6th Annual
Science Symposium
May 9, 2000
Paradise Valley Community College
Foreword

The 6th annual Science Symposium was held on May 9, 2000. Students enrolled in General Organic Chemistry II, CHM 236, participated in the event.

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

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

I would also like to dedicate this symposium to my friend and colleague, Dr. Fred G. Stahl, Dean of Instruction. Without his leadership, guidance and friendship, I would have had difficulty with my transition to education from private industry. He is and will always be regarded as a dedicated administrator and friend.

William L. "Hank" Mancini, PhD
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Albuterol
An Inhaled Reliever in Asthma Treatment

by Doreen Beard-Hites

CHM 236

Spring 2000
Abstract

Albuterol (Salbutamol) is a reliever and/or B-agonist that reverses induced broncho spasms in the asthmatic. Its history begins from adrenal extract, adrenal preparations and steroids. Epinephrine, one of the first steroid based compounds derived an entirely new group of anti-asthmatic drugs called Catecholamines. Within this group of drug compounds, Albuterol was born. Its unique hydrophilic character promotes rapid absorption in the airways. And, its chirality produces an active enantiomer of the R-configuration. With newly designed drugs and drug therapies targeted for specific levels of asthma, asthmatics will be able to enjoy a fuller quality of life.

What is asthma? Asthma is a chronic lung disease. An inflammation of the tubes of the lungs causes these tubes, the bronchioles, to be obstructed, making it difficult for air to pass through them. Asthma is essentially caused by an allergic type of reaction of the immune system. It affects approximately 14 million people in the United States. The main symptoms are: difficulty in breathing or "shortness of breath", associated with chest tightness. Wheezing and/or coughing is often present.

It is believed that the genes which cause asthma are in place from birth, but the condition is activated by outside factors such as: house dust, pollen, cat and dog fur, cigarette and tobacco smoke, pollutants from factories, car exhausts, household cleaners, perfumes, exercise and even low temperatures. All of these can cause the tubes in the lungs to narrow which results in difficulty of breathing.

As with most conditions, asthma can be treated with drugs. There are two main types of drugs used for treating asthma, and these are most commonly taken using an aerosol inhaler or nebulizer. The first group of drugs used for treating asthma are collectively called preventers. These medications reduce the sensitivity of the cells in the lungs to allergens, which helps reduce the swelling of the airways. These steroid-based inhaled drugs should be administered every day, if prescribed, even if one feels well. The second type of drug used for treating asthma is known as the reliever, which is the focus of
this written presentation. These drugs relax constricted bronchial muscles to relieve the asthmatic wheezing.

The history of respite care is broad based. Three thousand years ago in China, it is said that Ephedrine, a reputed antiasthma drug, was first formulated. At the other end of the cultural spectrum were ancient Indian civilizations that prosifically used nature's backyard as a medicine cabinet to cure their ailing. Medicinal plants were burned, the smoke inhaled, and respiratory discomfort was relieved. During the turn of the twentieth century, it was thought that cocaine may contribute to vasoconstriction through the action of adrenergic transmitters (by causing their release). However, severe side effects such as: profound depression, an intense desire for another dose (the "cocaine habit"), mental fatigue, restlessness, and irritability were reported. As a matter of fact, the cocaine-induced pain and blockage of nasal passages in some patients was worse than the condition prevailing when therapy had first been initiated. While cocaine became an obsolete decongestant, adrenal extracts were coming to fruition.

George Oliver, a physician in England, claimed to have observed that ingestion of adrenal extract reduced the diameter of the radial artery in his son. His report was of great interest to the Physiological Society of London.

An ophthalmologist named Bates gave a detailed account of two years clinical experience with adrenal extract given topically on the eye. Bates described how to prepare, sterilize, and maintain stability of the extract. He reported on its powerful vasoconstrictor effects. He stated that the extract could be applied daily for several months without irritation and with no ill effects. The adrenal extract replaced cocaine as a decongestant. Nasal spray was the method of delivery. The technology of oral inhalation was years away.

The 1920's gave way to the synthesis of adrenal preparations. Solomon Solis-Cohen, an MD who was also an asthmatic, experimented by substituting adrenal extract with tabloids containing powder of dried adrenal substance. The dose required was up to 6g of dried adrenal substance daily. The improvement in himself and severe asthmatics was striking. Nocturnal attacks became less frequent and less severe. Recovery was not rapid but was continuous. Adrenal preparations were definitely an effective vasoconstrictor and decongestant. Solis-Cohen's work is considered the first to show the effects of epinephrine in the treatment of asthma. However, he did not know the agent at the time and it took 50
years before purified steroids were shown shown to be beneficial in asthmatics.

Epinephrine (also known as adrenaline) was the basis for the development of the "reliever" also known in the scientific community as beta agonist, which reverses induced broncho spasms by causing the release of adrenergic receptors that influence airway blood vessels. This causes dilatation and increased blood flow in the bronchial circulation which subsides the wheezing and chest tightness.

The first compounds of this kind are called catecholamines. Catecholamines are synthesized from the amino acid tyrosine.
In the body, catecholamines are secreted in response to positive or negative stress - everything from extreme pleasure to increased cold to life-threatening danger. Their release into the blood gives the body a rapid bioenergetic boost, increasing metabolic rate and having dramatic effects on several target areas of the body. One of those target areas is the respiratory system. Epinephrine has a profound effect on the respiratory system. It dilates the bronchioles in the lungs, which increases the rate of oxygen delivered to the body’s cells. This is why doctors prescribe epinephrine — to open breathing tubes during asthma attack. The catecholamines also cause smooth muscles of some blood vessels to contract and muscles of other vessels to relax.


Albuterol's molecular formula is: C13 H21 NO3. Its molecular wt. is 239.31. It is 65% carbon, 9% hydrogen and 20% oxygen. Its mp is 157-158. Albuterol is a unique beta-agonist compared to others because it has a more hydrophilic character. When inhaled it appears to be completely absorbed. Experiments in animals suggest that the more hydrophilic compounds like albuterol and terbutaline reach the lung receptors more efficiently. This gives a favorable concentration gradient promoting rapid absorption in the airways. The inhalation technique and the devices used to deliver the drug are of utmost importance for the degree of drug deposited in the airways. Early studies with nebulized albuterol suggested that although there were great losses in the nebulizer, tubing, and
expelled air, the dose that did reach the patient was better targeted to the lung than a dose delivered from a pressurized metered-dose inhaler. And a greater proportion of the nebulized drug was deposited at outer boundaries of the airways.

Albuterol is a chiral molecule. It has a stereo center, by which four completely different substituents are bonded. This chirity brings rise to what is known as racemates. B-agonist are administered as racemates; that is, equivalent mixtures of a pair of enantiomers (2 separate molecules, both having identical molecular formulas. They are mirror images of each other. But, the mirror images are not superimposable, meaning; if the two racemates are placed directly on top of each other they would not be identical). Again, the physicochemical properties of enantiomers are the same but they have different pharmacological potency. Pertaining only to the B-agonists — the more active enantiomer has the R-configuration at the carbon adjacent to the primary ring structure (B-carbon). The less active enantiomer has the S-configuration at the B-carbon. The R/S format determines the configuration of one enantiomer from another. Substituents are prioritized by their atomic number. You look at the chiral carbon, set a numerical priority to the four groups. And then, going from the group that has the highest priority (highest atomic number) to the lowest priority (lowest atomic number) traceable by an arc. If it traces an arc clockwise we refer to it as R. If it traces an arc counterclockwise we refer to it as S.

A newly developed therapy known as the step-wise approach announced by the National Heart, Lung, and Blood Institute-World Health Organization (NHLBI-WHO) is a progressive therapy that is indicated when control of asthma is not achieved. For example, if B-agonists are required more than three times weekly, or if daily anti-inflammatory treatment is required, the step-wise approach is initiated. Step 1: Intermittent; Step 2: Mild Persistent; Step 3: Moderate Persistent; Step 4: Severe Persistent. Each directive formulated for a specific levels of asthma.

With new and improved technologies, it is just a matter of time before future generations will no longer suffer from this chronic disease called asthma.
Works Cited


Methadone Treatments

Dolophine®
80 mg

Michelle Cassidy
Chemistry 236
April 20, 2000
Abstract-
What is methadone? This paper will discuss the main usage for methadone and the usage that is being researched and tested. The methadone treatment programs will be discussed briefly using information obtained from experiments performed by other experts in the field. The usage of methadone as a management for pain will also be discussed briefly.

Introduction-
Methadone hydrochloride, 6-dimethylamino-4, 4-diphenyl-3-heptanone hydrochloride (1) was derived in Germany in the 1940’s. (2) Methadone is a racemic mixture on two enantiomers, d-methadone and l-methadone. The one that is the cause for the pharmacodynamic effects is the l-enantiomer. (3) Methadone is used for detoxification in people who are addicted to illicit drugs. Methadone is an opiate, however, it does not provide the euphoric rush that most illicit drugs do. Methadone actually blocks the effects of illicit drugs, which in turn, causes addicts to not want to take the illicit drug(s). (4)

\[
\begin{align*}
\text{CH}_2\text{CH}_3 & \\
\text{CO} & \\
\text{CH}_3 \\
\text{C} & \text{CH}_2\text{CHN(CH}_3)_2 = \text{HCl}
\end{align*}
\]

Several studies have shown that the use of methadone as a detoxification drug has actually cut down on the risk of AIDS infections due to not sharing needles for injecting illicit drugs such as heroin. (2) The table below shows how many people, by percentages, were hospitalized for various injection-related infections. The data from this table was obtained from a study done using people who were dependent on heroin. (5)

<table>
<thead>
<tr>
<th>Reason for Initial Hospitalization</th>
<th>% Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cellulitis/abscess/osteomyelitis</td>
<td>28.4</td>
</tr>
<tr>
<td>Bacterial pneumonia</td>
<td>22.4</td>
</tr>
<tr>
<td>Trauma</td>
<td>10.4</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>9.0</td>
</tr>
<tr>
<td>Opportunistic infection/HIV</td>
<td>7.5</td>
</tr>
<tr>
<td>Endocarditis</td>
<td>6.0</td>
</tr>
<tr>
<td>Mental status change</td>
<td>6.0</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>4.5</td>
</tr>
<tr>
<td>Other</td>
<td>6.0</td>
</tr>
</tbody>
</table>

HIV = human immunodeficiency virus.
Since methadone is an opioid antagonist with few side effects, it is an ideal pain management drug. Methadone is cheaper than other pain medications and has a longer half-life than other pain management drugs like morphine. Methadone has high lipid solubility, is highly bound to alpha-1-acid-glycoprotein, and is extensively metabolized in the liver to inactive metabolites. Absorption of methadone is almost all in the gastrointestinal tract. It has a half-life of 2 to 3 hours followed by a beta half-life of 15 to 60 hours. (6)

**Regulations**

Methadone is highly regulated by the Food and Drug Administration (FDA) and the Drug Enforcement Agency (DEA) in the United States. The manufacturing, labeling, and dispensing of methadone have to meet the requirements set by both the FDA and the DEA. Since methadone is a narcotic drug, it is considered to be a schedule II controlled substance. This classification of drug means that it is a highly addictive and possibly abuse able.

Some of the regulations set by the FDA for methadone are as follows. There are standards set by the Department of Health and Human Services (HHS) that tell how prescribing and under what circumstances methadone can be prescribed. The state governments, county, may also regulate treatment further and municipal levels. Section 3 of the Narcotic Addict Treatment Act of 1974 requires prescribing doctors be registered each year with the DEA if the physician is going to be prescribing methadone for maintenance or detoxification treatments.

There are three major factors as to why methadone is regulated so highly. Methadone is the only opiate approved for treating opiate-dependent people. This may cause diversion and abuse of methadone. There is no apparent public urging to reexamine the regulations set for methadone even after the regulations were modified in 1980, 1989, and 1993. The final factor as to why methadone is regulated as such high standards is that the methadone treatment programs have not been supported very strongly. (1)

**Administration of Methadone**

Methadone has been studied to see which formulation works better, the oral dosage or the injected dosage. Studies show that the patients who were taken the methadone treatments intravenously had higher occurrences of schizophrenia, depression, medical status, employment and support status, alcohol usage, drug usage, family and social status, and psychiatric status than the patients who took the oral form of methadone. The table below shows the results of the test. This study shows the physical and psychological problems associated with intravenous methadone. (10)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Intravenous methadone (n = 30)</th>
<th>Oral methadone (n = 20)</th>
<th>Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>BPRS schizophrenia score (scale 0-48)</td>
<td>1.2 ± 1.77 (0-6)</td>
<td>0.2 ± 0.41 (0-1)</td>
<td>P&lt;0.05</td>
</tr>
<tr>
<td>BPRS depression score (0-24)</td>
<td>5.5 ± 3 (0-11)</td>
<td>3.8 ± 4 (0-12)</td>
<td>NS (P&lt;0.10)</td>
</tr>
<tr>
<td>ASI, medical status (scale 0-1)</td>
<td>0.36 ± 0.29 (0-0.83)</td>
<td>0.22 ± 0.28 (0-0.78)</td>
<td>NS (P&lt;0.10)</td>
</tr>
<tr>
<td>ASI, employment and support status (scale 0-1)</td>
<td>0.88 ± 0.12 (0.58-1)</td>
<td>0.65 ± 0.24 (0.24-1)</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>ASI, alcohol use (scale 0-1)</td>
<td>0.11 ± 0.14 (0-0.58)</td>
<td>0.06 ± 0.08 (0-0.22)</td>
<td>NS</td>
</tr>
<tr>
<td>ASI, drug use (scale 0-1)</td>
<td>0.33 ± 0.11 (0.13-0.64)</td>
<td>0.23 ± 0.09 (0.09-0.46)</td>
<td>P&lt;0.005</td>
</tr>
<tr>
<td>ASI, legal status (scale 0-1)</td>
<td>0.19 ± 0.21 (0-0.62)</td>
<td>0.21 ± 0.2 (0-0.55)</td>
<td>NS</td>
</tr>
<tr>
<td>ASI, family and social status (scale 0-1)</td>
<td>0.28 ± 0.24 (0-0.85)</td>
<td>0.19 ± 0.23 (0-0.74)</td>
<td>NS</td>
</tr>
<tr>
<td>ASI, psychiatric status (scale 0-1)</td>
<td>0.33 ± 0.21 (0-0.8)</td>
<td>0.16 ± 0.2 (0-0.61)</td>
<td>P&lt;0.01</td>
</tr>
</tbody>
</table>
There are three formulations of methadone used in the United States. They are Methadose Dispersible tablets, Methadose liquid, and Methadone hydrochloride diskets. Studies show that the three different formulations have the same effect when being used to treat drug withdraws. The table below shows the range of the three different formulations and plasma levels for each drug. (11)

<table>
<thead>
<tr>
<th></th>
<th>Diskets</th>
<th>Liquid</th>
<th>Tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma peak, day 4 (ng/mL)</td>
<td>509 (272–1099)</td>
<td>533 (176–1572)</td>
<td>519 (178–1087)</td>
</tr>
<tr>
<td>Plasma trough, day 5 (ng/mL)</td>
<td>226 (121–584)</td>
<td>281 (71–693)</td>
<td>236 (91–773)</td>
</tr>
<tr>
<td>Absolute change, trough to peak (ng/mL)</td>
<td>246 (108–458)</td>
<td>245 (76–908)</td>
<td>251 (50–624)</td>
</tr>
<tr>
<td>Percent change, trough to peak (ng/mL)</td>
<td>97% (27–360%)</td>
<td>97% (24–209%)</td>
<td>95% (39–197%)</td>
</tr>
<tr>
<td>Slope of rise from trough to peak</td>
<td>52 (22–113)</td>
<td>55 (10–386)</td>
<td>46 (14–101)</td>
</tr>
<tr>
<td>Area under the curve, day 4 (ng h/mL)</td>
<td>7,750 (4,042–18,426)</td>
<td>8,615 (2,321–22,919)</td>
<td>7,928 (2,786–18,966)</td>
</tr>
</tbody>
</table>

*Note: n = 18 subjects in each group.
*p = not significant for all differences among preparations.

Very few studies have been done for the rectal administration of methadone. The one study that had data available showed that the rectal administration worked longer and better for most patients. However, this formulation was tested on how well it works for pain management not for detoxification. The patients in the study group were all cancer patience. This test was done by giving one-half the patient an oral formulation and the other one-half and enema. The one who received the enema had the side effects of constipation, nausea, and mild sedation. These are all normal side effects of methadone. The patients who received the oral dosage had to have more methadone sooner than the ones who where given the enema. (6)

For women who are pregnant and going through the methadone treatment program, it is recommended that the woman stay on the methadone throughout the pregnancy because interruption of the treatment could cause a relapse in illicit drug use. In cases like this, the newborn may need to go through withdraws from the methadone. (1)

Methadone is not recommended for children. It is not recommended for nursing mothers either as it may pass on to the infant through the breast milk. Detoxification should not extend 21 days and should not be repeated earlier than 4 weeks after completion of the preceding course. Methadone can be used for relief of pain but will do nothing for relieving anxiety. (12)

**Methadone Treatment Programs-
**
There are many treatment centers for illicit drug dependency in the United States. However, the treatment centers that are more willing to participate in studies for methadone maintenance programs are in New York. The information for these Studies came from the centers in New York.
Methadone maintenance treatment is the most effective treatment for heroin and other opioid dependence, a means for reducing the transmission of AIDS, and the most progressive and misunderstood form of substance abuse treatment. (7) This synthetic narcotic is cheap and lasts longer than morphine. Methadone was found to work as a detoxification drug by accident in a study done at Rockefeller. Researchers put test subjects on methadone before they proceeded to "detox" them. The subjects were beginning to act differently and were not requesting or requiring the drugs they were addicted to. (7)

One study done by two doctors and a representative form a public health services center from 1988 to 1995 showed that methadone treatment is more likely to reduce the use of drugs and prevent HIV transmission. This study showed that the majority of the treatment centers are not using effective doses of methadone. The effective dose of methadone is usually 60 to 120mg per day. These treatment centers are using less than 60mg per day per patient. This particular study showed that the average dose of methadone in 1990 was 40 to 50mg per day. This study also showed that the public treatment centers had longer treatment duration than the private treatment centers. This study looked at three different areas of concern. They were the mix of clients in treatment, the organization of the treatment, and the external and geographical location. The definition of methadone treatment for this study according to the people conducting the study is as follows, "a physical facility with resources dedicated specifically to treating opiate addicts with methadone." (8) The following table shows the average dose per day, the length of treatment in months, the upper limit dose, the decreased amount of the dose, urge for detox, and the client influence. This data is from 1988 and 1990 surveys and has taken into account and adjusted for the people who did not or were unable to participate in the study from 1988 to 1990. (8)

<table>
<thead>
<tr>
<th>Treatment Practice</th>
<th>1988 Data</th>
<th>1990 Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average dose (mg/day)</td>
<td>44</td>
<td>46</td>
</tr>
<tr>
<td>Time in treatment</td>
<td>21</td>
<td>21</td>
</tr>
<tr>
<td>Upper limit dose (mg/day)</td>
<td>78</td>
<td>79</td>
</tr>
<tr>
<td>Percent of decreasing dose</td>
<td>33</td>
<td>35</td>
</tr>
<tr>
<td>Urge to detox</td>
<td>3.0</td>
<td>3.0</td>
</tr>
<tr>
<td>Client influence on dose</td>
<td>3.3</td>
<td>3.4</td>
</tr>
</tbody>
</table>

The data table showed three differences between the groups. They are the units who were unable to participate in the 1995 study had a lower dose level in 1990 than other units. Nonrespondents in 1995 had shorter treatment times in 1990 than others, and ineligible units in 1995 had a lower limit on dose levels in 1990 than respondent units. The units that treat methadone only clients are financially worse and have more severe medical and social problems. Units that have mixed clients are more likely to be ineligible to participate in the study. (8) This research shows that there is geographic variation in treatment practices. The three different surveys indicate that methadone treatment has changed since 1988. This next table shows the difference in treatment among client factors, unit factors, and environmental factors. (8)
<table>
<thead>
<tr>
<th>Predictor variables</th>
<th>1988</th>
<th>1990</th>
<th>1995</th>
</tr>
</thead>
<tbody>
<tr>
<td>Client factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unemployed (%)</td>
<td>45</td>
<td>49</td>
<td>49</td>
</tr>
<tr>
<td>Black (%)</td>
<td>27</td>
<td>30</td>
<td>35</td>
</tr>
<tr>
<td>Male (M)</td>
<td>64</td>
<td>64</td>
<td>63</td>
</tr>
<tr>
<td>Average age (years)</td>
<td>31</td>
<td>33</td>
<td>36</td>
</tr>
<tr>
<td>Methadone clients (%)</td>
<td>65</td>
<td>69</td>
<td>73</td>
</tr>
<tr>
<td>Unit factors (%)</td>
<td></td>
<td></td>
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<td>Staff characteristics</td>
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<td>Staff physicians</td>
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<tr>
<td>Staff ex-addicts</td>
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<td>12</td>
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<td>Parent organization</td>
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<td>Hospital</td>
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<tr>
<td>Community mental health</td>
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<tr>
<td>Free-standing</td>
<td>55</td>
<td>58</td>
<td>52</td>
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<tr>
<td>Ownership</td>
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<td></td>
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<tr>
<td>Public</td>
<td>34</td>
<td>31</td>
<td>35</td>
</tr>
<tr>
<td>Private for profit</td>
<td>9</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Private not for profit</td>
<td>57</td>
<td>62</td>
<td>59</td>
</tr>
<tr>
<td>Service intensity</td>
<td>-0.6</td>
<td>-1.5</td>
<td>-2.6</td>
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<td>Profit margin</td>
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<td>Environmental factors</td>
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<tr>
<td>Northeast (%)</td>
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<td>Midwest (%)</td>
<td>13</td>
<td>16</td>
<td>17</td>
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<tr>
<td>South (%)</td>
<td>26</td>
<td>25</td>
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<tr>
<td>West (%)</td>
<td>21</td>
<td>17</td>
<td>14</td>
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<tr>
<td>Influence of government regulations on treatment practices</td>
<td>3.6</td>
<td>3.3</td>
<td>3.2</td>
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<tr>
<td>Dependent variables</td>
<td></td>
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<td></td>
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<tr>
<td>Average dose (mg/day)</td>
<td>45</td>
<td>46</td>
<td>59</td>
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<tr>
<td>Time in treatment (months)</td>
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<td>19</td>
<td>21</td>
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<tr>
<td>Upper limit dose (mg/day)</td>
<td>78</td>
<td>82</td>
<td>93</td>
</tr>
<tr>
<td>Percentage decreasing dose</td>
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<td>31</td>
<td>22</td>
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<tr>
<td>Urge detox</td>
<td>3.6</td>
<td>3.6</td>
<td>4.1</td>
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<tr>
<td>Client influence on dose</td>
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*The influence of government regulations, time until detox is urged, and client influence on dose are measured with a 5-point extent scale, where 1 = no extent and 5 = a very great extent.

This study shows that effective treatment of methadone does reduce the transmission of HIV. It also shows that the average dose is still under the recommended dose that other studies have shown to be effective. This study also shows that treatment has only increased one month in duration since 1988. (8)

The Office of Alcoholism and Substance Abuse Services (OASAS) regulate the methadone maintenance programs in New York. They define methadone maintenance as, "an outpatient treatment that administers methadone over a period of time to relieve withdrawal symptoms and reduce opiate craving." (9) For their programs, the person must be over 21 years of age and dependent on an illicit drug for one year. If the person is under the age of 21, they must be dependent on illicit drugs for 2 years or longer. The treatment programs in New York are required to provide certain services to their patients. These services are annual medical exams and referrals to appropriate medical services. The centers must also review the case history quarterly for the first year of treatment and semiannually after that. Rehabilitation services that must also be provided are individual or group counseling, vocational training, education programs, legal assistance, mental health, alcoholism treatment, and social services. (9)
Pain management-
Just recently, methadone has begun to be used as a pain management drug. It is still preferred second to morphine though. As mentioned before, methadone is an opioid agonist, has a long and unpredictable half-life, and is absorbed well. These reasons make it a good alternative to morphine as a pain management drug. Methadone does not have the side effects that morphine does either. Methadone does have some side effects. They include mild sedation, constipation, nausea, and proctitis. Methadone provides more effective pain relief and the relief lasts longer than the relief patients get with morphine.

Conclusion-
From the research that has been done, methadone appears to be a very effective drug for getting patients off of illicit drugs. However, I agree that methadone is being used in some cases as a replacement legal drug for an illegal drug. People who have an addiction problem will still have an addiction problem after they are taken off of the illicit drug. It may not be a physical dependency, but a mental dependency. People who are addicted to drugs like heroin tend to develop a mindset that they cannot go on without their “fix”. They may not need the “fix” physically, however, they are still psychologically addicted to taking the drug. Methadone may be better for the person because they don’t physically need or want the heroin, but the person still has the need mentally for it.

I believe that methadone will be used more for pain management for cancer patients over morphine. I do not think the change will happen soon. There are not enough studies being done for the pain management usage of methadone. Until there are more studies for using methadone in this way, it will continue to be linked to heroin addicts as a detoxification drug and not as a drug that can help end suffering in many people.
References:


XENICAL; Another attempt to combat obesity

Prepared for
Dr. Hank Mancini, Instructor Organic Chemistry

By
Karol L. Hess

April 21, 2000
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Abstract

This report pertains to newest pharmaceutical product introduced to combat obesity. The mechanism of action is described as well as benefits and side effects. Details of clinical trials are included along with predictions of future problems associated with the medication.

Introduction

The issue of weight in respect to physical health is a major concern in America today. It is a fact that nearly one-third of America’s population is overweight.\(^1\) Obesity is to be blamed for the poor health of many Americans. For example, obesity is linked to type 2 diabetes mellitus, heart disease, some cancers, and hypertension just to name a few.\(^1\) It has been estimated that obesity can be linked to approximately 300,000 deaths per year\(^1\). With this in mind it is no wonder that obesity related health problems costs number in the billions of dollars every year.\(^1\) Much of this money is spent on weight loss drugs that pharmaceutical companies manufacture. The most common of these are in the “speed” family and include meridia, fastin, redux and the notorious phen phen. The problems with these types of medications have become apparent. Although they speed up metabolism, decrease appetite, and do help those who take it lose weight, they can also cause adverse side affects. Phen phen, for example, is known to have caused heart valvular problems and was taken off the market due to this. In response to these and other problems associated with these medications, pharmaceutical companies are working to synthesize new drugs that exert their therapeutic action in a different manner. These drugs are known as fat blockers.

The first of these types of drugs to appear on the market is orlistat, known as Xenical by its trade name. The FDA approved Orlistat in April of 1999.\(^3\) Some are prematurely calling it the miracle drug of weight loss. Rather than suppress the appetite, orlistat prevents the body from absorbing fats from ingested foods by up to 30%.\(^1,2,3,4\) The lack of these fats results in weight loss. An examination into the mechanism of action of orlistat, clinical studies, its benefits, and adverse effects will show that it may not be a miracle drug at all but simply a tool not to be relied upon by itself to help obese persons with significant health threats gain control of their weight.

Background

Orlistat, produced by Roche Pharmaceuticals in Kingsland New Jersey, was approved by the FDA for prescription use in April of 1999\(^3\). The IUPAC name for orlistat is, (S)-2-formylamino-4-methyl-pentanoic acid (S)-1-[(2s, 3s)-3-hexyl-4-oxo-2-oxetanylmethyl]-dodecyl ester.\(^2\) “It is a chemically synthesized hydrogenated derivative of lipstatin.” The empirical formula for orlistat is C\(_{25}\)H\(_{33}\)NO\(_5\). It contains 4 chiral centers highlighted in fig1.1. “It is a diastereomeric molecule with a negative optical rotation in ethanol at 529nm.” Orlistat is a white crystalline powder that is dispensed in
recommended dosage is 120mg orally three times per day\(^2\). Orlistat is a reversible gastric and pancreatic lipase inhibitor that inhibits the absorption of dietary fats\(^2\).

\[
\begin{array}{c}
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\text{O} \\
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\end{array}
\]

Fig 1.1 (1)

Orlistat is recommended to those who are obese with a BMI (body mass index) greater than or equal to 30kg\(\text{m}^2\), or greater than or equal to 27kg\(\text{m}^2\) for those with additional risk factors such as hypertension and diabetes\(^1,2\). BMI is calculated by dividing weight in kilograms by height in meters squared\(^1,2\). Table 1.1 illustrates BMI of varies heights and weights.

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Table 1.1 (2)

**Mechanism of action**

When fats are ingested most of the lipid digestion takes place in the small intestine\(^5\). Triglycerides and their breakdown products are insoluble in water\(^7\), therefore, bile salts emulsify lipids prior to hydrolysis by lipase\(^6\). After hydrolysis by lipase enzymes triacylglycerols are converted to 2-monoacylglycerols and free fatty acids that are absorbed and used, or stored by the body in adipose tissue\(^6,7\). This process is illustrated in figure 1.2.
Orlistat works as a reversible inhibitor of these lipases by forming a covalent bond with the active serine residue sites of the enzymes\(^2\). The lipases are hence rendered unavailable to hydrolyze triacylglycerols, and the body does not absorb the fats resulting in weight loss\(^1,2\). Systemic absorption of orlistat is minimal, below the limits of detection (less than 5 ng/ml)\(^1,2\).

**Benefits**

Because lipase enzymes are indirectly involved in the uptake of cholesterol, orlistat has also been shown to lower cholesterol levels by 4%-5%, and LDL levels from 5%-10\(^\%\)\(^2\). "Other effects of orlistat include reducing the release of trypsin,
cholecystokinin, and bilirubin and increasing gastric emptying in the presence of a fatty meal. It has also been suggested that orlistat may present benefits to those suffering from type 2 diabetes. There were reported increases in insulin and c-peptide levels following administration of orlistat, but no comparison data was obtained in the administration of a placebo. Contrary to these findings however, during two, 104 week studies both insulin and glucose concentrations declined compared with placebo recipients. Researchers believe that the better glycemic control is related to the weight loss attained by those taking orlistat, and typical increases postprandially of insulin levels may explain the decline of insulin and glucose levels.

In two trials significant reduction of blood pressure was observed in those receiving orlistat. This again might be attributed to weight loss.

Adverse effects

There are several vitamins that depend on pancreatic carboxylester lipase for absorption. These include vitamins A, D, E, K and beta-carotene. While orlistat inhibits the absorption of lipids into the bloodstream, it can also inhibit the absorption of these vitamins. While studies have shown reduction of the presence of these vitamins in subjects, most levels remained within normal limits. Those who dropped below normal limits need only take a vitamin supplement. Although orlistat appears to have many benefits, there is significant side affects documented among test subjects. The most notable of these being gastrointestinal discomfort. Some reported abdominal pain and flatulence, others reported fecal urgency. All reported to some extent oily, fatty fecal evacuation due to the body not absorbing the fats. This can be controlled to some extent by limiting the fat content in the diet.

It has also been reported that orlistat may be associated with an increased risk of gallstone formation. The chemical cholecystokinin plays a role in gallbladder motility. The release of this chemical is dependant upon the presence of free fatty acids. Because orlistat inhibits the ability of the body to produce these free fatty acids there is an increased risk of developing gallstones.

Clinical trials

Clinical trials have been conducted in 8, 12, 24, 52 weeks and 2 year studies. Table 1.2 compiles the results of each. In general it was found that doses greater than 120mg three times per day did not significantly increase the percentage of lipase inhibition. Adjustment of dosage to accommodate weight or sex appears unnecessary. This is because nearly 95% of orlistat is eliminated in the feces. It has also been suggested that increasing the fiber in dietary meals may have an impact on the severity of gastrointestinal side effects.

There has been no studies conducted of peoples of special population, i.e.: pediatric, geriatric, different races, or patients with renal and hepatic insufficiency. "Drug-drug interaction studies indicate that xenical had no effect on pharmacokinetics and/or pharmacodynamics of alcohol, digoxin, glyburide, nifedipine (extended release tablets), oral contraceptives, phenytion or warfarin."
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**Duration:** 8 weeks

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**Duration:** 12 weeks

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**Duration:** 24 weeks

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**Duration:** 52 weeks

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**Duration:** 104 weeks Table 1.2 (1)

**Legend for table:**

Tid – three times per day
Conclusion

Obesity is without a doubt one of the biggest health concerns in the United States today. There have been numerous drugs marketed to help the overweight loss weight. However, the number of obese people continues to grow and include a younger and younger population. It seems unlikely that yet another drug, orlistat, is the answer to the problem.

Although clinical studies indicate that orlistat does increase weight loss, it is unclear if the weight loss is a direct result of reduced fat absorption. Perhaps due to the gastrointestinal side effects, participants were nearly forced to change dietary habits for the better to avoid extreme discomfort. This would certainly be an incentive to take the medication, however, it should be used as a last resort and only for those who are significantly obese with other health related risk factors.

Sadly, it is unlikely that only people within the recommended categories of BMI will be prescribed orlistat. The potential for abuse is high. There is no documentation as to the extent of vitamin loss while using this product over an extended period of time (over 2 years) or of the consequences that persistent oily stools may have on the colon and/or intestinal tract. Until these questions can be answered orlistat should be prescribed with caution and physicians should be sure to thoroughly educate patients about nutrition and exercise in conjunction with medication.
Bibliography


Bacillus Antracis: The Virulence Factors

Jacinta B. Hines

21 April 2000
ABSTRACT

Anthrax was recognized for many centuries as a serious disease of animals and man, one that inflicted great losses in agricultural economies and caused significant disease in humans. Anthrax was a major concern to the pioneers of microbiology, and its study by Pasteur, Koch, Mechnickoff and others established many of the basic principles of infectious diseases. The active form of anthrax protective antigen forms a heptameric ring-shaped oligomer that is believed to represent a precursor of the membrane pore formed by this protein.

The Disease
Anthrax, also called Splenic Fever, Malignant pustule, or Woolsorters' Disease, acute, specific, infectious febrile disease of animals, including humans, caused by Bacillus anthracis, an organism that under certain conditions forms highly resistant spores capable of persisting and retaining their virulence in contaminated soil or other material for many years.

Anthrax, named from the Greek word for coal, is one of the oldest recorded diseases of animals, being mentioned by Moses in Exodus 9:9. Anthrax was the first disease of humans and other animals in which the causative agent was definitely demonstrated as a specific microorganism. Robert Koch isolated the organism in pure culture. He found that dried spores could remain viable for years, even under exposed conditions. Louis Pasteur in 1881 found a bacterial vaccine, which was effective against the organism. He succeeded in vaccinating a herd of sheep against the disease. The natural history of B. anthracis remains obscure.

In comparison with herbivores, humans are moderately resistant to anthrax. Human anthrax is classified as non-industrial when the disease results from close contact with infectious animals, leading to cutaneous anthrax. Those classified as industrial, are employees that acquire the disease in processing plants.

Anthrax in humans occurs as a cutaneous, pulmonary (inhalation), intestinal or oropharyngeal infection. The most common type occurs as a primary localized infection of the skin in the form of a carbuncle. Lesions occur mostly on the face, hands, arms or neck as a small pimple that develops rapidly into a large vesicle with black necrotic center which is a malignant pustule. The pustule ruptures, exposing a black eschar at the base. Cutaneous anthrax is readily amenable to therapy with any number of antibiotics, and is rarely fatal. The pulmonary form (inhalation
anthrax) affects primarily the lymph nodes, lungs and pleura and results from inhaling anthrax spores in areas where hair and wool are processed. About 5 days after inhalation, a viral syndrome develops, followed by severe respiratory distress. The time to death may be as short as 24 hours after exposure. Death is apparently due to oxygen depletion, secondary shock, increased vascular permeability, respiratory failure and cardiac failure. The level of the lethal toxin in the circulation increases rapidly quite late in the disease and it closely parallels the concentration of organisms in the blood.

The organism finds a favorable milieu for growth and is induced to vegetate in the lymph nodes. It then begins to produce an antiphagocytic capsule and at least three proteins, which appear to play a major role in virulence.

**Virulence Toxins**
The virulence of *B. anthracis* for animals and man depends on the production of two recognized virulence factors, the gamma-linked poly-D-glutamic acid capsule, and the three component protein exotoxin that is termed anthrax toxin (Leppla et al., 1999). The capsule appears to protect the bacteria from phagocytosis, and therefore plays an essential role during establishment of an infection. The protein exotoxin may also help to establish an infection by incapacitating phagocytes (Leppla et al., 1999), but its more obvious role is to cause the extensive tissue edema that appears to be a principal cause of death. It is generally accepted that the pathological effects causing death in infected animals are due to the action of the (Leppla et al., 1999).

All virulent strains of *B. anthracis* form this capsule. The gutamyl-polypeptide capsule is itself nontoxic, but functions to protect the organism against the bactericidal components of serum and phagocytes. The capsule plays it most important role during the establishment of the infection and a less significant role in the terminal phases of the disease, which are mediated by the anthrax toxin. Virulent strains of *Bacillus anthracis* produce three distinct antigenic components that are related to a complex exotoxin called the anthrax toxin. Each component of the toxin is a protein that is subject to destruction by the action of moderate heat.

This toxin complex contains three proteins that are individually nontoxic. These are designated protective antigen (PA), lethal factor (LF) and edema factor (EF). Toxic activity is obtained only when the proteins are administered in pairwise combinations. Two different toxic activities are produced. The protein known as the edema factor (EF) is responsible for the flow activity of the toxin, the lethal factor (LF), is the main virulence component and is essential for the lethal effects of the anthrax toxin and the protective antigen (PA), which induces protective anti-toxic antibodies. These three factors exhibit no significant biological activity in an animal. By itself, PA has little or no toxic effect upon cells, but serves to bind cell surface receptors and
mediate the entry of EF and LF into the cell. Edema toxin results from the combination of EF and PA; lethal toxin results from the combination of LF and PA. These toxins result in necrosis of the lymphatic tissue, which in turn causes the release of large numbers of B. anthracis.

Work in recent years demonstrated that PA binds to receptors on eucaryotic cells and mediates the internalization of LF and EF to the cytosol. EF is an adenylate cyclase; it converts ATP to unphysiologically high concentrations of cAMP that cause metabolic perturbations (Leplla et al., 1999). LF was recently proven to be a metalloprotease (Leplla et al., 1999), and it was shown to cleave the mitogen-activated protein Kinase Kinases 1 and 2 (Duesbery et al., 1998). PA remains the principal and essential immunogen in both killed and live anthrax vaccines (Leplla et al., 1999). Therefore, study of anthrax has direct application to development of improved vaccines.

The Lethal factor is a protease and pinpoints its amino acid substrate. Lethal factor may also have a role in inhibiting cancer cell growth by disrupting the mitogen activated protein kinase pathway.

Anthrax Toxin protective antigen crystal structure (Petosa et al., Nature 385:833-838 (1997))

PA crystal structure and function
The structure of PA was solved by X-ray diffraction (Petosa et al., 1997). PA is a long flat protein that is rich in β-sheet structure. Domain 1 (aa 1-258) contains two tightly bound calcium ions, and a large flexible loop that includes the sequence that is cleaved during proteolytic activation. Domain 2 contains several very long strands and forms the core of the membrane-inserted channel. It also has a large flexible loop implicated in membrane insertion. Domain 3 has no known function. Domain 4 is loosely associated with the other three domains and is involved in receptor binding. The structure of PA flexible loop containing the chymotrypsin-sensitive site has the properties of an amphipathic beta hairpin, with alternating hydrophobic and
Sequences from PA family that are known or proposed to form amphipathic hairpins that assemble into membrane-spanning barrel structures. Hydrophobic residues (underlined) will face the lipid bilayer and the alternating hydrophilic residues will face the lumen of the channel. Residues in the central region (SF) form the bend of the hairpin on the cytosolic side of the membrane.

(Leppla et al., 1999)

hydrophilic residues (Petosa et. Al., 1997). In staphylococcal alpha toxin, a similar beta hairpin assembles into a 14-stranded beta barrel where the hydrophobic residues face the lipid and the hydrophilic residues face the lumen of the channel (Leppla et al., 1999). It is reasonable to assume that PA forms a very similar structure, and a model has been presented based on the similarity to the alpha toxin.

Mechanism of the anthrax toxin
The pathogenicity of B. anthracis depends on two virulence factors: a poly-D-glutamate ploypeptide capsule and a toxin produced in the log phase of growth. Host proteases in the blood and on the eukaryotic cell surface activate protective antigen by cutting off a segment, exposing a binding site for LF and EF. The activated polypeptide binds to specific receptors on the host cell surface, thereby creating a secondary binding site for which LF and EF compete. The complex is internalized by endocytosis and following acidification of the endosome, the LF and EF cross the membrane into the cytosol via PA-mediated channels. This mechanism is sometimes referred to as a prepore to pore conversion.

Toxin internalization and translocation
Proteolytically activated PA can bind LF and EF with high affinity. The anthrax toxin enter cells by receptor-mediated endocytosis and pass through acidic vesicles, because the effects of the toxins are blocked by pharmacological agents that block this process. The effects of the edema toxin are blocked by cytochalasin D and by amines (Leppla et al., 1999) and the effects of lethal toxin are blocked by amines (Leppla et al., 1999) and by specific inhibitors of the endosomal proton pump (Leppla et al., 1999).

It is clear from the research that the anthrax toxin is the principal protein virulence factor of B. anthracis. Strains unable to produce the toxin are avirulent, and animals are protected against infection only if they
posses antibodies to the toxin. Other bacterial pathogens depend on

**Figure above:** steps in anthrax intoxication 1. PA binds to a host cell receptor, 2. Furin cleaves and releases PA; 3. PA forms a heptamer, 4. The toxic enzymes bind to the PA, 5. Receptor-mediated endocytosis; 6. Acidification of the endosome leads to membrane insertion of PA; 7. Translocation of the toxic enzymes into the cytosol. LF, EF.


The new knowledge about toxin structure and function will be useful in design of candidate vaccines. However, much need to be learned about the mechanisms of immunity to anthrax before the knowledge about toxin structure can be used in ration design of improved immunogens.

There remain important questions about how the edema and lethal toxins act in cells and animals to cause the pathology associated with anthrax infection. We can anticipate important progress in connecting the initial catalytic steps, in particular the proteolytic action of LF, to the subsequent pathologic effects in cells and tissues. The fact that these protein exotoxins for their virulence, but in most cases the toxins have a less complex design.
dominant virulent factors, LF and EF, act by enzymatic mechanisms offers the possibility that small molecule inhibitors might be developed to block these effects.

**Vaccines**
Anti-anthrax serum, arsenicals, and antibiotics are used with excellent results. Antibiotic resistant strains of *B. anthracis* occur naturally and can be readily isolated in laboratories.

Ciprofloxacin and Doxycycline are the antibiotic choice for many experts. The only licensed vaccine is produced by the Biopart Corp. of Lansing, Mich.

Arthur Friedland, an anthrax researcher in the US Army, cautioned that more than one antitoxin might be needed to disable anthrax. The lethal factor toxin may not be the only culprit in the devastating disease. Other researchers have found that the systemic inflammatory response that occurs after the toxin is discharged ultimately kills the patient. It is unclear if a lethal factor inhibitor would prevent this response.

It is possible that the US has produced other vaccines and that these were used to vaccinate troops during the Gulf War of 1991. If anthrax-causing agents are being developed as weapons, then it is likely that biologically engineered varieties of the *Bacillus* are being used.

**Conclusion**
Anthrax has been a challenge for industries for many years. To comprehend the strategies used to control anthrax, it is important to understand the cycle of infection. Legislation had once required that contaminated livestock be burned or buried in calcium oxide. However, with today’s environmental concerns, it is believed that the past burials in calcium oxide have left contaminated sites with viable anthrax spores. It is hoped that this has changed. There is no evidence of person-to-person transmission of Anthrax. However, with the current concern over potential germ warfare in the Middle East, the US has all US military troops vaccinated against anthrax.
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Propecia

Lacramioara Iovin
Organic Chemistry 236
Dr. William Mancinni
April 21, 2000
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Abstract

Propecia, the first drug approved by the FDA to maintain (and sometimes regrow) hair which is lost as result of androgenic alopecia. It influences the hair growth cycle and increases the length and diameter of the existing hair. Propecia may have minimal side effects for men, however, women who are or may potentially be pregnant should not come in contact with the drug.

Hair plays an important role in defining one’s self-image. Men have been willing to try almost anything and to spend excess amounts of money in search of a cure for male patter baldness. In total, an estimated nine hundred million dollars are spent each year on the efforts to regrow hair (2). Clearly, a large population of men eagerly awaits remedies for the distressing symptoms of male pattern baldness.

Background

The growth of hair is cyclic which is divided into three phases: the first phase is anagen, which lasts two to six years; the second phase is catagen, which last for two to three weeks; and the third and final phase of the cycle is telogen, which lasts two to three months. At the end of the telogen, the hair begins to shed, which initiates the start of the next cycle.

Every day, an estimated one hundred hairs are shed form the head in the telogen phase and about the same number of follicles enter the anagen phase (5). The duration of the anagen phase determines the length of the hair. The thinning of the hair usually begins between the ages of twelve and forty years in both sexes, and approximately half of the
population expresses this trait to some degree before the age of fifty(5). Hair loss is a condition known as androgenetic alopecia, or commonly referred to male pattern baldness. As androgenetic alopecia develops, the hairs in the affected areas of the scalp become shorter, finer and less pigmented with successive growth cycles. This androgenic alopecia seems to be associated with the presence of dihydroxytestosterone (DHT) and 5-alpha-reductase, metabolites of testosterone.

5-alpha-Reductase

There are two isoforms of 5-alpha-reductase enzymes. Type I enzyme has an optimal pH level between 6 and 9, and it is present in all skin tissue. Type II enzyme is found primarily in prostate, seminal vesicles, and epididymes that has an optimal pH level of about 5.5 (7). Propecia (1 mg of finasteride) is a competitive inhibitor of type II 5-alpha-reductase and can lower DHT levels in tissue.

The inhibition of both isozymes by finasteride is accompanied by the reduction of the inhibitor to dihydrofinasteride and adduct formation with NAPD+. The turnover for the enzyme complex is slow, approximately thirty days for the type II enzyme complex and fourteen days for the type I complex (1,6).

The structural requirements for synthesis of 5-alpha-reductase inhibitors include stable configuration in the A ring of the steroid molecule that imitates the transition state in the conversion of testosterone to dihydrotestosterone (figure 2) (6). This allows the inhibitors to bind tightly to the active site of the enzyme.

![Figure 2. The structures of Testosterone, Dihydrotestosterone, and the 5-alpha-Reductase Inhibitor Finasteride.](image)

History

Finasteride was originally used for the treatment of benign prostatic hyperplasia and was marketed under the trade name of Proscar by Merck and Co. Proscar is 5 mgs of
oral finasteride, where as Propecia is 1 mg of oral finaseride (3). It was during and after the original studies that it was realized that finasteride could induce hair growth, further studies were initiated which resulted in the approval of Propecia being submitted for approval in December of 1996 and approved in December of 1997.

Description

The active ingredient in Propecia is finasteride, a synthetic 4-azaseroid compound. The chemical name of finasteride is (5-alpha, 17-beta)-N-((1,1-dimethylethyl)-3-oxo-4-azaandrost-1-ene-17-carboxamide. It follows the empirical formula of C_{23}H_{36}N_{2}O_{2}, and its molecular weight is 372.55. The structural formula for finasteride is

![Structural formula of finasteride](attachment:image.png)

Finasteride is a white crystalline powder with a melting point near 250 degree Celsius. It is freely soluble in lower alcohol solvents and in chloroform, but it is practically insoluble in water. Propecia tablets for oral administration are film coated tablets which contain 1 mg of finasteride and the following inactive ingredients; lactose monohydrates, microcrystalline cellulose, pregelatinized starch, sodium starch glycolate, docusate sodium, magnesium stearate, hydroxypropyl methylcellulose 2910, hydroxypropyl cellulose, titanium dioxide, talc, yellow ferric oxide, and red ferric oxide.

Pharmacokinetics

Once an oral dose of 14C-finasteride was ingested in a man, an average of 39% (range of 32-46%) of the dose was excreted in the urine in the form of metabolites (3). The major compound isolated from urine was the monocarboxylic acid metabolite. The t-butyl monohydroxylated metabolite on the side chain has been isolated from plasma. Approximately 90% of circulating finasteride is bound to plasma proteins (3,6,4). These metabolites did not possess more than 20% of the 5-alpha-reductase inhibitory activity of finasteride.
In a study conducted by the Merck & Co., fifteen healthy male subjects, the mean biological availability of finasteride 1 mg tablets was 65% (range of 26-170%), based on the ratio of AUC relative to a 5 mg intravenous dose, which was infused over a 60 minute time period. Following intravenous infusion, the mean plasma clearance was 165 ml per minute (6).

There is a slow accumulation phase for finasteride after multiple dosing. Following a steady state dose of 1 mg a day, the maximum Finasteride plasma concentration averaged 9.2 ng/ml (range of 4.9-13.7 ng/ml) and was reached 1 to 2 hours after the administered dose (6, 7).

Clinical Studies

The effectiveness of Propecia has been evaluated in three studies involving a combined total of 1,879 men with mild to moderate androgenetic alopecia between 18 and 41 years of age (3). All the men in these studies, regardless if they were treated with Propecia or placebo, were instructed to use a specified, medicated tar-based shampoo (Neutrogena T/Gel Shampoo). Two of the three studies included men with predominantly mild to moderate vertex hair loss. The third study enrolled men having mild to moderate hair loss in the anterior mid-scalp with or without vertex balding (8).

Out of the men who completed the first 12 months on the two vertex baldness trials, 1,215 were elected to continue in a double-blinded, placebo-controlled, prolonged 12 month study. There were 547 men who were receiving Propecia for both the initial and prolonged (up to 24 months) and 60 men were receiving placebo for the same amount of time. In addition, 65 men who were received Propecia for the initial 12 months followed placebo for the prolonged 12 month period, and 543 men who were received placebo for the initial 12 months followed by Propecia in the prolonged 12 month period (Figure 4) (5, 8).

*Figure 4*

- Mean Change in Hairs from Baseline
- PROPECIA (N=679)
- Placebo (N=672)

† Pooled data from vertex hair loss studies (mean baseline hair count = 676)
‡† At the end of initial 12-month period, treatment switched from PROPECIA to placebo (- - - - PROPECIA/Placebo) or from placebo to PROPECIA (------- Placebo/PROPECIA).
In these two studies in men with vertex baldness, a significant increase in hair count were demonstrated at six and twelve months in men treated with Propecia, as opposed to significant hair loss from the hair baseline was demonstrated in those treated with placebo. After twelve months there was a 107-hair count difference from placebo. Hair counts were maintained in those men who took Propecia for twenty-four months, while the placebo group continued to show progressive hair loss (2,8). After 24 months, a difference in 138 hairs resulted between the treatment group within the same area. Patients who switched from placebo to Propecia at the end of the initial twelve months had an increase in hair count at twenty-four months. A change of treatment from Propecia to placebo at the end of the initial twelve months resulted in the reversal of the increase in hair count twelve months later, at twenty-four months (3,5,6,7).

At twelve months, 14% of men treated with Propecia had hair loss (any decrease in hair count from baseline) compared with 58% of men in the placebo group. In the men treated for up to twenty-four months, 17% of the men treated with Propecia demonstrated hair loss compared with 72% of those in the placebo group.

Dosage and Administration

The recommended dosage is 1 mg once a day, it may be taken with or without meal, since food has no effect on the reaction rate of the drug. In general, Propecia needs to be used on a daily bases for three months before any results can be visible, since hair grows only about half an inch each month. Continued use is recommended to sustain benefits. If the treatment is discontinued the hair obtained during the twelve month period will thin out and shed (1,8). The dosage administered to a patient needs no adjustment on the basis of age or renal function. Since it is metabolized in the liver, caution should be used in men with abnormal liver function. Men who are of age sixty or older, finasteride may not be an effective treatment for male pattern hair loss, because type II 5-alpha-reductase activity in the scalp may not be as high as in younger men (5).

Adverse Reactions

Propecia has been well tolerated in all studies, however the following clinical adverse reactions were reported to be drug related in patients treated with Porpecia or placebo for twelve months, 1.8% of patients treated with Propecia reported a decreased libido, compared with 1.3% of patients in the placebo group, erectile dysfunction were also reported in 1.3% of patients taking Propecia, as opposed to 0.7% (3,8). Other reactions included itching, hives, swelling of the lips and face, breast tenderness and enlargement. These adverse effects gradually disappeared during prolonged treatment and disappear completely in days or weeks after the treatment is discontinued.

Propecia is a drug which should only be used by men. Although alopecia occur as often in women as in men, however, the use of Propecia is constricted in women when they are or may be potentially pregnant. Due to the ability of 5-alpha-reductase inhibitors
to inhibit the conversion of testosterone to DHT, finasteride may cause abnormalities of the external genitalia of a male fetus, a condition referred to as hypospadias. Hypospadias is a birth defect found in boys in which the urinary tract is not at the tip of the penis, a condition which occurs in about 8 of 1000 male births. Correction of hypospadias involves undergoing surgical procedures.

Women should not handle crushed or broken Propecia tablets when they are pregnant or potentially pregnant because of the possibility of absorption of finasteride and the subsequent potential risks to the male fetus. Propecia tablets are coated and will prevent contact with the active ingredient during normal handling, provided that the tablet is intact (4).

In female rats, low doses of finasteride was administered ranging from 100 micrograms/kg/day to 100 mg/kg/day which resulted in dose dependent development of hypospadias in 3.6 to 100% of male offsprings with decreased prostatic and seminal vesicular weights. The changes described above are expected pharmacological effects of Propecia. However, no abnormalities were observed in female offsprings exposed to any dose of finasteride.

Conclusion

The treatment of hair loss has been advanced by Propecia. This modestly effective medical treatment for male pattern baldness appear to be safe, since the minimal side effects are outweigh by the benefits, hindering hair loss and hair growth. Propecia is going to become extremely popular in the near future.

The future also foreshadows a Propecia like drug made especially for androgenetic alopecia in women, which will not only help the hair growth process, but also erase any fears that a women or pregnant women might posses.
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Ecstasy

by Camille Knudsen

April 21, 2000
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Abstract

Ecstasy is the common name for a drug that has caused several deaths, in the last decade. It is used as a party drug by youth who attend raves throughout the world. The effects of this drug are wonderful at first, but in the long run they can cause permanent damage to the brain which can lead to death. This paper will discuss the history, manufacture, effects, synthesis, infrared spectroscopy, stereoselectivity, and neurochemistry of Ecstasy.

History

Ecstasy is the new hot drug on the black market. In 1914, the drug was used as an appetite suppressant. Ecstasy became popular in the 1980's as part of the rave culture in the United Kingdom. One to one and half million people use Ecstasy every weekend.10 There are many other names that refers to the drug Ecstasy, Such as E, Adam, X, and Empathy. Other mixtures of drugs are used in place of Ecstasy. A mixture of LSD and amphetamines or caffeine is sold as Ecstasy.9

The chemical name of Ecstasy is 3,4-methylene-dioxy-N-methylamphetamine or Methyleneoxyamphetamine (MDMA.) Even though amphetamine is in the name, MDMA does not contain amphetamine. MDMA is a compound not a mixture. The numbers 3, 4 indicates the position of the substrates of the molecule. An isomer can be easily formed by rearranging the substrates (figure 1).9

![Image of Ecstasy molecule]

* chiral

Figure 1

MDMA is a white, crystalline solid and does not decompose in the environment, giving the drug a long life. It is soluble in water and the taste is bitter and strong.9

Manufacture

There are no health benefits to manufacture MDMA. Manufacturing MDMA is illegal. When manufacturing is complete, the end product in 80% to 90% MDMA. The weight of MDMA is 100 mg to 600 mg. When color is added to the pill form of MDMA, it seems that there are other active ingredients, but actually the combination of the different colors gives it that appearances. Since MDMA is poorly manufactured common
drugs such as aspirin are sold on the streets as Ecstasy. All that is done to the pill is the removal of the marking. There are two other forms other than the pill form, loose powder or capsules.  

Effects

There are positive and negative effects taking MDMA. The effects of the drug will start 20 minutes to one hour after taking the drug. The positive effects are: feeling a rush like 'butterflies in the stomach', calm and happy. These feelings start as a tingling feeling lasting for four to six hours. It can raise blood pressure and heart rate, which can diminish the appetite. A few days later a user can be depressed, moody, tired, and gain appetite back. The danger of the drug is its long term effects. MDMA can damage the overall health of a user. Studies in Britain show that Ecstasy can permanently damage brain cells. If the drug is taken in excessive amounts, chronic brain damage can occur. The amount of enzymes for breaking down MDMA in the body is different for each individual. The effects come quickly for users who have a high account of enzymes. Users who have a low account of enzymes take a larger amount to feel the effects, which increase the dangerous health side effects.

MDMA has several effects on activity. One is the duration of action of MDMA is lessened. Another is the overall effects of MDMA are less powerful and the hallucinogenic quality is destroyed. To reduce the harmful effects of MDMA, the structure is altered. A mechanism releasing endogenous monoamine neurotransmitters can change the structure of MDMA.

Synthesis

\[
\begin{align*}
\text{MDA} & \quad \text{NH}_2 \\
& \quad \text{Me} \\
\text{Me} & \\
\text{Me} & \\
\text{MDMA} & \\
& \quad \text{NH} \\
& \quad \text{Me} \\
& \quad \text{Me} \\
\end{align*}
\]

* Tritium

Figure 2

A N-alkylation was performed on the free base of MDA using tritium (\(^3\text{H}\) methyl iodine), the methyl group becomes positive, the nitrogen loses the hydrogen and the methyl group come in bonding with the nitrogen, giving the product MDMA (figure 2).
Figure 3

There are several steps in preparing the drug MDMA. As shown in Figure 3, the compound that starts the reactions is piperonal. The piperonal reacts with a Grignard reagent to get compound four. Compound four is then oxidized with potassium hydrogen sulfate and heat to produce compound five. The next reaction occurs in two steps. First, it reacts with acid; second, with alcohol and heat. This oxidizes compound five into compound six. Using ammonium acetate and sodium cyanoborohydride with compound six produces a mixture of MDMA (2a) with compound six. Then that mixture reacts with a methyl which attaches to the MDMA. Compound six is reduced with (R) or (S)-a-methylbenzylamine and W-2 Raney nickel. The intermediates N-a-phenylethylamines 7a is then catalyzed by PD-C. This produces the enantiomers of the primary amines 1a. The primary amine is then rearranged to their N-formyl derivatives and reduced with lithium aluminum to get the enantiomers of MDMA (2a). 7

Infrared spectroscopy

Figure 4 8
Structure of MDMA is determined by the use of infrared spectrum. There are distinct peaks to give the functional groups of the compound. The numbers on the bottom of the graph are the wavenumbers (cm⁻¹). These numbers help in determining the composition of the compound and the arrangement. There is a strong peak at 3000 cm⁻¹ which is the aromatic. The ether that is attached to the aromatic has a strong peak at 1250 cm⁻¹ and one at 1050 cm⁻¹. The arrangement of the substrates on the aromatic are unsymmetrical, this shows several peaks at 1650 cm⁻¹, 1500 cm⁻¹, 1000 cm⁻¹, 850 cm⁻¹, and 850 cm⁻¹. The secondary amine has a weak peak at 1580 cm⁻¹ and a medium peak at 1150 cm⁻¹. Lastly, the methyl group shows a medium peak at 1400 cm⁻¹.

Stereoselectivity

A racemic mixture is formed by the synthesis. To separate the R(-) and S(+) of MDMA, HPLC is used with chiral column. The retention time of the S (+) MDMA was 17.9 minutes and the retention time of the R(-) MDMA was twenty minutes. The optical resolution of the mixture in 1% ethanol solution at 28 degrees Celsius is +9.4 degrees Celsius for S(+) MDMA and -6.7 degrees Celsius for the R(-). Radiochemical purity is also found by the use of HPLC.⁴

Separation is done by placing a mixture of MDMA solution and methyl chloride onto the HPLC. The fractions were compiled and evaporated(figure 5).⁴

Figure 5

The enantiomers show different properties. The R(-) is not as strong of a pharmacodynamic agent as the S(+) enantiomer. This has been proven, the substrate interactions show chiral specificity when enzyme enantiomers are synthesized.²⁵

To determine the stereoselectivity of the drug, rats and mice brains are used in studies. In rats, the S(+) enantiomer is found to effect the 5-HT neurotoxicity compared
to the R(−) enantiomer which does not. The 5-HT is a transmitter system in the brain that releases HT. This can cause effect on metabolism and cause hyperactivity.  

A study was conducted to find which enantiomer of MDMA and its metabolites were more concentrated in the frontal cortices, hippocampi, and the whole brain. In figure 6, the graphs show that the S(+)- is in lower concentration than the R(-) enantiomer. There is very little difference of the concentrations in the frontal cortices, hippocampi, and the whole brain.  

---

**Figure 6**

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**Neurochemistry**

MDMA targets the 5-hydroxytryptamine (5-HT) and decreases the level. The 5-HT is released from presynaptic vesicles. After three hours the drug has been injected, more than 80% of 5-HT has depleted. Within twenty-four hours the brain concentrations of 5-HT are restored. Tryptophan hydroxylase (TPH) activity also decreases, and the concentration is reduced in the frontal cortices and the hippocampi for two weeks or longer.
Some species are sensitive to MDMA in different ways. A dose of 10 mg/kg of MDMA in rats cause short and long term effects in TPH activity and 5-HT, whereas in mice there was no effect which a dose of 15mg/kg. The metabolic route in rats is via ring para-hydroxylation. In mice, there are two metabolic routes, side-chain deamination and ring hydroxylation, rejecting the drug faster from the brain. This shows that mice are insensitive to the effect of the drug.6

The effects of neurotoxicity is unknown in humans. There is no concrete clinical evidence to test the 5-HT levels in the brain. Until experiments can be performed with reliable data, MDMA create helpful tools for neurochemists and possible health dangers of human users.5

Conclusion

The effects of MDMA in the brain are still unknown. More testing on humans needs to be done. When the mechanics of MDMA in known to the public, there will be a decline in the use. MDMA will always be around since this drug gives good effects, but hopefully people will look for the good effects in something else that does not kill. If life is to throw away, then why is life given to us.
Work Cited


Thalidomide: Black Scar or Ray of Hope?

Prepared for
Dr. Hank Mancini
Paradise Valley Community College

by
Elizabeth Mansolf

April 21, 2000
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Abstract

This scientific paper discusses the drug thalidomide. In the past, thalidomide had disastrous effects on people and society but is presently being researched further for use in the treatment of a multitude of diseases and conditions. The structure and properties of thalidomide are also explained.

I. Introduction

Thalidomide—this drug name conjures horrible images of malformed babies, with shortened limbs, loosened skin, and deformed faces, in the minds of anyone alive during the early 1960s. Thalidomide was administered to pregnant women as an anti-nausea drug in Europe and other countries in the world; fortunately, it was not distributed in the United States. Tragically, many babies were born with devastating and life threatening defects due to this drug. Since that time, thalidomide has been a black spot in the medical and pharmaceutical history.

With the advances in science and medicine, thalidomide has been researched more thoroughly. The structure and properties of this drug have been identified. Using this information, scientists have discovered that thalidomide is useful in treating a wide range of diseases. Despite the initial failure of thalidomide, new information regarding its structure and properties have helped in the conclusion that thalidomide is effective for treating illnesses such as myeloma blood cancer, oral ulcers, and cachexia.

II. Background

Thalidomide has been a controversial medication since it was synthesized in 1954. In Germany, an event took place that changed the medical and pharmaceutical community. Wilhelm Kunz, a pharmacist working for Chemie Grunenthal, synthesized a new organic compound while trying to make a new antibiotic. Grunenthal, a drug manufacturing company, labeled this new molecule K17. Laboratory testing of the drug on animals began immediately upon discovery and was found to have sedative properties. A paper describing the pharmacological and toxicological activities of thalidomide in comparison with other sedative drugs, such as phenobarbitone, was written by Kunz and two of his colleagues, Keller and Mueckter. This paper showed that the animals exhibited no adverse side effects from thalidomide. These findings prompted the onset of clinical trials in humans.

In 1955, clinical trials of thalidomide began with the initial understanding that thalidomide was non-toxic. At first, patients only experienced minor side effects such as constipation. For example, Dr. Herman Jung reported, “We have a substance that, at the correct dose level, has no undesirable side effects.” As the trials continued, reports came out that described significant
side effects caused by thalidomide. They included giddiness, nausea, buzzing in the ears, constipation, a "hangover" effect, and allergic reactions. Amazingly, Grunenthal released the medication in 1957, sold it over the counter, and touted that the drug was "completely non-poisonous and safe."³ This proved to be a disastrous move for Grunenthal.

Grunenthal released thalidomide although unfavorable and potentially severe side effects existed. The company was distributing a "liquid or suspension version of thalidomide on the market called Contergan Saft and was pushing it as a safe and reliable sedative for children."³ Dr. George Somers, a pharmacologist, discovered that this liquid thalidomide was actually poisonous because thalidomide is more readily absorbed by the body when it is mixed with sugar.¹ It was found that the original version of thalidomide was not toxic because it was not easily absorbed by the body. This was the first concrete evidence that thalidomide was not completely safe.

Thalidomide had been exported to 11 European, seven African, 17 Asian, and 11 North and South American countries before reports of serious side effects surfaced. Peripheral neuritis, a "condition of progressive neurological impairment that begins in the toes as a tingling sensation, numbness, and cold, progressing to muscular cramps, weakness, and impairment,"² was the first serious effect noted to be caused by thalidomide. "In 1962 in Germany—where thalidomide was available without prescription—it was estimated that 40,000 people suffered nerve damage."² Although peripheral neuritis is a debilitating and sometimes irreversible condition caused by thalidomide, it was mild in comparison with other side effects of this dangerous drug.

Other severe side effects were observed. Internal damage was caused. An example of this damage is anal atresia: it is a condition in which the anus is closed. Brain damage was another extremely serious side effect. Babies exhibited slippage and reddening of the skin. Furthermore, kidneys, ears, eyes, and genitals were malformed due to thalidomide.

Thalidomide caused a much more severe effect called phocomelia. Phocomelia is a malformation in which "the hands, feet, or both start from the main joint (shoulder or hip), like the flippers of a seal."² A phocomelia outbreak occurred in 1960-1. Initially, thalidomide was not connected to the outbreak. This may have occurred because thalidomide was marketed under a total of 51 names, including Distaval, Contergan Saft, and Softenil.¹ According to Muggleton, "Only 410 babies survived in the United Kingdom, contributing to a world total of 10,000. As 40% of the original group of babies died, this figure may have been much higher."² This outbreak occurred because doctors administered thalidomide to pregnant women as an anti-nausea medication.
Consequently, thalidomide was pulled from the market in December 1962. Figure 1 shows a picture depicting the characteristics of phocomelia.

The first thing to notice is the features of intrauterine fetal demise: skin slippage and reddening. These features are those of maceration and not trauma or birth defect. Note the shortened lower extremities, known as phocomelia. It was idiopathic in this case, but in the 1950's the drug thalidomide was responsible for many cases when pregnant women took it. Thus, it is very important that pregnant mothers be advised that drugs (including cigarette smoking and alcohol consumption) may have profound effects on the fetus.
In 1994, a study was conducted which determined that thalidomide also causes autism. Two scientists, Miller and Stromland, were studying autism and the factors that cause its occurrence. “All their subjects—Swedish adults born in the late 1950s and early 1960s—exhibited some of the malformations for which thalidomide is infamous: stunted arms and legs, mis-shaped ears and thumbs, and neurological dysfunctions.”

Scientists now understand which organs develop at each stage of gestation and are able to determine the exact days during which a malformation can occur. “Because motor neurons develop at the same time as the external ears, one might predict that the thalidomide victims with autism would also suffer from dysfunction of the cranial nerves. They found that all the subjects with autism had abnormalities of eye movement or facial expression or both.”

Figure 2 is a timeline that shows on which day of gestation that thalidomide affects different organs.

### Figure 2

**Thalidomide Timeline**

| Age of embryo (days) | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29 | 30 | 31 | 32 | 33 | 34 | 35 | 36 |
|----------------------|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|
| Damage caused by thalidomide exposure at this time | MISSING EARS | SMALL EARS AND OTHER EAR MALFORMATIONS | MISSING OR SMALL THUMBS | THUMBS WITH AN EXTRA JOINT | STUNTED ARMS | STUNTED LEGS |

### III. Synthesis

A new organic compound was synthesized in 1954 with the molecular formula, C_{13}H_{10}N_{2}O_{4}. It is commonly known as thalidomide: the chemical name is N-(2,6-Dioxo-3-piperidinyl) phthalimide or 2-(2,6-Dioxo-3-piperidinyl)-1H-isooindole-1, 3(2H)-dione. The system is a tri-cyclic, chiral molecule whose molecular weight is 258.233 grams. Since it is chiral, it readily racemises or exists in a 50/50 mixture of its enantiomers. This chirality is the reason for its high teratogenicity or toxicity in the human body. It was determined that (R)-(+-)thalidomide causes malformations whereas (S)-(--)thalidomide passes through the system without any interactions. The exact mechanism of the reaction that takes place is still not fully understood even after approximately 50 years of research. Figure 3 shows thalidomide’s structure and chiral carbon.

### Figure 3

![Chiral Carbon](image-url)
The tragic effects of thalidomide overshadowed its potential for treating other illnesses. One disease thalidomide treats with an extremely high degree of effectiveness is erythema nodosum leprosum or leprosy. According to the *American Heritage College Dictionary*, leprosy is "a chronic, mildly contagious granulomatous disease...characterized by ulceration of the skin, loss of sensation, paralysis, gangrene, and deformation." In 1964, Sheskin conducted a study that proved thalidomide reduces the actual reaction of leprosy. This surprised Sheskin because he was only trying to reduce the pain associated with leprosy. "This is now its [thalidomide] major use worldwide, its effectiveness being greater that 90%." Thalidomide treats leprosy, and other diseases, effectively.

Along with treating leprosy, thalidomide is showing hope in the treatment of several HIV-related conditions. These include aphthous ulcers and cachexia. Aphthous ulcers can occur in the mouth, pharynx, and esophagus. They are often very painful and can interfere with eating. In May of 1997, a study, published in the *New England Journal of Medicine*, concludes, "thalidomide is an effective treatment for aphthous ulceration of the mouth and oropharynx in patients with HIV infection." The AIDS Clinical Trial Group also conducted a study regarding the treatment of mouth ulcers with thalidomide. The results of this study are shown in Figure 4.

### Table 2: Thalidomide and Mouth Ulcers

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Number in group</th>
<th>Complete response at 4 weeks</th>
<th>Complete OR partial response at 4 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thalidomide</td>
<td>23</td>
<td>14 (61%)</td>
<td>21 (91%)</td>
</tr>
<tr>
<td>Placebo</td>
<td>22</td>
<td>1</td>
<td>4</td>
</tr>
</tbody>
</table>

Thalidomide treats cachexia, another HIV-related condition. According to Larkin, cachexia is "a syndrome of progressive weight loss and muscle wasting that occurs in HIV disease and cancer." Larkin reports on the findings of a study conducted by Gilla Kaplan, an immunologist from Rockefeller University. "Thalidomide seems to be at least as good as some of the other drugs that reverse wasting in terms of the percent of gain that is lean-body mass, not just fat or fluids," says Kaplan. The AIDS Clinical Trials Group conducted a study on thalidomide and weight gain. Figure 5 lists the results.

### Figure 5

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Average weight gain at 8 weeks</th>
<th>Average weight gain at 12 weeks*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thalidomide 100 mg/day</td>
<td>3.3% (4.5 lbs)</td>
<td>4.2% (6 lbs)</td>
</tr>
<tr>
<td>Thalidomide 200 mg/day</td>
<td>1.2% (2.2 lbs)</td>
<td>3.9% (5.7 lbs)</td>
</tr>
<tr>
<td>Placebo</td>
<td>0.5% (0.9 lbs)</td>
<td>3.3% (5 lbs)</td>
</tr>
</tbody>
</table>
Myeloma blood cancer is another condition which thalidomide is effective against. Myeloma is an incurable bone marrow cancer. "In 2000, multiple myeloma will be diagnosed in about 13,700 patients in the United States." The major belief is that thalidomide prevents angiogenesis, or the formation of blood vessels. A tumor dies when it has no blood supply. "Thalidomide may inhibit vascular endothelial growth factor and basic fibroblast growth factor, which stimulate angiogenesis." Figure 6 displays some roles thalidomide may have in inhibiting myeloma cancer. "Current clinical studies of thalidomide open possibilities for novel treatments that target the tumor cell and its microenvironment."
IV. Conclusion

The tragic results of the use of thalidomide during the early 1960s caused a profound change in the medical and pharmaceutical community. It taught scientists the necessity of extremely extensive and sensitive testing of new drugs before releasing them to the public. In the United States, a new drug takes approximately 10 years before it is approved by the FDA and released because drugs must be tested thoroughly and the test results scrutinized down to every last dot of an I or crossing of a T. This strict examination can be contributed to the havoc which thalidomide caused around the world. Every United States citizen should be immensely grateful for the strict rules regarding drugs.

Thalidomide has been shown to cause terrible effects in fetuses. These effects should not overshadow thalidomide's potential effectiveness in the treatment of a variety of diseases. As long as proper caution is taken, thalidomide can be a ray of hope for many individuals. With further investigation of its properties, thalidomide may prove to be the wonder drug of the future as originally believed in the past by the scientific community.
Bibliography

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The Dioxin TCDD

By Bianca Mendez
Abstract: There is a lot of speculation about 2,3,7,8-tetrachlorodibenzo-p-dioxin and its effects. One purpose of this paper is to provide scientific information about dioxin. Another purpose of this paper is to discuss how dioxin effects our environment.

The first published synthesis of TCDD was in 1957. This synthesis hospitalized the laboratory worker. The following are some important historical events involving TCDD. TCDD first gained serious notice in 1970. In 1970, the public learned of the presence of a mystery chemical, TCDD, in sprays that were used to defoliate large areas in Vietnam (4). In 1974, studies in Missouri revealed that waste oil, applied to dirt roads and horse arenas to suppress dust, contained TCDD and was responsible for sickness and death in horses and possibly accounted for illness in tow youngsters (4). In the summer of 1976, thousands of people in the town of Seveso, Italy, were contaminated with TCDD when an overpressured reaction vessel in a chemical plant vented its contents to the outside air (4). Many hundreds of animals became sick, some died (the effects were only partially due to TCDD; many were caused by other chemicals, a fact that was not grasped, and therefore poorly reported by the media) (4). The 1979 Alsea, Oregon, episode, widely reported on television, brought the issue of aerial spraying "home" in that it was U.S. forests that were sprayed, domestic watersheds that were possibly contaminated with TCDD, and American women who feared that their miscarriages resulted from the spraying (4).

The term "dioxin" is frequently used to describe the single compound 2,3,7,8 tetrachlorodibenzo-p-dioxin or TCDD (refer to top figure). TCDD belongs to a group of 75 different aromatic tricyclic dioxin where the number of chlorine atoms can vary from one to eight. TCDD is the most potent representatives of the 75 different chlorinated dioxins however all have similar biological and toxicological effects.

There are 22 isomers of TCDD, all of which have been synthesized. TCDD is symmetrical across both horizontal and vertical axes. At room temperature it is a colorless crystalline solid. It melts at 295°C. It is lipophilic, and it binds strongly to soils and other particulate matter. Chemically it's quite stable; for example, its thermal destruction requires temperatures of more than 700°C. Because dioxin is not easily broken down, it ends up in soil, water, and on plant surfaces.
The last important property of TCDD with respect to treatment is that the vapor pressure is very low. Its vapor pressure is \(6.4 \times 10^8\) mm Hg at 20°C and \(1.4 \times 10^9\) mm Hg at 25°C (6). Consequently, volatilization of TCDD from waste streams or soil is not expected to be a rapid process (8). Of more concern is the wind transport of soil particles with absorbed TCDD (8).

TCDD is a highly toxic contaminant produced as a by-product during the manufacture of chlorinated phenols and phenoxyherbicides, chlorine bleaching of paper pulp and combustion of chlorine-containing waste (3). The best known source of TCDD used to be the unwanted synthesis during the production of 2,4,5-trichlorophenol. However, production of 2,4,5-T and 2,4,5-trichlorophenol has been discontinued in the United States (7). The amount of TCDD formed during the production of 2,4,5-trichlorophenol depended on the chemicals used in synthesis and the temperature of the process; some TCDD levels were in the range of 1 to 20 parts per million (4). Trichlorophenol has been used to synthesize the bactericide hexachlorophene and the herbicide 2,4,5-trichlorophenoxyacetic acid or 2,4,5-T (refer to reaction below). The amount of TCDD contained as impurities in hexachlorophene and 2,4,5-T depends on how much was present in the original trichlorophenol (4).

Dioxins

Sources and structures
The mass spectra of 2,3,7,8-TCDD pictured below (refer to first mass spectra) shows the molecular ion and its isotope peaks at m/e 320, 322, and 324. Major ions are at m/e 257.259 (M+-COCl), 194 and 196 (M+-2 COCl). Minor ions at m/e 285, 287 (M+-Cl), 250, 252 (M+-COClCl), and doubly charged molecular ions at m/e 160, 161, and 162.

Only minor differences in the intensity of ions in the in the higher mass range are observed for different TCDD isomers. However, significant differences in the mass spectra of some isomers are found in the low mass range, at m/e 74, 75, and 76. Partial mass spectra of 2,3,7,8-, 1,2,3,8-, and 1,2,3,4-TCDD are shown below (refer to second mass spectra). 2,3,7,8-TCDD shows a significant peak at m/e 74 (C6H2+): the spectrum of 1,2,3,8-TCDD shows peaks at m/e 73, 74, and 75 (C6H3+) and that of 1,2,3,4-TCDD at m/e 74, 75, 76 (C6H4+).

Mass spectrum of 2,3,7,8-tetrachlorodibenzo-p-dioxin.

Partial mass spectra (m/e 70-80) of 2,3,7,8-, 1,2,3,8-, and 1,2,3,4-TCDD.
From there dioxin enters the food chain and the fats of fish, meat, and into dairy products. Since dioxin is fat-soluble, it bioaccumulates up the food chain and it is mainly found in meat and dairy products. The chart below shows North Americans daily intake of dioxin.

This is where you get your dioxin from:

<table>
<thead>
<tr>
<th>Source</th>
<th>TEQ (pg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beef Ingestion</td>
<td>38.0</td>
</tr>
<tr>
<td>Dairy Ingestion</td>
<td>24.1</td>
</tr>
<tr>
<td>Milk Ingestion</td>
<td>17.6</td>
</tr>
<tr>
<td>Chicken Ingestion</td>
<td>12.9</td>
</tr>
<tr>
<td>Pork Ingestion</td>
<td>12.2</td>
</tr>
<tr>
<td>Fish Ingestion</td>
<td>7.8</td>
</tr>
<tr>
<td>Egg Ingestion</td>
<td>4.1</td>
</tr>
<tr>
<td>Inhalation</td>
<td>2.2</td>
</tr>
<tr>
<td>Soil Ingestion</td>
<td>0.8</td>
</tr>
<tr>
<td>Water Ingestion</td>
<td>Negligible</td>
</tr>
</tbody>
</table>

North American Daily Intake (pg/day) of TEQ

Is this a good case for vegetarianism or what?
[A TEQ is a dioxin Toxic Equivalent]

There are several important properties of TCDD to consider with regard to waste treatment. They include the following: very low water solubility, much greater solubility in organic solvents, strong binding agent to organic matter, rapid decomposition at temperatures above 1350° C, low vapor pressure, and absorption of ultraviolet radiation.

Chlorinated dibenzo-p-dioxins are characterized by low polarization, which results in very low water solubility, but a much higher solubility in organic solvents (8). The half-life of TCDD in soil has been estimated to range between 1.5 and 10 years (8).

Another property of TCDD is that it absorbs ultraviolet light strongly with a wavelength of maximum absorption lying within the sunlight region (above 290nm)(8). As a result, TCDD has been shown to degrade significantly when exposed to light of this wavelength in the presence of a hydrogen donor such as hexane or some other organic solvent (8).

One of the most important properties of TCDD with respect to treatment is that it is destroyed at temperatures between 1200 and 1400° C (8).
Long term carcinogenesis studies involving laboratory animals exposed to TCDD conclusively demonstrate that this chemical is a complete carcinogen which is a chemical that caused cancer in laboratory animals that have not been exposed to any other known carcinogen (5). In a series of studies beginning in 1977 with rats and ending in 1988 with the TCDD-resistant hamster, TCDD consistently induced cancers in a variety of organs and systems, frequently causing tumors not ordinarily observed or having low background incidence in control animals (5).

The International Agency for Research on Cancer (IARC) which is part of the World Health Organization announced February 14, 1997, that 2,3,7,8-TCDD is now considered a Class 1 carcinogen, meaning a "known human carcinogen." According to the EPA humans are exposed to 119 pg/day. The EPA has set an acceptable daily intake of 0.006 pg/day. The World Health Organization on the other hand, considers 10 pg/day to be acceptable.

A report released for public comment in September 1994 by the US Environmental Protection Agency (EPA) clearly describes dioxin as a serious public health threat (1). According to the EPA report, not only does there appear to be no "safe" level of exposure to dioxin, but levels of dioxin and dioxin-like chemicals have been found in the general population that are "at or near levels associated with adverse health effects (1). The US Environmental Protection Agency report confirmed that dioxin is a cancer hazard to people; that exposure to dioxin can also cause reproductive and developmental problems (at levels 100 times lower than those associated with its cancer causing effects); and that dioxin can cause immune system damage and interfere with regulatory hormones (1). Another finding of this report is that the "major route of humans exposure is through ingestion of a wide variety of common foods containing small amounts of dioxin, especially dairy products, meat and fish; this has resulted in widespread low-level exposure of the general population"(2). One last important finding of this report is that the "principal sources of dioxin in the environment are incineration, chemical manufacturing and processing, industrial and municipal processes and reservoir sources"(2).

Acute health effects of TCDD may occur immediately or shortly after exposure. One acute health effect is that contact with it can cause skin and eye irritation. A second acute health effect is that exposure to it can cause headache, weakness and digestive disturbance. Chronic health effects of TCDD can occur at some time after exposure and can last for months or years. One chronic health effect is that it may be a carcinogen in humans since it caused lymphomas in humans and it has been shown to cause liver, lung, mouth, tongue, and skin cancer in animals. A second chronic health effect is that it may be a teratogen in humans since it has been shown to be a teratogen in animals. A teratogen is a substance that caused birth effects by damaging the fetus. A third chronic health effect that it may decrease fertility in males and females however, there is only limited evidence of this. TCDD presents chronic health effects other than cancer and
reproductive hazards. TCDD exposure can cause severe acne-like skin rash called chloroacne to develop and possibly persist for years. TCDD exposure may damage the liver. TCDD can affect the nervous system with symptoms of lack of energy, loss of energy, loss of sex drive, personality and mood changes, weakness, pain in the legs, and numbness.

Despite the amount of research devoted to the mechanisms of TCDD-associated toxicological effects, including carcinogenesis, no complete step by step or even stage by stage model has yet been established (5). The growing consensus among researches is that most, if not all, of TCDD's biochemical and toxic effects require interaction with Ah receptors (5). However, it must be kept in mind that formation of the Ah receptor-TCDD complex is only the first of many steps involved in the production of biochemical, toxic, and carcinogenic effects (5). Although our understanding of subsequent steps is increasing, we still know little about certain components of the Ah receptor-mediated responses (5). Clearly, however, cell-specific factors other than the Ah receptor must be involved in determining tissue responses once TCDD binds that receptor (5).

Decisions made with regard to use of TCDD may continue to be based upon the assumption that it is much more dangerous to people than data seems to indicate, but strict controls may prevent harm to other organisms and the public may feel more secure. In addition, consideration must be given to disposal since no acceptable method currently exists for the efficient destruction of dioxins. Waste dioxins are currently being stored until efficient means of disposal or destruction are developed.
Bibliography


Vitamin C

Kimberly Nichols

Organic Chemistry

May 2000
Abstract

Vitamin C, or ascorbic acid, is surely the best known of all vitamins. It was the first vitamin to be discovered, structurally characterized, and to be synthesized in the laboratory. This paper will focus on the chemical make up of vitamin C, the roles it plays as an antioxidant, how it is synthesized, and how it makes the human body better.

An English naval doctor was given the task of finding a solution to the problem of scurvy in the ranks of Her Majesty’s Fleet. Dr. Lind found that simply feeding these men citrus fruits, oranges, and lemons cured the disease and prevented it from occurring again. Dr. Lind achieved this is 1747. Fifty-three years later, in 1800, the British Royal Navy finally took advice and introduced lemon juice into the diet of shipboard seamen (1). It was not until 1928 that the Nobel laureate, Albert Szent-Gyorgi, isolated the chemical responsible for curing scurvy, it became known as vitamin C, or ascorbic acid (2).

Vitamin C is a sugar acid that is synthesized in plants and in the livers of most vertebrates, but not human beings. Vitamin C is water soluble and is carried through the body in water with excess discarded daily. L-ascorbic acid, the active form of vitamin C is a six carbon chain with eight hydrogen and six oxygen atoms attached (Fig 1). It’s molecular weight is 176.13 (1).

Fig 1
(Source: Encyclopedia Britannica)

A good food source of vitamin C should contain a substantial amount of vitamin C in relation to its calorie content and contribute at least ten percent of the U.S. Recommended Daily Allowance (RDA) for vitamin C in a selected serving size. The recommended dosage for this vitamin is 100-300 milligrams per day (1). The U.S. RDA given is for adults (except pregnant or lactating women) and children over four years of age. Ninety-three percent of vitamin C in diets of Americans comes from fruits and vegetables. Citrus fruits and tomatoes contribute almost half of the vitamin C provided by the fruits and vegetable groups. Figure 2 is a sample list of foods that are considered a good source for vitamin C (3). Foods that contain small amount of vitamin
C, but are not considered good sources can contribute significant amounts of vitamin C to an individual's diet if these foods are eaten often or in large amounts.

Fig 2
(Source: Ohio State University Extension Fact Sheet)

The major role of vitamin C is as an antioxidant. As our body turns oxygen into energy, there are byproducts formed, free radicals, these are the oxidants that cause oxidative damage to cells (1). These free radicals have an unpaired electron in the atom's outer orbit (Fig 3). This

Fig 3
(Source: Organic Chemistry Text Book)

A free radical

unpaired electron tries to steal an electron, or maybe a whole hydrogen atom, from something around it (1). Unfortunately, what is around is the human body. A little tear can be made in the cell wall, changes in the chemistry of mitochondria in the cell, or it can rip a little piece of DNA out of the nucleus (4). This is where antioxidants, vitamin C, come in. They clean up as many free radicals as they can before damage occurs and where damages have already happened, they come in and correct the problem. If these free radicals are left unchecked damage can be done to tissues and an increase of cancer, heart disease, arthritis, premature aging, and other degenerative
diseases are all other possible effects (5). Sometimes the antioxidant gives the free radical an electron to stabilize it, other times the antioxidant neutralizes the free radical by combining with it to form a different stable compound (1). For example, research has shown it is best to take estified C (Ester C), which is created by linking ascorbic acid with a dietary mineral like calcium, potassium, or zinc (1). This form of vitamin C is non acidic and is absorbed by the body better.

As an antioxidant vitamin C should be considered an important part of antioxidant supplementation. One of its greatest benefits is that it fights the effects of pollution (1). As the human body takes in pollutants in the air and water, all of this toxicity produces free radicals. Vitamin C comes in and neutralizes these free radicals that are formed as mentioned earlier. Researchers have also discovered that smokers are especially prone to have lower vitamin C levels because their reserves are eaten up with each cigarette. This leaves the smoker’s immune system weakened and depletes his or her antioxidant capability, thereby opening him or her up to the possibility of cancer, cardiovascular disease, and other sickness (1). Researchers have also found that vitamin C helps fight cardiovascular disease. By protecting the endothelium (the lining of the artery) from oxidative damage, it promotes better blood flow, even in patients with high blood pressure (6). A study in 1997 demonstrated that vitamin C reduced the number of super oxide radicals in the arteries, an thereby reduced the number of low density lipoproteins (LDL) particles that oxidized (1). Simply by reducing the number of free radicals floating around, vitamin C has an indirect effect on stopping lipid oxidation, which can lead to atherosclerosis, hardening of the arteries (6).

Diabetics tend to have problems with vitamin C because this nutrient likes to ride on insulin to be carried thought the body (1). Diabetics tend to have low vitamin C levels simply because there is not enough insulin to circulate it. This means that diabetics also have problems with not having enough antioxidant activity, at least those diabetics who do not take insulin, therefore this lack of antioxidant activity results in poor control of the diabetes. Patients who are aware of this and are supplementing their vitamin C may slow that progress. Researchers have also been aware for quite some time that vitamin C helps reduce cataracts (1). New research is now showing that women age fifty-six to seventy-one who had used vitamin C supplements for ten years or more had a seventy-seven percent lower incidence of lens opacities. The key in this study was the long term use of supplements, which gave these women long term protection and turned back the clock to reverse the effects of aging (1).

It has often times been said that vitamin C can stop a cold. However, vitamin C is not known to even clearly interact with invading cold germs. Rather, it has a general immune boosting effect; in other words, it helps the body protect itself (5). Vitamin C’s most basic role in the body is to create collagen, which is needed to form and maintain body tissue. Therefore, taking in plenty of vitamin C maintains the strength of the body’s physical barriers to infectious invaders (7). Vitamin C also strengthens the immune system by increasing the production and activity of white blood cells, which are responsible for destroying foreign invaders such as viruses and bacteria. Research has shown that there is a reduction in white blood cell formation when vitamin C is deficient in the diet (5). In addition, vitamin C boosts production of interferons. Interferons consist of groups of glycoproteins that increase resistance to viruses and prevent them from replicating. Thus, the body’s resistance to infection and disease improves when vitamin C
intake is increased. Although there are far fewer studies examining the effects of vitamin C on the flu than on vitamin C and the common cold, it makes sense that the overall immune boosting effect of vitamin C would help people who have the flu. The common cold is not the only respiratory infection that vitamin C benefits; this vitamin seems to have an affinity for supporting healthy lungs (7). Asthma, although not an infectious disease itself, can be worsened by the presence of a respiratory infection. A recent study took twenty young asthmatics and suspended their use of regular asthma medication and instead took two grams of vitamin C or a placebo one hour before engaging in seven minutes of exercise on a treadmill. This single large dose of vitamin C prevented flare up of asthma in forty-five percent of the asthmatics, and lessened the severity of the attack in another ten percent (6).

For some time now researchers have been putting a link between cancer and vitamin C. The immunological defense system has the difficult task of distinguishing foe from friend by first recognizing "not self", such as bacteria or malignant cells. Recognition depends upon the evaluation of differences in molecular structure. For the viral and bacterial vectors of disease these differences are striking and their recognition is relatively easily accomplished, whereas for the cancer cells the differences are slight and the immune mechanisms must be highly competent in order to be effective (8). There is increasing evidence that vitamin C is essential for the efficient working of the immune system. The mechanisms of the immune system involve both certain molecules, mainly protein molecules, that are present in solution in the body fluids and certain cells. The immunoglobulins are these protein molecules, often called antibodies or antitoxins, that have the power of recognizing "not self" cells and combining with them, thus helping to mark them for destruction (8). It has been found that human beings with a high intake of vitamin C manufacture more antibody molecules than those with a lower intake. There is another complex of protein molecules called a complement, which is involved in an essential way in the process of destruction of foreign cells and malignant cells. Studies have shown that in guinea pigs an increased intake of vitamin C significantly increases the amount of the first component of complement, C1 esterase, without which the whole component cascade is inoperative and the "not self" cells would not be destroyed (8). Researchers have no doubt that vitamin C is required also in man for the synthesis of C1 esterase, because the component of the complement contains protein molecules that are similar to the molecules of collagen that are known to require vitamin C for their synthesis (8). In summary, cancer patients generally exhibit decrease effectiveness of their natural immune protective mechanisms and almost invariably have low ascorbate content of their lymphocytes. The simplest and safest way to enhance immunocompetence in these patients is to ensure that their molecular and cell mediated defense systems are working at maximum efficiency, which means to increase their intake of vitamin C (8).

Now that some of the most important benefits of vitamin C have been discussed, let's take a closer look at the structure. Ascorbic acid may be described as no more toxic than ordinary sugar, and far less toxic than ordinary table salt. Ascorbic acid (vitamin C) is a white, crystalline powder with large solubility in water (9). Ordinary ascorbic acid is also called L-ascorbic acid. There is another substance, D-ascorbic acid, that is closely related (Fig 4). The two substances contain the same atoms bonded together in essentially the same way, but with a spatial relationship corresponding to a reflection in the mirror, therefore they are enantiomers of each
other (9). The letters D and L indicate right-hand (dextro) and left-hand (levo). Only L-ascorbic acid has vitamin C activity.

Fig 4
(Source: Organic Chemistry Text Book)

L-ascorbic acid
(active)

D-ascorbic acid
(inactive)

Vitamin C can be obtained two different ways, directly within the body of some vertebrates or by industrial synthesis. Vitamin C's industrial preparation involves an unusual blend of biological and laboratory organic chemicals. The Hoffman-LaRoche company synthesized ascorbic acid from glucose through the five step process shown in Figure 5 (2).

Fig 5
(Source: John McMurray Organic Chemistry Book)

Glucose

Sorbitol

Acetobacter suboxydans

NaCl

HCl

Ethanol

Ascorbic acid
Glucose, a pentahydroxy aldehyde is first reduced to sorbitol, which is then oxidized by the microorganism, *Acetobacter suboxydans*. No chemical reagent exists that is selective enough to oxidize only one of the six alcohol groups in sorbitol, so an enzymatic reaction is used (2). Treatment with acetone and an acid catalyst then protects four of the remaining hydroxyl groups in acetyl linkages and the unprotected hydroxyl group is chemically oxidized to the carboxylic acid by a reaction with aqueous NaOCl (household bleach). Hydrolysis with acid then removes the two acetyl groups, causing an internal ester forming reaction to take place and catalyzes a keto-enol tautomerization to give ascorbic acid. The Hoffman-LaRoche company states that each of the five steps takes place with a better than ninety percent yield, which in organic chemistry is considered very good.

In most vertebrates, with the exception of humans, ascorbic acid can also be derived from glucose within the organism. After the organism has taken up all the glucose it requires, a secondary pathway for glucose leads to two specialized products: D-glucuronate, which is important in the detoxification and excretion of foreign organic compounds, and L-ascorbic acid (Fig 6) (10). Although the amount of glucose diverted into this secondary pathway is very small, the products are vital to the organism.

Fig 6
(Source: Principles of Biochemistry)

In this pathway, glucose-1-phosphate is first converted into UDP-glucose by reaction with UTP (uridine triphosphate), which can be used the same way ATP (energy) is used to catalyze a
reaction. The glucose portion of UDP-glucose is then dehydrogenated to yield UDP-glucuronate. UDP-D-glucuronate can then be converted to D-glucuronate, which is an intermediate in the conversion of D-glucose into L-ascorbic acid. It is reduced by NADPH to the six carbon sugar acid L-gulonate, which is converted into its lactone, a cyclic ester formed when a carboxyl and hydroxyl group are present within the same molecule. L-gulonolactone then undergoes dehydration by the flavoprotein gulonolactone oxidase to yield L-ascorbic acid (vitamin C) (10). Humans, guinea pigs, monkeys, some birds, and some fish lack the enzyme gulonolactone oxidase, which is why they cannot synthesize ascorbic acid in the body and are required to get it ready-made in their diet (10).

In conclusion, this paper has discussed the many valuable effects vitamin C can have on the human body. Including boosting the immune system to help fight off colds and even more devastating illnesses including cardiovascular disease, diabetes, and even cancer. Since the human body is unable to synthesize vitamin C on its own, it is important for people to either take a supplement or to eat foods rich with vitamin C. Vitamins, in general, are essential in helping maintain good health. Vitamin C is considered a “protector” nutrient, which is the body’s first line of defense against oxidative damage. Researchers are continually doing research on many kinds of antioxidants. They have already proven the benefits taking vitamins have on the body, so start taking vitamins, especially vitamin C, today and enjoy the health benefits for life.
References


Provigil(modafinil) used to promote wakefulness in people with Narcolepsy

Laura A. Schick, 20 April 2000
Abstract

Clinical studies have shown modafinil to have no long-term side effects and dependence. Comparing the data of Hypocretins, and the mechanisms of modafinil, there appears to be a definite linkage. In addition the mechanisms for the cause of narcolepsy are also left undefined except for their possible relation to the Hypocretin 2 gene. Although the role of Hypocretins has not yet been exclusively established, it has been thought that they affect wide regions of the brain, possibly affecting many different neuronal activities. The administration of modafinil and its effects on Hypocretins may cause some beneficial outcomes, but there must be regions of the brain in which modafinil doesn’t act as kind.

Sleep Introduction

Sleep is a period of rest during which the sleeper loses awareness of his or her surroundings. This vital behavior of unknown function consumes one-third of any given human life. All human beings and many kinds of animals must have a certain amount of daily sleep at regular intervals. Studies have shown that sleep is a heterogeneous state most classically separated into rapid eye movement (REM) sleep and non-REM sleep. REM and non-REM sleeps are indispensable to survival; both REM and total sleep deprivation are lethal in mammals. Sleep restores energy to the body, particularly to the brain and nervous system. Extra sleep of either kind does not make up for a lack of the other.

As a person falls deeply into sleep, the brain sends out slower but larger and larger waves. The slowest, largest waves occur during the first two or three hours of a period of sleep. During slow-wave sleep, also called non-REM (Rapid Eye Movement) sleep, mental activity slows down but does not stop. Non-REM sleep is characterized by synchronized EEG activity, partial muscle relaxation, and less frequent dreaming mentation. Persons awakened from non-REM sleep can often recall unclear thoughts that they had while asleep. Non-REM sleep may help especially in building proteins and restoring the control of the brain and nervous system over the muscles, glands, and other body systems.

Periods of small, fast waves, similar to those of an awake person, occur at intervals during sleep. During these periods of fast brain wave activity, the sleeper's eyes move rapidly as though they were watching the events of a dream. A sleeper who is awakened during such a period probably will recall dreaming and remember details of the dream. Sleep during these periods is called dreaming sleep or REM (Rapid Eye Movement) sleep. REM sleep is characterized by vivid dreaming, muscle atonia, desynchronized EEG activity, and REMs. REM sleep may be especially important for maintaining such mental activities as learning, reasoning, and emotional adjustment.

Independent of REM and non-REM sleep is the propensity to sleep or stay awake. This is regulated by homeostatic (sleep dependent) and circadian (clock-dependent) processes. Circadian processes are believed to be generated at the genetic level within the suprachiasmatic nucleus of the hypothalamus. Circadian rhythmicity both on molecular and neuroanatomical levels is still poorly understood.

Scientists are still seeking answers to many questions about the need for sleep. They do not know, for example, why human beings cannot simply rest, as insects, or the exact mechanisms in how sleep restores strength to the body. Understanding the
processes of sleep could give insight and maybe cure some neurological and sleep disorders.

Narcolepsy
Narcolepsy is a life long neurological disease that affects more than 1 in 2,000 Americans.\(^1\) It is a sleep disorder characterized by attacks of disabling daytime drowsiness and low alertness. The normal components of rapid eye movement (REM) sleep, dreaming and loss of muscle tone, are separated and occur while a person is awake. These symptoms are known as excessive daytime sleepiness, hypnagogic hallucinations, cataplexy and sleep paralysis. Unlike normal sleep, that of a narcoleptic often begins with REM activity and the time taken to fall asleep is shorter than normal.

**Excessive Daytime Sleepiness**
People who suffer from Narcolepsy experience sleep attacks along with persistent daytime drowsiness.\(^3\) The onset of sleep can occur at any time or place. Sleep episodes vary from few to many in a single day, and each episode may last minutes or hours. The ability to resist the desire to sleep remains only temporary, although arousal from narcoleptic sleep occurs as readily as from normal sleep. Sleep attacks are described as irresistible and may occur with or without warning. Sleep tends to occur during monotonous conditions, as for normal sleep, but may also occur during hazardous circumstances such as when a person is driving. The quick onset of sleep may also occur when a person is working, eating, talking, or engaging in other activities. This makes it hard for narcoleptics to live a normal life. Excessive daytime sleepiness is usually the first symptom of narcolepsy and often the most difficult symptom to control.\(^5\)

Narcoleptics go through life feeling the way most of us would feel if we had been awake for 24 hours. They awake refreshed from naps, but soon are sleepy again within a few minutes. Total daily sleep time usually does not increase despite the frequent sleep episodes. The onset of REM sleep is almost instantaneous. This pattern differs from normal sleep, in which non-REM sleep usually lasts about 60 to 90 min, preceding REM sleep. Their nighttime sleep is unsatisfying by being fragmented with less of the deeper stages of sleep and may be and interrupted by vivid, frightening dreams.\(^13\)

**Cataplexy**
Cataplexy is triggered by sudden strong emotions and results with the loss of muscle tone. This momentary paralysis occurs while remaining conscious and is evoked by sudden emotional reactions, such as anger, fear, joy, or, often, by surprise.\(^3\) Weakness may be confined to the limbs or may cause a limp fall when a person laughs heartily or is suddenly angry. These attacks resemble the loss of muscle tone that occurs during REM sleep or, to a lesser degree, in a person who is "weak with laughter." Attacks of cataplexy are usually over within seconds but in some narcoleptic patients they can last for minutes and be disabling. In most narcoleptic patients, sleepiness rather than cataplexy is the more troublesome symptom.\(^13\)

**Sleep paralysis**
Sleep paralysis occurs when a person is just falling asleep or immediately upon awakening and results with temporary immobilization.\(^3\) In sleep paralysis,
a person may try to move, but realize that he cannot. When this occurs it may last a few seconds to a few minutes. These occasional episodes may be very frightening.

**Hypnagogic hallucinations**

Hypnagogic hallucinations are particularly vivid, often frightening, dream-like images that occur when a person is dozing off, falling asleep, or on awakening.[3] These visual illusions or hallucinations are so vivid that they are hard to distinguish from reality. They are somewhat similar to vivid dreams, which are normally occur in REM sleep.

**Diagnosis**

Narcolepsy is usually developed in the second or third generation of life with symptoms progressing over a period of 1 or more years and then stabilizing.[13] Excessive daytime sleepiness, sleep fragmentation, and abnormal REM sleep, such as cataplexy, sleep paralysis, and hypnagogic hallucinations contribute to narcolepsy, although some symptoms are not always present. The full tetrad of daytime somnolence, cataplexy, sleep paralysis, and sleep-associated hallucinations is present in only about 15% of patients.[7] Severity of the disorder can fluctuate which leads doctors to misdiagnosis narcolepsy as other conditions and vice versa. Clinically the diagnosis is confirmed by polysomnography, a technique that employs simultaneous recording of EEG and the electromyogram (EMG). This procedure reveals “sleep-onset REM periods,” REM sleep occurring at sleep onset or within 15 minutes of sleep onset.

**Recent Discoveries About Narcolepsy**

Narcolepsy is the only known neurological disorder that specifically affects the generation and organization of sleep. Several studies have reported a strong association between certain class II HLA haplotypes on human chromosome 6 and narcolepsy. The disorder has a genetic basis: most affected persons carry the human leukocyte antigen (HLA)HLA-DQB1*0602, and first-degree relatives of narcoleptics have a 40-fold increased risk of developing narcolepsy. However most persons with HLA-DQB1*0602 do not develop narcolepsy, the concordance rate in identical twins is low, and narcolepsy does not cosegregate with HLA-DQB1*0602 in some multiplex families. Although familial cases of narcolepsy have been reported, most human occurrences are sporadic, and the disorder is generally believed to be multigenic and environmentally influenced.[2]

Narcolepsy has also been reported to occur in animals and has been most intensively studied in canines. A large number of physiological and pharmacological studies have been performed throughout the last 20 years, which demonstrate a close similarity between human and canine narcolepsy. In the August 6 issue of Cell, Lin et al. (1999) report that canine narcolepsy is caused by a mutation of the Hypocretin receptor 2 gene (Hcrtr2). Hypocretins, also called orexins, are recently identified neuuropeptides with homology to the gut hormone, secretin. Within the central nervous system, cell bodies containing Hypocretins are present exclusively in the tuberal region of the hypothalamus. The projections of these Hypocretins are widely distributed throughout the brain and are shown to affect the sleep/wake cycle and appetite.[4]
Neurotransmitters Associated With Narcolepsy

It is important to understand certain functions of the brain and its neurotransmitters to comprehend the complexity of narcolepsy. The brain produces many kinds of chemicals that are used as neurotransmitters. The most important ones that affect narcoleptic patients include Hypocretins (orexins), gamma aminobutyric acid (GABA), glutamate, and dopamine. The chemicals are not distributed evenly throughout the brain. Each is found only or primarily in specific areas.

**Figure 1**

![Diagram showing neurotransmitters]

**Hypocretins/Orexins**

In 1998, de Lecea et al., described a hypothalamus-specific mRNA that encoded "prohypocretin," which was thought to be the precursor of two peptides, Hcr 1 and Hcr 2. They named these peptides Hypocretins (Hcrts) to indicate their hypothalamic localization and similarity to the gut hormone secretin. At the same time, Sakurai et al., were researching DNA sequences and identified peptides on the G protein that bind to and activate two related receptors. They named these peptides “orexins” after the Greek word for appetite because of their correlation with food intake. The peptides described by both are identical.[13]

Hypocretins include a group of neuropeptides called Orexin A and Orexin B. Neurons containing Hypocretin are located exclusively in the lateral hypothalamus and send axons to numerous regions throughout the central nervous system, including the major nuclei implicated in sleep regulation. They are also shown to be involved in the regulation of food and energy homeostasis.[7]

Hypocretins are restricted to neuronal cell bodies of the dorsal and lateral hypothalamus which act concurrently within the central nervous system as homeostatic regulators. The orexin-1 receptor binds orexin A only, whereas the orexin-2 receptor binds both orexin A and orexin B.[7] The orexigenc neurons in the lateral hypothalamus project widely in the brain. Research has showed that the brain region receiving the densest innervation from orexinergic nerves is the locus coeruleus, which is a key modulator of attentional state. At this location the application of orexin A increases cell firing of intrinsic nonadrenergic neurons, therefore increasing arousal and locomotor
activities and modulating neuroendocrine functions. This suggests that orexin A plays an important role in coordinating the sleep-wake cycle.

The orexin peptides are unique among hypothalamic peptides because they act directly at axon terminals. Therefore they can increase the release of the major inhibitory transmitter, GABA, as well as the major excitatory transmitter, glutamate. Together these two neurotransmitters are responsible for almost all fast synaptic activity in the hypothalamus. Studies have also shown that Hypocretin release raises cytoplasmic calcium levels by opening plasma membrane channels.

Hypocretins and orexins were recently discovered so scientists are still conducting research to determine their exact functions and mechanisms. These statements are summarized conclusions from previous research projects. Hypocretins can be found in the region of the hypothalamus where peptides are encoded therefore, their physiologic role is likely to be complex.

**Figure 2**

The synapse is a very dynamic region consisting of a presynaptic axon terminal, a synaptic cleft or space, and a postsynaptic neuron (dendrite, soma, sometimes an axon or another dendrite). Neurotransmitters are released from storage vesicles and diffuse across the synaptic cleft to bind to a specific receptor site on the postsynaptic neuron. The neurotransmitter then activates (excites or inhibits) the next neuron and is then reuptaken into the sending neuron or destroyed either in the cleft or in the presynaptic neuron. It is at the synapse that most drugs or chemicals work to alter the brain and thus the mental state of the person.

**GABA (gamma-aminobutyric acid)**

GABA (gamma-aminobutyric acid), $\text{C}_6\text{H}_7\text{NO}_2$, is a neurotransmitter found in the central nervous system. It is the main inhibitory neurotransmitter in the brain. Its actions, which are anxiety reduction, are mediated by the entry of chloride into a cell
when GABA binds to its postsynaptic receptor site. The brain produces substances which enhance anxiety like beta-carbolines, as well as substances which reduce anxiety like allopregnanolone. These substances modify the GABA receptors in the brain to produce their effects.

**GLU (glutamate)**

Glutamate is the main excitatory neurotransmitter in the brain. Its actions are mediated at two types of receptor sites. At one receptor glutamate binding will cause calcium to flow into a neuron. These receptors are involved in the process of memory formation in the brain. Excess glutamate is neurotoxic and neurons are killed by the excessive calcium which enters the cell due to glutamate binding.

**Dopamine**

Dopamine is a monoamine with the general formula, C₈H₁₁NO₂. It is formed as an intermediate compound from dihydroxyphenylalanine (dopa) during the metabolism of the amino acid tyrosine. Dopamine, also called hydroxytyramine, is a decarboxylated form of dopa and occurs especially as a neurotransmitter in the brain. The cell bodies of neurons that contain dopamine are in the midbrain of the brainstem. The axons of these cells reach into other areas, including the frontal lobes of the cerebrum and an area near the center of the brain called the corpus striatum. It inhibits the transmission of nerve impulses in the substantia nigra, basal ganglia, and corpus striatum. These dopamine pathways function in the regulation of emotions and in the control of complex movements.

Dopamine is a precursor of the hormones epinephrine and norepinephrine. Norepinephrine plays a role in attention and general arousal level. Waking behavior is enhanced by drugs which activate norepinephrine systems while REM sleep (dream sleep) occurs when norepinephrine systems are at their lowest level of activity. Epinephrine stimulates the breakdown of glycogen and glucose in the liver, which results in the raising of the level of blood sugar. It is also referred to as the emergency hormone, because it is released during stress.

*Figure 3*[^15]

![Diagram of dopamine pathway](image_url)


Dopaminergic receptors are located on the postsynaptic membrane. They undergo reactions that regulate calcium and potassium channels on this membrane. Dopaminergic receptors terminate dopamine by uptake into the presynaptic terminal.[8]

**Treatment of Narcolepsy**

Although there is no known cure, the sleepiness of narcolepsy can be treated by a number of agents. Pharmacologic treatment of narcolepsy has depended on the use of central nervous system stimulants to increase wakefulness, vigilance, and performance. The medications considered effective in the treatment of narcolepsy include dextroamphetamine, pemoline, methylphenidate, methamphetamine, and modafinil. Currently only methylphenidate hydrochloride, dextroamphetamine, and modafinil are approved for use in the United States. The first two available stimulants are associated with dangerous side effects, limiting efficacy, and negative effects on nighttime sleep. In contrast to these, modafinil has been shown to be effective in reducing daytime sleepiness in patients with narcolepsy causing only an acute amount of side effects.[9]

**Modafinil**

Modafinil, known in the United States as Provigil, is a wakefulness promoting agent approved for the treatment of narcolepsy. The U.S. Food and Drug Administration (FDA) approved marketing for PROVIGIL® (modafinil) Tablets [C IV] in December 1998. Modafinil is the first non-amphetamine drug to improve wakefulness in patients with excessive daytime sleepiness associated with narcolepsy in 40 years. The DEA has proposed that Provigil be placed into Schedule IV of the Controlled Substances Act.[10]

The chemical name for modafinil is 2-[(diphenylmethyl)sulphonyl]acetamide. The molecular formula is C₁₅H₁₅NO₂S and the molecular weight is 273.36 g/mol.[11] The chemical structure is: (fig. 4)
The chirality of modafinil is at its sulfur atom. Modafinil is a racemic compound whose enantiomers have different pharmacokinetics. The enantiomers of modafinil exhibit linear kinetics but do not interconvert. At a steady state the total exposure to that of the l-isomer is three times that of the d-isomer.\[12\]

**Synthesis**

Modafinil may be synthesized in two different ways. The preferred method for preparation comprises reacting an acid halide with an amine.\[4\] This is shown (fig. 5) using two different halides, chlorine and an alkoxy group. Acid chlorides and acid anhydrides transfer acyl groups to ammonia to give amides. In one scenario benzhydrylsulphinylacetic chloride reacts with ammonia to give 2-(benzhydrylsulphinyl)acetamide, (modafinil), and a byproduct of hydrogen chloride. The other scenario reacts an ester with an amine to give an amide and an alcohol. In this case methyl benzhydrylsulphinylacetate reacts with ammonia to give 2-(benzhydrylsulphinyl)acetamide, (modafinil), and methanol.

**Figure 5**

benzhydrylsulphinylacetic chloride 2-(benzhydrylsulphinyl)acetamide methyl benzhydrylsulphinylacetate (Modafinil)

The second method of preparation reacts a sulpho derivative with an amine to obtain a sulphur amide(fig. 6). This is oxidized with hydrogen peroxide to give a sulphinyl derivative.\[4\] The synthesis begins with a nucleophilic substitution reaction on a carboxylic acid. The activation of the carboxylic acid converting the hydroxyl group on the carboxyl group into a good leaving group occurs with difficulty and can only be done with the aid of an acylating agent. In this case thionyl chloride acts as the acyl-transfer agent because it has a low boiling point of 79°C and leaves gaseous byproducts which are easily removed. The thionyl chloride separates, converts the hydroxyl group into a good leaving group, and replaces it with a chlorine. The major product is benzhydrylthioacetyl chloride with byproducts of sulfer dioxide and hydrogen chloride. The resulting acid chloride will react with ammonia, as explained above, to give benzhydrylthioacetamide. Oxidation with hydrogen peroxide will relieve strain on the sulfur group resulting with a
major product of 2-(benzhydrylsulphinyl)acetamide, (modafinil), and water as a byproduct.

**Figure 6**

![Chemical structure of modafinil and related compounds](image)

**Effects of Modafinil**

Modafinil is effective in promoting daytime wakefulness without interfering with nighttime sleep. It improves a patient's ability to participate in daily activities without fearing sleep attacks and drowsiness. Provigil is generally well tolerated, as hasn’t shown drug dependence in the body. Nervousness, headache, nausea, anxiety, and insomnia are the most common reported side effects. Unlike traditional stimulants, modafinil’s cardiovascular side effects are minimal, and there are fewer nervous system and GI side effects.

**Pharmacologic activities in preclinical models**

<table>
<thead>
<tr>
<th>Activity</th>
<th>PROVIGIL</th>
</tr>
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<tbody>
<tr>
<td>Wakefulness</td>
<td>++</td>
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<tr>
<td>Wakefulness mediated by dopamine</td>
<td>–</td>
</tr>
<tr>
<td>Locomotor activity</td>
<td>–/-/+</td>
</tr>
<tr>
<td>Anxiogenic</td>
<td>–</td>
</tr>
<tr>
<td>Blood pressure/Heart rate</td>
<td>–</td>
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<tr>
<td>Rebound hypersomnia– = no activity</td>
<td>–/-/+ = minimal activity</td>
</tr>
<tr>
<td>++ = marked activity</td>
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**Suggested Mechanisms for Action**

The precise mechanisms through which modafinil promotes wakefulness are unknown. Modafinil has wake-promoting actions like amphetamine and methylphenidate, although the pharmacologic profile to these amines is not identical. Modafinil is not a direct or indirect dopamine receptor agonist and is inactive in several preclinical models capable of detecting enhanced dopaminergic activity.

Recently studies have shown that modafinil activates Hypocretin-containing neurons in the lateral hypothalamus. These neurons have been discovered to regulate...
sleep/wakefulness states. Although modafinil also produces neuronal activation in other brain regions, so it is unlikely that this is the sole mechanism of action.\textsuperscript{[7]}

It has also been shown that modafinil dose-dependently inhibits the activity of GABA neurons in the cerebral cortex and in the nucleus accumbens, as well as in sleep-related brain areas such as the medial preoptic area and the posterior hypothalamus. Modafinil showed a maximal increase in glutamate release in these brain regions, associated with the lack of effect on GABA release. Therefore it has been suggested that an increase in excitatory glutamatergic transmission in these regions, alters the balance between glutamate and GABA transmission.\textsuperscript{[14]} This could, in turn, suggest an ill-defined mechanism by which modafinil contributes wake-promoting effects.

**Modafinil vs. Amphetamines**

Although the mechanism for action is unknown, modafinil appears to be unlike classic amphetamine stimulants. Modafinil appears to act on a specific subset of brain pathways which regulate sleep and wakefulness, whereas amphetamines affect a greater number of cerebral structures involved in the regulation of these behavioral states(fig. 7)\textsuperscript{[17]}

Sleep initiation was not altered by modafinil in comparison to amphetamine which marked a decrease in total sleep time and sleep efficiency. Amphetamines caused no REM stages of sleep. Severe symptoms, like tachycardia has been reported with regular use of amphetamines. The body becomes dependent on the use of amphetamine, so it must be regulated carefully.\textsuperscript{[18]} Unlike amphetamines that work by stimulating the nervous system, modafinil targets the hypothalamus, thought to be responsible for wakefulness. Neither does it produce the emotional highs and lows associated with amphetamines.

*Figure 7*

PROVIGIL is thought to act selectively in areas of the brain believed to regulate normal wakefulness. Here, it shows highly selective CNS activity, distinct from amphetamine and methylphenidate\textsuperscript{[16]}
Theory

The hydrolysis of amides to amines and carboxylic acids is one of the most important types of chemical reactions in the body. Proteins are large molecules held together chiefly by amide groups known as peptide linkages. Digestion breaks down proteins into smaller units by the hydrolytic cleavage of amino bonds. The smallest units resulting from such hydrolysis of proteins are the amino acids. Peptides are created when the amino group of one amino acid forms an amide bond with the carboxylic acid of another one. These actions allow living organisms to maintain homeostasis. In certain circumstances the specific amino acid or peptide may be under or over produced which will cause a hormonal imbalance along with many other side affects. This is where pharmaceuticals, like Modafinil, come in and adjust the imbalance of amino acid and peptide formation. As a result homeostasis will be maintained.

Although the mechanisms for modafinil are ill-defined, I have come to the conclusion that there are four major neuro contributors to take into consideration. Hypocretins (orexins), dopamine, GABA, and glutamate all undergo mechanisms to affect the sleep/wakefulness cycles in the brain. The complexity of these neurotransmitters makes it difficult to understand the exact processes by which they contribute to neurohomeostasis.

It can be suggested that Hypocretins (orexins) are the initiating factors for narcolepsy. Studies have already shown that narcolepsy correlates with a mutation on the Hypocretin-2 receptor.\[1\] If the mutations cause moderately diminished responses to neurotransmitter functionality, then the administration of Hypocretins might improve the symptoms. Since Hypocretins can be found in the region of the hypothalamus where peptides are encoded, it can be safe to suggest that they are the basis of peptide formation. The lack of Hypocretins can cause the underproduction of certain peptides causing reverse effects in the brain from normal function. If the Hypocretins are produced at a lower rate or if the signals are transferred incorrectly then that would cause an insufficient production of GABA and glutamate balance. Also, if Hypocretins have a role in monoamine and acetylcholine release similar to the role they have been shown to have in GABA and glutamate release, than Hypocretin hypofunction could cause the accumulation of dopamine and the upregulation of several receptor sites that is observed in narcoleptics.\[13\]

Furthermore, clinical studies have shown modafinil to have no long-term side effects and dependence. I would have to disagree. Comparing the data of Hypocretins, and the mechanisms of modafinil, there appears to be a definite linkage. In addition the mechanisms for the cause of narcolepsy are also left undefined except for their possible relation to the Hypocretin 2 gene. Although the role of Hypocretins has not yet been exclusively established, it has been thought that they affect wide regions of the brain, possibly affecting many different neuronal activities. The administration of modafinil and its effects on Hypocretins may cause some beneficial outcomes, but there must be regions of the brain in which modafinil doesn’t act as kind. Like all molecular processes in human anatomy, each single, minute aspect contributes to all bodily functions. Sometimes these aspects are so minute, they are difficult to find, like Hypocretins. Hypocretins, more than likely, affect other tiny neuroaspects that are yet to be discovered, and modafinil has an affect on these aspects as well, whether they be good, bad or both.
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Naltrexone Hydrochloride: An Opiate Antagonist

Prepared for Dr. Mancini
Professor of Organic Chemistry
Paradise Valley Community College

by
Erica Takimoto
Organic Chemistry Student
Paradise Valley Community College
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Abstract

Naltrexone Hydrochloride is a revolutionary drug that is proven to be extremely effective in opiate antagonist activities. It has lead to monumental new discoveries in the treatment of opiate addiction. Its efficacy is attributed to its structure and stereospecific binding at opiate receptor sites. Pharmacokinetic and pharmacodynamic activities are of great importance and are addressed within the following composition. The synthesis of a chosen opiate (heroin) as well as naltrexone will be examined as well as the similarities between structures. Several current methods of naltrexone use are also discussed, and a final deduction is stated.

Introduction

For centuries, man has sought relief from pain and discomfort through the use of medicaments which contain opiates. In the early 19th century, an opium derivative called morphine was introduced as an analgesic. It was soon discovered that opium derivatives caused tolerance, dependence, and addiction, therefore resulting in abuse.

In the late 19th century, morphine was acetylated with acetic anhydride (see figure 3) to form a more potent analgesic called heroin 1. Initially, this new drug was also used as a remedy for pain and was a proposed treatment for morphine addiction. Although heroin was indeed a more effective analgesic, unfortunately, it also created greater dependence. More than one hundred years later, opiate addiction is still a prevalent problem without a cure.

It is this problem that has given chemists the initiative to create another division of drugs known as "narcotic antagonists." These new drugs do not possess the same characteristics as analgesics, instead they counteract the effects of opiates.

Naltrexone Hydrochloride is one of the more effective narcotic antagonists that is used to treat opiate addicted individuals. The rationale behind the development of narcotic antagonists suggests that addicted individuals who receive the narcotic antagonists, such as naltrexone, will discontinue to search for opiates because euphoric reinforcements brought on by self administration cannot be felt 2.

Although terminating an addiction is not completely a physical task, naltrexone has been proven to be successful in blocking the euphoric effects associated with opiate use. This phenomena has been achieved by producing a specific chemical structure through many complex chemical reactions. This structure is stereoselective when binding to receptor sites and the "lock and key" bind that results is stronger than that of the opiate binding. The result is a blockage of opiate binding and therefore feelings of pleasure do not occur (see figure 1) 2.

Figure 1.
Structure and Physical Properties

Naltrexone is a synthetic congenor of oxymorphone (a derivative of morphine). The structures differ as the methyl group on the nitrogen atom is replaced by a cyclopropylmethyl group. The methyl group on oxymorphone gives the molecule an agonist characteristic, and just by substituting the methyl group for a cyclopropylmethyl group, the molecule character (now naltrexone) changes to that of an antagonist. (see figures 3 and 4). The structures are very closely related and only differ slightly, which again proves the importance of stereochemistry. (The structure of naltrexone is shown in figure 4). The chemical name for naltrexone is (5a)-17-(cyclopropylmethyl)-4,5-epoxy-3,14-dihydroxymorphinan-6-one. The molecular formula for naltrexone is C20H23NO4. Its melting point is 168-170 C, and its molecular weight is 341.412.

Pharmacokinetic Activity

Naltrexone has been introduced to the human body by both oral tablets and occasionally, pellet implantation. The drug has an oral absorbency rate of 96%. As naltrexone enters the body, it is converted into metabolites, some of which have great therapeutic effects and others which have little or no antagonistic effects at all. Naltrexone is converted in the liver, by a reduction of the 6 keto group, to its major metabolite 6-B-hydroxynaltrexone. (see figure 2).Naltrexone's major metabolite, 6-B-hydroxynaltrexone, is a pure opiate antagonist. It has a high affinity for opiate receptors and is responsible for the antagonistic efficacy of the drug. (The structure of the metabolite is shown in figure). Other minor metabolites such as 2-hydroxy-3-methoxy-6-B-naltrexol (HMN) have weak opiate receptor affinity and exert primarily little or no antagonistic characteristics 3.

\[\text{Naloxone} \rightarrow \text{6-B-Hydroxynaltrexone}\]

Figure 2.

Pharmacodynamic Activity

Naltrexone is a revolutionary drug that competetively binds to opiate receptors. As the drug binds to these receptor sites, the effects of the opiates, such as feelings of euphoria and detachmenet, cannot be felt. Not only does the naltrexone eliminate feelings of euphoria, but it also completely reverses the physical symptoms associated with overdose.

As in most cases of a heroin overdose, vital signs diminish which include respiration depression and the lowering of blood pressure. If naltrexone is administered to an individual who has overdosed, the naltrexone will occupy the receptor sites by "kicking out" the opiates, and within one to two minutes, respiration and blood pressure begin to return to normal 4.
For individuals who are physically dependent on opiates, naltrexone will trigger an immediate withdrawal. Naltrexone has very few intrinsic actions besides opiate blocking although it causes constriction of the pupils by an unknown mechanism. Naltrexone does not cause physical dependence or tolerance and therefore is safe to use for extended periods of time. There are no withdrawal symptoms that occur if the user suddenly stops taking naltrexone.

**Synthesis**

Naltrexone was created to counteract the actions of detrimental opiate drugs that cause dependence and addiction as well as horrifying side effects. In order to synthesize a drug that would competitively bind to opiate receptors stronger than the opiates themselves, chemists had to design a molecule that would sterospecifically attach to receptor sites. Ironically, this antidote is formed with molecular and physical likenesses of the original opiate. Just by altering certain functionalities within the molecule, the behavior of the opiate is completely reversed from agonist activity to antagonist. (Figures 3 and 4 below show the synthesis mechanisms of both heroin and naltrexone.) The molecular and physical similarities of heroin and naltrexone can be easily observed.

The synthesis of heroin is done by obtaining morphine, an extraction of opium, and then acetylation it with acetic anhydride. This was discovered in the 19th century and was done to increase the analgesic properties of morphine. Originally this was thought to be a non-addictive pain killer.

![Synthesis of Heroin](image)

**Figure 3.**

Naltrexone is synthesized by acetylayting 7,8-dihydro-14-hydroxymorphinone, then the N-methyl group is removed by cyanogen bromide. The acetyl groups are hydrolyzed with a dilute solution of hydrochloric acid, and the nitrogen is then alkylated with cyclopropyl bromide.

![Synthesis of Naltrexone](image)

**Figure 4.**
Uses of Naltrexone Hydrochloride

The most common use of naltrexone hydrochloride is to prevent a relapse for individuals who wish to remain opiate free by a method of daily oral administration. Naltrexone hydrochloride is also used in emergency situations such as an accidental opiate overdose, to reverse detrimental effects and sustain vital signs. Occasionally it has been used to treat individuals with chronic alcoholism however it is more common for opiate addicted individuals to receive the drug.

Naltrexone hydrochloride is also used in a method known as rapid opiate detoxification under general anesthesia (RODA) and naltrexone induction followed by naltrexone pellet maintenance therapy, which was first successfully completed in Cairo, Egypt in October of 1995. This is the most intense and intriguing use for naltrexone thus far.

Many individuals who have a chronic opiate addiction cannot independently and successfully withdraw from opiates because the physical withdrawal is too strenuous on the body. This method allows a rapid detoxification while under anesthesia so that the painful effects cannot be felt. Although this seems like a quick fix for addicts who desire to escape the hardship of coming clean, this is a rather complex procedure.

The patient who wishes to be detoxified is first put under a combination of anesthesia and muscle relaxers such as Propofol and Norcuran respectively. Respiration and blood pressure are closely monitored. Then, approximately 1.6 to 2 mg of naltoxone, which is similar to naltrexone except that is is milder in its antagonistic activities and has a shorter half life, is intravenously injected. This milder version of naltrexone is administered initially so that the body eases into the detoxification process, however without the anesthesia, the body would almost instantly precipitate violent withdrawal symptoms. Approximately twenty minutes to one-half an hour after the naltroxone is administered, 12.5 to 25 mg of naltrexone are given. Further doses of naltrexone are given two or three hours later so that the total dosage given is approximately no less than 50 mg and no more than 200 mg.

Following the naltrexone administration, few signs of withdrawal can be seen such as sweating or tremors which are alleviated by dispensing more Norcuran. The final step of the procedure is the implantation of the naltrexone pellet.

The area of pellet implantation, which is usually the lower region of the abdomen, is sterilized and anesthetized with 2% Lidocaine. An incision approximately one-half inch in length is made with a #15 blade. A pocket is then created adjacent to the incision with blunt curved scissors. A naltrexone pellet weighing 1 gram is inserted into the pocket and the incision is closed with two simple stitches.

As the individual emerges from the anesthesia, they may experience withdrawal symptoms such as shaking, muscle cramps, drowsiness, nausea or even restlessness. Most individuals are released within the same day of detoxification, although some are not discharged if withdrawal symptoms are persistent.

With the naltrexone pellet implanted in under the skin, the individual will not be able to feel the pain relieving effects of opiates as well as most analgesics. Therefore, in case of an injury, patients are advised to wear a medic alert tag that communicates this so that proper pain medication can be prescribed.
There is a loss of tolerance to the effects of opiates as the individual remains on naltrexone. Should the individual decide to relapse after the naltrexone wears off, and use the same dose of opiates as before, there is a very high risk of overdose in which death can result.

Although there are detoxification clinics located around the world in London, Cairo, and Athens, there are very few clinics in America that offer the rapid detox procedure. Several clinics located in New Jersey and Atlanta, Georgia continue to engage in the procedure. Rapid opiate detoxification was also performed on a number of individuals at a surgery center in Tempe, Arizona.

Conclusion

Naltrexone is one of the more astonishing drugs that modern chemistry offers today. It is an extremely efficient narcotic antagonist, possibly the best in its class. It is known to be one of the best because as it reverses the detrimental effects of opiate overdose, it produces no side effects of its own.

It is more logical to use naltrexone in the aid of heroin abstinence rather than methadone because it does not produce euphoric reinforcements, tolerance or dependence. Heroin is thought to be the most addictive drug and with this new remedy, many addicts have a chance at sobriety who would otherwise remain addicted. Many heroin addicts fear the withdrawl that can linger for up to six months in some cases. The rapid opiate detoxification process is an ideal alternative for individuals who have a high risk for relapse. The pellet implantation is a sure way to prevent regression while the individual adjusts to necessary lifestyle modifications. Oral self-administration of naltrexone should be reserved for the more highly motivated individuals.

Although naltrexone will unequivocally prevent a relapse, it is imperative that the recovering individual seek other methods to remain opiate free such as a support groups and lifestyle modifications. Naltrexone is a "crutch" that can be used in recovery, and should not be looked upon as an instantaneous cure.
References


Carbon fiber composite

By Eric Weiss, April 2000
Introduction:
PAN based carbon fibers were developed by Dr. Shindo of Japan around 1960(1). These fibers, when mixed with a resin in the form of a composite, form a material that has low weight, high rigidity, high strength and great resistance to heat. Due to these unique properties, carbon fiber is becoming the material of choice for many applications ranging from aviation to architecture, with new uses being discovered each day. Demand for this product's remarkable qualities has prompted investigation into the invention of new materials and improvement of existing ones through the addition of carbon fiber. This paper will explore some of these uses and some of the research that is currently underway.

Background:
Vince Kelly of Tenax, a subsidiary of Toho Rayon Co. of Japan, explains what carbon fiber is and how it is made:
Carbon fibers are derived from one of two precursor materials PITCH and PAN (Polyacrylonitrile fibers) PITCH based carbon fibers have lower mechanical properties and are therefore rarely used in critical structural applications. PAN based carbon fibers are under continual development and are used in composites to make materials of great strength and lightness. The raw material of PAN, acrylonitrile (AN), is a product of the chemical industry and can be manufactured as follows:
Acrylonitrile (AN) is used as a raw material in acrylic fibers, ABS resin, AS resin, synthetic rubber (NBR), acrylamide and other materials. Global production capacity is 4.67 million tons, approximately 60% of which is consumed for acrylic fibers. In the early manufacturing processes acetylene and hydrogen cyanide (HCN) were used as a raw material, whereas today nearly all AN is manufactured using what is called the Sohio process, whereby an ammoxidation reaction are applied from inexpensive propylene and ammonia. Technological advances, particularly surrounding research into improved catalysts for the Sohio process, are proceeding, promoted by a concern for energy conservation and lessening the environmental loading. The research aims include improved productivity, reduced byproducts, and lesser wastewater and waste gas.
2. Sohio process. The Sohio process was perfected in 1960 by The Standard Oil Co. of Ohio, owing to the development of an epoch-making catalyst that synthesizes AN in a single-stage reaction using propylene and ammonia. The reaction took place using the fluid-bed method. The P-Mo-Bi group is used as the catalyst and favorable fluidized conditions are maintained by adjusting the physical properties of the catalyst.

\[
\text{CH}_2=\text{CHCH}_3 \text{+ NH}_3 \text{+ 3/2O}_2 \rightarrow \text{CH}_2=\text{CHCN} \text{+ 3H}_2\text{O}
\]

The reaction gas contains not only AN, but also acetonitrile, hydrogen cyanide and other byproduct gasses, so AN products are obtained by having the reaction gas absorbed into water, then using evaporation separation.
5. Improved processes
The Sohio process was epoch-making at the time it was developed, but improvements have been made in response to the following conditions:

(1) The AN yield of approximately 60% was not very high.
(2) The process circulated and used large amounts of water, requiring a lot of energy.
(3) Approximately 1.5 tons to 2 tons of wastewater was generated for every ton of AN produced.
(4) Treatment technology for the waste gas was incomplete. I. Improved catalyst.

![Sohio process diagram]

II. Steam reduction
Monsanto Corp. improved the water extractive distillation stage of the Sohio process, reducing the amount of steam required to produce one ton of AN by three tons.

III. Wastewater and waste gas treatment
AN wastewater normally contains ammonium sulfate, along with small amounts of nitrile compounds, hydrocyanic acid and compounds with a high boiling point. Alkali used to be added to the wastewater before discharging, but nowadays wet oxidation processes and biological treatment processes are being employed. Bayer Inc. has developed the technology to recover high-grade ammonium sulfate from the gas generated as a byproduct of the reaction.

Polymerisation of acrylonitrile produces PAN, the most common carbon fiber feedstock.

*The basic unit of PAN is:*
Polyacrylonitrile

\[
\begin{align*}
&\text{CH - CH}_2 - \text{CH - CH}_2 - \text{CH - CH}_2 - \text{CH - CH}_2 - \text{CH - CH}_2 - \text{CH - CH}_2 \\
&\quad | \quad | \quad | \quad | \quad | \quad | \\
&\quad \text{CN} \quad \text{CN} \quad \text{CN} \quad \text{CN} \quad \text{CN} \quad \text{CN} \\
\end{align*}
\]

The Manufacturing Process
The conversion of PAN to carbon fibers is normally made in 4 continuous stages
- Oxidation
- Carbonisation (Graphitisation)
- Surface treatment
- Sizing

**OXIDATION** involves heating the fibers to around 300 deg C in air. This evolves hydrogen from the fibers and adds less volatile oxygen.

<table>
<thead>
<tr>
<th>Polyacrylonitrile</th>
<th>Oxidised Polyacrylonitrile</th>
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<tbody>
<tr>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>C</td>
<td>CH_2</td>
</tr>
<tr>
<td>CH - CH_2 - CH - CH_2</td>
<td>CH CH CH + heat</td>
</tr>
<tr>
<td>CN</td>
<td>CN</td>
</tr>
<tr>
<td>Air to 300°C</td>
<td></td>
</tr>
<tr>
<td></td>
<td>C C C</td>
</tr>
<tr>
<td></td>
<td>N N NH</td>
</tr>
</tbody>
</table>

The polymer changes from a ladder to a stable ring structure, and the fiber changes color from white though brown to black. The resulting material is a textile fiber which is fireproof, some companies actually sell this as an end product for example SGL Technic (Scotland), under the tradename PANOX. (OXidised PAN)
CARBONISATION (GRAPHITISATION) involves heating the fibers up to 3000 °C in an inert atmosphere, the fibers are now nearly 100 % carbon.

Comparison of standard grade carbon fiber to high tensile steel.

<table>
<thead>
<tr>
<th>Carbon Fiber Vs. Steel</th>
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<tbody>
<tr>
<td>Series 1 = Carbon Fiber</td>
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<tr>
<td>Series 2 = Steel</td>
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</table>

<table>
<thead>
<tr>
<th>Tensile Strength (Gpa)</th>
<th>Tensile Modulus (Gpa * 10^-2)</th>
<th>Density (g/ccm)</th>
<th>Specific Strength (Gpa)</th>
</tr>
</thead>
</table>

Chart based on information from Vince Kelly (2)
The first of these terms, tensile strength, refers to the materials ability to resist loads without breaking. The second, tensile modulus refers to the materials stiffness or elasticity. Density is a measure if grams per cubic centimeter. And, specific strength is a measure of strength per specific gravity.

Now that we understand what carbon fiber is, how it’s made and what it’s properties are, we will explore what research is underway and what carbon fiber is currently being used for.

Architectural:

Carbon fiber is being researched for use in construction of marine and other structures such as bridges and buildings. This research involves among other things the effects of the environment such as UV light and water absorption on carbon fiber reinforced structures as well as strength considerations when added to concrete, wood and steel (3)(4).

Toho Rayon Co. developed a new carbon fiber based material for architectural purposes with the advent of carbon fiber reinforced, glued laminated timber. “This new (CFR-glulam) based on a new phenolic resin and new development methods, demonstrated increased fire endurance while doubling flexural modulus and strength.”

Clean energy:

According to Toho Rayon Co., “new industrial uses have increased markedly in keeping with the major concerns of the 21st century such as safety, low carbon dioxide emission, new and clean energy, environmental conservation of the earth. For example, the demand for compressed natural gas (CNG) and natural gas tanks produced with CF for vehicles has increased because of their effective uses for low carbon dioxide emission and clean exhaust gas. In the clean energy field, carbon fiber reinforced carbon (C/C) plates for fuel cells and carbon fiber reinforced plastic (CFRP) blades for wind power generators have also begun to be used.” One such study, investigates the use of a carbon fiber anode in an H2O2 fuel cell (5). Filtration of hazardous materials such as Ammonia gas is another example of environmentally friendly use of carbon fiber (6).

Medicine:

Carbon fiber is used for medical applications such as the use of carbon fiber microelectrodes in the field of neuroscience (7). And, “in the field of dentistry carbon fiber posts (CFP) are widely used in the restoration of endodontically treated teeth to enhance the mechanical behavior in spite of metallic posts and to prevent vertical fractures of the tooth under chewing loads” (8).
Leisure and sporting goods:

Carbon fiber is becoming the new standard in the sporting goods industry. Carbon fiber, or carbon based tennis rackets and fishing rods have been around for years. Recently, the use of carbon fiber has extended to golf clubs and is quickly becoming the standard for bicycles with entire bicycle frames being made from this low weight, high strength material. Other high-end applications include yacht and windsurfing masts (9). One study was conducted to determine the influence of stiff shoe mid-soles on vertical jump performance. A carbon fiber plate was used to stiffen the mid-sole of the shoes. It was found that the stiff soled shoes did increase vertical jump height on average of 1.7 cm for a group of 25 subjects (10).

Transportation:

The automotive industry is seeing more and more use of carbon fiber. Toho Rayon Co. is currently producing friction parts such as break pads and clutch components that use carbon fiber, and the durability of carbon fiber mechanical components such as carbon fiber reinforced gears are being investigated (11).

Aviation and aerospace:

Due to its high strength and low weight, carbon fiber is quickly becoming the material of choice for the aviation and aerospace industry with such innovations as deployable solar wings for the Scientific Microsatellite for Advanced Research and Technology, (SMART) (12). And, the pride of the U.S. military and perhaps the most technologically advanced aircraft in the world, the B-2 stealth bomber is made almost exclusively of carbon fiber (Northrop Grumman).

B-2 Stealth bomber
The future of carbon fiber:

Carbon fiber's combination of low weight, high strength and high modulus make it a unique and remarkable material. With so many conceivable uses and so much effort currently being put into the improvement of carbon fiber, there is no doubt that the use of carbon fiber will increase and that improvements will continue. As improvements continue and as increasing environmental concerns pressure our transportation industry for the design of lighter and hence, more fuel-efficient vehicles, we should see carbon fiber being used with greater frequency and in an increasing number of applications where strong, rigid and lightweight materials are desired.
Reference list


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