those patients with diabetic peripheral neuropathy pain. The exact manner by which the drug works is unknown but two studies performed on over 1000 patients showed a greater reduction in pain when compared to a placebo. Its side effects can include: nausea,dizziness, lack of appetite and constipation. (17)

In addition to new drugs being added to the arsenal for fighting diabetes, there are also attempts being made to improve upon existing transplant efforts regarding the islet cells of the pancreas. While transplants are already done from cadavers to diabetic patients, it generally takes as many as three pancreases to provide the necessary cells. Recently, a procedure was done whereby a mother donated a portion of her islet cells to her daughter. The possible benefit is that it may show that with healthy cells from a live donor, less are required for success helping to solve the shortage of available cells. There are potential risks, however. First, it is possible that the same problem leading to the patient’s original cells destruction could repeat itself. Also, there is increased risk of diabetes developing in the donor. Finally, this procedure was only recently performed and long-term issues could develop. (11)

Conclusion
The areas of chemistry and pharmaceuticals have come a long way towards improving the lives and prognoses of diabetic patients. With the proper combination of nutrition, exercise and medications such as insulin and oral pills, most diabetics can live long productive lives. It was over 80 years ago when doctors began using animal insulin to treat the disease. Now, we have synthetically produced varieties that are much safer for all patients. With that, we now have numerous methods for administering the insulin from the traditional syringe to “pens” to insulin pumps. There is also a wide range of drugs that offer aide to those suffering from Type II diabetes. With all of that there is still no cure available to stop the disease in its tracks. It will likely be science in the form of better medication or perhaps some form of genetic therapy or transplant that will save the day for millions of people around the world.
Bibliography


2) Aventis: Lantus (insulin glargine [rDNA origin] injection). FDA Approved Label, Submitted 2004


Fluoxetine: the side effects and unknowns

Darcy Kibler

April 2005
In the past decade, drug therapy for mood disorders has become prevalent in American and English society. The most popular drug is fluoxetine hydrochloride, most commonly known as Prozac. For a drug that is prescribed to over 54 million people, fluoxetine's potential effects on pregnancy, physical performance, and its side effects are generally not commercialized (1).

Fluoxetine is selective serotonin reuptake inhibitor, a new class of antidepressant. It effects the chemical messengers in the brain called neurotransmitters. The imbalance of neurotransmitters is what researchers believe to be the cause of depression (2). In depressed patients, their uptake pump in their sending nerve cell reabsorb the released serotonin from the receiving nerve cell. Fluoxetine is believed to block the uptake pump from the reabsorption. This blockage allows the correct amount of serotonin to transmit from one nerve cell to the next (1).

![Picture of normal, depressed, and Prozac treated nerve cells]

Figure 1. Illustrations of the differences of a normal nerve cell, a depressed patient's nerve cell and a nerve cell treated with Prozac, fluoxetine.

The fluoxetine structure is a N-methyl-3-phenyl-3-[(α,α,α-trifluoro-p-toly)-oxy]propylamine hydrochloride (2). Figure 2 shows the makeup of the structure.

![Fluoxetine HCl structure]

Figure 2. Fluoxetine HCl

Eli Lilly Company developed Fluoxetine in the 1970's and has been researched ever since. Scientists have yet to find what mechanism causes the blockage on the sending nerve cell. However, scientists know that SSRI's selectively block the re-uptake of the neurotransmitter group 5-hydroxytryptamine, serotonin. Serotonin is a Tryprophan derivative, which synthesizes in multiple stages. Since the mechanism of Fluoxetine is unknown, the importance of Tryprophan enzymatically converting to 5-hydroxytryptophan, then one of the additional enzymes converts 5-hydroxytryptophan to 5-hydroxytryptamine is vital to uncover Fluoxetine’s
pathway (2). Figure 3 displays the chemical equation

Figure 3. Biosynthesis Pathway of 5-hydroxytryptamine from Tryprophan

Some scientists suggest that fluoxetine inhibits potassium ions induced by [3H]5-HT release by antagonizing voltage-dependent calcium ion entry into the nerve terminals. These scientists are saying that fluoxetine may not inhibit, but signals an increase of serotonin production (10). Since the mechanism of fluoxetine is still remains unknown, researchers are continually searching.

Fluoxetine's biochemistry may not be well-known, but the side effects should be very familiar. Within the first few weeks of taking Fluoxetine, a person may experience headache, nervousness, insomnia, drowsiness, fatigue, anxiety, tremor, dizziness or lightheadedness, nausea, diarrhea, dry mouth, anorexia and excessive sweating (1). Eli Lilly's researchers say most of the side effects will go away after the trial basis (3). However, Phillip W. Long, MD, the creator of Internet Mental Health informs the public of possible continuing side effects. In a clinical trial of 4000 patients, fifteen percent discontinued treatment because of an adverse event such as anxiety, nausea, dizziness, pruritus, etc. The side effects effect the psyche, digestive system, nervous system, and the epidermal system (4). If the Fluoxetine can effect all these areas of the body, what effect can it have on women and pregnancies?

Women have additional conditions they need to be aware about when taking fluoxetine. Women do not need as high a dose of antidepressant as men because women tend to have higher serum levels of the fluoxetine based on their physiology. However, women's menstrual cycle specifically during PMS, requires higher doses of medication to balance the fluctuation of hormones, which effect the neurotransmitters. Since women undergo broad fluctuations in hormone levels, so does their brain chemistry. If that is not enough, women who do not fluctuate the milligrams of their dosage can experience excessive side effects, like sexual side effects. Most women are not aware that antidepressants like fluoxetine may decrease interest and/or inability to have an orgasm (6). If the female patient does get the interest and gets pregnant, the safety of her child is also in question.

Fluoxetine is widely unknown, therefore, trial researches are the best way to guide scientist. The
scientists put their trials to the test of fluoxetine's effects on pregnant women and their babies via case studies. There are multiple areas of pregnancy that need to be examined from the first term to years after the baby is out of the womb.

The changes in the women's bodies during pregnancy can alter the concentrations of drug absorbed and used throughout the body. An increase in total body water may potentially lower serum concentrations of fluoxetine. The decrease in the amount of protein is important because drugs have to bind onto the proteins in order to be absorbed. Less binding sites cause an increase in serum concentration. The step in absorption of fluoxetine is altered also because the gastrointestinal tract decreases in its emptying rate as well as decreasing in gastric acid secretion. Glomerular filtration rate is increased causing the volume of water filtered out of the plasma through glomerular capillary walls. In other words, the increase in the GFR in pregnant women causes faster excretion of some drugs, antidepressants, so higher doses are required. Increases of medicatin doses is not uncommon in pregnancies in order to achieve therapeutic serum level; however, after delivering, she must decrease the dosage to prevent toxicity (6).

In The New England Journal of Medicine, a study of 482 pregnant women from 1989 through 1995 compared the outcome of pregnancies from one group being treated in the first trimester, one group being treated at the third trimester and one control group. The results did not show any

| TABLE 1. CHARACTERISTICS OF WOMEN TAKING FLUOXETINE AND CONTROL WOMEN AND OUTCOMES OF PREGNANCY. |
|-----------------------------------------------|------------------|---------------|------------------|------------------|------------------|
| VARIABLE | **FLUOXETINE GROUPS** | **CONTROL GROUP** | **P VALUE** |
|          | EXPOSED EARLY | EXPOSED LATE |          |            |
| Maternal characteristics* | | | | |
| Age — yr | 32±6 | 32±6 | 30±5 | <0.001 |
| Gravidity — no. | 3.0±1.8 | 3.3±1.9 | 2.4±1.4 | <0.001 |
| Parity — no. | 0.9±1.1 | 1.0±1.2 | 0.8±1.0 | 0.35 |
| No. of previous spontaneous abortions | 0.4±0.8 | 0.4±0.7 | 0.3±0.7 | 0.43 |
| No. of previous therapeutic abortions | 0.7±1.0 | 1.0±1.4 | 0.4±0.7 | <0.001 |
| Weight gain — kg | 17±7 | 14±7 | | 0.01 |
| Average dose of fluoxetine — mg | 28±15 | 26±10 | | 0.15 |
| Trimester of entry into the study — no. of women (%) | | | | 0.001 |
| First | 82 (83.0) | 45 (61.6) | 137 (61.4) | |
| Second | 16 (16.0) | 16 (21.9) | 57 (26.6) | |
| Third | 2 (2.0) | 12 (16.4) | 29 (13.0) | |
| Trimester of fluoxetine therapy — no. of women (%) | | | | |
| First only | 93 (93.0) | | | |
| First and second | 7 (7.0) | | | |
| First, second, and third | 60 (82.3) | | | |
| Second and third | 7 (9.6) | | | |
| Third only | 4 (5.5) | | | |
| First and third | 2 (2.7) | | | |
| Cesarean section | 35 (35.0) | 29 (39.7) | 45 (20.2) | <0.001 |
| First cesarean section | 22 (22.0) | 20 (27.4) | 33 (14.8) | 0.04 |
| Birth outcome and examination‡ | | | | |
| Live-born infant — no. (%) | 101 (45.2)§ | 73 (50.6)§ | 226 (37.6)§ | <0.001 |
| Mode of infant examination — no. (%) | | | | 0.07 |
| By investigator | 60 (59.4)§ | 44 (60.2)§ | 153 (67.7)§ | |
| By own physician | 33 (33.7)§ | 21 (28.8)§ | 43 (19.0)§ | |
| By maternal report | 8 (7.9)§ | 8 (11.0)§ | 30 (13.3)§ | |
| Spontaneous abortion — no. (%) | 23 (10.0)¶ | 22 (8.5) | | 0.59 |
| Stillbirth — no. (%) | 0 | 1 (0.4) | 2 (0.9)§ | 1.00 |
| Ectopic pregnancy — no. (%) | 1 (0.4) | 0 | | 0.47 |
| Therapeutic abortion — no. (%) | 22 (9.6) | 7 (2.7) | | 0.002 |
| Lost to follow-up — no. (%) | 8 (3.5) | 1 (0.4) | | 0.02 |
alarming differences, but any risk seems to much when the health of a baby is at involved. Table 1 shows how the numbers do not range at extremes, but vary dependently from each other. The results showed the spontaneous pregnancy loss did not differ significantly between the women treated with fluoxetine and the control women (7).

The difference in the major structurally anomalies only differed 5.5 percent vs. 4.0 percent, shown in Table 2. The minor structural anomalies are significantly higher for infants exposed to fluoxetine then those infants in the control groups. Infants exposed to fluoxetine treatment in general have a 15.5 percent chance of a minor structure anomaly compared to only 6.5 percent of infants from the controlled group (7).

<table>
<thead>
<tr>
<th>TABLE 2. MAJOR AND MINOR STRUCTURAL ANOMALIES IN INFANTS OF FLUOXETINE-TREATED WOMEN AND CONTROL WOMEN.</th>
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<tbody>
<tr>
<td><strong>VARIABLE</strong></td>
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<tr>
<td>Major structural anomalies*</td>
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In Table 3 shows the small, but significant difference between pregnancies treated in the first trimester and pregnancies treated in the third trimester. A higher risk is involved when fluoxetine is used later in the gestation period. Premature deliveries are more likely to happen by 4.8 percent with pregnant

<table>
<thead>
<tr>
<th>TABLE 3 RELATIVE RISKS OF SELECTED OUTCOMES IN INFANTS OF WOMEN WITH LATE EXPOSURE TO FLUOXETINE AS COMPARED WITH INFANTS OF WOMEN WITH EARLY EXPOSURE.</th>
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<tr>
<td><strong>OUTCOME</strong></td>
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</tr>
<tr>
<td>Prematurity (&lt;37 wk of gestation)‡</td>
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<tr>
<td>Admission to special-care nursery</td>
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<tr>
<td>Poor neonatal adaptation¶</td>
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women using fluoxetine in their third trimester in comparison to earlier treatment of pregnant women. Poor neonatal adaptation is at 8.7 percent higher, which would include respiratory difficulty, cyanosis on feeding and jitteriness. The birth weight was also consistently lower and birth length shorter in infants. The good results from the findings by the New England Journal of Medicine is that there are no extreme risks with taking fluoxetine during pregnancy, but does bottom line some severe risks like perinatal complications when fluoxetine was used in the third trimester (7).

Since a human may have withdrawal symptoms from fluoxetine, logic says an infant may too. If the mother was being treated with fluoxetine to the point of her babies birth, the child may experience withdrawals. Spanish researchers thought the same. In February of 2005, they found selective reuptake inhibitors like fluoxetine were associated with neonatal withdrawal syndrome. Neonatal withdrawal syndrome can cause infants to experience convulsions, irritability, abnormal crying and tremors. The researchers from the University of La Laguna advise doctors to “avoid prescribing SSRIs to pregnant women” or have mothers-to-be use them cautiously (5).

Though the researchers from University of La Laguna may think fluoxetine does more damage than good in a pregnancy, Dr. Gail Erlick Robinson seems to believe there is no real evidences to suggest a severe risk in the children whose mothers were treated with fluoxetine through the pregnancy and nursing. She sided more to health of the mother which would directly effect the child’s safety. The situation depends on the severity of the mothers depression if she would be more of a risk to the baby without fluoxetine or if the baby has a higher risk with fluoxetine. Dr. Robinson writes, “infants older than ten weeks showed no accumulation doxepine or fluoxetine and were at low risk for adverse effects.” She also goes on to say that “infants exposed to fluoxetine or tricycles during the first trimester of pregnancy have now been followed up to school age with no evidence of malformation or behavioral teratogenicity.” There have not been any true, long term effects of breast-feeding while taking antidepressants, but scientists still seem to pick their research to back up their opinions (6).

With all the drug hype in athletics, Doctors express their theories of what fluoxetine may have on competitive athletes. In one doctors research, he observed rats’ endurance of running or swimming to exhaustion and decreased central fatigue while being treated with an SSRI, but the rats also had cardiac conduction abnormalities, which seems like a contradiction for an athlete if the effects turn out the same for he or she. The athlete may die participating in heart failure, but the chance of the edges is still possible. In retrospect many, so called, performance enhancing drugs do have grave effects down the road like steroids. If an athlete was initially depressed and started treatment with fluoxetine, the sheer lack of depression would promote motivation and self-esteem in training (8).

In a human study, researches have linked fatigue with serotonin and the hypothalamic-pituitary-adrenal axis regulation during exercise. The importance of this connection involving fluoxetine is the serotonin. A hypothalamic-pituitary-adrenal axis is part of the neuroendocrine system that controls reactions to stress, including physical stress. HPA is the mechanism for a set of interactions among glands, hormones and parts of the mid-brain. They in turn mediate a general adaptation syndrome. Neurotransmitters are one of the interactions HPA has. When HPA goes
under stress it would signal a neurotransmitter to react by increasing or decreasing its own production. Since fluoxetine can alter the levels of serotonin, it potentially can alter the effects HPA initiate. This hypothesis proved wrong for these researchers because no increase in performance occurred. In some trial performance actually decreased, but all the 90 minute trials involving well-trained athletes resulted in no effect at all (9).

The lack of knowledge of fluoxetine mechanism will continually leave a blind gap for researchers to stumble around in trial and error. Through the research collected, the conclusion of this popular drug has many undesired risks. If a patient is not deterred by nausea, sexual disorder, or the risk of poor neonatal adoptions of one’s child then the patient’s need for his/her mood disorder outweighs undesirable additions.
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Possibilities Concerning Homeopathy

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ABSTRACT

This paper encourages insight into the area of homeopathic mechanisms. The approach does not contradict atomic theory but extends the theories of chemical structure and ionic mechanisms to give a hypothesis as to how homeopathic remedies might work. A combination of inorganic metal ion chemistry and some electrokinetics aid in showing that increasing dilution can promote species of extremely high activity due to their charge. This electrical charge is produced in unison with the rearrangement of the water surrounding the atom. Consecutive dilution with water reduces the metal concentration but may preserve small domains of water structure which are homogeneously redistributed by proper succession technique.

INTRODUCTION

Homeopathy is founded on the application of highly diluted remedies which are derived from chemical systems. Many people see disparity between homeopathy and chemistry, especially in the factor involving dilution. Dilution of a simple remedy, such as Natrium Muriaticum (i.e., sodium chloride or NaCl) for instance, is looked upon as a placebo because the concentration remaining is usually below Avogadro's number, so that "less than one molecule remains." In the subdivision of matter, the ions dissociated from the molecule are the furthest subdivision known within the measurable energy of dissolution.

Certain hypothetical cases can occur during strong dilution. First of all, all molecules might disappear. This is the understanding of the biological and medical sciences. What it means is that no molecule is left and that the remedy is acting as a placebo with much left to the patient's imagination and desire to retrieve wellness. The desire to feel well again can have a strong effect on the physical. However, to those who practice homeopathy, this hypothesis cannot explain how it works and the enhanced effects seen as dilution is increased. Homeopaths not only believe that the activity of a remedy is present below Avogadro's value, but also that the remedial effect actually increases with increasing dilution, upon proper succession, or rigorous shaking. That is, that the potential energy for remedy action is increased upon dilution.

A second theory states that one molecule remains. Upon successive dilutions, there is a possibility that every time an aliquot is taken and diluted, that the one molecule which may exist, is chosen each time. Without going into any detailed mathematics, it can be seen that such probability is quite small. With continued dilution, everything hypothetically disappears. Only the solvent remains.

The last possibility is that an essence remains of the molecule. If the molecule is dissolved and diluted past the Avogadro value, what actually remains that pertains and relates to the more concentrated solution is in question. A field might exist that is passed on upon successive dilutions. This field might be electrical, magnetic, electromagnetic, or others.

It is always best to use hypotheses that we can sense and measure. The hypothesis proposed here, for explaining and understanding the law of the minimal dose, uses the following areas of science: catalysis; ionic mechanisms; chemistry of simple and complex inorganic ions; colloid chemistry; chemistry of water structures; and the science of electrokinetics.
CATALYSIS

From the laws of chemistry, the chemical activity of a species increases with its concentration. Homoeopathy, however, is formulated upon the law that dilution (and succussion) increases the remedial activity of a species. At first this seems to be in complete contradiction. However, chemical activity and biological activity can be quite different. Also, homoeopathic activity may be more related to a sort of catalytic activity, which falls more in the realm of colloidal and surface phenomena. In chemistry, when a reaction is normally impossible to produce, a tiny amount of a small particle size material (i.e.: a colloidal system), which seems completely uninvolved, can cause the reaction to go with great ease. This is the principle of catalysis. Chemists can make non-reactive molecules react with great force by using a catalyst. Usually, the catalyst is a small particle size material which, itself, does not seem to enter into the beginning or final product of a reaction.

Catalysts can be homogeneous or heterogeneous depending on their state, i.e.: soluble or insoluble (colloidal). Their mechanism is difficult to understand. Having been found in an empirical manner, they are one of the basic components of modern chemistry. Without them many new products would not even exist.

Catalysis not only involves chemical ones but also biological ones. Certain reactions in the human anatomy cannot occur effectively or at all if the salient biocatalyst is not present. Many times the concentrations of these are very small and difficult to measure. Soluble metals can play a major role as biological catalysts. Such is the role of chromium which may be needed in the proper form at minute concentrations. To get it to the individual before it is spent or absorbed it must be chelated (i.e.: hooked up) to preserve its action for the right time.¹ Therefore, the salt form is used for this purpose of efficiency. The metal catalysts such as these can play a major role in proper control of metabolism.

It may be reasonable to assume that homoeopathic remedies can act as catalysts. They behave somewhat like homoeopathic remedies. Small concentrations are needed. They control the main reaction, but don't partake in the reaction or the final product. They are energetically illogical. Finally, they can be destroyed or contaminated by a minuscule amount of contaminant.

IONIC MECHANISMS

An example molecule serves as a model and does not have to be of a remedy which is used exhaustively. Also, it may be quite difficult to begin with a remedy which is organic in origin unless the exact formula of the species in known which does the curing. By dividing the remedies into organic and inorganic chemicals, some distinctions can be made. Conventional medicine uses very little inorganic chemistry. Homoeopathy uses a lot. One only needs to scan the remedies used and see such as Arsenicum, Natrium salts, Kali salts, Silver and salts, Copper and salts, Aurum, Clay, Silica, among others. One could say that allopathic medicine relies almost entirely on large organic molecules while homoeopathy uses quite extensively the chemistry of inorganic materials. By organic we mean compounds containing carbon and by inorganic we mean everything else. This does not mean that organic materials are not used in homoeopathy. Inorganics play a strong role, a concept not deployed very well at all in conventional medicine.
In order to propose mechanisms in homeopathy, certain corollaries need to be expressed before going further. First of all, the remedy either contains nothing at concentrations less than Avogadro’s number, and if so, can have nothing that relates to the chemistry of the system greater than Avogadro’s number. In this case, the remedy is looked upon as a placebo and the homeopathic evidence is dismissed. On the other hand, the evidence for homeopathy cannot all be imaginary and must be, to a good portion, reliable human observations. In this case, each remedy is specific and differentiable and must have a relationship above and below the Avogadro value. Finally, there exists a species of the chemical which specifies, below Avogadro’s value, that a remedy will perform in a certain way. These species are of interest.

Inorganics can have various forms: elemental; e.g., Argentium (Silver), Aurum (Gold); or Electrolytes (salts): Kali Bi (Potassium Bichromate), Natrium Mur (Sodium Chloride). The metals, which are inorganic cations (i.e.: positive ions, ions are charged atoms), can be divided into two major groups of Simple and Complex. A simple metal ion would be one which has a small charge such as Na(+) (sodium, a monovalent cation) while a complex ion is usually a multivalent (charge greater than one) cation. In this case, for purposes of a hypothetical model, salts or metals will work, as long as they dissolve, interact with water, and form ions or charged species. The charge of the species is most important. In theory, homeopathy uses the various salts, exploring their delicate variations and providing remedies which use each’s specific nature.

This ionic concept will then lead us to the field concept of remedies, the last of the proposals. To further the argument, one must accept the idea of an electric field surrounding the ion. After all, the ion has an electric charge and must therefore have an accompanying field of the same nature.

Structure is also important, in that it is closely related to charge. It is necessary to show that the charge of the species mentioned above depends on the structure of the water surrounding the species. The structure and charges are important to homeopathy and the consequent conclusions. When one speaks about infinitesimal doses, one imagines dilution to a point where no more molecular nature exists; one must then assess what remains: possibly the electric field left by the ions; or a structure which has been stored in the water molecules. Another plausible hypothesis is that water which is structured around a species remains after the central atom is gone. This water has a different structure than bulk water.

The example will be the aluminum ion, a very commonly used ion in academia and industry. In order to expand this theory to other more applicable metals, or at least to some which are used more frequently in remedy prescribing, more research needs to be accomplished. Aluminum is usually thought of as a tri-valent ion and usually represented as Al(+3). Therefore it forms salts such as AlCl(3), Al(2)(SO(4))(3), Al(NO(3))(3), which are the chloride, sulfate and nitrate salts respectively. However, aluminum is much more complicated than this. It reacts with water in a specific way. Around the aluminum ion there exists, very close to the central atom, a shell of coordinated water. This is the first shell of coordinated water. This water shell has a particular structure. This is special water; it is coordinated to the aluminum ion. It actually plays a role in making aluminum what aluminum is and is the essence of the homeopathic electric field proposed.
The charge on a metal ion is controlled by the dissociation of the water molecules in the first coordination shell of the metal ion.

Now observe Figure 1. In this figure, the coordination water shell can undergo the phenomenon of hydrolysis. In this case, hydrolysis is simple and just means that a water molecule can lose a Hydrogen ion (H(+) which is the anion (the negative ion) of the water molecule. When this occurs, the hydroxyl ion which has a negative charge of -1 neutralizes one positive aluminum charge and the remaining ionic charge on the aluminum is now reduced to +2. The structure of the water in the first coordination shell has changed and controlled the overall charge on the aluminum. This is extremely important since it means that water structure controls the electric field around the ion. If one continues with this hydrolysis, then we should wind up with Figure 2. The final charge on the aluminum ion diminishes as the water adds OH ions, one at a time (by one with each degree of hydrolysis), until the resultant charge is zero. This can go on even further until the resultant charge is reversed to negatively charged aluminum species. This is shown in Figure 3.

Water controls not only the degree of charge but even the sign of the charge itself. Remember that at zero charge, the aluminum is not soluble any more exactly because it is not ionic or charged. It is in the precipitate form, and is called aluminum hydroxide. Any one of these species can be a remedy. So, in the case of aluminum the remedy make-up could be complex. However, the most highly charged species probably does all the work, i.e.: transfers the most energy. That means that an aluminum system will vary with degree of hydrolysis of its coordinated water.

Concerning hydrolysis of a metal ion, hydrolysis is promoted by the following: temperature, because heat promotes hydrolysis; water, because the more water there is, and the purer the water, the more hydrolysis has a chance to occur. For instance, a 50% solution of an aluminum salt does not hydrolyze much if at all; pH, because the promotion of hydroxyl ions (OH(-)) also promotes hydrolysis.

ELECTROKINETICS

Electrokinetics is the science of the movement of small particles under an applied electric field. A voltage is applied to a dispersion of small particles in water and the particles move to an oppositely charged electrode. So, if the particles are positive, they move towards the negative electrode (the cathode). If the particles are negatively charged, they move toward the positive electrode (the anode). It is to be determined whether the disappearance of the metal ion leaves behind a shell of water whose charge remains, or if the structure of that water is more important.

Homeopathy would hope that ionic remedies of great dilution could cause electric gradients to move around the vital system. In order to prove that water plays a major role, the electrokinetic
The charge as a function of pH (addition of OH ions) is shown in Figure 4. The hydrolysis of the aluminum ion proceeds from left to right. As one can observe, there is a peak in the middle range.

Colloid chemists have been able to find the reason for the peak. A special ion is formed at a certain specific degree of hydrolysis and its formula has been derived to be: [Al(8)(OH)(20)](+4). The presence of such an ion is extremely minute and the concentration of all the other ions drown out its existence such that it is impossible to measure it by ordinary concentration chemical methods. Nevertheless, its activity is so strong that it completely dominates as an electrical entity. This ion is so strong that it coagulates negatively charged particles at extremely low concentrations, which are not measurable by chemical or physical means. That means that it had to actively be working at even lower concentrations. This is another instance of where colloid science resembles homeopathy. There are now two instances-catalysis and coagulation by complex ions - when extremely small concentrations are active. The domain of homeopathy also use extremely active systems at extremely high dilutions. To match concentrations and dilutions so as to go from chemistry to homeopathy is not the goal. It is desirable to show that dilution with water causes these ions to hydrolyze and this greatly affects their ionic properties, providing a hypothesis to the homeopathic standpoint.

Another point to be made is that if one were to prepare a remedy from these theoretical aspects, one could, in theory, produce more than one remedy from the same metal ion. Also, if one prepared a metal at different degrees of hydrolysis, then the proofs of these different species may correlate with chemistry, thereby proving scientifically a relationship between homeopathy and good science.

MECHANISM OF SIMPLE IONS

The simple ions, such as sodium and potassium, might also leave a water structure which can be memorized by a diluted system. Sodium and potassium are both from the Group I family in the periodic table and have a lone electron in their outer electron shell. They form monovalent ions and should be quite similar. But they are different with respect to water.
An illuminating example is found in biology. Blood is a colloidal system where the particles (the corpuscles) flow in a serum medium. The particles need to interact with each other just right. Too much causes aggregation and high blood pressure. Too little causes too thin a blood flow and will retard coagulation when it is needed. One the controlling factors will be the sodium/potassium ratio in the system. Too much sodium causes excess water swelling of the corpuscles and this increases the viscosity (resistance to flow) of the fluid. This can lead to high blood pressure and other circulatory diseases. Potassium is then needed to replace some sodium in the corpuscles and reduce particle swelling. Thus, the two elements, though similar in structure, cause opposing phenomena of water retention in the blood. As relates to homeopathy, perhaps the interaction of these ions with water effects their water structure in their first hydration shell, differing their overall interactions. In the case of these Group I monovalent simple ions, the water structure is again playing a major role in their activity. This water structure may remain during infinite dilutions and succussions and leave its imprint for remedy action.

IMPORTANCE OF VICINAL WATER TO INSOLUBLE REMEDIES

Surface chemists have discovered the anomalous nature of water when it is in contact with a solid surface. It has been suggested that liquid water molecules, in the presence of a solid surface, are "ice-like" in structure and physical behavior. Water molecules situated at solid boundaries are known as "vicinal water". The structuring of water around colloidal particles is thought to be due to enhanced hydrogen bonding). Vicinal water is less dense than regular water (i.e., 0.965 vs 1 g/cc). Vicinal water is more viscous than regular water. Environmental researchers who study the separation (dewatering) in order to purify water cannot remove certain water associated with sludge particles. This is a big problem in that industry. Vicinal water cannot be separated from colloidal particles. Vicinal water is sometimes referred to as bound water. It freezes at about -20°C instead of 0°C. It is also much more difficult to evaporate. Pathogens survive in unfrozen vicinal water. All in all, there is considerable evidence of the existence of a form of water, different from regular water, which manifests itself when colloidal systems are formed in water. If, upon extensive dilution, this water disappears, then its existence is inconsequential to homeopathy. If, however, the process of succussion, for some unknown reason, preserves vicinal water arrangement in a specific way, then maybe an explanation of the homeopathic mechanism is arising, as far as the insoluble remedies go.

DISCUSSION

The mechanism of how homeopathy works is a challenge to understand. Theories were offered to help understand possible homeopathic mechanisms. Established theories usually only work with ideal systems. Real life has few ideal systems. The best tool that we have for solving problems is our imagination. They are the images, outside of our limited space-time border, which can and will help us use bodies of knowledge (such as homeopathy) to greater logical extents. One must remember, however, that new experimental evidence and facts should dictate changes in the mechanism if the need arises. Homeopathy is still a young science in many respects. Other sciences were also held back for similar reasons, that main reason being: the inability to measure and quantify relatable data and turn them into mathematical functions. The lack of observation is not necessary proof of the non-existence of a form of matter or energy.
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Imatinib Mesylate- Targeted Drug Development

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Abstract
Imatinib mesylate is a drug recently approved by the Food and Drug Administration on a fast-track approval for the treatment of Chronic Myelogenous Leukemia (CML) and Gastrointestinal Stomal Tumors (GISTs) in a new class of cancer agents called signal transduction inhibitors (STIs). The unprecedented development of this drug as a “targeted therapy” has become a new blueprint for cancer drug development. Its mechanism of action makes this drug unusual by pinpointing one step of the cellular signaling cascade and inhibiting the proliferation of the cancer cells. The case studies show an incredibly high response rate in patients at each of the three stages of CML. The drawbacks are that some patients develop resistance to imatinib mesylate due to a mutation of the cancer cells and the very high price of treatment. However, clinical trials are in progress for the future use of this drug to fight other types of cancers.

Introduction

Imatinib mesylate (brand name Gleevec\textsuperscript{TM}, ST1571) is being hailed as the new prototype for targeted drug therapy development against Chronic Myelogenous Leukemia (CML) and Gastrointestinal Stomal Tumors (GISTs). Imatinib is considered a “targeted therapy” due to its attack only on cancer cells, and, unlike traditional therapies, it does not affect normal cells.\textsuperscript{1} It is an overnight success story that took over 40 years to develop and incorporates basic biology from the Human Genome sequence released in February of 2001 and chemistry to target a particular step of cancer cell proliferation and block it. Fighting cancer on a molecular level is considered a new paradigm, and one that is much more effective than past drug therapies.

The human impact of stopping the proliferation of cancer cells with imatinib must be addressed. According to the figures from the Leukemia and Lymphoma Society, in the year 2004 an estimated 111,000 people in the United States will be diagnosed with new cases of leukemia, lymphoma or myeloma and every 10 minutes another person is expected to die from these diseases.\textsuperscript{2} These diseases will account for approximately 8% of the nearly 1.4 million new cases of cancer diagnosed in 2004.\textsuperscript{2} My sister is included in these statistics, since she was diagnosed with the chronic phase of CML in August, 2004.

What is Chronic Myelogenous Leukemia? CML is a slowly progressing disease that makes the bone marrow produce too many cancerous white blood cells. There are three distinct phases of CML as defined by the National Cancer Institute. The first is the chronic phase when there is 5% or less of blast cells present in the blood, followed by the accelerated phase when there are 6-30% blast cells present; and finally the blastic phase when blast cells comprise over 30% of the blood.\textsuperscript{3} A patient diagnosed with CML in the past was usually given a life expectancy of 3-5 years and Figure 1 below shows the average time in a patient is in each phase. Case studies show that imatinib’s effect is “to normalize white blood cell counts in nearly all patients afflicted with CML,”\textsuperscript{4} which is why it received an “accelerated approval” by the FDA in May 2001.\textsuperscript{4} Patients have experienced significant results of a dramatic decrease in the abnormal white blood cells count with the use of this drug therapy, but there is no long term data on its effectiveness to prevent CML.
**Figure 1**

**Development History**

The “overnight” success of imatinib first began in 1960 with the discovery of the “Philadelphia chromosome” by Doctors Peter Nowell and David Hungerford. They found a short segment on one part of the 22nd chromosome which was consistent in all CML patients. The next breakthrough came in 1973 when a new staining technique enabled researchers to observe that the long arm of chromosome 9 was lengthened by about the same amount that was missing in the long arm of chromosome 22. This suggested that a translocation of pieces of each chromosome had occurred. Nine years later, in 1982, one of the human cancer genes, the Abelson (or ABL) proto-oncogene, was found on chromosome 9 in non-CML patients and traced to the Philadelphia chromosome in CML patients. This discovery led researchers to theorize that the ABL oncogene could have become active by the translocation to chromosome 22. Between 1984 and 1987, multiple labs worked to determine how the translocation could generate a cancer-causing protein. The ABL translocation to chromosome 22 fuses with the broken part of the gene called BCR (BCR stands for breakpoint cluster region), which causes the formation of an abnormal gene referred to as BCR-ABL. The BCR-ABL gene is found in nearly 95 percent of CML patients and considered the source of CML.

In 1986, Dr. David Baltimore and his team worked to isolate the BCR-ABL gene to determine its function. They learned that the normal gene carries a protein tyrosine kinase which regulates cell growth, division and death. The fused, abnormal BCR-ABL also carries the protein tyrosine kinase in an “on” position and cannot turn off due to the missing part of the gene. This results in the rapid division of the abnormal cells. Furthermore, the abnormal white cells do not go through the normal life span of a cell, which includes programmed cell death, so the number of white cells present is even higher.

In the late 1980’s N. Lydon and A. Matter lead a team of scientists at Ciba-Geigy (now Novartis Pharma) on research into compounds that would inhibit the activity of the protein kinases. A 2-phenylaminopyrimidine derivative was identified as a lead compound to target protein kinase C (PKC) which is the backbone shown in black in Figure 2A. It did not have the specificity or potency desired, and inhibited both serine/threonine and tyrosine kinases. Derivatives were synthesized from this compound, including the addition of a 3’-pyridyl group at the 3’-position of the pyrimidine, as shown...
in blue in Figure 2A. This addition resulted in an improvement of the cellular activity. When a benzamide group was added at the phenyl ring (shown in red in Figure 2B), the inhibitory activity against tyrosine kinases was further increased. The researcher noted a key observation that substitutions at the 6-position of the aniline phenyl ring caused the loss of PKC inhibition. A “flag-methyl” group attached at this position increased selective activity against tyrosine kinases, as shown in purple in Figure 2C. This series of compounds had low water solubility and poor bioavailability. A highly polar side chain, N-methylpiperazine, was added and is shown in green in Figure 2D.\(^6\)

![Chemical structures](image)

**Figure 2**

In 1990, Dr. Brian Druker was researching how the BCR-ABL protein fit into the cascade of intracellular signaling. He learned about complementary research into cellular pathways by Ciba-Ggigy, a Swiss pharmaceutical company, and started testing the protein kinase inhibitors they had developed. He found that STI571 (now imatinib) stopped the leukemia cells with little or no effect on the surrounding healthy cells. In 2001, the Human Genome sequencing was released which explain the small RNAs that control the on/off switches during cell development. This is the missing switch on the fused BCR-ABL gene which is why the cancer cell is in the “on” position and leads to rapid proliferation. Imatinib was also found to inhibit autophosphorylation of the c-kit receptor and its cognate ligand, stem-cell factor, inhibit the signal cascade of the platelet-derived growth factor (PDGF), and inhibit the adenosine triphosphate (ATP) binding site on cellular and viral ABL protein kinases.\(^5\) It was inactive against serine/threonine kinases, showed little or no disruption to the kinase receptors for vascular endothelial growth factor, fibroblast growth factor receptor 1, tyrosine kinase with immunoglobulin and EGR homology-2, as well as the SRC family nonreceptor tyrosine kinases. Last, they found it was not effective against the epidermal growth factor receptor intracellular domain.\(^6\)
Structure

Imatinib mesylate’s chemical name is 4-[(4-Methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-93-pyridinyl]-2-pyrimidinyl]amino]-phenyl]benzamide methanesulfonate with a molecular formula is C_{29}H_{31}N_{7}O \cdot CH_{4}SO_{3} and has a relative molecular mass of 589.7. The chemical structure is show below in Figure 3.

![Chemical Structure](image)

**Figure 3** Novartis.com

Imatinib mesylate is manufactured by Novartis Pharma AG Basle, Switzerland. Its color is white to off-white to brown to yellow crystalline powder. It has an elimination half-life of 18 hours from plasma, and it takes approximately 7 days to eliminate 81% of the drug. According to the summary approval from the FDA, “it is very soluble in water and soluble in aqueous buffers <pH 5.5 but very slightly soluble to insoluble in neutral/alkaline aqueous buffers. In non-aqueous solvents, the drug substance is freely soluble to very slightly soluble in dimethyl sulfoxide, methanol, and ethanol, but is insoluble in n-octanal, acetone and acetonitrile.” The FDA has approved imatinib mesylate for use with patients diagnosed with Chronic Myelogenous Leukemia and metastatic and/or unresectable malignant Gastrointestinal Stromal Tumors (GISTs). The medication comes in 100mg or 400mg tablets as shown in Figure 4. Standard doses in patients with CML-CP are 400mg/day and 600mg/day in patients with CML-AC and CML-BC.

![Tablets](image)

**Figure 4** Gleevec.com

Mechanism of Action

Imatinib mesylate is classified in a new class of cancer agents called signal transduction inhibitors (STIs). It is a protein kinase inhibitor that specifically and
selectively inhibits the BCR-ABL tyrosine protein kinase found in patients with Chronic Myelogenous Leukemia and inhibits the autophosphorylation in receptor tyrosine kinases for platelet-derived growth factor, stem cell factor and c-kit. The inhibition of the c-kit phosphorylation by imatinib resulted in significant tumor response in patients with metastatic and/or unresectable malignant Gastrointestinal Stomal Tumors.

The function of the protein kinase is a mediator of cell growth, development and death. Imatinib mesylate works by binding to the adenosine triphosphate (ATP) binding site on the tyrosine kinase and interrupts the signaling pathways. It stabilizes the protein kinase in its close, inactive conformation. This blocks the protein kinase from causing the transfer of the phosphate from ATP to the hydroxyl group of a tyrosine residue in the substrate. The result is that the BCR-ABL gene cannot proliferate and cell death occurs in the cancer cells without affecting the normal cells as shown in Figure 4.

![Figure 5 wikimeida.org](wikimeida.org)

Case Studies

Response rates of patients with CML on imatinib mesylate therapy are truly amazing overall. In a report by Blood Weekly dated January 6, 2005, 98% of newly diagnosed CML patients treated with Gleevec™ had achieved complete hematologic response, 91% of the patients had achieved a major cytogenetic response, and 84% had achieved a complete cytogenetic response at the 42 month follow with 1106 patients. This article describes the correlation of higher doses of Gleevec™ to newly diagnosed CML patients and an early cytogenetic response. A possible new measurement of success is major molecular response (MMR) which occurs when there is virtually no sign of the disease on the molecular level.

A second study discussed in the January 6, 2005 Blood Weekly report describes three consecutive trials conducted at the MD Anderson Cancer Center in Houston, Texas. The total number of patients with previously untreated early chronic phase CML was
222, and they were split into two controlled groups. The first group received a standard 300mg daily dose of Gleevec™ and the second group received a higher daily dose of 800mg. The patients who had received the higher dose saw a 99% progression-free survival rate twelve months versus 92% in the standard 400mg dose group. Their conclusion was that the patients who received the higher dose experienced both complete cytogenetic and molecular remissions at a higher rate. However, the high dose group also experienced extramedullary toxicity at higher rates. Approximately 7% of the high dose patients had severe anemia, 39% neutropenia, and 27% thrombocytopenia.¹⁰

Another study in the Clinical Cancer Research journal compared the survival advantage of patients using imatinib therapy in the chronic-phase CML (CP-CML) after interferon-α (IFN-α) failure which was the traditional therapy for CML. In this study 261 patients with CML-CP and post failure on IFN-a therapy were compared to a historical group of 204 patients. The complete cytogenetic response to imatinib mesylate was 62% versus 19% on the INF-α and 80% of imatinib patients showed some level of response versus 29% of IFN-α patients with some level of response.¹¹ Upon taking a close look at the cytogenetic response at the three month point, 98% of patients on imatinib who achieved a major response were predicted to have a 3 year survival rate. Patients who experienced a minor response were predicted to have a 92% three year survival rate. Even patients who experienced no response to imatinib were predicted to have an 84% three year survival rate.¹¹ The researchers concluded that the early cytogenetic response to imatinib mesylate was a strong predictor of the patient’s long term survival and that imatinib mesylate therapy was “superior” to other therapies traditionally used to treat CML.¹¹

Drawbacks

The drawbacks of imatinib mesylate are the resistance that some patients have experienced as well as the cost of the therapy. Some patients have experienced a resistance which researchers believe is a mutation of the cancer cells and more common in the advanced stages of the disease.⁶ Imatinib mesylate binds to the ATP site in a close, inactive conformation. Researchers have identified 17 relevent point mutations. It is believed that amino acid substitutions interact directly with the BCR-ABL kinase or affect the ability of the BCR-ABL kinase to attain the closed, inactive conformation. New second generation protein tyrosine kinases are being tested to override this resistance.¹²

The second drawback is the cost of the therapy. The cost is approximately $35,000 per year for a standard dose of imatinib mesylate. Patients are advised to check with their insurance companies to verify if they cover this treatment.¹³

Conclusion

The development of imatinib mesylate has to date become the success story for targeted drug development. There are drawbacks, such as the small percentage of patients who have become resistant to the drug. However, more applications of imatinib are in progress. Studies include its effect on lung cancer tumors, ovarian cancer and the possible effectiveness against solid tumors with c-kit or PDGFR signaling or hematologic tumors that show ABL signaling. Even though the final results have yet to be seen on imatinib mesylate’s long term effectiveness, researchers have made huge strides in the fight against cancer by working in a smarter, targeted manner.
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Melatonin, From Pineal Gland to Everyday Medication

Chemistry 236

Dr. Hank Mancini

By: Shahab Mohebbi

April, 22, 2005
Abstract

This paper is an overview on melatonin, which is a natural hormone secreted from the pineal gland, and also name of a medication available in every drug store throughout United States. This article contains information about how melatonin works in human’s body and some diseases that might be prevent by using melatonin as pills. Also it will demonstrate structure, synthesis, side effects, stereochemistry and at the end the opinion of the write about melatonin.

How Melatonin Is Related With the Pineal Gland

Melatonin is one of the neurohormones and is present in many species, processing the pineal gland. It plays important roles in controlling neuroendocrine functions including sleep in human, which probably is the most important factor that makes it a "wonder drug" for at least the last twenty years. Melatonin or 5-methoxy-N-acetyltryptamine is a very amazing hormone. It plays an important role in the regulation of the circadian sleep-wake cycle. It also controls essential functions such as metabolism, sex drive, reproduction, appetite, balance, muscular coordination and immune system in fighting off diseases triggered by bacteria, viruses, chemical pollutants and excessive free radical activity. But ability of fighting some diseases has not been determined for sure. It is released during the night in response to environmental changes in light levels by the pineal gland, which is a small gland buried deep in the brain behind the eyes of mammals. The pineal itself is controlled by a paired cluster of nerve cells located just above the optic chiasm in the hypothalamus. These cells are known as the suprachiasmatic nuclei (SCN) and they contain the circadian pacemaker. Each night the SCN send impulses, via a series of neurons in the hypothalamus and spinal cord, up to the pineal gland to stimulate melatonin secretion. The timing mechanism in the SCN itself is controlled by sunlight that enters the retina and reaches the SCN via the retinohypothalamic pathway. The amount of melatonin circulating in the blood has been shown to rise and fall during a day.

Molecular Structure of Melatonin

The molecular structure and configuration of melatonin (N-acetyl- 5 - methoxy tryptamine) can be determined by X-ray diffraction method. “It is crystallized from benzene solution as yellow plates (m.p. 118-119 °C ), which are shown to be monoclinic with unit cell parameters of a= 7.711, b=9.282, c=17.107 A° and β =96.77° from systematic extinctions. The density value of 1.269 g/cc measured by the flotation method in calcium chloride aqueous solution indicates that there are four molecules in a unit cell. The main C-C distance in the benzene ring is 1.402 A°, while those of C-C and C-N distances in the pyrrole ring are 1.405 A° and 1.394 A° respectively. The indole part of melatonin is planar, the average deviation of the atoms from the plane is 0.011 A° and the maximum deviation is 0.022 A° for N(2). C(1), C(2) and O(1) of acetyl groul and N(1) are almost strictly in a plane. This plane forms a dihedral angle of 12 ° with that of the indole ring.” The NMR and IR on the next pages show the configuration, structure, shifts and coupling constants of the melatonin.
**$^1$H NMR Assignment**

<table>
<thead>
<tr>
<th>Bond</th>
<th>Chemical Shift/ppm</th>
<th>Coupling constant</th>
<th>Peak</th>
</tr>
</thead>
<tbody>
<tr>
<td>3H, 2-CH$_3$</td>
<td>1.87</td>
<td></td>
<td>SINGLET</td>
</tr>
<tr>
<td>3H, Acetone</td>
<td>2.32</td>
<td></td>
<td>SINGLET</td>
</tr>
<tr>
<td>2H and β-CH$_2$</td>
<td>2.87</td>
<td>6.5 Hz</td>
<td>TRIPLET</td>
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<tr>
<td>2H and t-CH$_3$</td>
<td>3.48</td>
<td>6.5 Hz</td>
<td>QUATET</td>
</tr>
<tr>
<td>3H, OCH$_3$</td>
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<td>SINGLET</td>
</tr>
<tr>
<td>N$_2$NH</td>
<td>5.7</td>
<td></td>
<td>BROAD and SINGLET</td>
</tr>
<tr>
<td>1H and 6- H</td>
<td>6.78</td>
<td>2 and 8.5 Hz</td>
<td>QUATET</td>
</tr>
<tr>
<td>1H and 4H</td>
<td>7.00</td>
<td>2 Hz</td>
<td>DOUBLET</td>
</tr>
<tr>
<td>1H and 7H</td>
<td>7.17</td>
<td>8.5 Hz</td>
<td>DOUBLET</td>
</tr>
<tr>
<td>H, NH</td>
<td>8.3</td>
<td></td>
<td>BROAD and SINGLET</td>
</tr>
</tbody>
</table>
**IR Spectrum**

**Bond**  **Wavenumber / cm**⁻¹

NH 3240

C=O, amide I 1627

C=O, amide II 1555

Aromatic C=C 1620, 1587, 1492

C-O 1217, 1180

Aromatic Substitution 828, 810, 800

**Melatonin As sleeping pill**

Melatonin is an effective sleeping pill. Taking low doses of melatonin on a nightly basis at appropriate sleep times allows the body to naturally adapt to alter day and night patterns. Synthesis of melatonin in human body decrease by increase of age. This is one of the reasons why elders have more sleep disorder problems than children. Research shows that the administration of melatonin improves the sleep onset in blind subjects unable to synchronize with the solar cycle. It may also be an effective hypnotic for insomniacs or travelers who suffer from jet lag. In 1994 Wurtman et al. at the Massachusetts Institute of Technology reported the results of a sleep laboratory study involving 20 subjects with normal sleep habits. Subjects were
administered melatonin in low doses (1-10 mg) or placebo, and sleep was monitored in the lab during five 8-hour test sessions. Compared with placebo, melatonin (all doses) decreased the time subjects took to fall asleep and increased sleep duration. Subjects who received melatonin 1 mg fell asleep in an average of 6 minutes compared with 17 minutes for subjects who received placebo. The investigators concluded that melatonin may be as effective a hypnotic as the benzodiazepines. Apart from its treatment with sleeping disorders, there is also a correlation between the low level of melatonin and increase in risk of cancer. Research studies have demonstrated that melatonin can prevent chemically induced mammary tumors in laboratory rats and can also inhibit the proliferation of human breast cancer cells in tissue culture. The pineal gland as an integral constituent of the neuroendocrine system seems to play an important role in modulating the immune response via circadian release of its main neurohormone melatonin and/or some other substances. There is a substantial body of evidence suggesting an antimitotic action of melatonin in mammalian cells in vitro.

Possible mechanisms of interacting between the immune system and the pineal gland hormones seem to come full circle with the path physiology of the immune disorders. Neuropeptides and neurotransmitters such as endorphins, encephalin, vasoactive intestinal peptide and the pineal hormones all have significant influence on the immune system, and have been shown to modulate antibody production, natural killer cell activity and response to mitogen. The products of the immune system, on the other hand, have substantial influence on the pineal gland and neuroendocrine system. Similar antineoplastic effect of the pineal gland and its hormone melatonin was observed in fibro sarcoma, in a transplantable form of leukemia and various form of carcinoma. The enhancement of transplantable tumor growth in pineal ectomised animal was reported along time ago.

Modern investigations have revealed that about 50% of pineal tumors in humans are germinomas. Pineal tumors are most common in the Japanese population and occur four to five times more often in males than in female. According to Doctor Olcese the writer of Melatonin after Four Decades “In the United States, as many as 40% of tumors in the region of the pineal gland are mixed historical type. However, studies on the link between the pineal gland and tumor development did not always yield consistent results, though many of the reports pointed to an costatic action of the pineal.” There have also been several papers reporting that melatonin has no or even stimulatory effects on the growth of some tumors. Differences in the results obtained may depend on a number of reasons. In fact, precise comparison of the studies on relationship between the pineal neurohormones and neoplastic growth is very difficult due to the diversity of the experimental approaches i.e. various tumor models used, different methods of measurement of tumor growth (neoplastic cells proliferation, tumor weight, and tumor volume), differences in mode and timing of melatonin administration and various photoperiodic environments.

**Consideration about Melatonin**

The first thing to consider is that sometimes, less is more. Although melatonin plays an extremely important role in our bodies, it is present only in small amounts, even when human are at youthful peak. Melatonin capsules vary in dosage from less than 0.1 mg up to 6 mg. Although no severe side effects have been reported at dosages up to 10 mg daily, in some people it may
cause morning drowsiness. Melatonin is not recommended for pregnant women nor intended to be used by persons under 25 years of age. People who have serious illnesses such as autoimmune disorder, leukemia or lymphoma should consult a physician familiar with melatonin before usage. Immune suppressing drugs such as cortisol and cyclosporine may react adversely with melatonin as may anti-depressants. People who are diabetic, experience major depression or have a hormonal imbalance should also take caution. Pregnant and nursing mother should avoid melatonin supplements. On the other hand the researches for drug interaction for melatonin is not perfectly enough so there might be chances of other drugs interaction with melatonin.

Chemical Synthesis of Melatonin

The methods for the chemical synthesis of melatonin are generally not so complicated and do not involve more than three steps of conversion.

Reaction 1

In 1958 melatonin was first isolated and characterized by A.B.Lerner. It was known as one of a substituted 5-hydroxyindole derivative in the pineal gland that could lighten pigment cells. It had not been known to exist in biological tissue although it had been isolated as a urinary excretion product in rats after administration of 5-hydroxytryptamine.

“Melatonin or N-acetyl-5-methoxytryptamine (40 mg) was prepared by reducing 100 mg of 5-methoxyindole-3-acetonitrile with 160 mg of sodium and 2 ml of ethanol. Then the product was acetylated with 4 ml of both glacial acetic acid and acetic anhydride at 100 °C for 1 minute. Purification was achieved by countercurrent distribution and silicic acid chromatography.”

\[
\begin{align*}
\text{5-methoxy-indol-3-yl-acetonitrile} & \xrightarrow{\text{Na, EtOH}} \text{2-(5-methoxy-1H-indol-3-yl)-ethyl-acetamine (melatonin)}
\end{align*}
\]

Reaction 2

“5-Methoxytryptamine hydrochloride (1g, 4.75 mmole) was dissolved in pyridine (10 ml) and acetic anhydride (10 ml) and kept overnight at 20 °C. The solution was poured onto ice, neutralized with diluted hydrochloric acid and extracted with chloroform (2x25 ml). The combined extracts were washed with water, dried in MgSO₄ and evaporated to afford a liquid of N,N diacetyltryptamine derivative. The liquid was then poured into water (50 ml) and extracted with chloroform (2x25 ml). The combined organic layers were washed with water (25 ml), dried in MgSO₄ and evaporated to dryness. The residual solid crystallized from benzene to afford melatonin 819 mg, 80% yield.”
Reaction 3

"The more reactive indoles (1a-1d) were alkylated at the 3 position by reaction with nitroethene generated in situ by thermolysis of nitroethyl acetate. The nitroethyl acetate used for this purpose was prepared by acetylation of nitroethanol with acetic anhydride using NaOAc as a catalyst. These conditions constitute a substantial improvement of the overall yield of the reaction. Reduction of the nitroethylated indoles (2a-d) by hydrogenation over PtO₂, followed by acetylation for the resulting tryptamines with acetic anhydride-pyridine completed the synthesis of melatonin and its derivatives (4a-d)."
Biological Synthesis and Metabolism of Melatonin

The biosynthesis of melatonin is initiated by the uptake of the essential amino acid tryptophan into pineal parenchyma cells. Tryptophan is the least abundant of essential amino acids in normal diets. It is converted to another amino acid, 5-hydroxytryptophan, by action of the enzyme tryptophan hydroxylase and then to 5-hydroxytryptamine (serotonin) by the enzyme aromatic amino acid decarboxylase. Serotonin concentrations are higher in the pineal than in any other organ or in any brain region. They show a striking everyday rhythm remaining at a maximum level during the daylight hours and falling by more than 80% soon after the onset of darkness as the serotonin is converted to melatonin, 5-hydroxytryptophol and other methoxyindoles. Serotonin's conversion to melatonin involves two enzymes that are characteristic of the pineal: SNAT (serotonin-N-acetyltransferase) which converts the serotonin to N-acetyl serotonin, and HIOMT (hydroxyindole-O-methyltrasferase) which transfers a methyl group from S-adenosylmethionine to the 5-hydroxyl of the N-acetyl serotonin. The activities of both enzymes rise soon after the onset of darkness because of the enhanced release of the epinephrine from sympathetic neurons terminating on the pineal parenchyma cells.

Conclusion

In conclusion, melatonin is a hormone secreted by the pineal gland that has many effects on human's body. One of the most important effects is sleep-wake cycle. These days people use melatonin as pills which they can buy anywhere in drug stores.

People use melatonin pills for sleep problems and jet lag. It seems like an important drug because there is no evidence about severe side effects of melatonin. However, there are some restrictions about use of melatonin for certain ages and conditions, which has not been taken seriously, but overall melatonin has become a part of everyday life for some people. It also has effects on immune system and cancer growth. It is cheap and worthy to use. There have not been lots of complains from consumers of melatonin. There have been some complains about drowsiness, which is the least side effect that melatonin has shown yet.

If people use melatonin every day for irregular sleep or jet lag, wouldn't it affect the secretion of the pineal gland? There have been some drugs that were not showing side effects at first but it harmed the body after so long of usage. The human's body itself can adapt very easily, usage of melatonin every day can make the pineal gland very lazy so it would not secrete melatonin as needed. That way melatonin could become addictive. If the human's body needs melatonin for sleeping and it’s not regularly secreted by the pineal gland, it would make the body addicted to a supply from out side.

Use of melatonin in younger people should be considered. For older people it is reasonable because there body is not producing enough melatonin anymore, but in younger people who want to go to sleep whenever they want, it could become a big problem later, there for using melatonin should be limited by age. Further more, there have not been enough studies yet showing that melatonin is a safe sleeping drug.

Also there are not many studies about drug-drug interaction of melatonin. Many of people who are taking medications and need to get some sleep might use melatonin with out
consultation with their physicians. Lack of research might end up harming lots of people who take the medication now and are happy to go to sleep easily every night.
On the other hand, people with chronic sleeping problems will use melatonin as a mask to cover their illness. The proper way is to talk to the physician before using melatonin. This way melatonin will become a cover for people who have chronic sleep problems or depression. People with depression normally would not seek for help at the first sight of the illness; instead they look for ways to calm down themselves or try to go to sleep. That’s when they look for drugs like melatonin to satisfy their needs. Selling melatonin over the counter of pharmacies might cause problem for these kinds of people. It’s better to use drugs when is perfectly tested and harmless. So far melatonin is the safe sleeping pill to use but lack of research about side effects, drug-drug interactions and abuse of melatonin should be considered.
References

Ketek (Telithromycin)

Prepared for Dr. Hank Mannncini
Organic Chemistry 236
Spring 2005

By: Siamek Mollaei
Abstract:

This research paper is about a medicine called 'ketek', which in this paper we will discuss all about it in details from how it was invented and what effects it has, what side effects it has and how it works on human body.
Introduction:

Every year, millions of Americans suffer from respiratory tract infections, which are among the most prevalent infectious diseases among adults in the developed world and the leading reason for seeking medical care in the United States. These conditions include sinusitis, which is an upper respiratory infection, and community-acquired pneumonia (CAP) and acute exacerbations of chronic bronchitis (AECB), which are lower respiratory infections.

Sinusitis is one of the most prevalent diseases encountered in general practice. It affects up to 35 million adults in the United States each year.\(^\text{1,3-6}\) People with sinusitis make 12.3 million visits to the doctor and 1.3 million hospital outpatient visits each year.\(^\text{3}\) It is the fifth most common diagnosis for which an antibiotic is prescribed and accounted for 9\% of all adult antibiotic prescriptions written in 2002, at a cost of $400 million to $600 million.\(^\text{4}\) It typically begins as a viral respiratory tract infection; bacterial superinfection occurs in 60\% of adults whose respiratory infection has lasted at least 10 days.\(^\text{1,6}\) The direct cost of health care for adults with sinusitis has been estimated to be up to $4 billion per year.

Community-acquired pneumonia is a significant cause of morbidity and mortality worldwide. Estimates range from 4 million to 5 million cases in the United States per year, half a million to 1.3 million hospitalizations, and 1.3 million visits to the emergency room.\(^\text{7,8}\) Patients with CAP make approximately 10 million physician visits a year.\(^\text{9}\) The mortality rate of pneumonia in the outpatient setting is low, in the range of less than 1\% to 5\%; however, the mortality rate averages 12\% among those who require hospitalization.\(^\text{8}\) It is higher among those with bacteremia and those from nursing homes, and approaches 40\% in those who are most ill and require admission to the intensive-care unit.\(^\text{8}\) It is the fifth leading cause of death in people 65 years of age and older.

About half of all pneumonias are caused by viruses; these are less severe than bacterial pneumonia. However, patients with viral pneumonia may develop bacterial pneumonia. Community-acquired pneumonia also is a common complication of influenza, especially in the elderly.

Chronic bronchitis affects more than 11 million people in the United States; it is estimated that each of them will have one to four acute exacerbations each year, frequently following a cold. About half of acute cases are bacterial. The cost to treat AECB was determined to be $1.6 billion for inpatient care in 1994; costs for outpatient care were estimated to be $769 million in 1999.\(^\text{6}\)

Chemical Structure:

Telithromycin (ketek) is a new semisynthetic antibiotic, the first in a new class of antibacterial agents known as ketolides, which are structurally related to macrolides. Telithromycin has been developed specifically for the treatment of community-acquired respiratory tract infections caused by common and atypical pathogens, including resistant strains. The mechanism of action of the ketolides is very similar to that of erythromycin, from which they are derived.\(^\text{4,8}\) They exert their bactericidal effect by inhibiting the synthesis of new proteins; they do this by
preventing the bacterial ribosome from translating its mRNA. 49,50 Telithromycin has important structural features that differentiate it from the macrolides and are responsible for its novel mechanism of action and unique microbiological profile.

The chemical structure of telithromycin differs from that of the macrolides in three major ways: (A) a methoxy group at C6 improves acid stability and prevents internal hemiketalization; (B) 3-keto function avoids induction of MLSB resistance and improves ribosome binding; (C) the c11-12 carbamate side chain increases affinity for the ribosomes and improves interaction with resistant ribosomes.

Antibacterial efficacy of the macrolides, has been replaced with a keto group. Combined with a methyl group at position 6 to prevent ketalization, this confers excellent acid stability. The ketolides are therefore an improvement over the others, which quickly degrade in acid environments, causing erratic oral absorption and increasing gastric irritation. The keto group also is thought to be responsible for the fact that ketolides do not induce resistance to macrolides, lincosamides, and streptogramin B in vitro (4), as the macrolides The side chain at positions 11 and 12 allows tighter binding to the ribosome at 2 different sites. In fact, telithromycin binds 10 times more tightly than erythromycin and 6 times more tightly than clarithromycin to wild-type ribosomes Telithromycin belongs to the ketolide class of antibacterials and is structurally related to the family of antibiotics. Telithromycin concentrates in phagocytes where it exhibits activity against intracellular respiratory pathogens.
KETEK® has an innovative mechanism of action. Unlike the macrolides, KETEK® has 2 strong binding sites on the bacterial ribosome. This strong dual binding helps provide coverage against resistant strains of S pneumoniae in vitro.

**Macrolides Target the 50S Subunit of the Bacterial Ribosome**

- AA-tRNA
- Peptidyl tRNA
- mRNA
- 23S and 5S tRNA + 32 proteins
- Exit site for the growing peptide
- 16S tRNA + 20 proteins

- Macrolide binding inhibits protein synthesis by interfering with elongation of peptide synthesis and preventing 50S subunit assembly
Metabolism. Telithromycin is metabolized primarily by the cytochrome P-450 (CYP) enzyme system in the liver. The drug circulates in the plasma mainly in its unchanged form. Approximately two thirds of the dose is eliminated as metabolites; the final one third is unchanged drug. It is estimated that approximately 50% of its metabolism is mediated by CYP 3A4, and the remaining 50% is independent of the CYP system.

Telithromycin is rapidly accumulated to high concentrations in alveolar macrophages and white blood cells and is eliminated more slowly from these cells than from plasma. Such accumulation may facilitate transport of the antibacterial agent to the site of infection and aid in killing intracellular pathogens. In vitro studies have demonstrated that telithromycin is bactericidal and that its effects are concentration-dependent. This differs from the macrolides, whose bactericidal activity is time-dependent.

Indication
- Bronchitis
- Haemophilus Influenzae
- Pharyngitis
- Pneumonif
- Sinusitis
- Upper Respiratory Tract Infection
- Lower Respiratory Tract Infection

Since the ketek is a very common and popular medicine for Bronchitis. So we will get into it a little bit more in depth so we understand it better.

Bronchitis is an inflammation of the lining of the bronchial tubes, or bronchi, which connect the windpipe with the lungs. When the bronchi are inflamed and/or infected, less air is able to flow to and from the lungs and a heavy mucus or phlegm is formed in the airways.

Acute bronchitis is usually a short illness that commonly develops from a severe cold or following other viral infections and is characterised by cough with green sputum and a soreness in the centre of the chest and perhaps fever and some (usually mild) shortness of breathe.

The approval process for ketek started on 04, 2004 and ended on 02, 2005 and that is pretty much is the time it took the government to approve ketek.

Chronic bronchitis is defined by the presence of a mucus-producing cough most days of the month, three months of a year for two successive years without other underlying disease to explain the cough. People with chronic bronchitis also have varying degrees of breathing difficulties. Periodically these people may get infections in their lungs which makes their breathing problems worse.

List of Microorganisms that ketek affect them:
- Aerobic gram-positive microorganisms
  Staphylococcus aureus (methicillin and erythromycin susceptible isolates only) Streptococcus pneumoniae (including multi-drug resistant isolates
- Aerobic gram-negative microorganisms
  Haemophilus influenzae
  Moraxella catarrhalis
- Other microorganisms
  Chlamydia (Chlamydia) pneumoniae
  Mycoplasma pneumoniae (2)

In general, against gram positive organism such as: Saureus enterococcus
leecalis, streptococcs,... Kelek is more affective than erythromycin (3).

Dosage:
The dose is two 400-mg tablets taken once every 24 hours. The duration of
therapy depends on the infection, as detailed in Table 6. The tablets may be
taken with or without food. A missed dose should be taken as soon as
remembered, but patients should not take more than two doses (i.e., four tablets)
of telithromycin in a 24-hour period. 40 Once-daily dosing and short-course
therapy are seen as positive factors in increasing patient compliance with their
prescribed regimen (4)

Precautions:
- Diarrhea
- Hepatitis
- Elderly
- Pregnancy
- Viral Infection

Out of the five existing Precautions, Hepatitis is the most important which
we’ll discuss more about it now. Hepaticic dysfunction, including elevated
Hepatitic enzymes and Hepatit has been reported with a use of ketek.
Additionally, Hepatitic metabolism and terminal elimination half-life of ketek is
reduced in patients with Hepatitic diseases. Since elimination of drug is via the
liver and the kidney reduced Hepatitic metabolism maybe offset by increased
renal exertion.

Ketek shouldn’t take in a patients with a history of hyper sensitivity to ketek or
any component of the commercial formulation.

Drug interactions:
Administration of ketek with a drug primarily metabolised by enzyme system
may result in increased plasma contrition of drug that could increase or prolong
both the tropic and advanced effect.
### Drug Interactions of Telithromycin

<table>
<thead>
<tr>
<th>Drug</th>
<th>Effect</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triphasic contraceptives</td>
<td>Slightly increased Cmax, AUC, and t1/2 of levonorgestrel; does not affect efficacy endpoint or the ability of the contraceptive in preventing ovulation</td>
<td>Interaction not clinically significant</td>
</tr>
<tr>
<td>Simvastatin, atorvastatin</td>
<td>Significant increase in Cmax and AUC of simvastatin</td>
<td>Avoid concomitant use; suspend statin therapy during the course of telithromycin treatment</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>Increases Cmax and AUC of isoniazid</td>
<td>Contraindicated</td>
</tr>
<tr>
<td>Rabeprazole</td>
<td>Risk of increased plasma concentrations</td>
<td>Contraindicated</td>
</tr>
<tr>
<td>Itraconazole, ketoconazole</td>
<td>Slight increase in Cmax and AUC of telithromycin</td>
<td>Not clinically significant; no dosage adjustment necessary</td>
</tr>
<tr>
<td>Theophylline</td>
<td>Moderate increase in theophylline concentrations</td>
<td>Monitor daily to minimize gastrointestinal side effects</td>
</tr>
<tr>
<td>Diphenhydramine</td>
<td>Moderate increase in Cmax and AUC of digoxin</td>
<td>Use with caution; monitor digoxin side effects or serum concentrations</td>
</tr>
<tr>
<td>Warfarin</td>
<td>No clinically significant interaction</td>
<td>Avoid concomitant use</td>
</tr>
<tr>
<td>Rifampin, phenytoin, carbamazepine, phenobarbital</td>
<td>Possible subtherapeutic concentrations of telithromycin</td>
<td>Avoid concomitant use</td>
</tr>
<tr>
<td>Methadone</td>
<td>Significant increase in concentrations of methadone</td>
<td>Consider dosage adjustment</td>
</tr>
<tr>
<td>Benzodiazepines (e.g., lorazepam)</td>
<td>Significant increase in concentrations of midazolam</td>
<td>Consider dosage adjustment</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>50% increase in Cmax and AUC of metoprolol</td>
<td>Contraindicated with caution</td>
</tr>
<tr>
<td>Sotalol</td>
<td>Decreased concentrations of sotalol</td>
<td></td>
</tr>
</tbody>
</table>

AUC = area under the concentration-time curve; Cmax = maximum plasma concentration; t1/2 = terminal plasma half-life.

*These agents were not studied with telithromycin; however, since they are in the same class as those studied, health care practitioners should use professional judgment regarding their use.

Drugs may interact with ketek, there are many medicine that they have which may interact with ketek such as Alfentanil-alozetron. Lidocaine, rifampin, theophylline, ...

It is obvious using of caffeine drinks or alcohol or even smoke can affect the ketek. (1)

In regard to resistance, the resistance mechanisms are interesting. Bacteria have learned to put a little methyl group on their RNA, and then the antibiotics such as erythromycin, Biaxin, azithromycin or Z-Pak, can't attach to it. Or they have a little pump inside and they recognize the macrolide and they pump it right back out of the cell as well. It's different for erythromycin and telithromycin. Telithromycin (Ketek) has a very low affinity for this pump so it actually stays in the cell, which is different from Biaxin and Z-Paks, which actually get pumped right back out of the cell.

One of the innovations of Ketek was developing a mechanism to resist these typical forces that get rid of bacteria. It is bad news to have resistant organisms. A couple of studies show that people who have been infected with resistant organisms have a higher risk of being hospitalized.

Telithromycin is from the family of macrolides. It actually has its own category called ketolides. It was derived from the erythromycin family. Its
ancestors are clarithromycin and azithromycin. However, it has a fourteen-member ring, a little different from azithromycin, Z-Pak. It has some properties that make it very different chemically. For example, it overcomes resistance to methylation and avoids that pump that pumps it out of the cell. It has two binding sites to the bacteria, so even if the bacteria has gotten smart and methylated an area, it has a second place it can bind on a bacteria and avoid the usual resistance. It also kills very quickly. It kills with something called concentration dependent killing. That means that if a level of it hits the tissue or your blood it is what kills the bacteria. So as soon as you take those two tablets and within an hour or two, you get a high enough blood level, the bacteria die. That’s very different from beta-lactams, which require time dependent killing. You need to have amoxicillin, for example, hanging around in the bloodstream for many, many hours, probably 60% of the day, in order to effect killing. It doesn’t have to be a particularly high level necessarily unless you’ve got resistance but it needs to be there a long time. That’s called time dependent killing. It is very different from concentration dependent killing.

Side effects may be noticed by taking ketek

- Anorexia
- Anxiety
- Blurred vision
- Dizziness
- Fatigue
- Hepatitis
- Insomnia
- Nausea-vomiting
- Muscle cramp

Out the above list Blurred vision, and Muscle cramp are the most common ones out there when taking ketek, therefore using ketek is always and should always be under the provision of Doctors.

Conclusion

Ketek is the first of the ketolide class of ketek with FDA approval. Ketek is similar to the macrolide antibiotics, and it may show some benefit against penicillin and erythromycin resistant pathogens And should be used only to treat infection that are proven strongly suspected to be caused by bacteria. I think ketek will be in pharmaceutical industry for the benefits that it provides to medical improvement.
Work Cited & References


PSEUDOTUMOR CEREBRI

Prepared by
Janice L. Munnell

March 31, 2005
Abstract

Pseudotumor Cerebri is a condition in which high cerebrospinal fluid pressure inside a patient’s head can cause headaches and vision problems. Cerebrospinal fluid is the clear fluid that surrounds the brain and spinal cord. The term “Pseudotumor,” means “false tumor”. In Pseudotumor Cerebri, the flow of cerebrospinal fluid is blocked from flowing back out of the head as it should, leading to high pressure inside the head. This pressure results in swelling of the optic disc at the back of the eye, which can damage (sometimes permanently) the optic nerve, causing vision loss. High pressure may also cause damage to the nerves that move the eyes, resulting in double vision.

Discussions of Findings

This report provides an overview of what is Pseudotumor Cerebri, who is affected by Pseudotumor Cerebri, what drugs are currently being used to treat this condition and what surgical procedures have been successful in providing treatment for this condition.

Pseudotumor Cerebri is a clinical syndrome characterized by increased intracranial pressure with normal neuroimaging and cerebrospinal fluid composition. It is typically associated with papilledema . . .” (9:8). Usually the flow of cerebrospinal fluid is blocked from flowing back out of the head as it should, leading to high pressure inside the head. This pressure results in swelling of the optic disc at the back of the eye (commonly referred to as papilledema), which can damage the optic nerve, causing vision loss or blindness. High intracranial pressure may also cause damage to the nerves that move the eyes, resulting in double vision or seeing spots. One might also experience the loss of peripheral vision in one or both eyes.

Symptoms Associated with Pseudotumor Cerebri

The most frequent symptom of Pseudotumor Cerebri is headaches. These headaches are not in any single specific area or location and their frequency varies. “The headache is aggravated by factors that affect the cerebrospinal fluid pressure, such as straining, coughing, and changing position” (6:249). Another symptom is tinnitus, or ringing in the ears. This ringing noise may be heard in
one or both ears and may intensify when bending over. Spencer Weig notes that in children, the “Headache is still the most common symptom . . . in addition, diplopia, head tilt, intracranial noises, spinal pain, apathy, and irritability are all well described” (15:242). Diplopia also known as double vision may be present in one of two forms of diplopia, binocular and monocular. Binocular diplopia can be corrected by covering either eye; monocular diplopia persists in one eye despite covering the other eye. Physiologic diplopia is a normal phenomenon depending on the alignment of the ocular axes with the objects of regard. Head tilt is where the child tilts his head to one side to help improve his vision. The head tilt action forms a wider separation of images, which allows the patient to suppress or ignore one image (1:0).

**Diagnosing Pseudotumor Cerebri**

When diagnosing a patient with Pseudotumor Cerebri, the physician will term the patient as positively having Pseudotumor Cerebri if the patient meets all the conditions of the modified Dandy criteria. “The inclusion criteria include only a confirmed diagnosis of Pseudotumor Cerebri (past or present) in a patient with nephropathic cystinosis. Patients will be diagnosed as having Pseudotumor Cerebri based upon the modified Dandy criteria:

1. signs and symptoms related to increased intracranial pressure;
2. no localizing neurological signs with the exception of unilateral or bilateral sixth nerve palsy;
3. neuroimaging study showing no mass lesion or hydrocephalus; and
4. elevated opening pressure with normal cerebrospinal fluid contents on lumbar puncture” (12:2).

Although the Modified Dandy Criteria is the current published test that is used to diagnose Pseudotumor Cerebri other test criteria are currently being researched and a revision to the Modified Dandy Criteria should be published soon.

**The edges of the optic nerve (the yellow disc in the center) appear blurred and indistinct when swollen**
Papilledema is often diagnosed during a routine eye examination. The ophthalmologist usually suspects something is wrong when he sees limited abduction of one or both of the eyes through various tests. One test commonly performed is one where the patient follows the examiner’s hand to the right and the left with both eyes. The involved eye does not move fully outward, leaving some white sclera showing lateral to the cornea on the involved side compared to the other side. The speed of the abducting movement in the affected eye is usually slower than in the normal eye. Additional tests that show a potential for papilledema are the alternate cover test wherein the eye makes involuntary jumps from one fixed point to another. When the ophthalmologist dilates the patient’s eyes, he may discover disc hyperemia, subtle edema of the nerve fiber layer can be seen with a slit lamp biomicroscopy and direct ophthalmoscopy; although nerve fiber layer edema obscures the fine peripapillary vessels, small hemorrhages of the nerve fiber layer are detected most easily with the red-free (green) light and spontaneous venous pulsations that are normally present in most individuals may be obliterated when the intracranial pressure rises above 200 mm water. Also, the ophthalmologist may do an Optomap Retinal eye scan, shown in the picture on page two, which will also show enlarged vessels in the eye. If the ophthalmologist has a patient with papilledema, he informs the patient of this condition and would recommend that the patient see his or her regular physician for additional diagnostic testing and treatment (1:0).

Another test used in the diagnosis of Pseudotumor Cerebri is a lumbar puncture. A lumbar puncture (an “LP”) is the insertion of a needle into the fluid within the spinal canal. It is termed a "lumbar puncture" because the needle goes into the lumbar portion (the "small") of the back. An LP is most commonly performed to diagnose a disease, namely to obtain a sample of the fluid in the spinal canal (the cerebrospinal fluid) for examination. The patient is typically lying down sideways for the procedure. After local anesthesia is injected into the small of the back (the lumbar area), a needle is inserted in between the nearby bony building blocks (vertebrae) into the spinal canal. (The needle is usually placed between the 3rd and 4th lumbar vertebrae). Spinal fluid pressure can then be measured and cerebrospinal fluid (CSF) removed for testing. A normal lumbar pressure is between 70 – 180 mm, “any value greater than 250 mm H2O is abnormal; a value ranging from 200 to 250 mm H2O is in the grey zone” (8:58). The lumbar puncture is the most conclusive indicating factor of Pseudotumor Cerebri (4:0).

Usually if there is a continued increase in pressure of the patient’s lumbar puncture, the doctor will usually request a venogram. A venogram is a procedure that looks at your blood vessels (veins) by injecting x-ray dye and taking x-rays. The x-ray dye will show the radiologist the path of the blood flow through the veins back to the heart and measure the pressure at designated points throughout the brain and in the heart. This procedure will detect if there are any blockages causing an increase in the spinal fluid pressure or if there are any areas that show an increase in pressure. This procedure is done in a few hours on an outpatient basis and is primarily used to rule out any other factors that may be causing the increase in cerebral spinal fluid (4:0).
Magnetic resonance imaging ("MRIs") is also used in the diagnosis of Pseudotumor Cerebri. MRIs are used to provide insight in the diagnosis process. "A 1998 study by Brodsky identified specific MRI findings in cases of papilledema with elevated intracranial pressure. Posterior sclera flattening was present in 80%, empty sella in 70%, perioptic subarachnoid space distention in 45%, periaminal optic nerve enhancement in 50%, along with other findings that gave an overall 90% prediction of elevated intracranial pressure when certain MRI criteria were present" (7:3). "The primary diagnostic role of modern neuroimaging in suspected Pseudotumor Cerebri is in the exclusion of other disorder, particularly space-occupying lesions" (14:10). Ct scans although less expensive than MRIs are not sensitive enough to be used in the diagnosis of Pseudotumor Cerebri.

**Patients Affected by Pseudotumor Cerebri**

Pseudotumor Cerebri usually affects women who are of a reproductive age and are obese. It has been proven that women who have endured a significant weight increase over a short period of time may suddenly develop Pseudotumor Cerebri. However, this disease also occurs in children and teenagers (both male and female) and adult males (3:0).

**Medical Treatment of Pseudotumor Cerebri**

Doctors recommend that patients with Pseudotumor Cerebri participate in a long-term weight management program that embodies both diet and exercise. If the patient is unable to participate is this type of program, he/she may consider gastric bypass as an additional alternative. However, it has been proven that by losing weight most patients become asymptomatic right away. This is not true in all cases and the doctor must take an alternative action by prescribing medication.

**Medication Used to Treat Pseudotumor Cerebri**

In additional to weight loss, doctors may also prescribe Acetazolamide (Diamox) which is a diuretic. Acetazolamide is a "Carbonic anhydrase ... enzyme responsible for forming hydrogen and bicarbonate ions from carbon dioxide and water. By inhibiting the enzyme, Acetazolamide reduces the availability of these ions for active transport. Hydrogen ion concentrations in the renal tubule lumen are reduced by Acetazolamide, leading to alkaline urine and an increased excretion of bicarbonate, sodium, potassium, and water. A reduction in plasma bicarbonate results in metabolic acidosis, which rapidly reverses the diuretic effect. Reduced intraocular pressure is the result of a 50 – 60% reduction in aqueous humor production by Acetazolamide and is likely due to decreased bicarbonate ion concentrations in ocular fluid" (13:1)
Acetazolamide provides the best results in patients with Pseudotumor Cerebri because it increases cerebral blood flow, reduces cerebral spinal pressure, decreases the intraocular pressure and is currently the drug of choice by doctors.

![Chemical Structure of Acetazolamide](image)

When using Acetazolamide to treat Pseudotumor Cerebri doctors usually prescribe between 1200 – 1500 milligrams per day. Since this is such a high dosage, many times the patient needs to build up a tolerance to this dosage. Some frequent side effects of this medication are tingling in the extremities, rashes, nausea, vomiting, drowsiness, etc. Patients should be cautious when taking such a large amount of Acetazolamide because it can also cause distal renal tubular acidosis. Distal renal tubular acidosis is the presence of acid in the urine and a low rate of urinary ammonium secretion is related either to decreased production of ammonia by the cells of the proximal convoluted tubule or to failure to accumulate ammonium in the distal convoluted tubule and excrete it in the urine. Decreased ammonium production is sometimes observed. Acid secretion is thus reduced because of the deficiency of urinary buffers. This type of acidosis is also observed in early renal failure, due to a reduction in renal mass and decreased ammonium production in the remaining proximal tubular cells (3:0).

In addition to weight management and management with medication, patients with Pseudotumor Cerebri should also consult an Ophthalmologist every two to three months to check their vision prognosis and to make sure that the patient does not sustain an increase in swelling while on Acetazolamide. If swelling occurs and is persistent, the patient should then consult a neurologist for surgical relief of pressure.

**Surgical Procedures Used to Treat Pseudotumor Cerebri**

Currently there are two surgical procedures being used to treat Pseudotumor Cerebri. The first is management with a lumboperitoneal shunt and the second is fenestration.

“A lumboperitoneal shunts is considered the preferred neurosurgical procedure for Pseudotumor Cerebri” (10:18). This procedure is performed in the operating room under general anesthesia. A flap is cut in the scalp and a small hole is drilled in the skin. A small catheter is passed into a ventricle of the brain. A pump (valve which controls flow of fluid) is attached to the catheter to keep the fluid away from the brain. Another catheter is attached to the pump and tunneled under the skin, behind the ear, down the neck and chest and into the peritoneal cavity (abdominal cavity). The pump is regulated through a device located in the small of the back of the patient. This device allows the doctor to adjust the
volume of fluid release with a magnet. Many surgeons have not had a high success with this procedure; however Dr. Harold Rekate, Pediatric Neurosurgery of Barrow Neurological Institute, Phoenix Arizona has had a good rate of success in using the shunt to relieve the symptoms associated with Pseudotumor Cerebri. However, Dr. Rekate has concluded that “In older patient, lumboperitoneal shunts are likely to need frequent revisions, particularly when used to treat Pseudotumor Cerebri” (11:41).

Lumboperitoneal shunts when used to treat Pseudotumor Cerebri become vulnerable to failure when the patient becomes pregnant. Patients with lumboperitoneal shunts have to be monitored by their Neurosurgeon very closely during pregnancy to ensure that the cerebral spinal fluid pressure does not exceed the regularly accepted levels and to ensure that the patient’s intracranial pressure maintains an acceptable level (4:0).

Another surgical procedure currently being used is the optic nerve sheath fenestration. An optic nerve sheath fenestration is usually performed on both eyes under general anesthesia. The surgeon creates access to the optic nerves via an orbitotomy, which is an incisional approach to the eye socket. The surgeon may proceed either medial or lateral to the eye itself. Once the surgeon gains access to the optic nerve itself, a small “window” is created in the optic nerve sheath using delicate instrumentation. Once the optic nerve sheath fenestration is created, cerebrospinal fluid (CSF) will begin to drain from the optic nerve sheath via the window, thereby releasing pressure on the nerve. This procedure results in reversal of optic nerve swelling and at least partial recovery of optic nerve function in most cases. (2:0)

Unfortunately, the optic nerve sheath fenestration may not be a permanent for these patients and they may also have to have a lumboperitoneal shunt in addition to the optic nerve sheath.

Optic Nerve Sheath Fenestration

![Diagram of optic nerve sheath fenestration](image-url)
Pseudotumor Cerebri is a very serious condition that is often misdiagnosed and mistreated. Since more and more physicians have become aware of this condition there has been a trend towards more timely and accurate diagnosis of this condition. Although weight loss is frequently the best remedy for this condition, in few cases medication and/or surgery can prevent the patient from suffering any serious side affects.
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Interviews


Articles


Cervical Cancer

Lauren Reinsch
Organic Chemistry 236
Dr. Mancini
April 22, 2005
ABSTRACT:

Cervical cancer is a major epidemic, causing premature death among women throughout the world. Cervical cancer affects the female reproductive system, parametria, and pelvic walls, potentially invading the bladder, rectum, or other pelvic sites.

GENERAL DESCRIPTION:

Cancer is a malignant mass of tissue that has the potential for unlimited proliferation, capable of developing locally by invading surrounding tissue, or metastasizing by systematic processes. Common ways to prevent cancer, which has now become the number one preventable cause of premature death, is to cease the use of tobacco products, exercise regularly, and consume adequate amounts of fruits, vegetables, and legumes providing essential vitamins and minerals.

The three major processes associated with cancer are initiation, promotion, and progression. Initiation is an irreversible chemical interaction with DNA causing a permanent change. However, a cell that has undergone initiation is not considered to be a cancer cell, rather a cell that has undergone mutation, there must be more than one error present in order for a cancer cell to grow. Promotion is the increase in cellular division and the reduction of apoptosis, which is a requirement for cancer to occur. However, agents that are promoters are not sufficient enough to cause cancer and must follow the initiation process to cause cancer. Progression is a series of independent mutations which are due to genetic or chromosomal instability and the loss of genomic surveillance. Progression encompasses the invasion of surrounding tissue, the metastasis of cancer cells to other parts of the body, the loss of hormonal regulation, avoidance of immune surveillance, and the formation and differentiation of blood vessels called angiogenesis.

Common ways in which cancer is eradicated from its host include destroying the neoplastic cells by the use of anti-cancer chemotherapeutics, ionizing radiation, the host may elicit an immune response, or surgically removing the cancer. These methods may be used independently, or in conjunction with one another depending on the severity of the cancer. Furthermore, it is easier to kill fast growing tumors than slow growing tumors if they are caught in time. Smaller tumors that have not yet formed a necrotic core are easier to kill allowing drugs to reach all of the tumor cells. The earlier cancer is detected, the less likely the cancer cells have metastasized, allowing treatment to be less invasive.

ETIOLOGY:

The cause of cervical cancer is unknown, but it has been associated with numerous factors including, sexual intercourse at a young age, numerous sexual partners, having other types of sexually transmitted diseases, the use of tobacco products, poor nutritional intake, and low socioeconomic status. Infection with two types of human papilloma virus (HPV), which is transmitted sexually, is strongly associated with cervical and vulvar cancer and is the primary risk factor. The most common type of cervical cancer is squamous cell carcinoma accounting for 85 percent of all cervical cancers. Adenocarcinoma is the second most common type of
cervical cancer accounting for 10 percent of all cervical cancers. The third type of cervical cancer is Adenosquamous carcinoma, which is a combination of both adenocarcinoma and squamous cell carcinoma accounting for about four percent of cervical cancers. The remaining one percent of cervical cancers encompasses a neuroendocrine malignancy, which is quite similar to lung cancer, cancer of the GI tract, and lymphomas, which spread to the cervix from other parts of the body. Since it is unclear what the primary onset for cervical cancer is, we can assume that the papilloma virus infection’s replication cycle is the optimum model for cervical cancer analysis 1.

DISTRIBUTION:

There are approximately 500,000 reported cases of cervical cancer each year, making it the second most common type of cancer, and the leading cause of cancer related death among women in developing nations 8. Those affected, range from 20-80 years of age, with the majority of incidences occurring between the ages of 40-60 and women of poor socioeconomic status 7. There is a higher occurrence of cervical cancer for African American, Hispanic, and Native American women 18. And, women in Haiti, Nicaragua, Ecuador and Mexico have the highest death rate caused by cervical cancer, ranging from 20 to 50 deaths per 100,000 9. In the United States there is an estimated 15,000 cases of cervical cancer resulting in about 5,000 deaths. With routine examinations the lifetime risk of contracting the disease is about 0.8 percent 10.

BIOMARKERS & PREVENTION:

Research has given evidence that HPV 16, 18, 31, 33, 45, 51, 52 and 56 are found in nearly 80% of all cervical carcinomas 1. Given that HPV may shed beyond the covered area, condoms do not provide complete protection as they would for other sexually transmitted pathogens such as HIV, syphilis, and gonorrhea. Nevertheless, the Centers for Disease Control and Prevention still recommends using prophylactic methods to reduce the risk of transmission, and prevent the transmission of other sexually transmitted diseases. Lifelong monogamy or abstinence are the most effective ways to avoid HPV infection. Moreover, sexually active women can reduce the risk of developing cervical cancer by having regular Pap smear tests. Therapeutic vaccines designed to prevent precancerous cells due to HPV infection are being developed, but are still years away from being available 14.

SIGNS AND SYMPTOMS:

Signs of cervical cancer will first present themselves in women who receive regular pap smear tests which generally present asymptomatic symptoms. Observable symptoms generally present themselves as abnormal vaginal bleeding, abnormal vaginal discharge, painful sexual intercourse, painful urination, or lower back pain. Cervical cancer cells that have metastasized from the primary site of infection to a secondary site of infection will present symptoms such as constipation, blood in the urine, dilation of the cervix, or obstructions of the uterus 5.

PROGRESSION:
Cervical cancer consists of five stages: stage 0, stage I, stage II, stage III, and stage IV. In stage 0, also called carcinoma in situ, cancer cells will only be found in the first layer of the cervix lining.

Stage I, cancer cells have spread markedly more but have still not progressed beyond the first layer of the cervical lining.

Stage II marks the point at which cancer cells have spread beyond the cervix to greater portions of the vaginal region but not to the extent of the pelvic wall.

Stage III cervical cancer cells will have spread throughout the vaginal region reaching the pelvic wall and any viable lymph nodes nearby. At this point, adverse symptoms such as blocks in the uterus and kidneys will present themselves.

Stage IV cancer cells will have spread throughout the bladder, rectum, and potentially metastasizing to other parts of the body such as the liver, GI tract, or lungs.\textsuperscript{7,12}

TREATMENT:

In 1895, Wilhelm Conrad Roentgen discovered ionizing radiation as a cancer treatment method, which is still being used for treatment.\textsuperscript{6} Currently, radiation therapy to treat cervical cancer directs x-rays toward the general region of the malignancy. A second beam of ionizing radiation delivers a higher concentration of radiation at the primary site of cellular mutation. This type of therapy is the choice cervical cancer treatment option for the elderly or those in poor fitness who may have some difficulties recovering from surgery. Yet, much like surgery, radiation may not remove all of the mutated cells within the patient.\textsuperscript{6}

Conization, also called a cone biopsy, is a surgical procedure used for stage I and stage II cervical cancers, that removes a “cone-shaped” piece of tissue from the cervical canal by using a cold knife. A cold knife is used because heat may alter the findings, preventing a pathologist from viewing the excised tissue under a microscope. Pathological findings from a conization may be used to diagnose or treat a cervical condition.\textsuperscript{12}

A total hysterectomy is an aggressive surgical procedure used to treat stage III and stage IV cervical cancers by removing the female reproductive organs. If removed through the vagina, the procedure is called a vaginal hysterectomy. If removed by making a large incision in the abdomen, the operation is called a total abdominal hysterectomy. If a small incision is made with the use of a laparoscope, the operation is called a total laparoscopic hysterectomy.\textsuperscript{12}

Bilateral salpingo-oophorectomy is a surgical procedure that removes both ovaries and both fallopian tubes.\textsuperscript{12}

Radical hysterectomy is a surgical procedure that removes the uterus, ovaries, fallopian tubes, and nearby lymph nodes.\textsuperscript{12}

Pelvic exenteration is a surgical procedure that removes the lower colon, rectum, and bladder.\textsuperscript{12}

If a woman undergoes a cervical procedure that removes the reproductive organs, plastic surgery may be needed to make an artificial vagina, and pathways to permit urine and feces to flow from the body.\textsuperscript{12}

In the 1940’s chemotherapeutic anticancer drugs were discovered serendipitously when soldiers were exposed to biochemical warfare during WWII. Unfortunately, it wasn’t until 20 years later that physicians were able to discover cancer treatment drugs are most effective when
administering more than one drug at a time. Although the strategies for treating cancer with chemotherapeutic cocktails has helped the war against cancer, the debilitating side-effects to rapidly multiplying normal cells still remains a major topic of research.

Chemotherapy may destroy cells independently of radiation therapy but, administering chemotherapy with radiation treatment is appealing because they may act together to increase the killing of cancer cells. Chemotherapeutic anti-cancer drugs used to treat cervical cancer include Platinol, 5-fluorouracil, 6-mercaptopurine (6-mp), 6-thioguanine (6-TG).

In 1942 George Hitchings set out to develop a treatment for cancer that was similar enough to normal nucleotides to be used in cells, but different enough to interfere with DNA synthesis. Gertrude Elion joined Hitchings in his quest in 1944, and by 1951 she was producing numerous chemicals such as, 6-mercaptopurine, resembling normal purines, which prevented cellular division. The 6-mercaptopurine antimetabolite drug they created, induced remissions without severely harming normal cells. It only took the FDA 10 weeks to approve widespread use of this drug.
In the late 1950's, Robert Duschinsky furthered anti-cancer chemotherapeutic treatment methods by developing drugs currently known as 5-FU (Adrucil, Fluouracil, Efudex, and Fluoroplex). Duschinsky's goal was to create a drug that was able to specifically antagonize uracil, functioning to inhibit DNA synthesis after incorporation into a growing DNA molecule, which proved to have a superior anti-cancer capability. The 5-FU and normal pyrimidine base structures and are illustrated below.

![Uracil, Thymine, 5-Fluorouracil](image)

**Research:**

Recent oncology research has shown how radiation therapy combined with drug therapy, considerably surpasses cancer treatment with radiation treatment alone. One of these clinical trails involved 403 patients that were treated with either radiation therapy alone, or radiation therapy plus 5-fluorouracil chemotherapy. Those with stage III or IV cervical cancer experienced a five year survival rate of 63 percent, opposed 57 percent survival rate for patients treated with radiation therapy alone. The chance of post cancer recurrence was 42 percent for patients treated with chemotherapy and radiation compared to 62 percent for those treated with radiation alone. Combined cancer treatment drugs and radiation therapy have been pleasingly tolerated with the exception of minimal, short-lived gastrointestinal and hematologic side effects.

**Conclusion:**

Cancer is a malignant mass of tissue that has the potential for unlimited proliferation, capable of developing locally by invading surrounding tissue, or metastasizing by systematic processes. It has now been proven that the best ways to prevent cancer is to stop smoking, exercise regularly, and have a healthy diet.

Common ways to destroy cancer include the use of anti-cancer chemotherapeutics, ionizing radiation, or surgically removing the cancer, which may be used independently, or in conjunction with one another depending on the severity of the cancer. Above all else an educated population will lead to a lower cancer related death rate and an overall healthy lifestyle.
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February 3, 2005.


Putting the “Sting” in Inflammation:
The Medicinal Use of Bee Venom

By Kyle Richmond

Prepared for Dr. Mancini
CHM 236 – Organic Chemistry
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April 22, 2005
Abstract

Apitherapy, the medical use of honeybee products, has been in use for centuries, but only recently, has been scientifically investigated for its advantageous effects on the treatment of inflammation as well as other human ailments. Despite the benefits of this product, there remains some controversy over its use and administration, as there are still many aspects of the serum that continue to be a mystery. This document will provide information concerning the uses of bee venom in clinical settings in treating inflammation along with other applications, encompassing multiple sclerosis.

Background

The complex social and chemical engineering practiced by *apis mellifera*, otherwise known as the common European honeybee, has bee a subject of great interest to scientists of many disciplines. Synthesized bee products have been utilized for centuries addressing health-related problems. Pliny, Confucius and Galen all describe the use of ointments made from bee products and treatments using the stings from these insects.¹ In fact, honey has been clearly documented in several religious texts, including the Veda (Hindu scriptures) and the Bible, while some documents, dating back 4000 years, delineate the use of honey for its healing benefits.²

The Ancient Egyptians described bees making propolis, a gummy material from trees, which was a component in embalming their dead. Hippocrates, the great Greek philosopher and physician, may have been the first to use bee venom to treat joint pain and arthritis.³ His experience with bee substances, encouraged him to endow his remedy to the ancient Greek athletes who used honey to heighten energy levels and venom to treat inflammation in sore joints.¹

Unfortunately, this practice lost luster during the mid-millennium and did not resurface in modern times until Austrian physician, Phillip Terc, reported on bee venom in the late 1800's. His discourse, "Report about a peculiar connection between the bee stings and rheumatism," rekindled interest in this field, and an extensive following in Eastern Europe and China ensued and proliferated throughout the 20th century.

The popularity of bee venom for treatment of a variety of conditions is currently on the rise, as the North American culture is moving toward a healthier lifestyle and shying away from the reactions and perils of modern synthetic drugs, not to mention the associated side-effects. In order to overcome these dangers, patients are seeking more natural means of treating their conditions.¹ The by-product of this cultural shift has resulted in a gain in popularity in natural treatments, namely bee venom, and more specifically, the key component in the venom, melittin. Moreover, significant clinical research has been recently conducted substantiating the benefits of this particular product. Though the true mechanism by which the product provides relief can only be theorized, the advantages seem to speak for themselves.

**Chemical Components and Structure of Melittin**

Researchers have identified more than 40 active compounds in bee venom, of which the most prevalent is a basic amino acid polypeptide, melittin.³ This compound is
a potent anti-inflammatory agent initiating a chain reaction by activating histamines and stimulating the pituitary to release adrenocorticotropic hormones. The production of adrenocorticotropic hormones stimulates the adrenal glands to produce cortisol. Excess cortisol in the system inhibits the inflammatory response while suppressing both cartilage and bone formation, and preventing vasodilation. The second most prevalent component includes phospholipase A₂, otherwise known as lecinthinase, which is an enzyme used to catalyze the splitting of a phospholipids molecule. Another important compound found in bee venom is apamin, which has displayed the ability to block calcium potassium channels in cells, enhancing long-term synaptic transmission and shortening the duration of the neuron action potential. The final researched ingredient involves a dolapin, instrumental in the lytic action of the phospholipids cell.

Melittin is considered a protein containing 26 amino acid residues and the main substituent of bee venom, comprising 50-60% of the substance by volume. Despite being considered water-soluble as either a monomer or tetramer, it readily integrates into the lipid bilayer of animal cells making it amphiphilic. Of the 26 amino acids, the first thirteen are hydrophobic, while four of the last six are charged and the remaining two residues are polar. This construction enables the substance to act as a lytic agent within animal cells, which is thought to enhance the activity of phospholipase A₂, producing numerous effects on living cells. The complete sequence of Melittin is illustrated by the following:

\[
\begin{align*}
\text{NH}_2 - & \text{Gly} - \text{Ile} - \text{Gly} - \text{Ala} - \text{Val} - \text{Leu} - \text{Lys} - \text{Val} - \text{Leu} - \text{Thr} - \text{Thr} - \text{Gly} - \text{Leu} - \text{Pro} - \text{Ala} - \text{Leu} - (1) \\
& \hspace{10cm} (7) \hspace{10cm} (14) \hspace{10cm} (15) \\
\text{Ile} - & \text{Ser} - \text{Trp} - \text{Ile} - \text{Lys} - \text{Arg} - \text{Lys} - \text{Arg} - \text{Gln} - \text{Gln} - \text{CONH}_2 \hspace{1cm} (21) \hspace{2cm} (26)
\end{align*}
\]

The overall structure of melittin is formed by four polypeptide backbones and is organized in a cylinder shape, while each individual melittin chain is formed much like a bent rod, constituting an angle of approximately 120°. The cylindrical shape and bending are a result of the distribution and alignment of polar and apolar side chains and are divided into three distinct regions: 1) a hydrophobic NH₂-terminal region, 2) a central section with hydrophobic and hydrophilic faces, and 3) an entirely hydrophilic C-terminal region. This configuration allows 156 out of 198 hydrophilic atoms to interact with a given solvent enabling interaction with a polar substance. The hydrophobic side chains, in contrast, only enable 66 atoms to interact with a solvent. Though substantially less, it is sufficient to categorize the molecule as amphiphilic, largely due to the presence of tryptophanyl. The unique structure of melittin provides the molecule with an ideal conformation for interacting with small proteins containing a majority of apolar residues. Furthermore, the hydrophilic exterior serves to protect the interior which possesses apolar side chains, while the overall positive charges of the melittin tetramers contributes its aqueous solubility. A schematic diagram of melittin is illustrated below.

| TABLE 1 |
| Amino acid sequences of selected channel-forming peptides. For RS-AFP1 the β-sheet (b) and α-helical (h) regions are indicated. The Cys-Cys bonds between residues 4 and 51, 15 and 36, 21 and 45 and 25 and 47 are also shown (Pant et al., 1998). |
| GIICAVLTKVT TLGLPA LIKSWI KRKRQR Q-CONH₂ |
| Melittin |
Included in the melittin chain are the amino acids lysine and arginine, which are important on several levels. First, the positive charge on the tetramer resulting from both components, prevent the tetramers from accumulating in solutions, enabling them to spread out and disperse. When used as a toxic defense mechanism by the bee or as an anti-inflammatory treatment, this aspect becomes increasingly important. Secondly, the equilibrium between melittin monomers and tetramers in solution is affected by the six positive charges of each monomer. When monomers and tetramers are in equilibrium with a concentration of 200μM and in a solution with an equal ionic strength and pH, it is able to produce 59% lysis of a dilute suspension of erythrocytes. This equals, approximately 1/100 the concentration of venom in the common honeybee. The previously mentioned important component of bee venom, adolapin, acts as a neurotransmitter, and has been shown to have an analgesic effect which may provide pain relief for those suffering from discomfort associated with pain.

Mechanism of Melittin on Inflammation

The water-soluble extract of bee venom contains peptides, proteins, carbohydrates and -OH attached small molecules. Important characteristics include melittin, phospholipase A₂ and adolapin in bee venom. Melittin, the major component of whole bee venom and water soluble bee venom, initially causes local pain and edema in animals, while also producing an axon reflex in humans. The vasodilatory effect induced by axon reflexes, including deep tissues, may exert a favorable influence upon the chronic inflammatory process by increasing tissue metabolism and eliminating endogenous and exogenous irritants or toxic substances. Further support for a role of peripheral nerves in joint inflammation illustrate unilateral subcutaneous injection of Freund’s adjuvant induces a significant decrease in prostaglandin synthesis affected joints. Research further demonstrates that chronic administration of capsaicin, which
blunts the normal response of C fiber stimulation, prevented the bilateral significant decrease in cartilage synthesis. Similarly, an intra-articular injection of MK-801, which blocks glutamatergic synaptic transmission at the dorsal horn of signal originating in primary afferent C fibers, eliminated the Freund’s adjuvant induced prostaglandin synthesis. These findings implicate a role for C fibers in the arthritic changes occurring in the joint. If melittin induces a local axon reflex in nerves innervating the joint or serves as a counter-irritant that affects central spinal cord mechanisms, this could contribute to both its anti-inflammatory and antinociceptive effects on adjuvant-induced arthritis.7

Additional theories have been submitted for the mechanism of bee venom after successful clinical trials. Several studies have been researched to fully understand exactly how the components of bee venom work. Attempts to isolate the components of the compound have proven successful, although the beneficial effects have not been appreciated when the constituents are administered individually. This can be attributed, in part, to the amphiphilic capability of the compound. An experiment conducted by J.T. Gergig was able to provide information indicating the conformational change in the melittin structure when mixed with a variety of alcohols, specifically 1,1,1,3,3,3-hexafluoro-2-Propanol (HFIP) and water. When dissolved in these substances, melittin’s conformational change displayed appreciable shifts of C[alpha]H.8 The result was a bent helical conformation, from the original rod shape, exposing a greater surface area of polar side chains.8

This configuration enables the amphiphilic amino acid to penetrate the polar surface of the phospholipids bilayer of the cell.5 As melittin crosses into the interior of the cell, the non-polar tails of the bilayer, repel the polar “face” enabling to once again reconfigure, exposing its soluble non-polar side chains.9 Due to the fact that “like dissolves like,” the melittin amino acid is able to cross the cell’s membrane forming a channel with at least three other melittin molecules. Upon completion of the channel, ions can diffuse across without the need of active transport or facilitated diffusion.9

After forming the channel, phospholipase A2, apamin and adolapin, work within the cell providing a lytic action and destroying the cell. The destruction sets off the chain reaction, previously mentioned, producing an excess amount of cortisol by the pituitary gland, which is known to suppress the inflammatory response mechanism in the body.9

Clinical Substantiation

Though the use of bee venom to combat inflammation and ease pain associated with arthritis was well known, many refuted the treatment, believing it was nothing more than a substituted circumstance, since there was no clinical proof of the “so-called” remedy. After all, the nociceptive effect of a bee sting, can cause patients to quickly alter their attention from one source of pain to another. It wasn’t until a gentleman, Charles Mraz, a beekeeper in Maryland, noticed the beneficial effects on his “rheumatism” after being stung numerous times at his apiary. Because of this experience, he began to pursue the advantages of the substance relieving his symptoms. Through his diligence, and after studying Phillip Tere’s publication, he was able to capture the attention of the medical community, 50 years later, after researching the topic and discovering other countries had employed this treatment for many years.
Many studies have been conducted on the synthesis of bee venom and the human body with only few providing a partial description of the interaction between the venom and cells affecting rheumatoid arthritis.\textsuperscript{4,5} Most have only been able to substantiate the benefits of the toxin, but fall short in describing the true mechanism, although they have been able to provide relatively similar theories of how the substance works and identifying the two major components of the venom, melittin and phospholipase A\textsubscript{2}.

The majority of the studies have been conducted on Sprague-Dawley rats, which have been widely used and accepted by the American Medical Association as viable specimens for such research, due to the successful history associated with research conducted on this species.\textsuperscript{7,10} In all studies, rats were injected with the Freund's adjuvant induced rheumatoid arthritis formula in a hind paw. In some clinicals, bee venom was introduced immediately, while others waited until day 14 before administration.\textsuperscript{7,10} In order to accurately test the bee venom, the substance was extracted into two solutions predicated on its solubility: a water soluble fraction, BVA, and an ethylacetate soluble fraction, BVE. Additionally, a control group was maintained and injected with a saline solution. All solutions were subcutaneously injected in a dosage equal to 0.9 mg/kg/day (0.9 mg per day, depending on the weight of the specimen).\textsuperscript{7,10}

An interesting aspect concerning the injection sites involved one group receiving the melittin injections at the site of inflammation, while another group received the dosage at the Zusanli acupoint, located below and lateral to the anterior tubercle of the tibia. The Zusanli acupoint is a common site of needle acupuncture. Ironically, the rats receiving inoculations at the Zusanli acupoint produced significantly greater anti-arthritis effects than rats receiving the injections at non-acupoint sites.\textsuperscript{7,10} This aspect of administration remains a mystery to researchers, although the clinical results are difficult to dispute.

Upon completing the course of administration, paw volume was calculated to determine the effects of the bee venom. In all cases, long-term bee venom treatment was found to successfully suppress the inflammation associated with the rheumatoid arthritis and in fact, suppressed the induction of the disease itself.\textsuperscript{7}
The X-ray images at three weeks after arthritis induction in normal animals (A), saline-treated animals (B), the water soluble fraction of BV (BVA) treated arthritic animals (C) and the ethylacetate fraction of BV (BE) treated arthritic animals (D).

![Graph showing Change of Paw Volume](image)

**Fig. 1.** The change of paw volume in saline-treated arthritic animals (RA-Sal, N = 10), the water-soluble fraction of BV treated arthritic animals (RA-BVA, N = 10) and the ethylacetate fraction of BV treated arthritic animals (RA-BVE, N = 10). Vehicle or fractions of BV was administered into the Zusanli acupoint for 3 weeks after RA induction. Graph depicts the change in the paw volume of the contralateral left hind limb. **p < 0.01:** significantly different from RA-Sal group.

Another significant finding resulted from these clinical trials, an antinociceptive effect on those specimens receiving the bee venom therapy. Not only did the components of the venom produce an anti-inflammatory treatment, it also provided an analgesic effect as well.7,10 Rats in the study were able to move more freely and experience a greater range of motion than those who received saline injections alone or the ethylacetate injections.

![Graph showing Mechanical Threshold](image)

**Fig. 6.** The changes of mechanical threshold (Randall-Selitto test) in saline-treated arthritic animals (RA-Sal, N = 10), the water-soluble fraction of BV treated arthritic animals (RA-BVA, N = 10) and the ethylacetate fraction.
of BV treated arthritic animals (RA-BVE, N = 10). Graph depicts the percent inhibition compared to the mechanical threshold of the normal animal value in the contralateral left hind paw. **> 0.01: significantly different from RA-Sal group.

During the clinicals, arthritic-induced thermal and mechanical hyperalgesia was reduced significantly with long term bee venom treatments. Evaluating potential inhibitory effects of bee venom on arthritic nociception required monitoring of spinal cord expression following bee venom treatments. It has been claimed that arthritis-induced nociception significantly increases expression in the lumbar spinal cord three weeks after adjuvant injections.7,10 The increased number of spinal cord expressions is appreciably reduced by treatment with aspirin or with whole bee venom.7,10 During the study, it was observed bee venom notably suppressed the increased number of spinal cord expressions induced by arthritic pain, indicating that BVA has a potent antinociceptive effect on rheumatoid arthritis. The mechanism responsible for acupoint stimulation producing an analgesia result is not yet entirely clear or understood. Whereas its action was widely explained by gate control theory in the past, acupuncture, like neurostimulation methods may also act by modulation of neurotransmitters in the central nervous system.7,10

Whole bee venom injections have been shown to produce tonic pain responses at the time of injection. During the current study, injection of water soluble bee venom produced a brief vocalization. Predicated on these results, it was theorized that water soluble bee venom at the Zusanli acupoint induced a brief nociceptive input to the spinal cord that in turn reduced RA nociceptive input according to the gate control theory and/or caused modulation of neurotransmitters.7 The information obtained in this study implies that water soluble bee venom activation of the Zusanli acupoint may be a valuable method for inducing the optimal analgesic effect of acupuncture, thus substantiating that bee venom acupuncture has a more potent anti-arthritic and antinociceptive effect than traditional needle acupuncture in humans.7

Future Implications and Discussion

The future of apitherapy remains unknown. Many scientists continue to research the substance everyday, searching for plausible new uses. Currently, the compound is showing promise in the area of inflammation and nociceptive treatments, which is becoming increasingly important as side effects of many synthesized drugs are beginning to be unveiled. The recent recalls of Vioxx®, and Bextra®, arthritic drugs, and Tysabri®, a Multiple Sclerosis treatment, are just a couple of examples of the dangers that can be associated with synthesized products.11 Bee venom, on the other hand, has not been synthesized at this juncture, and consists of naturally occurring substances. Though fatally toxic to approximately 3% of the general public, the rest constitute a virtually untapped market for the benefits that may be derived.

Currently, studies are underway, seeking the advantageous effects of bee venom in a variety of other uses. Antibiotic therapy uses bee venom to combat antibiotic resistant bacteria through the use of the enzymes contained in the substance to breakdown the "protein shields" utilized by these pathogens. Additionally, cancer research is experimenting with the "magical serum" to identify some benefits in the treatment of a variety of carcinomas and sarcomas.
As the public and Food and Drug Administration become increasingly aware of some of the detrimental effects of many synthesized drugs, they are seeking more safe and healthy alternatives to the current norm. Though not the answer to everything, bee venom seems to provide, at the most, some possible answers, and the least, a new place to start.
References


HYDROGEN CYANIDE
HCN

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Abstract:

The history of hydrogen cyanide is an interesting one, while the toxic nature of bitter almonds has been known since antiquity; it has only been since modern times that CN– has been identified as the source of the toxin. In addition, the structure and physical properties of hydrogen cyanide as well as it uses will be discussed. Lastly, the presence of hydrogen cyanide in food crops and its toxic effect upon the body will be looked at.

Cyanide in various forms has been used for centuries. As a poison, it has its source in various natural substances. It is found in bitter almonds and cherry laurel leaves. The Egyptians referred to it as the “penalty of the peach”.¹

Hydrogen cyanide, HCN, was first prepared by the Swedish chemist Scheele in 1786. He synthesized HCN from the dye Prussian blue and called his new preparation acidum berolissense.¹ It was first names Prussic Acid by Guyton de Morveau in 1789.

The actual structure of HCN was determined by Berthelot who found that it contained hydrogen, carbon and nitrogen, but on oxygen. It was the chemist Gay-Lussac, who in 1815 first prepared HCN in semi-pure form and proposed the name hydro-cyanic acid. He also named the cyanide radical, CN–, cyanogen.¹

From 1830 to the end of the nineteenth century, a series of investigations identified a large number of plants that contain cyanogenic compounds. This includes cassava and soybeans, which are major food crops for much of the world.

Structure, Physical properties and Synthesis:

The Lewis structure for HCN is H-C≡N:. Hydrogen has 1 valence electron; carbon has 4 valence electrons and nitrogen 5 valence electrons. There are 2 regions of electron density around the central carbon atom. Because there is no lone pair of electrons around the central carbon atom, the geometry of the molecule is linear with the bond angles 180°.

In the molecule the C-H bond is non polar. However, because nitrogen is more electronegative than carbon, C-N is polar with carbon being partially positive and nitrogen partially negative. The result of C-N bond is that HCN is a polar molecule.

HCN is a colorless gas that smells of bitter almonds. The molecule can also exist as a volatile liquid and in isotopic form. HCN is also known by several other names, such as hydrocyanic acid, Prussic acid or Formonitrile.

HCN can also be identified by its CAS registry number: 74-90-8. Its molecular weight is 27.026 g/mol and is percent composition is 44.44% C, 3.73% H and 51.83% N.³ The melting point of HCN is 13°C, the boiling point is 25.7°C with a molecular density of 0.72.³ HCN is flammable and burns with a bluish flame. HCN is soluble in
a variety of substances such as water, ethyl alcohol and di-ethyl ether, it also is a weak acid with a $pK_a$ of 9.89 which is close to phenol.\(^3\)

HCN can be fatal at fairly low doses, in humans exposure of 30-60 minutes at a concentration of 150 ppm can be life threatening.\(^4\) Death may result in just a few minutes from exposure at concentration of 300 ppm; in humans the average fatal dose is 50-60 mg. HCN poising can be treated by sodium nitrate and sodium thiosulfate.\(^4\)

There are several ways to commercially produce HCN. Among the ways in which to produce HCN, there is the Andrusow or Andrussaw process, the Degussa process, the Shawinagan process and the formamide process.\(^2\)

In this process methane, oxygen and ammonia are passed over either platinum or a platinum-rhodium catalyst with high heat, in the range of 1030-1090°C.\(^7\) The product is first cooled in a waste heat boiler and then any unreacted product is removed. The remaining gases are transferred to a cold-water absorber and then the HCN is quickly recovered. The HCN must be cooled quickly to prevent any polymerization; with this method, yields of greater than 99% are common.\(^7\)

The Andrusow process is an endothermic process, requiring more energy to be put in than is released. The reaction can be controlled by altering the oxygen and hydrocarbon concentrations so that the heat evolved from the methane is greater than is required for HCN formation. However, it is important that the concentration of oxygen not be great enough for complete combustion of the ammonia and methane.\(^7\)
From the typical material requirements:\(^7\)

Ammonia \hspace{1cm} 830 \text{ kg}
Methane \hspace{1cm} 1153 \text{ m}^3
Oxygen \hspace{1cm} 7500 \text{ m}^3
Phosphoric acid (stabilizer) \hspace{1cm} \text{small}
Sulfuric acid \hspace{1cm} 725 \text{ kg}

You can produce 1 metric ton of HCN, which is a yield of over 99%.\(^7\)

The reaction for the Andrussow process is given by:

\[2\text{HN}_3 + 3\text{O}_2 + 2\text{CH}_4 \rightarrow 2\text{HCN} + 6\text{H}_2\text{O} \text{ with a platinum catalyst.}\(^7\)

\[\begin{array}{c}
\text{H}^- + \text{N}_3^- + 3\text{O} = 3\text{O}^- + 2\text{H}^+ + 2\text{C} = \text{H} + \text{H}^+ + \text{C} = \text{H} + \text{H}^+ + 2\text{O}^- + 2\text{O}^- \\
\rightarrow \text{HCN} + \text{H}_2\text{O} + \text{H}_2\text{O}
\end{array}\]

The Degussa process is a modified version of the Andrussow process. The difference is that oxygen is left out and the reaction proceeds from direct contact between ammonia and methane, it also uses a platinum catalyst and high heat, about 1200°C. In this process, there is a higher concentration of HCN as a product. This process is useful for small-scale production because of its high yields.\(^2\) The reaction for this process is as follows:

\[\text{NH}_4 + \text{CH}_4 \rightarrow \text{HCN} + 3\text{H}_2 \text{ with heat and a platinum catalyst.}\(^7\)

\[\begin{array}{c}
\text{H}^- + \text{N}^- + \text{H} + \text{H}^- + \text{C} = \text{H} + \text{H}^+ + \text{C} = \text{H} + \text{H}^+ \\
\rightarrow \text{HCN} + \text{H}_2 + \text{H}_2 + \text{H}_2
\end{array}\]
If no methane is available, there is another process that can be used; it is the Shawinigan process. This is also known as the Fluohmic process. In this reaction, no catalyst is used but a high temperature is used 1370-1500°C. During this reaction a bed of petroleum coke is used, and the yields of HCN are 85-90%. The reaction for this process is as follows:

\[ 3\text{NH}_3 + \text{C}_3\text{H}_8 \rightarrow 3\text{HCN} + 7\text{H}_2 \text{ with high heat} \]

Another reaction is one that uses sulfuric acid:

\[ 2\text{NaCN} + \text{H}_2\text{SO}_4 \rightarrow \text{Na}_2\text{SO}_4 + 2\text{HCN} \]

Uses:

Besides the familiar use as a pesticide, HCN has many uses in chemistry and biology. HCN is used in the production of asymmetric amino acids. In this context, HCN is added to Schiff bases to produce amino acids. This reaction is a 4-step reaction and is as follows:

\[ \text{RCH} = \text{NR}^1 \rightarrow \text{HCN} \rightarrow \text{RCHNHR}^1 \rightarrow \text{H}_3\text{O}^+ \rightarrow \text{RCHNHR}^1 \rightarrow \text{Pd(OH)}_2/\text{C H}_2 \rightarrow \]

(1) \(\text{CN} \) \hspace{1cm} (2) \(\text{COOH} \) \hspace{1cm} (3) \(\text{RCHCOOH} \)

(4) \(\text{NH}_4 \)
Schiff bases, the R groups, are prepared from aliphatic aldehydes. The R\textsuperscript{1} group represents optically active benzyl ammines.\textsuperscript{5}

A major use of HCN used to be in the production of vinyl cyanide, also known as acrylonitrile. Vinyl cyanide was used as a component of nitrile rubber, which was used in self-sealing gas tanks during World War II.\textsuperscript{7}

Since then, it was used extensively in the manufacturing of acrylic fibers. In 1975 about 700 million pounds of HCN were produced, 52% was used for acrylonitrile, 18% for methyl methacrylate, and 7% for sodium cyanide production.\textsuperscript{8} However, since 1975 HCN has not seen much use in that capacity. One reason that HCN is not being used in that capacity any more is that regulations have become stricter regarding pollution and waste disposal. Another reason is that there is an alternative method for making vinyl cyanide. The reaction for making vinyl cyanide is:

\[ \text{H}_2\text{C} = \rightarrow \text{400-500°C, } \Delta \rightarrow \text{CH}_2=\text{CHCN} \]

**HCN in Crops:**

Soybeans are a major source of protein for much of the world's population. As of 1978, the United States alone consumed over 1 Billion pounds of soy products.\textsuperscript{9} This is less than 3 g of protein per person per day, compared to Japan which consumes 10 g/day and some other Asian countries which consume 30 g daily.\textsuperscript{9} In Nigeria up to 35 mg is consumed daily from cassava, this is about half the fatal dose.\textsuperscript{9} In addition to soybeans and cassava, cyanide has been found in the legume family and New Zealand spinach and in a variety of cereal grains. The concentration of HCN found in the grains ranged from 1 ppb to 450 ppb.\textsuperscript{9}

While most humans have a small amount of cyanide in additional intake of cyanide is definitely unhealthy. For raw soybeans the concentration was found to be 80 ppb, and for toasted soybeans is was 70 ppb. While for whole soybean meal the concentration was quite higher at 260 ppb, the hull contained the highest concentration of cyanide. In addition, for raw defatted soy flour it was 80 ppb.\textsuperscript{9}

**The effects of HCN upon the body:**

HCN is highly toxic in its gases form. It achieves its toxic effect at relatively low concentrations. While some sources report fatal exposure at 330 ppm, it has been reported as low as 270 ppm and at 0.3 mg/L.\textsuperscript{8}

The lethal dose in humans is achieved after only 10 minutes with a concentration of 0.6 ml/L and at 546 ppm. While after 30 minutes fatal exposure occurs at 0.15 mg/L and at 135 ppm.\textsuperscript{8} From this, it can be seen that fatal exposure happens in a very short time and at low concentrations. Even at 0.05-0.06 mg/L and 45-54 ppm, the body only tolerates exposure for 30 to 60 minutes without immediate effects.\textsuperscript{8}
Some of the effects of HCN exposure are tachypnea, particularly with high concentrations. In addition to tachypnea, dyspnea, paralysis, unconsciousness, convulsion and finally respiratory arrest can occur. With exposure to lower concentrations, headaches, vertigo, nausea and vomiting may occur.\(^4\)

HCN primarily enters the body through respiration, although it can be absorbed through the skin. HCN affects primarily the mitochondrial respiratory chain, the enzyme that is most affected in this chain is cytochrome c oxidase.\(^1\) Cyanide once in the body, targets the brain where cytotoxic hypoxia can occur. With cytotoxic hypoxia, decreased ATP levels and lactic acidosis, the body can experience loss of perception, loss of consciousness, and loss of control functions such as respiration and cardiovascular.\(^2\) Ultimately death occur from respiratory failure.

When cyanide abortion exceeds the minimum requirements to inhibit the respiratory chain, many other enzymes and systems are also affected. The list of effect enzymes is quite long: Succinic dehydrogenase, Xanthine dehydrogenase, xanthine oxidase, D-Amino acid oxidase, Superoxide dismutase, these are just some the effected enzymes.\(^2\)

Some the long-term effects of cyanide exposure/poisoning are demyelination, lesions on the optic nerve, an increase in thiocyanate, goiter, ataxia, hyperonnia and depressed thyroid functions. HCN poisoning can be treated with sodium nitrite and sodium thiosulfate and hydroxocobalamin. Thiosulfate is a substrate for the rhodanese enzyme. This enzyme converts cyanide to thiocyanate. Nitrite then converts the hemoglobin to methemoglobin, which then joins with HCN. The HCN-methemoglobin releases the cyanide, which is converted to thiocyanate. Then the cyanide reacts with hydroxocobalamin to form cyanocobalamin.\(^1\)

**Conclusion:**

HCN is a fairly simple molecule. You sometime do not realize how useful simple things are. You look at medications and see how large and complicated the molecule is and think the more complicated the more useful it is. However, there is and elegance in having so many uses for such a simple molecule. It is surprising that as toxic as cyanide is at such low concentrations, that it is so widely distributed in nature.
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Anesthetics and the Synthesis of Procaine Hydrochloride

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Abstract

This paper will focus on the history, mechanisms and effects of anesthetics in relation to the local anesthetic Procaine Hydrochloride. Procaine Hydrochloride was given the trade name of Novocain in 1905. Its structure, uses and effects on the body are explained. The synthesis of Novocain will also be discussed using diagrams. Finally, an IR spectrum of benzocaine, a similar ester compound is presented.

History of Anesthetics

Prior to 1846, surgical procedures were very rare due to the lack of knowledge of diseases and the treatment of such diseases. The main deterrent however was the pain involved in surgical procedures. Attempts to relieve the pain were very minimal, usually involving opiates, which had been used since ancient times. Prior to 1846, the most common method of dealing with pain during surgery was restraint of the patient. This eventually changed, due to the work of dentists of the period who were often faced with patients complaining of pain. William T.G. Morton, a dentist in Boston experimented with nitrous oxide as well as diethyl ether on patients. He was able to perform nearly painless operations on his subjects while they were conscious. News eventually spread to the medical community through demonstrations, revolutionizing the way in which doctors treat patients during surgery. Diethyl ether eventually became the preferred method of anesthesia for medical procedures, while nitrous oxide wasn’t used effectively until 20 years later. Diethyl ether however was hard to administer and did have some harmful side effects. Advancements in science and chemistry soon led to better and safer forms that are still in use today. (1.2.13)

Anesthetics

There are three types of anesthetics: general, regional and local such as Procaine Hydrochloride. General anesthetics are required for major lengthy surgeries such as heart surgery. These forms completely block all signals to the brain and the person undergoing treatment would be unconscious. They are administered via an intravenous infusion (IV) and the patients are closely monitored throughout the procedure. Regional anesthetics involve blocking large groups of nerves in the body in order to work on a larger area. Lastly, local anesthetics temporarily block the nerves in a specific area and are used in minor medical and dental procedures. (1)
How Anesthetics Work

Anesthetics work by blocking the signals your brain receives via the nervous system. The nervous system communicates signals through nerve cells, which use electric pulses to transmit messages to the brain and spinal cord. Nerve impulses are conducted by the exchange of sodium and potassium ions through the cell membrane. Local anesthetics prevent the initiation and conduction of nerve impulses by blocking passageways in the cell membrane. By altering the permeability of the membrane to sodium ions only, local anesthetics affect the nerves ability to create a pulse, thus rendering it temporarily inactive. The nerve is inactive for a duration of time and no damage occurs to the cell membrane. (1.2.10.)

History of Procaine Hydrochloride

One of the first local anesthetics used was cocaine. Cocaine is an alkaloid, which is produced from the coca plant. The problem with cocaine is that it is highly addictive and toxic to the body. Doctors of the period were well aware of these addictive properties, which prompted researchers to begin looking for substitutes. Alfred Einhorn, a scientist in Germany first synthesized Procaine Hydrochloride from cocaine in early 1905. After synthesizing the substance, Einhorn gave it the trade name of Novocain. Procaine Hydrochloride became very popular because it was easier to produce and had less side effects. Novocain instantly became a popular anesthetic for dental and medical purposes. Its high solubility, tolerance and stability made it the model for today’s local anesthetics. Novocain received FDA approval in 1939 and is still used to this day. Despite its current uses, Novocain has been fazed out of the dental industry by amide type anesthetics such as Lidocaine. (5.6.7.)

Procaine Hydrochloride

Molecular Formula: C13H21O2N2Cl
Molar Mass: 272.78g
Melting Point: 154°C
Procaine Hydrochloride, an alkaloid, is a small white crystalline powder. The molecule is composed of covalent bonds since all the atoms are non-metals. It is an ester anesthetic which acts a linkage between the hydrophilic and hydrophobic groups. (8)

Uses

Novocain was widely used in the Dental field. It allowed for painless tooth extractions. Novocain is injected directly into the tissue next to a nerve or nerve trunk. Being a local anesthetic, only a certain area will become desensitized. Within 3-5 minutes, the drug binds to the sodium channel of the membrane causing a buildup of sodium ions which blocks signals that are transmitted to the brain. The effects can last up to two hours. Sometimes Novocain is mixed with other drugs such as vasoconstrictors. These drugs constrict the blood vessels, which reduce the flow of blood allowing for a slower rate of absorption. This will allow the anesthetic effects to last longer. It is also used in spinal and rectal surgeries. In addition, it is helpful in healing wounds and found in anti aging supplements. (7.8.10.)
Side Effects

In addition to blocking nerve passages, anesthetics can interfere with all organs of the body and the central nervous system. This can lead to restlessness, tremors and even convulsions. This of course would only happen at higher doses and is also one of the reasons why local anesthetics are made in amide form instead of the ester form. For the most part, side effects are very minimal and include giddiness, headaches, nausea and vomiting. It is recommended that Novocain doses in a procedure do not exceed 400mg. The liver, kidneys and plasma in the body eliminate Novocain through hydrolysis. This can be harmful, cause it can lead to high plasma levels in the body. The plasma metabolizes Novocain to P-amino benzoic acid, which has minimal effects on the body and is water-soluble. (2.4.7.10.)
Synthesis of Procaine Hydrochloride

The synthesis of Procaine Hydrochloride begins with P-amino benzoic acid. This will be represented as "R".

\[
R = \begin{array}{c}
\text{CO}_2\text{H} \\
\text{H}_2\text{N} \\
\end{array}
\]

\[
1 \quad R - \overset{\text{O}}{\text{C}} - \overset{\text{H}}{\text{O}} \xrightarrow{\text{Na}_2\text{CO}_3} R - \overset{\text{O}}{\text{C}} - \overset{\text{O}^-}{\text{O}} + \text{HCO}_3^- \\
\]

\[
R - \overset{\text{O}}{\text{C}} - \overset{\text{O}^-}{\text{O}} \xrightarrow{\text{CO}_3^-} R - \overset{\text{O}}{\text{C}} - \overset{\text{O}^-}{\text{O}} + \text{HCO}_3^- \\
\]

The reaction is run under basic conditions using Na$_2$CO$_3$. The Na$_2$CO$_3$ seeks out the H proton forming a carboxylate ion.
An Sn2 reaction takes place where the CICH2CH2Cl comes in. Chloride, a leaving group is forced off allowing the ion to attach to the CH2CH2Cl.

The nitrogen's unpaired electrons bond with the CH2CH2Cl forcing the chloride to leave. This leaves the H+ proton, which is attracted, to the HCO3.
The H proton will attract to the HCO$_3$ forming H$_2$CO$_3$. As well, the H proton can bond to the negative ions of the chloride-leaving group forming HCL. Thus resulting in the final product of Procaine Hydrochloride. The reagent HCL does play an important role in making the molecule more polar so that it can be used in the body. The synthesis of Procaine Hydrochloride is an Sn2 reaction where the nucleophile does a backside attract on the leaving group. It is a concerted reaction, which means that it happens all at once.

**IR Data**

This is an IR spectrum of benzocaine, which is a similar ethyl ester. It does have similar qualities, which are reflected on the IR graph. The tertiary amine group is missing in Benzocaine, which would have been represented by additional peaks in the 3000-3500 range. You can however see the two peaks in the 3000-3500 range reflecting
the primary amine group (NH2). The peaks from 1200-1700 represent the C=O and the C-C bonds. The aromatic ring shows a peak around 800 (para).

Conclusion

Procaine Hydrochloride played a key role in anesthetics and the synthesis of modern day anesthetics. Its roots can be traced back to ancient times and its structure has provided the foundation for today’s amide type anesthetics. Although Novocain is not used in the dental field anymore, it is still used in spinal surgeries and for post surgical needs. Recently, the drug has seen new light in the dietary supplement Gerovital (GH3). Procaine is the active ingredient in GH3 causing anti-aging results and smoother tighter skin.
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Dental Fissure Sealants
Truman Seiler
4-22-05
Abstract

Dental fissure sealants are composed of monomers which, upon polymerization, harden to become polymers. They are used within the dental industry to prevent cavities, and are applied over the grooves in teeth. Dental fissure sealants are very useful, but can also have some negative side effects.

Introduction

Dental fissure sealants are commonly used in the dental industry as a preventative measure against cavities in teeth. The enamel covering on teeth consists primarily of hydroxyapatite (Ca5(PO4)3OH) (figure 1), which is slightly soluble in acidic conditions. Food becomes trapped in the small crevices (called pits and fissures), which attracts bacteria. Bacteria produce acid which wears away the enamel, and can lead to cavities (Figure 2). Dentists recommend brushing with fluoride containing toothpaste, because the F- in fluorapatite (Ca5(PO4)3F) is a weaker base than OH-, and thus creates a “competitive equilibrium” in which some hydroxyapatite is converted into fluorapatite.\(^1\)

\[ \text{Figure 1} \]
Hydroxyapatite\(^7\)

\[ \text{Figure 2} \]
Reaction of hydroxyapatite with acid\(^7\)

Dental fissure sealants consist of an organic resin matrix, frequently consisting of an ester called methacrylate.\(^1\) In practice, a thin layer of sealant is painted over the chewing surfaces of molars and premolars. By filling up the crevices within the teeth, a protective barrier is formed, and food and bacteria cannot congregate.\(^1,15\) The effects of dental fissure sealants are not fully known, and many speculate the usage of dental fissure sealants could have potential harmful consequences.
Composition:

The organic resin matrix comprising dental fissure sealants, is composed of a monomer system, filler particles, stabilizers and binding agents.

The monomers are normally based on a glycidyl methacrylate called bisphenol (2,2-bis[4-(2-hydroxy-3-methacryloxypropoxy)phenyl]propane, but abbreviated bis-GMA).\(^5,4\) Methacrylate (Figure 4) is the ester of methacrylic acid, and the organic structure of methacrylate is H\(_2\)C=CH(CH\(_3\))COOR (R is an organic radical)\(^1\). Bis-GMA is also sometimes referred to as Bowen’s monomer, in reference to its inventor Raphael L. Bowen.\(^3,14\) It was first synthesized in 1956, by the reaction of bisphenol A with glycidal methacrylate, and was approved by the American Dental Association Council on Dental Therapeutics for consumer use in 1972.\(^5,15\)

![Figure 4](image)

**Figure 4**
Methacrylate

An alternative to the bis-GMA monomer, is 1,6-bis(methacryloxy-2-ethoxycarbonylamino)-2,4,4-trimethylhexan (UDMA), a urethane dimethacrylate synthesized from hydroxyalkyl methacrylates and diisocyanates. UDMA can be used in concert with bis-GMA, alone, or with triethylene glycol dimethacrylate (TEGDMA).

Dental fissure sealants also commonly contain other monomers besides bis-GMA, such as bisphenol A dimethacrylate (bis-DMA), ethylene glycol dimethacrylate (EGDMA) and TEGDMA. These additional monomers are added to modify the properties of the sealant by reducing viscosity.\(^4,5\) These monomers, along with the bis-GMA, comprise the monomer system in the dental fissure sealant.\(^5\)
The following substances constitute common monomers and co-monomers used in dental sealants:  

<table>
<thead>
<tr>
<th>Monomer</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bis-GMA</td>
<td>Bowen Monomer</td>
</tr>
<tr>
<td>Bis-PMA</td>
<td>Propoxylated bisphenol-A-dimethacrylate</td>
</tr>
<tr>
<td>Bis-EMA</td>
<td>Ethoxylated bisphenol-A-dimethacrylate</td>
</tr>
<tr>
<td>Bis-MA</td>
<td>Bisphenol-A-dimethacrylate</td>
</tr>
<tr>
<td>UPGMA</td>
<td>Urethane bisphenol-A-dimethacrylate</td>
</tr>
<tr>
<td>UDMA</td>
<td>1,6-bis(methacryloxy-2-ethoxycarbonylamino)-2,4,4-trimethylhexan</td>
</tr>
<tr>
<td>TEGDMA</td>
<td>Triethylene glycol dimethacrylate</td>
</tr>
<tr>
<td>TEGMMA</td>
<td>Triethylene glycol monomethacrylate</td>
</tr>
<tr>
<td>TEEGDMA</td>
<td>Tetraethylene glycol dimethacrylate</td>
</tr>
<tr>
<td>DEGDMA</td>
<td>Diethylene glycol dimethacrylate</td>
</tr>
<tr>
<td>EGDMA</td>
<td>Ethylene glycol dimethacrylate</td>
</tr>
<tr>
<td>DDDMA</td>
<td>1,10-Decanediol dimethacrylate</td>
</tr>
<tr>
<td>HDDMA</td>
<td>1,6-Hexanediol dimethacrylate</td>
</tr>
<tr>
<td>PDDMA</td>
<td>1,5-Pentanediol dimethacrylate</td>
</tr>
<tr>
<td>BDDMA</td>
<td>1,4-Butanediol dimethacrylate</td>
</tr>
<tr>
<td>MBDDMA ½</td>
<td>BDDMA-methanol-adduct ½</td>
</tr>
<tr>
<td>DBDDMA ½</td>
<td>BDDMA-auto-adduct ½</td>
</tr>
<tr>
<td>PRDMA</td>
<td>1,2-Propanediol dimethacrylate</td>
</tr>
<tr>
<td>DMTCDDA</td>
<td>Bis(acryloxyethyl) triclodecane</td>
</tr>
<tr>
<td>BEMA</td>
<td>Benzyl methacrylate</td>
</tr>
<tr>
<td>SIMA</td>
<td>3-Trimethoxysilane propylmethacrylate</td>
</tr>
<tr>
<td>SYHEMA ½</td>
<td>½-Cyclohexene methacrylate</td>
</tr>
<tr>
<td>TYMPTMA</td>
<td>Trimethylolpropane trimethacrylate</td>
</tr>
<tr>
<td>MMA</td>
<td>Methyl methacrylate</td>
</tr>
<tr>
<td>MAA</td>
<td>Methacrylic acid</td>
</tr>
</tbody>
</table>

A filling agent is used to give the sealant appropriate viscosity, to help increase bond strength, to protect against abrasion and wear, and to minimize the shrinkage associated with polymerization. A certain degree of thickness is necessary as to ensure the sealant does not leak to the gums from the teeth, yet fluidity is also necessary to ensure application can be quick and unproblematic.  

Fillers are compiled from “finely ground quartz, borosilicate, lithium-aluminum-silicate glass and/or amorphous silica.”  

One specific type of fillers, are called glass fillers. Glass fillers are benign silicate compounds, which are used through the polymerization reactions to control desired the hardness or appearance of the resin.
In addition to the monomer system and fillers, an initiator system, stabilizers, and occasionally a coupling agent are added to the resin. The initiator system is added to instigate the polymerization of the monomer(s) from light treatment, the stabilizers are used to stabilize both the uncured and the cured resin, and the coupling agent connects the resin to the filler particles.\textsuperscript{3,4,5} Organo-silanes are commonly used coupling agents, such as \textsuperscript{.gamma.-}methacryloxypropyltrimethoxysilane, \textsuperscript{.gamma.-}aminopropyltriethoxysilane and \textsuperscript{.gamma.-}glycidoxypropyltrimethoxysilane. Organo-silanes are preferred because they increase the strength of the bonds of the uncured filler, as well as the cured filler.\textsuperscript{3}

**Application:**

![Figure 5](image)

**Figure 5**

Application of Dental Fissure Sealant

A thin layer of the dental fissure sealant is “painted” over the grinding section of the molars and premolars (the teeth located in front of the molars).\textsuperscript{6,15} The teeth are then exposed to UV or visible light treatment, which initiates a reaction called polymerization.\textsuperscript{4}

Polymerization of dental fissure sealant entails energy from light forcing monomers in the matrix to bond together, to form polymers.\textsuperscript{5} Polymers are “higher molecular weight molecules made up of repeating units of smaller molecules.”\textsuperscript{16} Methacrylate is a preferred resin, because it is easily polymerized at room temperature.\textsuperscript{12}

Upon polymerization, the monomers harden and create a protective seal. These dental fissure resins are thus called thermosetting resins, because they become highly cross-linked when heated, to solidify into a hard, insoluble mass. One characteristic thermosetting resin reaction, is that of Bakelite, in the following figure:\textsuperscript{9}
By providing a protective coating around pits and fissures, bacteria and food are less likely to become trapped in the crevices of teeth, and the chances of attaining a cavity are reduced. Studies have shown that if a sealant remains intact, it will provide 100% protection against decay.\textsuperscript{13}

Medical Concerns:

Dental fissure sealants have raised many concerns within the medical community since they were first released in the 1970’s. Filling agents have been shown to occasionally release fluorine, sodium, silicon, calcium, aluminum and strontium into the body. Full polymerization cannot be achieved, which generally leaves about 10% of the initial monomers unreacted. The manufacturing process can also place impurities in the unreacted resin, which may react when polymerized. The reacted resin can be cleaved into several oligomers by means of degradation caused by photo, thermal, mechanical, or chemical factors. Substances may then leak into the body from the dental sealant, a process called leaching.\textsuperscript{5}
Leaching of specific substances can be potentially harmful. Bis-GMA, bis-MA, DMBZ, TEGDMA, DEGDMA, DMTDA, and UDMA have all been found to be cytotoxic, TPSb is genotoxic, GMA and TEGDMA are mutagenic, and Formaldehyde is carcinogenic.\(^5\) Bisphenol-A can be leached from the resins and oligomers of dental fissure sealants, as published by *Environmental Health Perspective* in 1996.\(^5,10\) Bisphenol-A is estrogenic in that it can mimic human estrogen.\(^2,5\)

The following is a list of possible reaction by-products, decomposition by-products, contaminants, and additives:\(^5\)

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Chemical Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>CQ</td>
<td>Camphoroquinone</td>
</tr>
<tr>
<td>BL</td>
<td>Benzil</td>
</tr>
<tr>
<td>DMBZ</td>
<td>Dimethoxybenzoin</td>
</tr>
<tr>
<td>CEMA</td>
<td>N-(2-Cyanoethyl)N-methylanil</td>
</tr>
<tr>
<td>DMABEE</td>
<td>4-N,N-Diethylaminobenzoic acid ethyl ester</td>
</tr>
<tr>
<td>DMABBEE</td>
<td>4-N,N-Diethylaminobenzoic acid butyl ethoxy ester</td>
</tr>
<tr>
<td>DMBAEHE</td>
<td>4-N,N-Diethylaminobenzoic acid 2-ethylhexyl ester</td>
</tr>
<tr>
<td>DMAEMA</td>
<td>N,N-Diethyl aminoethyl methacrylate</td>
</tr>
<tr>
<td>DEMAEEA</td>
<td>N,N-(Bisethylmetacrylate)-2-ethoxyethylamine</td>
</tr>
<tr>
<td>HMBP</td>
<td>2-Hydroxy-4-methoxy benzophenone</td>
</tr>
<tr>
<td>TIPN</td>
<td>2(2'-Hydroxy-5'-methylphenyl) benzotriazol</td>
</tr>
<tr>
<td>TIN326</td>
<td>Tinuvin 326</td>
</tr>
<tr>
<td>TIN350</td>
<td>Tinuvin 350</td>
</tr>
<tr>
<td>Tin328</td>
<td>Tinuvin 328</td>
</tr>
<tr>
<td>HQME</td>
<td>Hydroxyquinone monomethyl ester</td>
</tr>
<tr>
<td>BHT</td>
<td>2,6-Di-t-butyl-4-methyl phenol</td>
</tr>
<tr>
<td>MBP</td>
<td>2,2-Methylenebis(6-t-butylphenol)</td>
</tr>
<tr>
<td>MBEP</td>
<td>2,2-Methylenebis(6-t-butyl-4-ethylphenol)</td>
</tr>
<tr>
<td>BPE</td>
<td>Benzoic acid phenylester</td>
</tr>
<tr>
<td>MMMA</td>
<td>Methyl methacrylate methanol adduct</td>
</tr>
<tr>
<td>CA</td>
<td>Camphoric anhydride</td>
</tr>
<tr>
<td>HC (\frac{1}{2})</td>
<td>2(3)-endo-Hydroxyepicamphor</td>
</tr>
<tr>
<td>TPP</td>
<td>Triphenyl phosphane</td>
</tr>
<tr>
<td>TPSb</td>
<td>Triphenyl stibane</td>
</tr>
<tr>
<td>DMDDA</td>
<td>Dimethyl dodecylamine</td>
</tr>
<tr>
<td>DMTDA</td>
<td>Dimethyl tetradecylamine</td>
</tr>
<tr>
<td>DCHP</td>
<td>Dicyclohexyl phthalate</td>
</tr>
<tr>
<td>DEHP</td>
<td>Bis(2-ethylhexyl) phthalate, Formaldehyde</td>
</tr>
</tbody>
</table>

Several research projects have addressed the growing concern over harmful contaminants leaching from dental fissure sealants. Two specific projects were conducted at the University of Grenada in Spain and at Tufts University in Boston. In this project, the
researchers analyzed the saliva of 18 people, an hour after they had a dental fissure sealant applied. Their research indicated large amounts of bis-phenyl A had leached from the dental resin into the subjects’ bodies.  

The panic caused by the study prompted the American Dental Association (ADA) to conduct their own tests. In the investigation of 12 brands of sealants accepted by the ADA, only 1 had detectable amounts of bis-phenyl A. The manufacturer of the twelfth brand implemented additional quality controls after being contacted, and did not leach bis-phenyl A in a later test. In a separate study, a research project done by UCLA could not find any bis-phenyl A in 7 commercially available dental sealants tested.  

This discrepancy in test results could be the result of different brands being tested. Dan Myer, Associated Executive Director of the Division of Science at the American Dental Association, reasons that the difference between the tests done in America versus the tests performed in Europe, is that the brands of sealants tested in Spain are generally not used by American dentists, and thus were not used in the American studies.  

Further studies reveal that the level of bis-phenyl A released in dental fissure sealants in past studies, does not come near the amount needed to cause acute toxicity in animals. In fact, the oral toxicity levels reported in animal studies, are 50,000 times higher than the highest levels reported from oral contact from dental fissure sealants. Further, the highest reported oral exposure is below the maximum acceptable dose for bis-phenyl A for a lifetime.  

Conclusion:  

In the last thirty years, the number of cavities in America has declined. This can be contributed to many factors, including the effectiveness in cavity preventing of fissure sealants. Fissure sealants are a tremendously effective measure for the prevention of cavities on the chewing surfaces of molars and pre-molars, by blocking off the cracks in which bacteria and food may become trapped. If a sealant remains intact, it will provide 100% protection against decay. However, they offer no protection against cavities between teeth, on the smooth surfaces of teeth or just below the gum line.  

Dental fissure sealants work through the polymerization reaction. Monomers in the dental resin become reactive when exposed to light or heat, and bond together to form polymers. These polymers are extremely hard-wearing, and create a protective coat around the tooth.  

Substances may leach out into the body from the dental fissure sealant. These substances may have already been there due to contamination during synthesis, or they may be created or released during the polymerization of the resin. The potential of harmful substances leaching in to the body is a drawback to this procedure. However, this threat appears to be minimal as the American Dental Association has approved 12 different brand of fissure sealants, all of which have been tested to release minimal amounts of unsafe chemicals.
Bibliography


Phototransduction:
The Transformation of Light Energy Into Neuronal Signals.

Prepared for
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Organic Chemistry 236

Prepared by
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April 21, 2005
Abstract

The conversion of light energy to neuronal signals by the human eye through a process called phototransduction is researched. The specific components of the eye responsible are discussed, and the molecules and mechanisms involved are examined. The paper includes images that accompany the text, and concludes with an overview of the material covered and current research being conducted today.

Introduction

The process of phototransduction is the means which light energy is received by photoreceptors in the eye, and then converted to an electrical signal that is transmitted to the brain. There are many elements and functions of the process that are known with most being clearly defined and documented in terms of their purpose and motivation for taking place. However, despite the tremendous amount of knowledge that has been acquired, researchers are still investigating aspects of phototransduction in order to develop a better understanding of the procedure and to identify specific details such as a role or driving force behind an enzyme or mechanism taking place. From a molecular standpoint, the first understanding of molecules responsible for vision began in the 1960’s with George Wald and his associates’ work illustrating the molecular structure of rhodopsin.

Cis-retinal and Vitamin A

“Vitamin A is essential for vision. George Wald was awarded a Nobel Prize in 1967 for his finding that the 11-cis isomer of vitamin A aldehyde (11-cis-retinal) is the chromophore (light-absorbing component) of visual pigments in rods and cones . . .”

Cis-retinal plays a vital role in the vision process. It is also something that the body cannot produce on its own and must be acquired through a diet that includes Vitamin A from which cis-retinal can be derived. Vitamin A is converted to 11-cis-retinal through a two step process where the molecule is first isomerized to a cis-form and then oxidized to an aldehyde. 11-cis-retinal will be combined with opsin and used by the photoreceptors in the retina of the eye to absorb light and begin the phototransduction cascade.

If there is not enough Vitamin A to convert into cis-retinal, photoreceptors will be unable to function in an ideal manner, and initial consequences will include night blindness. While there are numerous conditions that can lead to a Vitamin A deficiency, the most common is an inadequate dietary intake. The conversion process of Vitamin A to 11-cis-retinal must be rapid and numerous enough to meet the continuous needs of photoreceptors.
**Photoreceptors**

The retina of the eye contains millions of photoreceptor cells called rods and cones that absorb light. While similar, there are differences between the two. Both rods and cones can be divided into three segments: the outer segment, the inner segment, and the synaptic terminal. The synaptic terminal is where the neurotransmitter glutamate is stored and released.

“We now know that the neurotransmitter (chemical signal) passed through the vertical pathways of the retina-from photoreceptors to bipolar cells to ganglion cells is glutamate.”

The inner segment is where the biosynthetic machinery of the cell is located.

“Opsin is synthesized in the proximal region of the inner segment, and then transported . . . to the base of the connecting cilium.”

The outer segment is connected to the inner segment, via the cilium, and is most specialized part of the photoreceptor and where the majority of the proteins involved in phototransduction are found. It is also in this segment where rod and cone cells differ.

Rod cells are monochromatic and are used for night vision as they function in dim light. They are named for their shape and are concentrated along the outer edges of the retina. Rhodopsin is found in rods and is considered to be the beginning of the phototransduction process when it absorbs light. A rod cell can react with as little as one photon of light.

“Early psychophysical experiments indicating that photoreceptors were capable of responding to single photons were confirmed . . . by electrophysiological recordings showing that quantized events (quantum bumps) could be recorded in response to absorption of single photons of light.”

Cone photoreceptors are trichromatic and perceive color through three different cones. They are not as numerous as rod cells and require tens of thousands of light photons to react. While less sensitive to light, cones provide most of the visual information during the day. They also use three photopsins that respond to color differently with regards to the wavelength of light that they can absorb. While rods and cones differ in the wavelengths of light they detect, the protein called opsin is common to both.
Opsin (Rhodopsin and Photopsin)

Rod and cone photoreceptors contain transmembrane proteins called opsin which are produced in the inner layer of the photoreceptor, transported through the connecting cilium, and then to the outer layer as disks. This process of synthesizing and transporting opsin in the photoreceptor cell is continuous.

"It follows that 9-10 billion opsin molecules are synthesized and transported every second in each human retina."  

Photoreceptors are also consistently undergoing a renewal process whereby disks are generated to replace those that have been shed and phagocytosed. Rods and cones undertake this activity at different times and are directed by light. Rods tend to shed in the morning and cones in the evening. This regeneration process is ongoing and can vary on the amount of time required.

"Through this process they regenerate completely about every 12 days, but this process can take up to 3 weeks."  

Opsins are similar to one another, with only minor differences in their respective amino acid sequence. These differences allow them to absorb different portions of the visible light spectrum and account for the color they are able to perceive. When cis-retinal fits into the receptor site on opsin in rods, it is called Rhodopsin, and when it takes place in cones, it is called photopsins I, II, or III. Basically, opsin is attached to 11-cis-retinal through a protonated Schiff base on one of its lysine side chains. While it was suspected that the molecule was a protonated Schiff base based on its absorbance spectrum when compared to an unprotonated Schiff base, it was proven through studies of Rhodopsin where the molecule was suspended in D2O and observed to have a different vibration frequency resulting from the change in mass when H was replaced with D.  

![Opsin binding to cis-retinal](image)

Each of the opsin responds differently to light with regards to the wavelengths they can absorb. When a specific color or light wavelength is detected, it will cause that respective type of cone to respond. The differences in the signals that each type of cone sends to the brain, in terms of strength and frequency, let it perceive a wide range of colors based on the primary three, blue, green, and red. Consequently, the absorbance of light initiates the phototransduction process through the isomerization the 11-cis-retinal molecule.
The Isomerization of Retinal.

"The initial step of visual transduction is the light induced isomerization of 11-cis-retinal to an all-trans configuration."³

In a normal eye, a light photon enters the retina hitting a rod cell. This causes the isomerization of retinal from 11-cis-retinal to all-trans-retinal. The light photon causes the double bond to temporarily break, through the promotion of electrons to a higher energy orbital resulting from an increased state of excitation. With only a single bond, the molecule is able to rotate 180 degrees, becoming linear before the double bond reforms and locks into place.

"Phototransduction begins with the absorption of light by Rhodopsin, triggering the 11-cis to all-trans photoisomerization of the chromophore retinal...."¹

When the molecule was in the cis-form, it fits nicely with the opsin receptor. However, the trans-form, called Bathorhodopsin, does not due to its shape. As a result, the Schiff base linkage becomes unstable, and the molecule undergoes a rearrangement, (with intermediate states), that ultimately releases the protein opsin, all-trans-retinal, and initiates the signal cascade to send an electrical impulse to the brain.

"Light exposure changes 11-cis-retinal to the all-trans form and moves opsin into a conformation that catalytically activates a G-protein (transducin) and thereby transmits a visual signal through the phototransduction pathway."³

All-trans retinal will eventually be restored to 11-cis-retinal, via an isomerase enzyme, combined with opsin, and regenerated into Rhodopsin/Photopsin completing the cycle. Although most of the overall process is understood, there is still some uncertainty as to the precise steps involved.

"...all-trans-retinal dissociates from the binding pocket of opsin, yet the molecular steps leading to its release from the opsin-binding pocket remain not fully explained.

"...all-trans-retinol translocates to the RPE via a poorly defined process...."¹⁰

While there are still unknowns surrounding all of the mechanisms involved, the significance of one of the intermediate states known as metarhodopsin II is understood with respect to its contribution to the signal transduction process.
Signal Transduction

While undergoing intermediate shapes before returning to the all-trans-retinal, an essential intermediate called metarhodopsin II is formed during the process. Metarhodopsin II will initiate the process of generating a nerve impulse to the brain by activating an enzyme called transducin. Transducin triggers a second enzyme called phosphodiesterase which is capable of hydrolyzing cyclic GMP (cGMP); cGMP is constantly produced in photoreceptors.

![Figure 6](image_url)  
**Figure 6**
**Hydrolysis of cyclic GMP**

"The signal amplification of the phototransduction cascade is remarkable in that within a few hundred milliseconds in mammalian rods, each Rhodopsin photoisomerization can lead to the hydrolysis of 10^5 molecules of cGMP."  

As phosphodiesterase begins hydrolysis of cGMP to GMP, the Na+ channels in the cell membrane begin to close. cGMP is necessary to keep these channels open so that Na+ ions are able to enter the rod cell. As a result, Na+ ions start to accumulate outside the cell which leads to hyperpolarization of the rod membrane. The large potential difference will send an electrical impulse through the rod to bipolar cells that are connected to ganglion cells which will transmit the signal across the optic nerve to the brain where the information is processed.

"Retinal rods and cones share a phototransduction pathway involving cyclic GMP."  

The process is believed to be the same in cone cells, although research is underway to further clarify the photoreceptor cascade in cones. The entire process of phototransduction occurs on a millisecond time scale.

"Psychophysical and electrophysiologicalexperiments have revealed that the sequence of light can occur in less than 1 s in mammalian rods and is even faster in cones."
Summary and Conclusions

"Visual transduction covers the sequence of photochemical, biochemical and electrophysiological events through which the absorption of a photon in a pigment molecule in a photoreceptor cell generates an electrical cellular response that will be detectable at the level of the synaptic connection."\[14\]

Vision is one of the most important senses available to interpret the world around us. The process that makes it work is a combination of different optical components, chemical mechanisms and enzymes. Initially, light enters the eye and isomerizes retinal. The resulting molecule is too unstable to remain in this position for very long and begins to rearrange itself as to become more stable. Eventually, the molecule forms an intermediate called metarhodopsin II which activates the enzyme transducin. Transducin then activates another enzyme called phosphodiesterase whose function is to hydrolyze cGMP. The absence of cGMP causes Na+ channels to close, and the resulting accumulation of ions leads to the membrane becoming hyperpolarized, and an electrical impulse sent to the brain. The abbreviated order of events that take place during the process of phototransduction are shown on the right, but by no means are complete as to each and every detail involved. While there certainly has been a substantial amount of progress made in the last twenty years toward understanding each variable underlying phototransduction, it remains a process with areas that are comprehended, but require further research to be understood to the point of molecular and chemical precision.

For example, there are Postdoctoral research positions available to study the methods proteins are transported via intraflagellar transport in photoreceptors, and the related contributions made by microtubule associated proteins such as kinesin and dynein towards this purpose.\[17\] In addition, there is research being conducted by private laboratories such as Mary D. Allen Laboratories where emphasis is placed on the research of cone specific genes and products to understand with completeness the cone photoreceptor cascade. One of the goals is to bring the level of knowledge up to that of rod photoreceptors.\[16\] Also, analysis is underway at the University of British Columbia "investigating proteins that may be involved in the recycling of all-trans retinal to its 11-cis isomer as part of the regeneration of rhodopsin."\[15\]

These are just a few examples of current research regarding specifics of phototransduction. There have been significant breakthroughs over the past few decades which will eventually lead to a complete understanding that will encompass every facet of the process. As a greater awareness of the details of phototransduction is developed, it will undoubtedly shed light on methods to resolve diseases related to vision and the eye. This research will also be carried over and applied to the process of transduction in general which is a vital element of the nervous system overall in support of other sensory functions, and responses to stimuli in vertebrates.
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The Food of the Gods:
The Health Benefits of Dark Chocolate

Prepared for
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Organic Chemistry 236

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April 17, 2005
Abstract

The health benefits of dark chocolate are currently being researched and explored. The chemical structures and activities of the physiologically active constituents of dark chocolate that are promoting optimum health is investigated. The positive impact of dark chocolate toward alertness, euphoria, mineral deficiency and cardiac conditions is analyzed and discussed.

Introduction

Chocolate, of any type, has maintained a stigma of guilty pleasure, primarily because of its high calorie, fat, and sugar content. Together, these ingredients make chocolate extremely tasty, to some individuals, irresistible, creating so-called chocoholics. However, in recent years, chocolate has been researched to inquire about any health benefits attributed to chocolate. The results of these studies and research have concluded that dark chocolate, specifically, has many advantageous physiological attributes.

Other then the most commonly known benefits of dark chocolate, such as feelings of stimulation and euphoria, the more essential advantages are to the blood pressure and cholesterol levels, reduction of mineral deficiencies and cardiac conditions. The stimulation and alertness an individual may feel after consuming dark chocolate is a chief result of the combination of theobromine and 1,3,7-trimethylxanthine, commonly known as caffeine. The feel good effect is caused by Anandamide, which is found to have parallels with marijuana. Although dark chocolate contains fat, since it is stearic in nature, it is similar to olive oil, and considered favorable. In addition, cocoa is known to be the highest natural source of magnesium, which helps combat mineral deficiencies. Finally, the antioxidants that dark chocolate retains are primary advocates of healthy heart conditions.

Background

Theobroma cacao, “The food of the gods”, is the name given to the cacao tree by the 17th century Swedish naturalist, Linnaeus. The Cacao seed, known as the coco bean, comes from the fruit of the Cacao tree. There are three different types of Cacao trees the Forastero, Criollo, and the Trinitario, although, 90% of Cacao beans come from the Forastero Cacao Tree. The different types of cocoa trees are cultivated around the equator, including the Caribbean, Africa, and South-East Asia.

The history of the Cacao bean includes it being utilized as currency by the natives of Central, North and South Americas. The Aztec Indians were the first to prepare and consume a drink out of the Cocoa seed; ironically, the Aztec Indians consumed this chocolate drink because they believed it contained stimulant and restorative properties. Modern research, through the use of clinical and blind studies and the use of advancing technology is coming to conclusions in support of this belief. Columbus brought the cacao bean to Spain in the 1500s. Since the extraction of the coco butter, the addition of sugar and fat, chocolate has become a world obsession.
**Theobromine**

The main methylxanthine compound in cocoa is theobromine, about 2% to 3% by weight. Combined with caffeine, although the amount of caffeine is small, approximately 0.2%, these two ingredients are responsible for the increased alertness and stimulation an individual feels after consuming dark chocolate. Theobromine has little stimulating effect on the central nervous system, unlike caffeine. Since there is an insignificant amount of caffeine, any restlessness or hyperactivity is not the responsibility of the caffeine\(^8\).

![Chemical structure of 3,7-dihydro-3,7-dimethyl-1H-purine-2,6-dione](image1.png)  
**3,7-dihydro-3,7-dimethyl-1H-purine-2,6-dione**  
**Figure 1\(^5\)**  

![Chemical structure of 1,3,7-trimethylxanthine](image2.png)  
**1,3,7-trimethylxanthine**  
**Figure 2\(^5\)**  

Although the primary beneficial recognition of Theobromine is alertness and stimulation, other studies are revealing that Theobromine is effective against persistent coughs, up to a third more effective than codeine due to antitussive to effect by suppressing vagus nerve\(^7\).

**Anandamide**

The word Anandamide is derived from the Sanskrit word for "bliss". "Anandamide (N-arachidonylethanolamine), is a brain chemical that activates the same cell membrane receptors that are targeted by tetrahydrocannabinol, the active ingredient in marijuana and hashish. The pharmacological effects of anandamide suggest that it may play important roles in the regulation of mood, memory, appetite, and pain perception."\(^8\) The results of Physiological research are showing that Anandamide may be a primary component in the control of cognitive and emotional control, perhaps as important as the effects of dopamine and serotonin\(^8\).
Anandamide's long hydrocarbon tail makes it fatsoluble and allows it to easily slip across the hydrocarbon-rich curtain that isolates the brain from the bloodstream. Notice that its threedimensional shape strongly resembles that of THC. Figure 3

Anandamide is synthesized enzymatically in areas of the brain and is broken down accordingly, however, dark chocolate also contains the compound N-acylethanolamines that inhibits the breakdown of Anandamide. As a result, not only do the chemicals in dark chocolate provide an enjoyable feeling, it is also preserved longer than normal.

**Stearate**

"While chocolate is high in saturated fat, the stearic acid it contains does not raise cholesterol levels even though stearate is a saturated fat. However, unlike other lipids, due to the limited absorption through the intestinal tract, stearic acid does not seem to increase plasma cholesterol. Also, stearic acid is desaturated in the liver to yield lipoproteins with oleic acid. The monounsaturated fat in chocolate, oleic acid, is also found in olive oil. It can lower LDL and total cholesterol levels in the blood. Therefore, the fat in dark chocolate does not augment the risk of heart disease and most likely any of the nutritionally linked cancers. Total fat intake, as a percentage of calories, plays a key role in the development of cancer.

**Minerals**

Although dark chocolate contains many minerals essential for the function of the human body, dark chocolate is the leading source of magnesium, which is one of the most significant minerals necessary for the function of the human body. Other than potassium, magnesium is the most abundant intracellular nutrient, making it an integral part of the cell. "As a result of the necessity of magnesium in all cells, crucial organs, such as the heart, brain and kidneys, are dependent upon it. A lack of magnesium is associated with a variety of diseases affecting these organs, including coronary artery disease, hardening of the arteries, high blood pressure, heart arrhythmia, kidney stones, kidney infections, pyelonephritis, depression, anxiety, Alzheimer's disease, and Parkinson's disease. It has also been observed that magnesium deficiency has been correlated with a greater number of diseases than any other deficiency of a mineral.

Dark chocolates' high magnesium content also helps alleviate the common problem of Pre-Menstrual Syndrome among women. The typical mood swings that characterize PMS are a
result of a noticeable drop in progesterone levels. The addition of magnesium to a woman’s diet has been proved to increase pre-menstrual progesterone levels, thus alleviating the problem.

Cocoa and chocolate provide a treasury of minerals. Often working in conjunction with vitamins, these are also indispensable for normal physical function. The most significant of the minerals are: Figure 4

**Calcium:** 3 - 40% Needed for the formation and maintenance of bones and teeth. Together with vitamin A, aids coagulation of blood in wounds. Plays a role in muscle function.

**Magnesium:** 6 - 60% The greatest concentrations are found in dark chocolate. Helps maintain a strong skeletal system, primarily active in the promotion of memory and brain function and in preventing depression.

**Copper:** 0 - 60% Mostly found in dark chocolate has role in combating cardio vascular conditions

**Phosphorus:** 25 - 35% Involved in the maintenance of a strong skeletal system. Utilization of energy from food is a primary role

**Zinc:** 7 - 17% The highest concentrations are found in dark chocolate. Important in the take-up of nutritional elements from macro-nutrients. Cell growth and the repair of tissue is dependent on zinc

**Antioxidants in Cocoa and Chocolate.**

ROS, Reactive Oxygen Species, is associated with the carcinogenic processes and is related to the mechanism of heart disease. A major defense against ROS is antioxidants that can prevent the oxidation of Low Density Lipids. Eating Phytochemicals flavonoids slowed the time needed for blood clotting the antioxidants block arterial damage caused by free radicals. The free radicals may damage the arterial walls by blocking the artery wall. The chocolate inhibit platelet aggregation that causes an attack or stroke. Chocolate also positively affects casodilation- blood vessel’s ability to relax, and blood pressure drops. These factors reduce risks for stroke, heart attack, and related disease. Decrease blood-clotting risk by reducing platelet activity. “Cocoa seems to have an aspirin-like beneficial effect on platelets in the blood, thanks to flavonoids. Various flavonoids have been shown to prevent oxidation, stimulate the immune system, impede cancer cell growth, and protect against bacteria and viruses.”

A study published in 2003 in the Journal of Hypertension, showing the flavanols in cocoa stimulate nitric oxide production in blood vessels.

Dark chocolate contains effective antioxidants through specific constituents belonging to the epicatechin oligomer and polyphenol class. “Worldwide international research in geographic
pathology and epidemiology as well as laboratory investigations demonstrated that major chronic
diseases are associated with ROS, which lead to damage in various essential cells in the body and
destroy or inhibit their ability to function. For that reason, there is need for nutritional elements
that provide antioxidants to limit the effects of ROS. Extensive research has
demonstrated the presence in these foods of antioxidants of a
polyphenol nature that are more effective
than the antioxidant vitamins\textsuperscript{5}.
During the processing of an
extract of the cocoa beans, the
polyphenol oxidase-mediated
oxidation of the cocoa
polyphenols forms a series of
polymeric procyanidins, a critical
antioxidant against ROS\textsuperscript{5}.

<table>
<thead>
<tr>
<th>Monomer</th>
<th>9.8</th>
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<tbody>
<tr>
<td>Dimer</td>
<td>13.3</td>
</tr>
<tr>
<td>Trimer</td>
<td>9.9</td>
</tr>
<tr>
<td>Tetramer</td>
<td>10.5</td>
</tr>
<tr>
<td>Pentamer</td>
<td>10.5</td>
</tr>
<tr>
<td>Hexamer</td>
<td>12.7</td>
</tr>
<tr>
<td>Heptamer</td>
<td>8.0</td>
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<tr>
<td>Octamer</td>
<td>8.6</td>
</tr>
<tr>
<td>Nonamer</td>
<td>11.6</td>
</tr>
<tr>
<td>Decamer</td>
<td>5.4</td>
</tr>
</tbody>
</table>

Figure 5\textsuperscript{5}: The results of a cooperative
study by four laboratories using purified
oligomers from Brazilian cocoa beans,
polymers up to decamers have been
observed, although the main polymers
were the dimers to the hexamers. These
have been resolved by high-performance
liquid chromatography and their structure
has been explored by mass spectrometry.
The basic monomer has the structure of
(\textsuperscript{-})-epicatechin. Figure 5\textsuperscript{5}

Figure 6\textsuperscript{5}. Cacao bears, are known to
contain various polyphenolic substances
(6\textendash{}8). (\textsuperscript{-})-Epicatechin, (\textsuperscript{+})-catechin, and
their oligomers linked by C4 \textendash{} C8 bonds
such as procyanidin B2, procyanidin C1,
and cinnamtannin A2 have been determined
to be the major antioxidative components
of cocoa and chocolate chemical structures
of polyphenols in chocolate and cocoa
Figure 6\textsuperscript{5,7}
A research experiment was done in regards to the effects of daily intake of cacao powder on LDL oxidative resistance in healthy human volunteers. “The volunteers consumed 12 g of cacao powder after breakfast, lunch, and dinner for 2 weeks. The susceptibility of their LDL to oxidation induced by copper ions or MeO-AMVN was significantly decreased compared with the control group. In addition, when hypercholesterolemic rabbits were fed a high-fat, high-cholesterol diet containing 1% cacao liquor polyphenol fraction (containing 50% total polyphenols prepared by the method described in a previous report) for about 10 days, the oxidative resistance of their LDL was significantly increased compared with that before intake.”

Taken together, these findings suggest that the polyphenols in cocoa powder are absorbed and distributed in blood at an effective concentration, and that they enhance the oxidative resistance of LDL.

**Conclusion**

As research is proving, dark chocolate has a multitude of chemicals that have a positive impact on a person’s health.

- Theobromine and caffeine provide stimulation and attentiveness
- Anandamide is a chief component in mood, memory, appetite, and pain perception, normally creating a feel good effect
- Stearic acid is the main saturated fat found in cocoa butter. It doesn’t raise blood cholesterol levels. It decreases platelet activity, contributing to heart health.
- The monounsaturated fat in chocolate, oleic acid, is also found in olive oil. It can lower LDL and total cholesterol levels in the blood.
- Chocolate is a good source of essential minerals copper, magnesium and calcium. Dark chocolate is the richest source of magnesium, providing alleviation of mineral deficiency and assisting in the prevention of related illnesses
- Chocolate contains antioxidants called flavanoids, a category of polyphenols, which prevent cell damage and reduce the risk of cancer and other age-related chronic diseases. The antioxidants is a primary protector against ROS (Reactive Oxygen Species)

The principal benefits of dark chocolate must be preserved during the manufacturing process. Several manufacturers, such as Mars Corporation, have developed and are using non-degeneration processes that retain the beneficial constituents of dark chocolate. When selecting which type or brand of dark chocolate to consume, an individual should keep in mind that there are different types of dark chocolate available, varying in quality. The percent of cocoa used and any additional additives, such as sugar, should be considered when selecting a product. To achieve the benefits associated with dark chocolate, 2 ounces per day of plain dark chocolate with a minimum content of 70% chocolate solids is recommended. Also, with dark chocolate, it is crucial for an individual to understand that they should not over indulge in dark chocolate. An individual must maintain a well-balanced diet and remain diligent in a healthy calorie, sugar, and fat intake.
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Treatment of Chronic Wounds With Oxygen Therapy
Hyperbaric vs. Topical

Petra Tavernaro

Chemistry 236

Dr. Mancini

Mon, Wed, Fri

8:30 A.M.—9:20 A.M.
Abstract

This paper examines the importance of oxygen in the treatment of chronic wounds. It is known that microphages are the major source of Vascular Endothelial Growth Factors (VEGF), and data will be given to support that VEGF content is increased at elevated oxygen tensions. The use of Hyperbaric Oxygen Chambers to treat chronic open wounds will be compared with the topical therapy and discussed. The information provided in this paper strongly suggests that topical hyperbaric oxygen therapy is a valuable adjuvant to conventional therapy for chronic wounds.

Introduction

Wound healing represents a well-orchestrated reparative response that occurs after all surgical procedures or traumatic injury (1). A compromised wound frequently represents the convergence of multiple factors that disrupt the normal wound healing process (2). Hypoxemia is a key factor that limits wound healing, which is caused by the disrupted vasculature (3). It is generally accepted that correction of wound-hypoxia is required so that enough oxygen could support the growth of regenerating tissue.

Clinical use of O₂ to promote wound healing began in the 1960’s with the administration of systematic hyperbaric O₂ to treat wounds. Although conditions such as pressure, concentration, frequency and duration of administration have not been optimized for systemic hyperbaric oxygen therapy (HBOT), the FDA has approved the therapeutic method that is used in wound clinics. The success rates among individuals that have been treated with HBOT have been encouragingly high.

This paper will summarize findings regarding the mechanism through which oxygen promotes wound healing, address issues related to methods of oxygen therapy in the perioperative and dermal wound setting, and discuss possible hazards regarding the limitation of treatment using hyperbaric oxygen chambers. Benefits of the alternative treatment of the use of topical hyperbaric oxygen treatment will be addressed.

Reactive Oxygen Species and Healing

Recent discoveries have demonstrated that in addition to phagocytes, nearly every cell in the wound microenvironment is designed with a specialized enzyme to convert oxygen to reactive oxygen species (ROS), including oxidizing species such as free radicals and H₂O₂ (4). Studies have shown that oxygen derived reactive species (ROS) play a critical role as cellular messenger molecules that signal to heal as well as disinfect. Blood cells such as macrophages and neutrophils recruited to the wound area have a well-defined mechanism to generate ROS from molecular oxygen (4). ROS can be used in the body as defense mechanisms. Immune cells that engulf bacteria and other foreign substances can generate them. After uptake, these immune cells undergo an oxidative burst, increasing the amount of O₂ that they consume, leading to production of superoxide and hydrogen peroxide that can be used to kill the engulfed bacteria (Fig 1).
Figure 1: Molecular oxygen and its reactive derivatives support numerous key processes associated with wound healing. ROS-driven redox-sensitive mechanisms in healing have been recently reviewed (4). While ROS may be beneficial at low concentrations, excess ROS (e.g., 3% \( \text{H}_2\text{O}_2 \)) commonly used clinically for wound disinfection) may be detrimental for overall healing. ROS = reactive oxygen species; SOD = superoxide dismutase; GF = growth factor.

Recent articles by Wentworth et al. go even farther. They demonstrated that antibody molecules (protein which bind to foreign molecules and target them for clearance or further immune response) could also generate ROS when they bind to their target. The outcome achieved was unexpected, but not inconsistent with the observation that antibodies can have catalytic activity if made against transition state analogs of hydrolyzable substrates. Over 100 different antibodies were found to generate hydrogen peroxide through the reaction of singlet oxygen with water to form \( \text{H}_2\text{O}_2 \) (13). Singlet \( \text{O}_2 \) can be generated from ground state \( \text{O}_2 \) by excitation through UV light or through collisional activation with an excited state chromophore (a conjugated alkene or aromatic molecule). The following reaction is to explain the formation of hydrogen peroxide. The oxygen in the peroxide comes from water, as shown by labeling water with O:

\[
2\text{H}_2\text{O} + \text{O}_2 \text{ (singlet oxygen)} \rightarrow \text{H}_2\text{O}_3 + \text{H}_2\text{O} \rightarrow \text{H}_2\text{O}_2 + ?
\]

Antibodies show this effect to a much greater extent that other proteins studied (6).

**Oxygen used as an antibiotic**

Wound tissues \( \text{pO}_2 \) levels are a major determinant of susceptibility to infection. Wound tissue oxygenation is an extremely sensitive indicator for risk of infection in surgical patients (7). A study by Grief et al (8) provided clinical evidence that enhancing wound \( \text{O}_2 \) levels through the administration of supplemental \( \text{O}_2 \) can improve host immune responses. There were 500 patients involved, all of whom were undergoing abdominal surgery. All patients received prophylactic antibiotics, administration of \( \text{O}_2 \) at an 80% \( \text{FiO}_2 \) during surgery and for two hours postoperatively. The results displayed a 5.2% wound infection rate versus an 11.2% infection rate in patients given \( \text{O}_2 \) at a 30% \( \text{FiO}_2 \) (8).
The ability of supplemental O₂ to reduce infection is mediated by ROS generated by NADPH oxidases in wound neutrophils and macrophages (1). The concentration of O₂ necessary to achieve half maximal ROS production is in the range of 45-80 mm Hg, with maximal ROS production seen at pO₂ at >300 mm Hg (9). It is clear that the only way to maximize the effects of the process is through the administration of supplemental O₂ to obtain wound pO₂ levels beyond those encountered through breathing the environmental air. ROS are generated by nearly all wound-related cells at the wound site (4).

**Oxygen Therapy**

The availability of respired O₂ to wound tissue depends on the vascular supply, vasomotor tone, arterial pO₂, and the diffusion distance for molecular O₂ (7). Edema and necrotic debris both increase the diffusion distance for O₂ to reach the wound; consequently, debridement is an important step to diminish obstruction to wound oxygenation (10). Clinical trials have shown that keeping patients normothermic with the supplemental treatment of O₂ therapy decreases the rate of wound infection in surgical patients and shortens the average length (11).

There are many levels that the clinical application of O₂ to wound healing applies: diagnostic, preventative and therapeutic. Pertaining to diagnostics, surgeons use measurements of wound oxygenation to guide treatment planning when transcutaneous O₂ measurements (TcO₂) with noninvasive vascular studies are obtained. TcO₂ measurements provide reliable prognostic information regarding the ability of wounds to heal, which has been used to determine amputation levels (1).

In preventative applications, optimizing wound perfusion and providing supplemental O₂ in the perioperative period have shown clinically to reduce incidence of postoperative infections (11). For therapeutic applications to wounds, O₂ can be given to the patient systematically, using pure O₂ (pressurized or not), or can be delivered locally to the wound using a topical device (1).

**The Wound**

Wound healing is the process of repair that follows injury to the skin and other soft tissues. Wounds may result from trauma or from a surgical incision. In addition, pressure ulcers (also known as decubitus ulcers or pressure sores), which develop on areas of the body where the blood supply has been reduced because of prolonged pressure, might also be considered wounds. These ulcers may be because of diabetic neuropathy and loss of sensation or they may be because of ischemia as a result of Diabetic Vasculopathy. It is also known that there is negative chemotaxis, poor functioning of macrophages and opsonin. Infections may play a major role in causing more morbidity and mortality.

Shortly after the infliction of a wound, coagulation occurs, and neutrophils gather at the wound site to release bactericidal reactive oxygen species (ROS) and in an H₂O₂ oxygen-consuming respiratory burst. It is commonly understood that in the early phase of wound healing, oxidants serve mainly to kill bacteria and prevent infection (13). Oxidants also damage surrounding host cells, including macrophages, by creating DNA strand breaks and depleting NAD stores (12).
Chronic Wound Healing

Chronic or deep wound healing occurs when an injury extends to the dermis and subcutaneous layer. The healing process is more complex than that of the epidermal wound healing due to the fact that multiple tissue layers must be repaired. Because the wound has occurred into deeper layers, normal function is lost in the tissue. Chronic wound healing occurs in three phases: an inflammatory phase, a proliferative phase, and a maturation phase (Figure 2) (14).

![Diagram of wound healing phases]

Figure 2 (14): The healing of chronic wounds occurs in three overlapping phases.

**Inflammatory Stage**
This stage occurs during the first few days. The wounded area attempts to restore its normal state (homeostasis) by constricting blood vessels to control bleeding. Platelets and thromboplastin make a clot. Inflammation (redness, heat, swelling) also occurs and is a visible indicator of the immune response. White blood cells clean the wound of debris and bacteria.

**Proliferative Stage**
After the inflammatory stage, the proliferative stage lasts about 3 weeks (or longer, depending on the severity of the wound). Granulation occurs, which means that special cells called fibroblasts make collagen to fill in the wound. New blood vessels form and the wound gradually contracts and is covered by a layer of skin.

**Maturation and Remodeling Stage**
This stage may last up to 2 years. New collagen forms, changing the shape of the wound and increasing strength of tissue in the area. Scar tissue, however, is only about 80% as strong as the original tissue. The body's ability to heal during this stage is diminished in the elderly.
Hyperbaric Oxygen Therapy

Vague accounts of increased atmosphere pressures used on humans date back to the fifth century BC. Henshaw, a British clergyman, built the first sealed chamber, termed the "Domicilium," in 1662. This chamber compressed air (21% oxygen) for numerous ailments such as inflammation, scurvy, arthritis, and rickets but likely had too little compression to do any physical good.

A flurry of interest in therapeutic hyperbaric medicine was fostered by Dr I. Boerema, who, while in Amsterdam in 1956, reported hyperbaric oxygen (HBO) as an aid in cardiopulmonary surgery, particularly for congenital conditions such as tetralogy of Fallot, transposition of great vessels, and pulmonic stenosis. A colleague of Boerema's, W. H. Brummelkamp, also interested in hyperbaric medicine, discovered in 1959 (and subsequently published in 1961) that anaerobic infections were inhibited by hyperbaric therapy. Meanwhile, Boerema had published an article, "Life without blood," a report of fatally anemic pigs treated successfully with volume expansion and pressurized hyperoxygenation (19). Boerema often is credited as the father of modern-day hyperbaric medicine. The benefits of hyperbaric medicine subsequently were observed for split-thickness skin graft acceptance, flap survival and salvage, wound re-epithelization, and acute thermal burns (18).

Researchers conducting wound-healing studies continued to try to take advantage of the angiogenic properties of increasing oxygen gradients resulting from hyperbaric therapy. Foot wounds from diabetes, radiation ulcers, and other ischemic wounds have been manipulated and successfully treated with HBO. Prospective blinded randomized trials and well-executed laboratory studies continue to further define the role of hyperbaric therapy in medical therapeutics.

The application of HBO depends on the physical properties of gases under pressure, specifically, oxygen at pressure greater than 1 atm. Oxygen is essential in a variety of enzymatic, biochemical, and physiologic interactions that promote normal cellular respiration and tissue function. Mono-oxygenase, intradioxynogenase, and interdioxynogenase are specific enzymes that recruit oxygen as a cofactor to perform required biologic processes. Collagen deposition and synthesis depend on an oxygen-dependent prolyl-hydroxylase hydroxylation of proline. Angiogenesis and epithelization also are oxygen dependent.

Hyperbaric O₂ therapy (HBOT) delivers 100% O₂ at 2-3 atmospheres (atm) of pressure and patients receive approximately 10-30 treatments, depending upon diagnosis. The treatments given are usually 60-120 minutes long, and are given 5 days a week. These treatments are performed in specialized chambers at facilities with physician supervision (1) (Fig. 3).
HBOT is capable of elevating arterial $pO_2$ as high as 1200 mm Hg. The mechanism of action of hyperbaric treatments is attributed to the immediate direct physical affects of oxygen and other gases under pressure. The mechanism of action is also attributed to other gases under pressure and to the delayed secondary physiologic and biochemical effects that are set into motion with each hyperbaric treatment (15). These primary and secondary effects of hyperbaric treatment are listed in Table 1 and Table 2. Benefits of hyperbaric treatment often use both the primary and secondary mechanisms to promote the desired effect. Charles law states that if a volume of gas is kept constant, the temperature varies with the pressure. Together, Charles and Boyle laws are known as the general gas law, expressed as $D_1V_1/T_1 = P_2V_2/T_2$. Henry law states, "At a constant temperature, the amount of a gas that will dissolve in a liquid is proportional to the partial pressure of the gas."

Each of the physical laws directly governs the principles of hyperbaric medicine through hyperoxygenation bubble size change and the myriad secondary effects noted above. These principles account for the clinical application in the adjunctive therapies below.

Table 1: Primary effects.

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Effect</th>
<th>Clinical Utility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperoxygenation</td>
<td>□ Greater oxygen carrying capacity</td>
<td>□ Severe blood loss anemia (unable to carry oxygen)</td>
</tr>
<tr>
<td></td>
<td>□ Increased oxygen diffusion in tissue fluid</td>
<td>□ Crush injury, compartment syndrome graft, and flap salvage (decreased perfusion)</td>
</tr>
<tr>
<td></td>
<td>□ Diffusion distance proportional to the square root of dissolved oxygen</td>
<td>□ Edema (increased diffusion barrier)</td>
</tr>
<tr>
<td>Mechanism</td>
<td>Effect</td>
<td>Clinical Application</td>
</tr>
<tr>
<td>----------------------------</td>
<td>------------------------------------------------------------------------</td>
<td>-----------------------------------------------------------</td>
</tr>
<tr>
<td>Decrease gas bubble size</td>
<td>□ Boyle law - Gas volume inversely proportional to pressure</td>
<td>□ Decompression sickness</td>
</tr>
<tr>
<td></td>
<td>□ Hyperbaric diffusion gradient favors gas leaving the bubble and oxygen moving in, metabolizing oxygen in the bubble</td>
<td>□ Air embolus syndrome</td>
</tr>
<tr>
<td></td>
<td>□ Law of La Place p-4t/r</td>
<td></td>
</tr>
<tr>
<td></td>
<td>□ Bubbles unstable as they decrease in size</td>
<td></td>
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</table>

Table 2: Secondary effects.

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Effect</th>
<th>Clinical Application</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vasoconstriction</td>
<td>□ Decreased inflow into tissues</td>
<td>□ Crush injuries</td>
</tr>
<tr>
<td></td>
<td>□ Decreased edema</td>
<td>□ Acute burns</td>
</tr>
<tr>
<td></td>
<td>□ Increased oxygen gradient between wound and surrounding environment</td>
<td>□ Compartment syndrome</td>
</tr>
<tr>
<td>Angiogenesis</td>
<td>□ Increased fibroblast proliferation leading to increased collagen deposition and increased fibronectin, which aids in neovascularization</td>
<td>□ Graft and flap salvage</td>
</tr>
<tr>
<td></td>
<td>□ Increased fibroblast proliferation leading to increased collagen deposition and increased fibronectin, which aids in neovascularization</td>
<td>□ Osteoradionecrosis</td>
</tr>
<tr>
<td></td>
<td>□ Radiation endarteritis obliterans</td>
<td>□ Radiation endarteritis obliterans</td>
</tr>
<tr>
<td></td>
<td>□ Chronic wounds</td>
<td></td>
</tr>
<tr>
<td>Fibroblast proliferation</td>
<td>□ Oxygen-dependent proliferation</td>
<td>□ Chronic wounds</td>
</tr>
<tr>
<td></td>
<td>□ Radiation-induced injury</td>
<td></td>
</tr>
<tr>
<td>Leukocyte oxidative killing</td>
<td>□ Increased oxygen free radicals</td>
<td>□ Necrotizing soft-tissue infections</td>
</tr>
<tr>
<td></td>
<td>□ Anaerobes lack superoxide dismutase to control oxygen free radicals</td>
<td>□ Chronic osteomyelitis</td>
</tr>
<tr>
<td>Toxin inhibition</td>
<td>□ Decreased clostridia alpha toxins</td>
<td>□ Clostridial gas gangrene</td>
</tr>
<tr>
<td></td>
<td>□ Decreased cardio toxins</td>
<td>□ Decreased cardio toxins</td>
</tr>
<tr>
<td>Antibiotic synergy</td>
<td>□ Fluoroquinolones, amphotericin B, and aminoglycosides - Use oxygen to transport across cell membranes</td>
<td>□ Sepsis</td>
</tr>
<tr>
<td></td>
<td>□ Necrotizing infections</td>
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Topical Hyperbaric Oxygen Therapy

Topical oxygen therapy has been shown in studies to minimize scarring and shorten treatment times for skin wounds, such as pressure ulcers, diabetic foot ulcers, severe burns and plastic surgery (20). Topical O₂ therapy has the advantageous potential to oxygenate superficial areas of the wound not supported by intact vasculature. Because of this, topical oxygen therapy may correct pO₂ of cells at the wound core, which consequently may correct hypoxia-induced impairment of NADPH oxidase function in those cells (1). NADPH oxidase function in wound-related cells contributes to favorable processes such as cell motility, angiogenesis, and extracellular matrix formation (4). The problem is that oxygen delivery to the wound site by hyperbaric chambers can be limited by poor wound tissue vascularization.

The difference between systemic HBO and topical hyperbaric oxygen (THBO) in therapeutic approach is that systemic HBO increases blood oxygen levels. However, blood oxygen levels are normally adequate for wound healing (1). Topical hyperbaric oxygen delivers oxygen directly to the wound. Transcutaneous oxygen levels are increased, despite the lack of well-vascularized wound tissue. Because this therapy is topical and relatively low pressure, there is no systemic absorption of oxygen, and therefore no risk of pulmonary or central nervous system toxicity that can result from breathing high pressure (30 - 45 psi) oxygen in full body chambers (16). The treatment protocol for topical O₂ therapy consists of a 90-minute treatment per day for four consecutive days, followed by three days with no topical O₂ therapy. This application continues until the wound is healed. The process involves placing a thin, transparent membrane bag, completely covering the wound. The bag is then secured with tape to the patient and inflated with oxygen to optimal pressure (Fig. 4) (17).

Fig.4: A patient is treated for pressure sores with the use of topical oxygen therapy.
This pressure must be maintained within rigid bounds or the treatment will not be effective or even worse, the skin lesion can be further damaged. The pressure indicator measures the pressure inside the bag by detecting the tension of the bag wall (19).

The same characteristics that make Topical Hyperbaric Oxygen Therapy an effective treatment regimen for diabetes-related necrotizing fasciitis make it effective for treating biological-warfare related lesions. The U.S. federal government has licensed the special technique for use among the nation’s military. The technique is of interest to the military because not only is it considered to be an effective treatment for burns, diabetes, or post-operative infections, it is considered an effective treatment for smallpox and dermal anthrax (20). Another benefit is that the equipment used is inexpensive, portable and disposable.

Hyperbaric Oxygen Therapy vs. Topical Oxygen Therapy

Correction of wound pO₂ is a fundamental issue that by itself may trigger wound healing. Approaches to correct wound pO₂ are expected to have a favorable influence on other therapies, such as responsiveness to growth factors and acceptance of grafts (4). In preventive applications, optimizing wound perfusion and providing supplemental O₂ in the perioperative period have been shown clinically to reduce the incidence of postoperative infections (21). In the treatment of diabetic foot infection, adjunctive hyperbaric oxygen therapy is a useful tool to enhance wound healing (22). O₂ therapy has been established as a powerful tool to be used in the treatment of many chronic wounds. The determination of what type of treatment should be used must be addressed.

HBOT is capable of elevating arterial pO₂ as high as 1200 mm Hg, but systematically administered O₂ relies on the vasculature to be delivered to tissues. Since this is the case, HBOT therapy may efficiently improve the wound perimeter, the areas of the wound that are not supported by blood vessels will not benefit as much (1). Although topical O₂ may not diffuse into deeper tissues, it does have the advantage to oxygenate superficial areas of the wound not supported by intact vasculature. As a result, topical O₂ may correct pO₂ of cells at the wound core, thus correcting wound hypoxia-induced impairment of NADPH oxidase function in the cells (1). NADPH oxidase function in wound-related cells contributes to favorable process such as cell motility, angiogenesis, and extracellular matrix formation (4).

Another key issue that needs to be examined in the comparison of HBOT to topical O₂ is the risk of systemic pure O₂ toxicity. It is general knowledge that exposure of biological cells and tissues to pure O₂ may result in oxidative stress and genotoxicity (23). Table 3 displays signs and symptoms of hyperbaric oxygen toxicity (15).

<table>
<thead>
<tr>
<th>CNS</th>
<th>Pulmonary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea and vomiting</td>
<td>Dry cough</td>
</tr>
<tr>
<td>Seizures</td>
<td>Substernal chest pain</td>
</tr>
<tr>
<td>------------------</td>
<td>------------------------</td>
</tr>
<tr>
<td>Sweating</td>
<td>Bronchitis</td>
</tr>
<tr>
<td>Pallor</td>
<td>Shortness of breath</td>
</tr>
<tr>
<td>Muscle twitching</td>
<td>Pulmonary edema</td>
</tr>
<tr>
<td>Anxiety and/or respiratory changes</td>
<td>Pulmonary fibrosis</td>
</tr>
<tr>
<td>Visual changes</td>
<td></td>
</tr>
<tr>
<td>Tinnitus</td>
<td></td>
</tr>
<tr>
<td>Hallucinations</td>
<td></td>
</tr>
<tr>
<td>Vertigo</td>
<td></td>
</tr>
<tr>
<td>Hiccups</td>
<td></td>
</tr>
<tr>
<td>Decreased level of consciousness</td>
<td></td>
</tr>
</tbody>
</table>

Because of the risks involved, it is extremely important to avoid treatment that is not necessary. Topical O₂ therapy can provide the oxygen necessary directly to the wound to correct pO₂ and aid in wound repair without the risks of inhaling 100% oxygen.

**Conclusion**

Studies and data have supported the idea that oxygen therapy has a detrimental effect on wound healing. When the hyperbaric oxygen chamber was invented new doors were opened, tremendous strides have been taken in order to eliminate potential and post-operative infections pertaining to many chronic wounds focusing on the patient. Reduction of risk of oxygen toxicity has been introduced, at the same time having the ability to treat the wound with oxygen therapy and providing the oxygen straight to the wound. Topical oxygen therapy has given the patient the ability to receive treatment at home, not only reducing medical costs, but also eliminates the inconvenience of unnecessary treatment in a confined shell. Benefits of treating chronic wounds with topical O₂ far out weigh those of using the O2 method of the hyperbaric (Table 4).

Table 4: Comparison of systematic hyperbaric oxygen therapy to topical oxygen therapy

<table>
<thead>
<tr>
<th>Systemic hyperbaric oxygen</th>
<th>Topical delivery of oxygen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemically oxygenates blood at 2-3 atmospheres</td>
<td>Topically oxygenates wound tissue at 1 atmosphere</td>
</tr>
<tr>
<td>Requires specialized facilities and personnel</td>
<td>Portable devices: available bedside and in the field</td>
</tr>
<tr>
<td>---------------------------------------------</td>
<td>---------------------------------------------------</td>
</tr>
<tr>
<td>Relatively expensive</td>
<td>Inexpensive</td>
</tr>
<tr>
<td>Relies on vascular system to deliver O₂ to wound</td>
<td>Can deliver oxygen directly to wounded tissue severed from circulation</td>
</tr>
<tr>
<td>Poor vascularity of wound tissue limits O₂ diffusion</td>
<td>Oxygenation not dependant on vascular bed</td>
</tr>
<tr>
<td>Risk of multiorgan oxygen toxicity</td>
<td>No risk of oxygen toxicity</td>
</tr>
</tbody>
</table>

A paradigm shift occurred at the time topical oxygen therapy was introduced. Although more study and research must be done to optimize the potential benefits, it is clear that topical therapy is a much-needed adjunctive therapy in the modern treatment of chronic wounds.
Works Cited
Genital Herpes and Current Treatments

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Abstract

Herpes is a viral infection of the skin caused by the Herpes Simplex Virus (HSV). This paper delves into the affects that herpes simplex virus has on human’s health and also considers the use of the antiviral drugs for the prevention and treatment of the herpes virus in human populations. It is very important to know that there is no cure for herpes and even with treatment; it may be possible to spread herpes.

Introduction

Genital herpes is a sexually transmitted disease that can have a devastating impact on the health of newborn babies. Herpes is caused by herpes simplex viruses, which are similar to the viruses that cause chickenpox and shingles. There are two main kinds of herpes simplex viruses: type 1, which is usually associated with cold sores around the mouth and lips; and type 2, which is usually associated with genital sores. Herpes infections are transmitted by direct contact with an infected person.²

Herpes has been around since the time of the ancient Greeks, which explains why its name comes from the Greek word herpein, meaning "to creep" or "to crawl." But what causes herpes to break out again and again remains a medical mystery. Today herpes has become a widespread infection that doesn’t discriminate between social or economic class. Experts estimate that genital herpes affects up to 60 million people, or one in five Americans over the age of 12. In 1991 an estimated 45 million Americans were infected with the virus that causes genital herpes and millions more have cold sores.⁷ Herpes virus is spread though skin to skin contact from an area where the virus is present to a skin site that is susceptible. The virus may affect mucous membranes and the skin around the mouth, nose, vagina, urethra, anus or eyes. Oral, anal and vaginal sexual intercourse are sexual behaviors or activities that may transmit the virus. Kissing and close skin to skin contact without intercourse can also pass the virus.⁵

Individuals who have sexual contact with an infected partner may develop symptoms within two to ten days or longer.

A personal genital herpes history often repeats, as herpes, like a wart virus remains in the organism for life. Where evidence is lacking, reason suggests that anything contributing to an individual’s wellness, herbal or organic immune supplements can only serve to be beneficial. Since viral infections may disappear without any intervention, it is difficult to certify the effectiveness of natural treatments particularly as a food source.²

Symptoms

Herpes is caused by a virus (Herpes Simplex HSV). The most common symptom is a single blister or cluster of painful blister-like lesions. Lesions are generally found around the mouth, nose or genitals. In females the genital lesions appear around the vaginal opening, urethra, anus and buttocks. Local swelling, burning upon urination and unusual vaginal discharge may occur. Males may develop blisters on the penis and/or around the anus and buttocks. The fluid-filled lesions are highly contagious. The lesions may last up to three weeks. They will usually crust over, form a scab and then heal completely without scarring. Other symptoms may include fever,
headache, swollen glands, muscular aches and fatigue. These symptoms are most common during the first episode. Some individuals with Herpes develop mild symptoms or no symptoms at all. Most of the time when Herpes sores is not present on the skin the virus remains in a latent (inactive) state in the central nervous system, where it does no damage. At times the virus travels back to the skin sites or mucous membranes without causing active symptoms recognizable as Herpes. Once the virus is at these sites its presence there may produce something known as asymptomatic (no symptoms) viral shedding. This shedding creates a risk of spreading Herpes to others through sexual contact or intimate physical contact. Unfortunately, most exposure occurs when there is no identifiable rash (e.g., when the person is asymptomatic) as there is shedding of the virus through the skin about 1% of the time. Many people are unaware that oral cold sores may cause genital infection during oral sex. It is also possible for a person to transfer herpes from their own mouth to their genitals, and to their eyes. New lesions that are filled with fluid are the most infectious.

Diagnosis

Diagnosis is made by a physician when hearing the symptoms of the rash and examining the blistered area. If there is any question, a sample of the abnormal tissue (biopsy) can be sent to the lab for microscopic analysis. A viral culture of the wound can also be checked to verify the presence of the Herpes Simplex Virus.

What Risks Does Herpes Pose during Pregnancy?

At least one in five pregnant women has been infected with genital herpes, although most do not know it. Fortunately, only a small minority will pass the infection on to their babies or suffer other pregnancy complications. Women who acquire genital herpes for the first time near the time of delivery have a 30 to 50 percent chance of passing the infection on to their babies during a vaginal delivery, whether or not they have symptoms. The risk is so high because a newly infected pregnant woman has not yet produced the disease-fighting antibodies that could help protect her baby during delivery. Studies suggest that about 2 percent of pregnant women who have not had herpes previously acquire it during pregnancy. Women who have had herpes prior to pregnancy and have a flare-up or silent infection at the time of vaginal delivery have only about a 3 percent chance of infecting their babies. Sometimes, what appears to be a first, severe episode of herpes during pregnancy actually can be a flare-up of an initially silent infection. These women have a low risk of infecting their babies. Unfortunately, currently available blood tests cannot always distinguish between a new and old infection. Some studies also suggest that women who acquire herpes for the first time late in pregnancy face an increased risk of premature delivery and of having a low-birth weight baby. Women with flare-ups of an old infection are not at increased risk of these complications. While most babies get herpes from their mothers at delivery, on rare occasions, a baby can become infected before birth. Occasionally, a baby can also acquire herpes after birth if someone with a cold sore (oral herpes) kisses the baby. Someone with a cold sore should not kiss a baby or touch the baby after touching the cold sore. Herpes infections in newborns often spread to the brain and many internal organs. Infected babies may appear irritable, eat poorly and have seizures.
Steps of HSV Infection and Replication

HSV Structure

HSV is a nuclear replicating, icosahedral, enveloped DNA virus. The HSV envelope contains at least 8 glycoproteins. The matrix or tegument which contacts both the envelope and the capsid contains at least 15-20 proteins.  

Receptor Binding

Herpes simplex virus genome must enter the cell for the initiation of infection. The initial association is between proteoglycans of the cell surface and gC. This is followed by a specific interaction with one of several cellular receptors collectively termed "HVEM" for "herpesvirus entry mediators". These are related to receptors for nerve growth factors and tumor necrosis factor. The association requires the specific interaction with the glycoprotein gD. Fusion with the cellular membrane follows. This requires the action of a number of viral glycoproteins including gB, gH, gl, and gL. The viral capsid with some tegument proteins then migrates to nuclear pores along cellular microtubules utilizing cellular transport machinery. This "docking" is thought to result in the viral DNA being injected through the pore while the capsid remains in the cytoplasm. Some tegument proteins, such asa-TIF, also enter the nucleus with the viral genome.
RNA Transcription during Productive Infection

The transcription of the HSV genome during productive infection occurs with cellular transcriptional machinery and viral promoters utilizing cellular transcription factor binding sites. Most viral transcripts are not spliced. There are two main phases of transcription, early, which takes place prior to genome replication, and late, which takes place upon replicated genomes in virus replication compartments formed in the infected cell nucleus.

Latent Infections

Latent infection and reactivation by HSV takes place in sensory neurons, primarily in the trigeminal ganglia for HSV-1. The process of establishment involves virus entering neurons at the periphery, and the viral genome traveling up the axon and entering the nucleus. While some neurons are destroyed as virus replicates, most neurons are refractory to virus replication and the viral genomes become associated with host histones and persist as mini-chromosomes.
HSV DNA Replication

HSV initiates rounds of DNA replication at one or all of the three origins of replication (Ori 1, Ori 2, and Ori 3). The initial step of HSV DNA replication is denaturation of the DNA at the replication origin with origin binding protein (UL9). The helicase/primase (UL5/UL8/UL52) and single stranded DNA binding proteins (UL29) associate to allow the DNA polymerase/UL42 complex to begin DNA synthesis.

Encapsidation and Nuclear Egress

The procapsid proteins (UL18, UL19 and UL38) assemble around scaffolding proteins (UL26 and UL26.5) that are then digested away. The empty capsid incorporates DNA by means of the action of cleavage/packaging proteins (see the DNA replication animation). The capsid migrates to the nuclear membrane and buds into the lumen between the inner and outer nuclear membrane. This enveloped virion then enters the cytoplasm through fusion with the outer nuclear membrane.
Envelopment and Release

Viral glycoproteins are translated from HSV RNA on the rough endoplasmic reticulum then transported to the golgi body in vesicles to continue the glycosylation process. The glycoproteins are then transported in vesicles to the nuclear or plasma membrane. The HSV capsid associates with tegument proteins then acquires a mature envelope by budding into an exocytotic vesicle. The enveloped infectious virion migrates to the virus modified membrane and is released outside of the cell.²

Treatments

There are three antiviral drugs (acyclovir, valacyclovir, famciclovir) that can shorten the duration of an attack and help alleviate symptoms. When taken preventively, these drugs also reduce the number of attacks in patients who have them often. These drugs usually are not recommended during pregnancy. However, acyclovir (which has not been associated with birth defects in more than 10 years of use) is sometimes recommended for pregnant women with a primary episode of herpes and for those with severe herpes complications. A few studies have suggested that taking acyclovir during the last few weeks of pregnancy may help prevent active infections during labor and delivery in women who have had a primary infection during pregnancy or who have recurrent flare-ups. This treatment may possibly reduce the need for cesarean delivery, but it is not known whether treatment helps prevent herpes infection in the newborn. Acyclovir comes in both oral and ointment forms, but the oral form is more effective.⁶

Valtrex (valacyclovir hydrochloride) is the hydrochloride salt of L-valyl ester of the antiviral drug acyclovir. Valtrex Caplets are for oral administration. Each caplet contains valacyclovir hydrochloride equivalent to 500 mg or 1 gram valacyclovir and the inactive ingredients carnauba wax, colloidal silicon dioxide, crospovidone, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, povidone, and titanium dioxide.⁸

The chemical name of valacyclovir hydrochloride is L-valine, 2-[(2-amino-1,6-dihydro-6-oxo-9H-purin-9-yl)methoxy]ethyl ester, monohydrochloride. It is a white to off-white powder with the molecular formula C₁₃H₂₀N₆O₄•HCl and a molecular weight of 360.80. The maximum solubility in water at 25°C is 174 mg/mL. The pKₐ’s for valacyclovir hydrochloride are 1.90,
7.47, and 9.43. It is rapidly converted to acyclovir which has demonstrated antiviral activity against herpes simplex virus types 1 (HSV-1) and 2 (HSV-2) and varicella-zoster virus (VZV) both in vitro and in vivo.

Chemical structure of $\text{C}_{13}\text{H}_{20}\text{N}_{6}\text{O}_{4}\cdot\text{HCl}$:

Valacyclovir treats herpes zoster infection (shingles) or genital herpes infection. Valacyclovir is not a cure; it will help the sores heal faster and relieve the pain or discomfort. Valacyclovir can also be used to help prevent a genital herpes infection from coming back. Valacyclovir might help prevent genital herpes from being passed on to a partner who does not have genital herpes if it is used with ‘safer sex’ practices. All three drugs prevent the herpes simplex virus (HSV) from synthesizing its DNA, but the new compound (valtrex) target different molecules than acyclovir. They inhibit a complex of three proteins, called the helicase-primase enzyme complex, which plays a key role in DNA synthesis.  

Mechanism of DNA synthesis inhibition by acyclovir and the new drugs.
Episodic or Suppressive Therapy (your choice)

Episodic therapy means taking the medication only during an outbreak to speed healing. Your doctor will prescribe treatment to take at the first sign of prodrome and continue treatment for five days. For first episodes, the healing time can be dramatically reduced. For recurrences, the outbreak can be shortened by about two days. Suppressive therapy means taking an antiviral medication daily as a preventative to keep HSV in check, reduce flare ups and lessen symptoms. Suppressive therapy can lower the number of outbreaks and, for some, prevent them altogether. This therapy also reduces asymptomatic shedding, and research studies are determining whether on-going antiviral medication can help prevent transmission. People who have just been diagnosed with herpes regain a feeling of control over their lives with antiviral medication. It also brings great relief to people who have frequent or bothersome outbreaks. However, many people with herpes don’t feel the need to take medication because their outbreaks are mild. Remember that each person is different.  

Conclusion

The first and most important issue about a disease is to protect yourself against that and try to be safe before trying for treatments but as we all know, sometimes we have to face some of those unpredicted diseases like herpes. The first task is to recognize that Herpes does not change who you are. Although some persons with Herpes may at first feel depressed, angry or damaged, Herpes does not make you a bad person or reflect upon your inherent self-worth. Herpes is a treatable skin infection, with a variety of options to help reduce physical pain and emotional stress.

The second task is educating yourself. Almost everyone eventually finds some way to control Herpes or to feel in control. Paying close attention to body signals, recognizing the prodrome of an outbreak and immediately beginning anti-viral treatment, cool baths, pain relievers and stress relief is the start of control. The more you understand yourself and the virus the more in control you will feel.
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(7) <http://www.hmc.psu.edu/healthinfo/g/genitalherpes.html>

