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

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

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

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

I would like to dedicate this symposium to the Dr. Rick Vaughn, PVCC math faculty. Through his hard work and leadership, this college was able to receive reaccreditation from the Higher Learning Commission (HLC) for another 10 years. Over the two plus years of this project Dr. Vaughn never lost sight of his mission and purpose. His leadership and direction allowed a diverse group of faculty and staff to achieve this success. As educators and students we acknowledge his efforts.

William L. "Hank" Mancini, PhD
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COPAXONE
FOR TREATMENT OF RELAPSING REMITTING MULTIPLE SCLEROSIS

Prepared for
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By
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CHM 236
Paradise Valley Community College
April 22, 2005
ABSTRACT

Multiple Sclerosis (MS) is a chronic autoimmune inflammatory disease of the Peripheral and Central Nervous Systems (PNS, CNS). Although no cure has been found, the past decade has revealed many treatments useful in delaying the progression of MS. Copaxone (Glatiramer Acetate, GA) has been especially useful in Relapsing Remitting MS sufferers. GA is speculated to have anti-inflammatory and neuroprotective effects; GA reportedly works by blocking major histocompatibility complex and T cell activation receptor cites. Such qualifications may serve as an interceptor to the disease in early stages and prevent the disease from further demise on the patient.

INTRODUCTION

Multiple Sclerosis is a debilitating disease caused by inflammation of the Central and Peripheral nervous systems. The white matter of the CNS is specifically affected. Due to the inflammatory damage in the white matter, plaques (lesions) form in the brain. These lesions are also referred to as black holes. Research thus far indicates that certain types of white blood cells begin attacking the myelin tissue that surrounds the nerve cell. This myelin sheath acts as an insulator and conductor of nerve impulses. Because this myelin is deteriorated, the communications on the nerve cell do not function properly, if at all. Such autoimmune attacks result in damage to the myelin sheaths, oligodendrocytes and minimal damage to the axons and neurons.4

Due to the demyelination and other damage concerning the CNS, MS outbreaks include blurred vision, diplopia, sensory inhibitions in arms and legs, bladder and bowel dysfunction and impaired muscle coordination (ataxia).4 These symptoms are usually the first indications of an initial type of MS called Relapsing Remitting. Many Scientists believe that if MS can be diagnosed while in early progression and matched with an appropriate treatment, the patient may be able to slow the progression of the disease.2 The need for treatments to delay the progression of this disease is imperative so further studies can be performed to pinpoint the direct causes and establish a cure. In order for adequate treatment of such a mysterious disease, 4 clinical diagnoses have been developed, each with different standards of beneficial treatment outlined.
TYPES OF MS

MS usually presents first symptoms for sufferers while in their twenties or thirties, in twice as many women as men. The disease has been associated with genetic predisposition. The severities of the symptoms experienced depend on the type of MS. Four types or “Clinical Courses” of MS have been defined (from least to greatest severity): Relapsing/Remitting (RRMS), Secondary Progressive (SPMS), Progressive Relapsing (PRMS), and Primary Progressive (PPMS). The following pictures graphically demonstrate the disability over time for the specific type of MS indicated. The “peaks” (upward trend) represent periods of time in which symptoms (relapses) are experienced.

1. Relapsing/Remitting (RRMS):

RRMS entails periods of symptoms (also called relapses or exacerbations) followed by periods of remission. Remission can be swift or gradual and may incorporate full or partial recovery from symptoms. RRMS is usually indicative of mild or beginning stage MS.

2. Secondary Progressive (SPMS):

A RRMS sufferer may experience gradual worsening of the disease between relapses; this is defined as Secondary Progressive. In the early phases, the person may still experience a few relapses but after a while, these merge into a general progression with no minimal recovery. Studies indicate between 10-30 years after initial symptoms, 50-90% of MS sufferers will have transgressed to SPMS.
3. Progressive Relapsing Multiple Sclerosis (PRMS):

This form of MS is categorized by a progressive course. Recovery from relapses is often immediate, but in between each remission the degree of symptoms experienced worsen.

4. Primary Progressive (PPMS):

PPMS displays gradual a progression from its onset; however, no remissions are involved. Plateaus may occur in exacerbations characterized by initial disease activity in the spinal cord, not the brain. This type frequently migrates into the brain; however, it is usually not as damaging as RRMS in terms of cognitive disability. Men are just as susceptible to this form as are women and this course usually is encountered when a person is in their late 30’s to early 40’s.

TREATMENTS FOR MS

The tribulation of treatments for MS is still an ongoing endeavor. Treatments include the Interferon-betas such as Avonex, Betaseeron, and Rebif; a chemotherapeutic agent called Novantrone (Mitoxantrone); and another non-interferon called Copaxone. Different treatments are recommended for different types of MS.

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<th>Clinical Sub Form</th>
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<tr>
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<td>SPMS (secondary progressive) with relapses</td>
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<td>SPMS (secondary progressive) without relapses</td>
<td>1. Mitoxantrone</td>
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<tr>
<td></td>
<td>2. Cytoprophospholipid</td>
</tr>
<tr>
<td>PPMS (primary progressive)</td>
<td>None</td>
</tr>
<tr>
<td>PRMS (progressive relapsing)</td>
<td>None</td>
</tr>
</tbody>
</table>

<www.unitedspinal.org>
COPAXONE FOR RRMS

Many sources indicate that with the proper analyses performed over time, Copaxone has qualities characteristic of performing protective affects in the CNS and PNS, possibly preventing further damage to these areas and maybe helping to delay the progression of the disease while further studies are coordinated to find a curative result for the disease. Several clinical trial provide evidence indicating that GA when used for RRMS can successfully delay the demyelination process in early stages and possibly prevent the lesion from becoming a black hole. A black hole is a term used when a neuron is without myelination and therefore is rendered useless.

Copaxone, also known as Glatiramer Acetate (GA) and Copolymer-1 is the only approved non-Interferon treatment for Relapsing-Remitting Multiple Sclerosis (RRMS).² Copaxone is administered daily via 20 gram subcutaneous injections. GA causes site irritation but does not cause flu-like symptoms or depression like the interferon drugs. Copaxone users will not experience necrosis or blood abnormalities.² Studies evaluating the effectiveness of this treatment have been in the works since 1995.² Such studies have demonstrated a decrease in the exacerbation rate of sufferers of RRMS. Many sources indicate that with the proper analysis and time, GA will perform protective affects in the CNS and PNS and may possibly prevent further damage to these areas. It is also suggested that GA may be useful in not only delaying the progression of RRMS but possibly slowing the disease from advancing to another course (ie: RRMS to SPMS).

STRUCTURE

Copaxone
(Gla, Ala, Lys, Tyr)₉ CH₃COOH
(C₃H₉NO₄C₃H₇NO₂C₆H₁₄N₂O₂C₉H₁₁NO₃)₉ C₂H₄O₂
Cas-147245-92-9

<http://chem.sis.nlm.nih.gov/>
PHYSICAL AND CHEMICAL PROPERTIES

Glatiramer acetate (GA) is comprised of a mixture of 4 synthetic polypeptides: L-glutamic acid, L-lysine, L-alanine, and L-tyrosine. The average molar fraction of the synthetic polypeptide salt is 0.141, 0.338, 0.427 and 0.095, respectively. The average molecular weight is 5,000-9,000 atomic mass units. This long chain usually averages approximately 45-100 amino acids, and closely resembles that of the Myelin Basic Protein (MBP), a vital component in myelin sheaths in nerves.

Copaxone injections are unit dosed for daily subcutaneous injection. In each single dose vial contains 1 ml of liquid, comprised of 20 mg of Glatiramer Acetate in 40 mg of mannitol. The solution is generally clear or pale yellow in color. The pH is a general range of 5.5 to 7.0.

\[\text{L-glutamic acid} \quad \text{L-lysine} \quad \text{L-alanine} \quad \text{L-tyrosine}\]

SYNTHESIS

In 1971 The European Journal of Immunology printed the original synthesis of Copaxone. Originally named Copolymer 1, this large molecule was used in experimental allergic encephalomyelitis (EAE). Copolymer 1 demonstrated suppressive effects on the disease. The polymer reduced incidence of the disease in clinical trials as well as decreased the occurrence and size of EAE-induced lesions.

"Cop 1 was prepared form N-carboxyanhydrides of tyrosine [12], alanine [13], \(\gamma\)-benzyl glutamate [14] and e, N-tri-fluoroacetyllysine [15]. The polymerization reaction was carried out at room temperature in anhydrous dioxane with diethylamine as initiator. The deblocking of the \(\gamma\)-carboxyl groups of the glutamic acid was carried out with hydrogen bromide in glacial acetic acid [16], and was followed by the removal of the trifluoroacetyl groups from the lysine residues by 1 mole of piperidine [17]."
STRUCTURE DETERMINATION

The following IR spectrum is indicative of Copolymer 1. Characteristic peaks of the C=O at 1720 cm⁻¹, The C-H at right of 3000 cm⁻¹, are displayed.⁵ The presence of chromophores in the UV spectrum is indicative of unsaturated bonds in the glutamic acid, a major component of GA.

![Graph showing IR spectrum and UV absorption]

**Figure 1:** Espectros FTIR do copolímero 1 e dos homopolímeros PLA e PEO-4000

<http://probes.invitrogen.com>

MECHANISM

Over the past five years, clinical breakthroughs have confirmed speculations as to the mechanism GA takes in treating RRMS. In 2001, The Drug Information Handbook documented the mechanism as a result of studies to date. A look at a later article from the journal of Neurology confirms these mechanisms and presents data in support of in vitro versus in vivo. GA has demonstrated the ability to affect immune cells specific for MBP.⁴ "GA is thought to suppress T-lymphocytes specific for a myelin antigen, it is also proposed that GA interferes with the antigen-presenting function of certain immune cells opposing pathogenic T-cell function."⁵

Four major mechanisms of action have been defined in the treatment of multiple sclerosis with Copaxone.⁴ First, GA competes with myelin basic protein (MBP) for binding sites to major histocompatibility complex (MHC) molecules.⁴ Second, GA in conjunction with MHC competes with MBP/MHC for binding to the T cell receptor.⁴ Third, GA exhibits involvement in activating and withstanding the beginning phases of MBP-specific T cells.⁴ Fourth, the GA has demonstrated capability towards “induction of T-helper 2-(TH2) – like regulatory cells.”⁴
MECHANISM OF GLATIRAMER ACETATE

As displayed above, upon subcutaneous injection of 20 mg Copaxone, the drug incorporates itself onto the binding receptor and does not allow MBP to bind. This "promiscuous binding" allows for the GA to replace the MBP and therefore inhibits further attack on the neuron and prevents demyelination. GA also shows promising data in support of its anti-inflammatory and neuroprotective qualities by crossing the Blood Brain Barrier.

STEREOCHEMISTRY

The GA/MHC complex has also displayed in vitro evidence of competition for the MBP/MHC complex for binding to the T-cell receptor (TCR). In vitro studies have also displayed evidence of the ease with which GA binds to MHC class II molecules. Stereochemically, the D-isomer of GA binds to the MHC class II just as efficiently as the L-isomer, however this isomer does not suppress the disease in the animal model. The article suggests this competition for MHC binding is not the exclusive attributing factor to explain the benefits of GA treatment in RRMS.

D-glutamic acid vs. l-glutamic acid (chemfinder.com)
GA DECREASES BRAIN LESIONS

In addition to the neuroprotective factors, GA has also been reported to reduce the likelihood of new MS lesions becoming black holes. In vivo results displayed this potential neuroprotective effect. Several studies including MRI trials have displayed significant evidence concerning GA's potential to lessen the degree to which brain lesions effect the RRMS sufferer along with a total decrease in actual new lesions formed.

CONCLUSION

Although no cure for Multiple Sclerosis is on the horizon, the diligence of scientists and MS sufferers is certain to ascertain success. GA has shown a reduction in frequency of attacks and overall decrease in the rate of debilitation. This specific treatment has shown optimal results when used in patients with mild RRMS.

The clinical trials over the past decade have revealed that a Copaxone has potential to limit the RRMS sufferers cognitive attacks. GA attaches to the binding sites and exerts a somewhat neuroprotective effect by becoming like MBP. However, MBP seems to be linked with the disease's autoimmune pathogenesis. Instead of the axonal terminal becoming damaged and the myelin atrophying, the synthetic amino acid penetrates the blood brain barrier and assumes the MBP's position in a non-harmful way. Moreover, recent studies have indicated that Copaxone's anti-inflammatory effects have prevented new lesions from forming on the brain. Although the four types of MS are not linear in progression, these studies performed on initial RRMS sufferers offers a window of opportunity to the advancement in Multiple Sclerosis treatments.
References


PSYCHOSTIMULANTS AND ATTENTION DEFICIT DISORDER

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Course: CHM 236 ORGANIC CHEMISTRY
Date: April 20, 2005
PSYCHOSTIMULANTS AND ATTENTION DEFICIT DISORDER

Abstract
This report examines the use of psychostimulants in the treatment of ADD/ADHD. Common psychostimulants will be identified and their psychopharmacology/chemical and biological functions will be explored. This report also provides a discussion of one of the more effective medications used to treat ADD/ADHD, Dextroamphetamine, and its synthesis, mechanism of action, pharmacokinetics, and adverse effects.

INTRODUCTION: ADD/ADHD

Attention Deficit Disorder (ADD), also known as Attention Deficit Disorder Hyperactivity Disorder (ADHD), is the most commonly diagnosed behavioral disorder in children, estimated to affect 3 to 5 percent of school-age children in the United States\(^1\). Its core symptoms include developmentally inappropriate levels of attention, concentration, activity, distractibility, and impulsivity. Children with ADD/ADHD usually have functional impairment across multiple settings including home, school, and peer relationships. ADD/ADHD has also been shown to have long-term adverse effects on academic performance, vocational success, and social-emotional development.

Despite the progress in the assessment, diagnosis, and treatment of children and adults with ADD/ADHD, the disorder has remained controversial. For example, the diverse and conflicting opinions about ADD/ADHD have resulted in confusion for families, care providers, educators, and policymakers. The controversy raises questions concerning the literal existence of the disorder, whether it can be reliably diagnosed, and, if treated, what interventions are the most effective.

Although the diagnosis of ADD/ADHD can be made reliably using well-tested diagnostic interview methods, as of yet, there is no independent valid test for ADD/ADHD. Although research has suggested a central nervous system basis for ADD/ADHD, further research is necessary to firmly establish ADD/ADHD as a brain disorder. This is not unique to ADD/ADHD, but applies as well to most psychiatric disorders, including disabling diseases such as schizophrenia. Evidence supporting the validity of ADD/ADHD includes the long-term developmental course of ADD/ADHD over time, cross-national studies revealing similar risk factors, familial aggregation of ADD/ADHD which may be genetic or environmental, and heritability.

Another major controversy surrounding ADD/ADHD concerns the use of psychostimulants to treat the condition. Psychostimulants, including amphetamine and methylphenidate are, by far, the most widely researched and commonly prescribed treatments for ADD/ADHD. Since psychostimulants are more readily available and are being prescribed more frequently, concerns have intensified over their potential overuse and abuse.
This report will discuss the psychopharmacological/chemical and biological functions of common psychostimulants used to treat ADD/ADHD. One of the more effective medications available to treat ADD/ADHD is Dextroamphetamine (Dexedrine). This report will, therefore, examine the synthesis, mechanism of action, pharmacokinetic, and adverse effects of Dextroamphetamine.

PSYCHOSTIMULANTS

The primary medications used for the treatment of ADD/ADHD are psychostimulants. The most important of these stimulants are the original drug, amphetamine, and its close chemical relations, methamphetamine. Psychostimulant-related drugs are central nervous system stimulants whose actions resemble those of adrenaline and noradrenaline, produced by adrenal gland and CNS. Even though psychostimulant mimic the effects of adrenaline and noradrenaline, they act for a much longer time in the body.

I. Adrenaline

Adrenaline, also known as epinephrine, is a natural stimulant made in the adrenal gland of the kidney. Adrenaline is the body's activator, and is released in response to anxiety, exercise or fear. This is the basis of the so-called "fight-or-flight" reaction. When an animal is threatened, the options are usually either to stand its ground and fight, or run away as fast as possible. Both responses would require extra supplies of blood and oxygen in the muscles. This increases the heart and breathing rate in preparation for the ensuing action. Chemically, epinephrine is a catecholamine hormone, a sympathomimetic monoamine, derived from the amino acids phenylalanine and tyrosine. The chemical formula of epinephrine is C<sub>9</sub>H<sub>13</sub>NO<sub>3</sub>. Its chemical structure is:

![Epinephrine](image)

II. Noradrenaline

Noradrenaline, also called norepinephrine, is released from the adrenal glands as a hormone into the blood, but it is also a neurotransmitter in the nervous system where it is released from noradrenergic neurons during synaptic transmission. It is one of the "stress hormones", and affects parts of the human brain where attention and impulsivity are controlled. Norepinephrine affects the fight-or-flight response, activating the sympathetic nervous system to directly increase heart rate, release energy from fat, and increase muscle readiness. It is one of the main neurotransmitters, which means it is the chemical which jumps the gap (synapse) between nerve endings, transmitting the signal between one nerve and the next.
When it is working inside the brain, it gives rise to thought processes and emotions. The chemical formula for norepinephrine is C₈H₁₁NO₃. Its chemical structure is:

![Norepinephrine](image)

Note that the only change from adrenaline is a -CH₃ has been replaced by an H, shown in red. The basic structure of norepinephrine can be altered to produce a variety of drugs, including psychostimulants, which act on the nervous system, to either slow down or speed up certain bodily systems, or to make selected muscles contract or relax.

III. Amphetamines

Amphetamines (1-phenylpropan-2-amine) are synthetic chemicals based upon a structure closely resembling that of adrenaline and norepinephrine. These chemicals, therefore, can induce similar biological responses, such as acting as a stimulant, and creating a greater alertness and a feeling of prowess. The model for these chemicals, amphetamine, which was once widely available under the trade name Benzedrine, is very similar to norepinephrine, except that all the -OH groups are missing and an additional methyl has been added to the sidechain.

![Amphetamine](image)

Note that Amphetamine/Benzedrine is the name given to left-handed mirror image of the amphetamine molecule.

IV. Methamphetamine

Methamphetamine or Methedrine is composed of an amphetamine molecule with an additional methyl group attached to its nitrogen (amine group). The "meth" from Methamphetamine comes from methyl (-CH₃ group) replacing one of the hydrogens on the -NH₂.

![Methamphetamine](image)
Note that the methyl group added to the amphetamine structure is shown in red. For many of the known psychoactives, adding a methyl group slightly alters the effects, duration, and/or potency. For Methamphetamine, the methyl allows it a little better fat solubility and thus better penetration into the brain.

**MECHANISM OF ACTION FOR PSYCHOSTIMULANTS**

Psychostimulants produce their characteristic behavioral effects by increasing synaptic activity of the monoamine neurotransmitters, dopamine, norepinephrine, and serotonin. They are called indirect agonists because their primary effect is to increase the ability of the neurotransmitters to act, without having a direct effect on the postsynaptic receptors for these neurotransmitters. Although producing slightly different cellular and molecular effects, the final outcome for each drug in this class (an increase in monoamine activity) is quite similar.

Amphetamine, for example, has variety of cellular effects, increasing the activity of monoamines in several important ways: 1) Amphetamine stimulates the release of dopamine and norepinephrine from catecholamine nerve terminals, increasing the amount of these neurotransmitters in the synapse; 2) Amphetamine also inhibits reuptake of the catecholamines, increasing their ability to activate receptors; 3) In addition, amphetamine inhibits monoamine oxidase, the enzyme responsible for the destruction of monoamine neurotransmitters, further increasing the availability of these neurotransmitters; and 4) Finally, there is some evidence that amphetamine may directly activate catecholamine receptors, further contributing to monoaminergic activity.

Psychopharmacological research has revealed the specific brain areas and neurotransmitters responsible for the behavioral effects of psychostimulants. The most prominent monoamine neurotransmitter involved in the effects of these drugs is dopamine, which is responsible for the powerful reinforcing effects, the increase in activity, and the stereotypic and psychotogenic effects. Increased dopamine activity in a forebrain region, known as the nucleus accumbens, mediates the reinforcing effects and the motor stimulant effects of the psychostimulants. Dopamine in this brain region also appears to mediate the psychotogenic effects produced by
high doses of these drugs. Increased dopamine activity in an adjacent forebrain region, the striatum (or caudate-putamen), is responsible for the stereotypic effects of the stimulants.

**PSYCHOSTIMULANT MEDICATIONS USED TO TREAT ADD/ADHD**

Psychostimulants constitute the major pharmacological treatment of ADD/ADHD. Theoretically, these stimulants cause more blood flow to areas of the frontal lobe that are important for attention, as well as increasing synaptic activity of the monoamine neurotransmitters, dopamine, norepinephrine, and serotonin.

A variety of stimulant drugs have been utilized in the treatment of ADD/ADHD. They include Dextroamphetamine (Dexedrine), Methylphenidate (Ritalin), Adderall (Amphetamine Mixed Salts), and Pemoline (Cylert). Dextroamphetamine (Dexedrine) has been demonstrated to be one of the most effective psychostimulant in the treatment of ADD/ADHD.

**DEXTROAMPHETAMINE (DEXEDRINE)**

I. **History**

Dextroamphetamine was initially developed in the 1920's to treat depression and obesity. The use of dextroamphetamine to control hyperactivity in children has been known since its development, but dextroamphetamine did not receive FDA approval for ADD/ADHD use until the 1950's.

Dextroamphetamine became very popular in the late 60s and early 70s as a prescription diet aid because of its ability to suppress appetite. Dextroamphetamine was frequently (and illegally) used by college students, either for the stimulant high it provided or to keep them awake while studying.

Dextroamphetamine is twice as potent a CNS stimulator on a weight basis than racemic amphetamine. It also has greater CNS-stimulating activity than epinephrine or other catecholamines. Clinical uses of dextroamphetamine include the treatment of narcolepsy and as an adjunct in the treatment of attention-deficit disorder. Dextroamphetamine and other amphetamines are DEA Schedule II-controlled.

II. **Chemistry, Structure and Property**

Dextroamphetamine is the dextro isomer of the compound d,l-amphetamine sulfate, a sympathomimetic amine of the amphetamine group. Chemically, dextroamphetamine is d-amphetamine, 4-amino business. 4-hydroxyamphetamine, the d-isomer of amphetamine, and is present in all forms of Dexedrine as the neutral sulfate. Because of the presence of nitrogen molecule, dextroamphetamine and other amphetamine based compounds are considered as Alkaloids. Furthermore, the functional groups present in the molecule contribute to the activity of the compound from the chemical, the physical, and the physiologic standpoint.
Dextroamphetamine is white, odorless, crystalline powder with bitter taste and melting point of melting point of >300 and molecular weight of 368.50. It is freely soluble in water (1:10), slightly soluble in alcohol (1:800), and not soluble in ether. The empirical formal consist of C₉H₁₃N of which C 58.67%, H 7.66%, N 7.60%, and O 17.37%. The structural formula for dextroamphetamine is as follows:

![Structural formula of Dextroamphetamine (Dexedrine)](image)

**SYNTHESIS OF DEXTROAMPHETAMINE**

The synthesis of Dextroamphetamine sulfate began from D-phenylalanine. The reaction sequence proceeds through three intermediates, in which the absolute configuration of the asymmetric carbon atom is changed but the relative configuration remains the same:

**Step I:** Synthesis of (R)-(+) 2-Amino-3-phenylpropanol from D-phenylalanine

21 g (12.7 moles) of D-phenylalanine is added to a suspension of 1.3 g (34 moles) of lithium aluminum hydride in 75 ml of anhydrous tetrahydrofuran. After the addition, the reaction mixture is refluxed for 20 min and cooled to room temperature. The complex and the excess reagent are decomposed by dropwise addition of 2N aqueous sodium hydroxide and water. The white solids is collected by filtration and washed with 100 ml of tetrahydrofuran. The filtrate and washings are combined and concentrated under reduced pressure. The residual clear oil slowly crystallized and is recrystallized from ethyl acetate-hexane, 1.75 g (91%), mp 90-91° [lit. mp 91-92°], [α]D 23.8° (c 1.0, ethanol) [lit.[α]D 24.6°].

![Conversion of D-phenylalanine to (R)-(+) 2-Amino-3-phenylpropanol](image)

**Step II:** Synthesis of (R)-(+) N-(Benzzyloxycarbonyl) 2-amino-3-phenylpropanol from (R)-(+) 2-Amino-3-phenylpropanol

A mixture, of 1.5 g (9.9 moles) of (R)-(+) 2-Amino-3-phenylpropanol and 1.12 g (10.6 moles) of sodium carbonate in 25 ml of acetone and 25 ml of water is stirred at room temperature, and 1.5 ml (10.5 moles) of benzyl chloroformate is added. The reaction mixture is stirred for 3.0 hr, diluted with 50 ml of water, and acidified (to pH 2) with concentrated hydrochloric acid. The mixture is shaken with 300 ml of ethyl acetate, and
the organic phase is washed with 100 ml of saturated aqueous sodium chloride. After drying (magnesium sulfate), the filtered organic solution is concentrated in vacuo. The product is crystallized from ethyl acetate-hexane, 1.5 g (55%), mp 91-92°C, [α]D 41.3° (c 1.0, ethanol).

(R)(+)-2-Amino-3-phenylpropanol  (R)(+)-N-[Benzzyloxycarbonyl]-2-amino-3-phenylpropanol

Step III: Synthesis of (R)(+)-N-[Benzzyloxycarbonyl]-2-amino-3-phenylpropanol p-Toluenesulfonyl from (R)(+)-N-[Benzzyloxycarbonyl]-2-amino-3-phenylpropanol

(R)(+)-N-[Benzzyloxycarbonyl]-2-amino-3-phenylpropanol (1.25 g, 4.4 moles) and p-toluenesulfonyl chloride (955 mg, 5 moles) are dissolved in 100 ml of pyridine. The solution is stored at room temperature with the exclusion of moisture for 4 days. Water (2.0 ml) was added; after 30 min, the solvent is distilled under reduced pressure. The residue is partitioned between 300 ml of ethyl acetate and 75 ml of saturated aqueous sodium bicarbonate, and the organic phase is dried (magnesium sulfate).

After filtration of the drying agent and concentration of the filtrate, the residual semisolid is preparatively chromatographed on two 1-m x 20-cm glass plates coat with 750-um layers of silica gel GF, using 5% acetone in benzene as the developing solvent. The product band is removed from the plates and eluted with ethyl acetate. Concentration of the eluate afforded a clear syrup, which is crystallized from ethyl acetate-hexane, 985 mg (50%), mp 96-97°C, [α]D 29.7° (c 1.0, ethanol).

(R)(+)-N-[Benzzyloxycarbonyl]-2-amino-3-phenylpropanol  (R)(+)-N-[Benzzyloxycarbonyl]-2-amino-3-phenylpropanol p-Toluenesulfonyl


(R)(+)-N-[Benzzyloxycarbonyl]-2-amino-3-phenylpropanol p-Toluenesulfonylate (250 mg, 0.568 mmole) and 100 mg of 10% Pd/C are mixed in 30 ml of absolute ethanol, and the reaction is shaken under 50 psi of hydrogen for 1.0 hr. The catalyst is removed by filtration (celite), and the filtrate is concentrated in vacuo. The residue is partitioned between 30 ml of 1N aqueous sodium hydroxide and 200 ml of ethyl acetate. The organic solution is washed with 50ml of water.
The dried (magnesium sulfate) solution is concentrated under reduced pressure (bath temperature of 25°C), and the oily residue is distilled in vacuo (Kugelrohr apparatus) at 0.05 mm and 40-60°. The clear distillate is dissolved in 3.0 ml of ether and carefully acidified (to pH 4) by addition of 0.2N H2SO4 in ethanol. The white solid is collected by filtration, washed with ether, and dried in vacuo to give 40 mg (38%), mp >300°, [α]D 20.1° (c 1.0, water) [lit. [α]D 21.5°]. The IR spectrum is identical to that reported for this compound.5

![Chemical Structures]

**MECHANISM OF ACTION FOR DEXTROAMPHE TAMINE**

There is no conclusive evidence for the mechanism(s) of action of any amphetamines on the mental and behavioral conditions; however, the “potential” mechanism of action for Dextroamphetamine in CNS involves the release and reuptake of dopamine, norepinephrine and serotonin. The predominant mechanism of Dextroamphetamine's CNS effects is to stimulate the release of several biogenic amines from storage sites in the nerve terminal. Each molecule of Dextroamphetamine that is taken up by the nerve terminal displaces one molecule of neurotransmitter.

Finally, Dextroamphetamine may act as a direct agonist on central 5-HT receptors. Thus, Dextroamphetamine is both a direct and an indirect stimulant. Indirect agonists are associated with tachyphylaxis due to the ever-decreasing supply of endogenous neurotransmitter than can be displaced from the nerve ending. Dextroamphetamine may also inhibit monoamine oxidase (MAO), but this is a minor action.

At typical doses, Dextroamphetamine stimulates the release of norepinephrine. At higher doses, dopamine is released from its storage sites accounting for some of the behavioral changes seen with Dextroamphetamine. It is thought that the release of dopamine is responsible for the reinforcing properties of Dextroamphetamine. At still higher doses, Dextroamphetamine stimulates the release of 5-hydroxytryptamine (5-HT). It is this neurotransmitter that is thought to explain the overt psychotic behavior associated with Dextroamphetamine excess.

The primary sites of activity in the CNS appear to be in the cerebral cortex and the reticular activating system. Dextroamphetamine-induced CNS stimulation produces a decreased sense of fatigue, an increase in motor activity and mental alertness, mild euphoria, and brighter spirits. These effects are believed to be due to stimulation of norepinephrine release from central noradrenergic neurons. Lithium may offset Dextroamphetamine-induced euphoria.
I. Actions in ADD/ADHD

There is no conclusive evidence for the mechanism(s) of action of Dextroamphetamine on the mental and behavioural conditions in children. Improved attention spans, decreased distractability, increased ability to follow directions or complete tasks, and decreased impulsivity and aggression have been noted when stimulants are prescribed for the treatment of ADD/ADHD. Current research suggests that the modulation of serotonergic pathways by the Dextroamphetamine may contribute to the calming effects in the treatment of this disorder.

PHARMACOKINETICS, DISTRIBUTION AND EXCRETION

Dextroamphetamine is readily absorbed from the GI tract following oral administration. After administration of two 5 mg regular-release tablets to healthy volunteers, peak blood concentrations of 29.2 ng/ml were achieved at 2 hours post-dose. Following administration of a 15 mg extended-release capsule, peak blood concentrations were achieved within an average of 8—10 hours post-dose. However, the onset of action of Dextroamphetamine occurs before peak serum concentrations are reached; onset of action is typically within 1 hour of dosage administration.

Distribution is to most body tissues with high concentrations found in the CNS. Metabolism occurs in the liver and excretion is via the kidney. Under normal physiologic conditions, the plasma half-life of Dextroamphetamine is 6—8 hours in children and 10—12 hours in adults. The urinary elimination of amphetamines may be affected by agents that acidify or alkalinize the urinary fluids (see Drug Interactions). In general, for every 1 unit increase in urinary pH, there is a reported 7-hour increase in amphetamine half-life. Conversely, acidification of the urine speeds amphetamine elimination.

SIDE EFFECTS

The most commonly reported side effects of Dextroamphetamine are: Psychotic episodes at recommended doses; overstimulation; restlessness; dizziness; insomnia; euphoria; dyskinesia; dysphoria; tremors; headaches; exacerbation of motor and phonic tics, and Tourette’s syndrome; palpitations; tachycardia; elevation of blood pressure; dryness of the mouth; diarrhea; constipation; urticaria; and impotence.
CONCLUSION

The prescription of stimulants is the most commonly used treatment for ADD/ADHD with around 750,000 children receiving these drugs as of 1998. These medications are popular because they have been effectively shown to greatly improve the behavior of the majority of children with ADD/ADHD.

As such, the pharmaceutical industry has discovered and developed, at an unrelenting pace, a wide range of psychostimulant drugs for the treatment of varieties of psychiatric illnesses, including ADD/ADHD. Among them is Dextroamphetamine, which has already demonstrated its effectiveness placebo in the treatment of ADD/ADHD.

There are continued concerns over the safety of the long-term use of these stimulants, as well as the risks of dependence and abuse. It remains a major challenge to characterize the potential clinical significance of pharmacological differences among the many drugs already available to us, as well as their long term effects.
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Are Bacteria Smarter Than Us?

By:
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For:
Dr. Hank Mancini
CHM 236

April 22, 2005
Abstract:
Since the creation of the antibiotics, the issue of the bacterial resistance has created a shadow on its head. The scientists have come up with many ways to defeat this resistance; however, bacteria have also improved their way of defeating antibiotics. Many of these challenges have overcome with the help of the science of chemistry.

Introduction:
In the perfect world, once the first antibiotic was discovered, all the infections would have been cured and no fatality should have occurred as a result of an illness. Any bacteria would be killed as soon as we gave the patient the ideal antibiotic. Unfortunately, that is far from the reality. Although the discovery of antibiotics was a major breakthrough and saved many lives, we know today that bacteria do not give up the fight easy and find ways to survive. Intelligence level has become a question in the last decade and has puzzled the humans in the best way of overcoming the fight between us and them! So far, almost all the ways that we have found to kill them has not been completely successful and has raised the question of “Are the bacteria smarter than us?”, and “How is the science of chemistry helping scientists to win this battle?”

The revolution of antibiotics is an amazing story: the way that they were discovered; the way that they were initially used; and how they became to be the only hope of humans against infections. One of the first antibiotics discovered and used in large quantity was penicillin. At the time, it thought to be effective against most if not all the bacteria. Now we know that not all bacteria are the same. One major problem with why one antibiotic does not kill all bacteria lies in the structural differences between bacteria. Bacteria are divided into two main groups, gram negative and gram positive based on the results of the staining test, which reflects the cell wall structure of bacteria. Gram positive bacteria have much simpler cell walls with relatively large amounts of peptidoglycan. The walls of gram negative bacteria have less peptidoglycan and are more complex in structure. The outer membrane on the gram negative cell wall contains lipopolysaccharides, carbohydrates bonded to the lipids (1). Penicillin, for example, works best on gram positive bacteria, while other antibiotics work better on gram negative bacteria. However, finding antibiotics which killed gram negatives as well as positives still did not help the puzzle and they have survived through a mechanism called bacterial resistance.

Resistance is a technical term that is used to show the lack of desire for the bacteria to be killed. To survive, with time, prokaryotes evolved and they became resistant to antibiotics. There are three general mechanisms for resistance. First, bacteria can change structure to decrease the uptake or increase ejection of the antibiotics (E-flux mechanism). This is commonly used against antibiotics that are bacteriostatic. Second, they have evolved genetically to produce an enzyme to destroy the drug, so the drug is not effective any more (enzyme based resistance), which is most commonly used against bactericidal antibiotics. Lastly, bacteria can alter the drug’s target inside their cell, so the antibiotic can not bind to the receptor (acquired resistance) (2). Any of the mentioned
resistance can be passed along to the next generation which is called inherent resistance. The enzyme-based resistance is more prevalent and favored for the bacteria, since it saves energy in comparison to other methods. The following picture simplifies methods of resistance used by bacteria:

Figure 1

![Diagram of bacterial cell with antibiotic and enzyme interactions](image)

No peptidoglycan = penicillin resistant
Gram-positive = peptidoglycan = penicillin susceptible

Picture from Essential Biochemistry's website

Through years, we have learned how to overcome some of this resistance; however, this still remains a major fight. Biochemists and biologists have been using the chemical structure modifications as a way to fight bacterial resistance and to modulate bioavailability properties of antibiotics. There are many antibiotics available to us these days, with most belonging to one of the following groups: Beta-lactams, Cephalosporins, Macrolides, Ketolides, Fluoroquinolones, and Tetracyclines. Many newer generations were created by changes on a previous one to either decrease resistance or increase coverage.

**Penicillins:**

![Structure of penicillin](image)
Beta-lactams (penicillins) are by far the oldest and most commonly used antibiotics. They are grouped because of their similarities in structure or properties related to the structure, and they are further classified by antibacterial spectrum activity, called generations. There are four generations of penicillins. As shown in the picture above, there is a core for an antibiotic to be considered active penicillin. Any change to this core is undesirable and will make the antibiotic inactive. This is the main tactic used by bacteria to survive when attacked by penicillins. The property of penicillin is determined by the R group, and the COOH group is a must for activity (3).

Except for the first generation, the other generations of penicillins were merely formed to increase the spectrum and potency, not resistance. There have also been some other modifications to the structure to make it more available for the body (increased bioavailability). For example the substitution of methylene group (Pen G) with a phenoxy group (Pen V) at the R position, makes it more stable in the stomach acid, and is available orally in comparison to IV only for Pen G.

Figure 2
Comparing the Structure of Pen V versus to Pen G

Penicillin V

Penicillin 6
It did not take long for doctors to start seeing patients whose infections were no longer responding to penicillin. They came to realization that somehow the bacteria had been able to resist the penicillin. We now know that some bacteria can produce enzymes (penicillinase or beta-lactamase), which break down the beta-lactam bond and therefore destroys the four member ring. To overcome this, scientists came up with the changes to penicillin, which have a steric hindrance of methoxy groups that stabilizes to attack by the beta-lactamase. The following picture illustrates the main way that the enzyme beta-lactamase breaks down penicillin by hydrolysis:

Figure 3

**Penicillin Resistance**

Beta-lactamase is an enzyme with an available nucleophile (O-H bond) that approaches the carbon that is double bonded to the oxygen on the beta-lactam ring. The oxygen temporarily gets its pair of electron back and the OH group forms a covalent bond with the carbon. The neighboring nitrogen also is affected by this charge exchange, attracting a positively charged hydrogen ion. Double bond between oxygen and carbon must form again therefore forcing another member to leave; however, since nitrogen has the lowest electronegativity, it becomes the leaving group causing the C-N bond to break. When the 4-membered ring breaks, there is no more antibiotic activity. The following figure further illustrates the exchange of charges during the process:

Figure 4
Cephalosporins:

Cephalosporins compared to penicillins, have a broader spectrum. The first cephalosporin was isolated from natural sources of penicillins. Modifications of the C-7 side chain led to more active analogs. The structure can be modified at C-7 and C-3 to affect spectrum, potency, and stability of cephalosporins. Compared to 5-membered ring of penicillin, cephalosporin has a 6-membered ring. This makes cephalosporin more stable but less reactive. However, like penicillin, beta-lactamase can deactivate cephalosporins through hydrolysis. When the beta-lactam ring is opened by hydrolysis, the C-3 in cephalosporins becomes a leaving group; therefore, cephalosporin has a better potency than penicillin (4).

With all that in mind, the creation of cephalosporins did not improve much of the resistance issue. The main reason for their creation was probably the fact that at the time penicillins were not available orally because of acid stability problems with them, but cephalosporins could be used orally (up to 95% absorbed orally). The second and third generations of cephalosporin only improved the spectrum and stability. The other main reason for broader usage of cephalosporins is activity against some of the bacteria on which penicillins had no major effect. Second generation cephalosporins are more plasma protein bound (98%). This increases the half-life of the medicine letting doctors to dose this drug once a day. This was a major breakthrough since most antibiotics available at the time had to be taken four times a day. The third generation has less polarity, which allows the antibiotic to cross the blood brain barrier. This can be used to treat brain infection such as meningitis. On the other hand, the forth generation has super side chains, which makes the drug more potent and more penetrable into the bacteria cell wall. They are by far the less resistant of the cephalosporins. Although there have been four generation of cephalosporins, there was still a need for more potent antibiotics.
Macrolides:

Macrolides are known for their large size. Their name is driven from the characteristic large lactone (cyclic ester) ring found in these antibiotics. Because they carry sugar groups with amino groups attached to them, they are weak bases and water soluble. The molecular mode of action of the macrolide involves inhibition of program ribosomal proteins biosynthesis. Macrolides are clinically bacteriostatic, meaning they do not kill the bacteria they attack, but prevent them from reproduction. They cover mostly gram positive and some gram negative such as Legionella, Haemophilus and some anaerobes. Macrolides include clarithromycin, azithromycin, and erythromycin. Their structure is a 14- or 16-membered rings (4). The newer macrolides are more stable to acid and have a long half-life. This allows them to be dosed once daily. Azithromycin, prescribed commonly as Z-Pack®, is metabolized by liver to an even more potent active analog. This has made it one of the most commonly used antibiotics of today. However, with this fame come costs. Since doctors have over prescribed azithromycin, they see more and more cases of resistance these days. There are two known mechanism of resistance to Macrolides. First is the methylation of the bacteria’s own RNA. This changes the binding site of the antibiotic; therefore, prevents the antibiotic from stopping the reproductive process. Secondly, bacteria use an E-flux mechanism, in which it pumps the antibiotic out of its cell at cost of energy (5). As we continue to over use Macrolides, their chance of being effective against some serious bacterial infections is fading and the need for them to be replaced by a more effective antibiotic is already being studied.

Ketolides:

This is a new member of the antibiotic family. They are structurally related to macrolide, with a major difference of having a ketone replacing a sugar group at the 3-carbon position shown at the macrolide structure. Although the mechanism of action is similar to that of the Macrolides, it retains activity against bacteria that are resistant to Macrolides due to methylation (6).
References:

The Effect of the Fen-Phen Diet Drugs

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April 22, 2005
Abstract:

The body of this paper contains information about the history, some potential side effects, and the chemistry of the popular drug combination Fen-Phen. A description of some incidents and why this diet drug harmed many people, will be described in detail including the reason why only Fenfluramine was removed and physicians continue to prescribe Phentermine. The Food and Drug Administration approved Fenfluramine and Phentermine to be used independently and not in combination.

Introduction:

A major problem for many years through the nation has been obesity affecting many individuals. As a consequence, a number of diet drugs have been introduced to fight obesity. One of the most powerful and popular diet drug combination was the Fen-Phen diet in the 1990’s. Fen-Phen is a combination of Fenfluramine and Phentermine, two drugs that were approved to treat obesity by the Food and Drug Administration. Fenfluramine and Phentermine had the FDA approval for singular use although never was approved to be used as a combination. According to the results of a study done by Weintraub, Fenfluramine and Phentermine (Fen-Phen) were found to be possibly successful in the long-term treatment of obesity. This influenced physicians to prescribe this drug combination, with estimates of about 18 millions prescription written. However in 1997 another study done by Connolly caused controversy. The study associated such drug diets with valvular heart disease, forcing the Food and Drug Administration to withdraw Fenfluramine from the market.

Background:

In 1997 the Food and Drug Administration established a relationship between the combination of Fen-Phen and valvular heart disease. This was mostly seen in women using this diet. The Fen-Phen diet was used to treat obesity. Fen-Phen is the generic name for the combination of two prescription diet drugs, Fenfluramine and Phentermine, which were used to suppress appetite. Phentermine and Fenfluramine decrease appetite through the regulation of serotonin, a chemical in the body that affects appetite. Unfortunately, elevated levels of serotonin could cause damage to the heart. The combination of Fenfluramine (also known as Pondimin) and Phentemine (also known as fastin and Ionamin) are the drugs that form the Fen-Phen diet.

In September of 1997 the drug manufacturer, American Home Products, (now called Wyeth) removed Fenfluramine from the market due to the cause of two types of health problems. One of the problems was Primary Pulmonary Hypertension (PPH). Primary Pulmonary Hypertension causes elevation of the blood pressure in the passageway between the heart and the lungs. The other health problem was heart valve disease, which in some cases requires heart surgery. Some individuals who had used this diet suffered from regurgitation, which required surgery to replace or repair the valves.
Shortness of breath is one of the most common symptoms of heart injury from the Fen-Phen drugs. Another side effect is chest pain and in some cases pulmonary hypertension. Primary Pulmonary Hypertension is also known as Pulmonary Arterial Hypertension. It is an extremely rare, incurable and often-fatal disease. Primary Pulmonary Hypertension cannot be diagnosed until all types of secondary pulmonary hypertension have been excluded on clinical grounds. PPH is difficult to diagnose. The length of time from exposure to a patient's first developing symptoms of PPH varies greatly. It could take ten years or longer before an individual experiences the first symptoms of PPH.

**History:**

In 1973 Fenfluramine (also known as Pondimin) was approved by the Food & Drug administration to reduce appetite. However, Fenfluramine had several potential side effects, which included diarrhea, drowsiness and dry mouth. In 1959 the Food and Drug Administration also approved Phentermine. This was another diet drug that also had potential side effects such as insomnia and irritability. In 1992, a study found that by using Fenfluramine and Phentermine together that there was a reduction of side effects while maintaining effective weight loss. This combination of Fenfluramine and Phentermine became known as the Fen-Phen diet. The FDA approved Fenfluramine and Phentermine to be used independently. Despite this fact, many physicians prescribed the drugs in combination. By 1996 about 18 million prescriptions had been written and about 6,000,000 Americans took Fen-Phen.¹

By September of 1997 several lawyers proposed lawsuits against manufacturers and distributors of Phentermine, Fenfluramine and dexfenfluramine (also known as Redux). The litigation included allegations of possible physical problems caused by these drugs. Many users report similar symptoms such as shortness of breath, swollen ankles and fatigue. Other individuals reported more serious symptoms of heart valve damage, in which the valves in the heart developed a white coating. This allowed blood to flow backwards and caused heart muscle damage. In some cases it required surgery to replace the valve or even caused death. Other side effects reported were PPH (Primary Pulmonary Hypertension) an extremely rare and fatal disease of the lungs. In July of 1997 Mayo Clinic published a paper discussing a report that showed that one third of users of the drug combination reported heart valve damage. By September of 1997, many lawsuits had been filed from victims who had suffered heart valve damage or Primary Pulmonary Hypertension causing the FDA to remove Fenfluramine from consumer use.¹ On May 5, of 1997 the first lawsuit was filed in the state of Massachusetts (page 23).³
Chemistry:

The combinations of drugs in the Fen-Phen diet are also known as Pondimin, Ionamin, Ponderax Pacaps; Ponderex; and Fasta. Fenfluramine HCl has the following chemical name: N-ethyl-alpha-methyl-3-(trifluoromethyl) benzeneethanamine hydrochloride. 1,1-Dimethyl-2-phenylethylamine is the chemical name for Phentermine. Some of the Inactive Ingredients are Corn Starch, FD&C Yellow 6, Magnesium Stearate, Microcrystalline Cellulose, Silicon Dioxide, Sodium Lauryl Sulfate. The chemical structure of the combination of Fen-Phen (Fenfluramine and Phentermine) appears as follows:

![Chemical structures of Fenfluramine and Phentermine](image)

Phentermine  
Fenfluramine

As it can be observed in the structures both drugs contain amines. Amines are organic compounds that contain nitrogen as the primary atom in the amine functional group. The chemical formula for Fenfluramine is C_{12}H_{16}F_{3}N it has a molecular weight of 231.2603 and for Phentermine is C_{10}H_{18}N and the molecular weight is 149.2352. Both chemical structures are very similar however, one difference in the chemical formula between these two drugs is that Fenfluramine contains Fluorine.

The combination of the Fen-Phen diet can also be viewed in a three dimensional aspect.

![Three-dimensional structures of Fenfluramine and Phentermine](image)

Fenfluramine  
Phentermine
Description and Usage:

"Fenfluramine is a sympathomimetic amine the pharmacologic activity of which differs somewhat from that of the prototype drugs of this class used in obesity, the amphetamines, in appearing to produce more central nervous system depression and stimulation" (Page 1414). Anorectics or anorexigenics are drugs used to treat obesity. However it has not been established that the action of such drugs in treating obesity is primarily one of appetite suppression. Other metabolic effects or central nervous system actions may be involved. Fenfluramine was designed to increase the level of the neurotransmitter serotonin. This depresses the central nervous system to regulate appetite. Resulting in a feeling of fullness and loss of appetite.7

The average amount of weight loss associates with the use of an anorectic drug varies from trial to trial, and increased weight loss appears to be related in part to variables other that the drug prescribed, such as the physician-investigator, the population treated and the diet prescribed. Fenfluramine is available in 20 mg orange, scored compressed tablets monogrammed AHR, in bottles of 500. Users initiated at a dosage of one 20 mg tablet three times per day before meals. Dosage should be adjusted to the need and response of the patient. Dosage may be increased to a maximum of two tablets three times daily. If patient can't tolerate the initial dosage, then dosage is reduce to two tablets daily and thereafter gradually increased in order to minimize the change of side effects.7

Phentermine also works with neurotransmitters in the brain. Stimulation of the neuron bundles releases a group of neurotransmitters known as catecholamines. These neurotransmitters signal a flight response in the body which puts a halt to the hunger signal. As a result, loss of appetite is achieved because the brain does not receive the hunger message. Perhaps this occurs due to the effects of phentermine on leptin levels in the brain. Patient taking oral dosage for capsules should take 15 mg - 37.5 mg once per day, before breakfast, or approximately one to two hours after breakfast. Patient taking oral dosage for tablets should take 15 mg - 37.5 mg once per day, before breakfast, or approximately One to Two hours after breakfast. Also, instead of taking Phentermine once a day, some physicians recommend taking 15 mg - 37.5 mg in divided doses, thirty minutes before meals. Patients taking an oral resin dosage form (capsules) should take 15mg - 30 mg, once per day, before breakfast. A reduced dosage may be necessary depending on the patient. It is recommended to take Phentermine between four to six hours prior to going to bed because is known to disrupt sleeping patterns. Phentermine is NOT recommended for children under age 16. Phentermine should always be taken according to physician's orders, never too much since it could be habit-forming.
Cases:

Some of the cases reported by CNN are as follows:

Case #1

This 41-year-old woman was found to have systolic murmur. She had taken Fenfluramine 40 mg three times per day, as well as Phentermine, 16 mg three times per day for 18 months. She was sent to the Mayo clinic where an echocardiogram and cardiac catheterization showed severe mitral regurgitation and mild tricuspid regurgitation. These tests were performed three months after the systolic murmur. It was decided that surgery would be necessary to repair the mitral valve. During the surgery several pathologic features were noted. There changes in the posterior and anterior leaflets of the mitral valve and the chordae additionally had pathology. Other changes in the valve resembled valves affected by drugs called ergot derivatives. However, this individual was not using ergot drugs. Ergot drugs are used to treat vascular headaches.

After the patient was discharged from the hospital, the patient developed symptoms of right heart failure. A repeat echocardiogram showed that the mitral valve had no regurgitation. However, pathology was noted in the tricuspid valve. The valve now demonstrated severe regurgitation. It was necessary to treat the patient with medical management but no surgery.5

Case #2

This case involved a 45-year-old woman that developed shortness of breath and was seen by a physician. On examination a heart murmur was noted. She had been taking Fenfluramine 20 mg three times daily and Phentermine 30 mg daily for approximately one year. An echocardiogram was performed and showed thickened tricuspid, aortic, and mitral valves with regurgitation. The patient had progressive shortness of breath and it was decided that a surgical procedure was indicated. Approximately six months after stopping the Fen-Phen diet symptoms were still evident. The surgery was then carried out to repair the valves. It was necessary to replace the mitral and aortic valve. The tricuspid valve also needed surgical repair. During the surgery specimens from the mitral and aortic valves were sent to pathology for inspection. Microscopic examination showed changes in the leaflet surfaces as well as the tendinous cords. These changes were similar on both the mitral and aortic valve. The majority of the changes were on the mitral valve.5
Conclusion:

The food and Drug administration withdrew Fenfluramine from the market due to the potential side effects reported; however Phentermine is still available for sale in the United States. The FDA approved these two drugs to be used separately not in combination. Fenfluramine showed that by combining it with Phentermine it caused potential side effects, but Phentermine didn't show any potential fatal side effects. Obesity is still a growing problem in the United States. Researchers continue to find a magic drug to promote weight loss. Although, better research should be done before it is promoted to the market.
References:


Babak Behbahani

"Amoxicillin"

April 22, 2005
ABSTRACT:

Since the beginning of time, infections have been a major cause of disability and death of humans in every part of the word. For centuries, there was not adequate knowledge about infections and how to prevent them, until the discovery of primary antimicrobial opened the doors of opportunity to develop new remedial antibiotics. The theme of this paper revolves on the applications and characteristics of amoxicillin as an antibacterial agent that specifically inhibits bacterial infection from occurring.

INTRODUCTION:

Amoxicillin is an oral semisynthetic aminopenicillin, a derivative of penicillin that has an antibacterial spectrum of action similar to ampicillin. Amoxicillin is considered as a moderate-spectrum β-lactam antibiotic employed to treat bacterial infections caused by susceptible microorganisms with a broad range of gram-positive and gram-negative (thin cell walls) bacteria. Gram negative bacteria such as N. Meningitides, H. Influenzae, Gardnerella Vaginalis, Bordestella Pertussis and some enteric Bacilli such as E. Coli, Proteus Mirabilis, and Salmonella (4). Amoxicillin’s gram-positive spectrum is similar to the natural penicillin. Amoxicillin is slightly active against S. Pyogenes, S. Pneumoniae, S. Agalactiae, and more active against Enterococci and Streptococci (4).

MODE OF ACTION:

As a beta-lactam antibiotic, amoxicillin is mainly bactericidal. It inhibits bacteria from growing and multiplying by preventing the bacterial cells from forming the cell wall that surrounds them. The cell wall protects bacteria form their environment and keeps the contents of the bacterial cell together. Bacteria cannot survive without the cell wall.
The cell wall is composed of a complex cross-linked polymer, called peptidoglycan, which consists of polysaccharides and polypeptides compound. The polysaccharide contains alternating amino sugars, N-acetylmuramic acid and N-acetylglucosamine and N-acetylglucosamine. A five-amino-acid peptide is linked to the N-acetylglucosamine acid sugar. This peptide terminates in D-alanyl-D-alanine. Amoxicillin inhibits the third and final stage of bacterial cell wall synthesis by preferentially binding to specific receptor penicillin-binding proteins (PBPs) that are vital for the completion of cell wall development, and are located inside the bacterial cell wall (1). PBPs catalyze the transpeptidation reaction that removes the terminal alanine to form a cross link with a nearby peptide, which gives cell wall its structural rigidity. Beta-lactam antibiotics are structural analogs of the natural D-Ala-D-Ala substrate and they are covalently bound by PBPs at the active site. At this point the transpeptidation reaction is inhibited, and peptidoglycan synthesis is blocked, which will result in termination of bacterial growth and ultimately cell lysis (1).

Amoxicillin has the ability to act synergistically with mecillinam, a new aminopenicillin. Mecillinam binds selectively to one of the penicillin-receptor proteins, and when combined with amoxicillin, it causes a synergistic reduction in the bactericidal level of each drug.(9)

EXPOSITION:

Amoxicillin is principally used for the treatment of infections caused by susceptible gram-negative bacteria (e.g., Neisseria, gonorrhoeae, Haemophilus influenzae, Escherichia coli, proteus mirabilis, Salmonella) and gram-positive bacteria (e.g., Streptococcus pneumoniae, enterococci, non penicillinase-producing Staphylococci, Listeria.) and also in high concentration, it inhibits gram positive and gram negative anaerobic species such as Clostridium fusobacterium, Peptostreptocci, and Bacteroides melaninogenicus. The general purpose of amoxicillin is to treat infection such as middle ear, tonsils, throat, larynx (laryngitis), bronchi (bronchitis), lungs (pneumonia), urinary tract, and skin.

Otitis Media is infection of middle ear diagnosed in early childhood. Amoxicillin is used for the treatment of acute otitis media (AOM) caused by Streptococcus Pneumoniae and nontypeable Haemophilus Influenzae, or Moraxella Catarrhalis bacteria. It is considered the drug of first choice for initial treatment of AOM. Unless the infection is suspected of being caused by β- lactamase-producing bacteria resistant to the drug. In which case amoxicillin and clavulanate potassium is recommended because it is highly effective, has a narrow spectrum of activity, is well distributed into middle ear fluid, and is well tolerated and inexpensive (8). To increase the efficacy of amoxicillin against penicillin resistant S. Pneumoniae in Otitis or respiratory infections, higher dosage regimens have been recommended (4). Pneumonia remains the most important causes of childhood mortality in developing countries, and three days treatment of amoxicillin is proven to be highly effective for such disease in children (2).

Amoxicillin is also used as an alternative agent for post exposure Prophylaxis, following exposure to Bacillus Anthracis spores, for the treatment of anthrax.
Amoxicillin is considered for the treatment of mild, uncomplicated cutaneous anthrax caused by susceptible strains of Bacillus Anthracis. It is also efficacious for treatment of Chlamydial Urogenital infections during pregnancy, and is used to prevent the Haemophilus pathogen in maxillary sinusitis. This antibiotic is used as the drug of choice for the treatment of early localized or early disseminated Lyme disease associated with Erythema Migrans in the absence of neurologic involvement or third degree atrioventricular heart block, and is preferred for the treatment of early Lyme disease in pregnant or lactating women. Amoxicillin is a successful drug of use for treatment of Helicobacter Pylori infection and duodenal ulcer disease in adults, and in acute exacerbations of bronchitis in the patient with chronic bronchitis or bronchiectasis. It is a very effective therapy for typhoid and an ideal agent to orally use to treat septic arthritis and osteomyelitis (4).

Acute pyelonephritis has caused 5% febrile episodes in very young infants. It comprises urinary tract infection with systemic features including fever, vomiting, abdominal or loin pain, and lethargy due to infection by Escherichia coli and Enterococcus faecalis bacteria. Oral antibiotic such as Amoxicillin is considered a great remedy (3).

DISCONTINUE OF USAGE:

Resistance can occur when bacterial cells produce anti beta-lactam enzyme called beta-lactamase which will destroy the drug (1). Amoxicillin is susceptible to beta lactamases from Staphylococci, and therefore it is not used to treat staphylococcal infection. It is also not administered to treat gram-negative enteric organisms, such as Klebsiella, Enterobacters, Serratia, Citrobacters, Acinetobacters, indole-positive Proteus, and Pseudomonas causing infections (4). Amoxicillin is not useful in treatment of Shigellosis or Salmonella gastroenteritis or brucellosis, and is not indicate as an approved form of therapy for either Str. Viridans or Str. Faecalis endocarditic infection causing valvular heart disease.

The safe use of amoxicillin during pregnancy has not been definitely established. There are not adequate or controlled studies using aminopenicillins in pregnant women, however amoxicillin has been administered to pregnant women without evidence of adverse effects to the fetus. Because amoxicillin is distributed into milk and may lead to sensitization of infants, the drug should be used with caution in nursing women.

STRUCTURE AND SYNTHESIS:

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\[
\text{Amoxicillin}
\]
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amoxicillin (Amoxil), (C16H19N3O5S), is an aminopenicillin with an addition of an hydroxyl group on the phenyl ring, which extends its anti bacterial activity. It is available as trihydrate and occurs as a white, practically odorless, crystalline powder, which is sparingly soluble in water (4). The chemical name for the compound is: [[2S-[2α,5α,6β(S*)]-6-[[amino(4-hydroxyphenyl)acetyl]amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxilic acid] (5).

This Smeisynthetic antibiotic can be produced by kinetically controlled synthesis (KCS), which promotes substrate activation. Amoxicillin is synthesized from p-hydroxyphenylglycine methyl ester. In kinetic model, Penicillin G acylase (PGA) immobilized on glyoxyl-agarose is used to catalyze the reaction between P-hydroxyphenylglycine methyl ester (POHPGME) and 6-aminopenicillanic acid (6-APA) in low temperate of $-30^\circ C$ engaged with toxic organic solvent such as methylene chloride and silylation reagents, yields the antibiotic amoxicillin and methanol. (6)

![Chemical diagram]

Amoxicillin differs structurally from ampicillin due to presence of a p-hydroxyl group. The difference alters the in-vitro activity and human pharmacology of the two agents. It is not stable to beta-lactamases of either gram positive or gram-negative bacteria. Amoxicillin is more stable to gastric acid than penicillin and more bioavailable than oral ampicillin. It is associated with a higher absorption after oral administration, and this is not altered by the concomitant ingestion with food (5).

RECONSTITUTION AND ADMINISTRATION:

Amoxicillin is commercially available for oral administrations capsules, film-coated tablets, chewable tablets, or powder for oral suspension containing 250 and 500mg (5). It is stable against gastric acid and is rapidly absorbed from the gastrointestinal tract. It undergoes minimal metabolism in the body and is widely distributed to tissues (5). It’s Peak serum levels of occur within 1-2.5 hours following an oral dose. Food in the stomach inhibits the rate of absorption but not its extent (4).
Amoxil trihydrate is administered orally. The general dosage for adult for the treatment of mild to moderate infections of the ear, nose, throat, skin is 500 mg every 12 hours or 250 mg every 8 hours and for the sever infections 875 mg every 12 hours, or 500 mg every 8 hours.

Amoxicillin is distributed into liver, gallbladder, prostate, middle ear effusions, bronchial secretions, maxillary sinus secretion and synovial fluid. Amoxicillin and its metabolites are excreted into the urine primarily via tubular secretions and glomerular filtration. And small percentage of drug is excreted in breast milk. Approximately 60% of an orally administered dose is excreted in the urine with 6 to 8 hours (1).

AUGMENTIN:

Amoxicillin-Clavulanic acid is a combination drug marketed under the trade name Augmentin. Clavulanic acid is a beta-lactamase inhibitor that possesses weak antibacterial activity, when combined with amoxicillin, it will expand amoxicillin’s spectrum of activity against infection due to beta-lactamase-producing bacteria H. influenzae and penicillinase-producing anaerobes and inhibits Klebsiella and E. Coli, Haemophilus, and Neisseria. Augmentin is Used For treatment of abscesses, cellulites, and impetigo caused by S. Epidermidis, Staphylococcus, Streptococcus Pyogenes or Corynebacterium and also used for treatment of acute otitis media or acute maxillary sinusitis (upper and lower respiratory system) caused by M. catarrhalis (1). It also inhibits Enterobacter, or P. mirabilis form causing urinary tract infections. Augmentin is a commonly used drug to treat infections such as acute sinusitis, acute bacterial cystitis, uncomplicated gonorrhea caused by penicillinase-producing strains of N. Gonorrhoeae, and Chancroid caused by susceptible organisms.

DURATION OF THERAPY:

The duration of amoxicillin therapy depends on the type and severity of infection and should be determined by clinical and bacteriologic response of the patient, but for most infections, except gonorrhea, therapy should be continued for at least 48-72 hours after the patient becomes asymptomatic, or evidence of eradication of the infection has been obtained. Persistent infections may require several weeks of therapy. Amoxicillin usually is continued for 60 days for post exposure prophylaxis or treatment of inhalational or cutaneous anthrax. If amoxicillin is used in the treatment of infections caused by β- hemolytic streptococci, therapy should be continued for at least 10 days to decrease the risk of rheumatic fever and glomerulonephritis. If amoxicillin is used in the treatment of chronic urinary tract infections, frequent bacteriologic and clinical appraisal is necessary during therapy and may be required for several months after therapy. (For proper dose amount patient must consult with their doctors)

SIDE EFFECTS:

Amoxicillin, also known as: (Amoxil, Trimox, Wymox) may not be taken without doctor’s prescription. People who have asthma, eczema, kidney disease, leukemia,
mononucleosis, intestinal problems (especially colitis), other chronic illness, viral infection, breast-feeding must consult with their doctor promptly prior to amoxicillin usage. Side effects include the following symptom: diarrhea, dizziness, heartburn, insomnia, nausea, itching, vomiting, confusion, abdominal pain, easy bruising and swollen joints, rash, dark yellow or brown urine, fever or chills, sore throat, increase thirst, pain or difficulty passing urine, pain on swallowing, redness, blistering, peeling or loosening of the skin, seizures, unusual bleeding, extreme weakness or tiredness, yellowing of the eye, headache, loss of appetite, and allergic reactions.

Amoxicillin is one of the most frequent prescribed medications, but patients can develop an allergy once they have been exposed to it. The allergic reaction can be triggered every time the drug is being utilized in the body. Allergic reaction occurs because the immune system responds to the drug as if it were a harmful substance instead of a helpful remedy. The body then creates anti bodies called immunoglobulin to attack the medication. The allergic reactions are rashes, hives, itchy eyes, swollen lips, tongue or face. In rare instances the allergy to amoxicillin can cause an anaphylactic reaction, which can be deadly. The reaction involves the entire body and usually develops within the hour of taking the medication which may constrict the airway tube (bronchi) making it hard to breathe, and the blood pressure may drop to life threatening levels. It may cause dizziness and loss of consciousness. The consumer of drug may also notice wheezing, rapid or weak pulse, bluing of skin including lips and nail beds, diarrhea, nausea and vomiting. In any of these cases the matter must be consulted with the doctor, and seek alternative medication.

CONCLUSION:

Amoxicillin is the leading global antibiotic in the market with sales of 2 billion along with additional of 1.5 billion in sales for Augmentin, a combination of amoxicillin and clavulanic acid. Overall amoxicillin accounted for over 50 percent of all penicillin sales. The total consumption of amoxicillin was 10,000 tons in 1998, and continued in an increasing rate of 10 percent annually. The largest regions of growth for antibiotic manufacture and consumption are in developing countries where antibiotics can be produced at lower costs and demands are high. India produces 20 to 25 percent of the world’s amoxicillin (7).

The primary focus of antibiotic research is now, to develop new antibiotics to combat resistant strains of bacteria, since antibiotics have become less effective against infectious diseases due to the evolution of bacteria that are resistant to the bactericidal properties of the drugs (7).
Work Cited


DICYCLOMINE

A SYNTHETIC METHOD OF RELIEVING PRIMARY SYMPTOMS
OF
IRRITABLE BOWEL SYNDROME (IBS)

Prepared for
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April 21, 2005
ABSTRACT

In 2002 Gastrointestinal (GI) disorders which can lead to a variety of diseases affected approximately 18% of the western world,\(^{(1)}\) today that number has increased to 25%.\(^{(2)}\) Irritable Bowel Syndrome (IBS) being the most common of GI disorders unfortunately presents patients with uncontrollable muscle spasms along the digestive tract which leads to bloating and excessive gas.\(^{(3)}\) Dicyclomine hydrochloride the generic form of Bentyl is a popular synthetic prescribed by doctors as an antispasmodic.\(^{(4)}\) Some people prefer a homeopathic form of therapy by taking supplements containing papain enzymes which are produced from the juices of the papaya fruit. Papain enzymes are similar to cysteine proteases which aid in the dissolution of proteins during digestion, therefore decreasing excess gas.\(^{(5),(6)}\)

I. BACKGROUND

Digestion begins with hydrolysis forming chyme which is a mixture of masticated food combined with stomach acids.\(^{(7)}\) Hydrochloric acids which are secreted by the stomach walls along with various enzymes such as amylase, maltase, lactases and many more are used in catalyzing further reactions to break down particular food molecules found in chyme.\(^{(8),(9)}\)

Pepsin along with the hydrochloric acid decomposes proteins. From the stomach the protein molecules have become small chains of amino acids which travel into the small intestines. Once in the small intestines trypsine, chymotrypsine, as well as carboxypolypeptidase enzymes are released by the pancreas introducing an alkaline environment. The enzymes along with the alkaline atmosphere transform the smaller amino acid chains into polypeptides. If the hydrochloric acid or pepsin are insufficient in breaking down the protein molecules complications will occur later in the digestive tract. Here too, in the small intestine is where the amylase uses the maltose and lactose to rearrange carbohydrates into sugar molecules. Now that the carbohydrates are simple sugars they are released sporadically according to their makeup into the bloodstream through the intestinal walls.

Gastric lipases are the enzymes that aid in the decomposition of fat molecules. These fat molecules consist of phospholipids and cholesterol compounds which are difficult to dissolve therefore they sit idly in the small intestine up to four hours. In the time it takes for these molecules to breakdown a process known as fermentation begins to take place causing irritation in the intestinal lining. Continuing to eat fatty foods without giving the digestive tract time to recuperate, will cause such severe irritation that symptoms of bloating, gas, diarrhea and abdominal pain begin to occur, (four symptoms which can be related to IBS). To assure further breakdown of fatty molecules an enzyme produced by the liver assists the gastric lipases. Bile, synthesized from cholesterol has a higher PH (5) than the normal PH (2.5) produced in the stomach due to the acid content required to breakdown fats. Bile is a combination of negatively charged ions of salts and bile acids that motivate only from the liver to the small intestine, the bloodstream and back again. The molecular structure of bile is so large that it can not squeeze through the
cell walls of the intestines. However occasionally some bile enzymes are lost but quickly replenished on an as needed basis. The fluid transporting the bile also neutralizes the hydrochloric acid from the stomach to the small intestine. This same fluid also assists in the release of unnecessary wastes left in the system, (i.e.: mucous, excess fatty acids, urea etc.) through the rectum.\(^\text{7,8,9}\) It is here in the small intestines that the majority of symptoms for IBS occur.

**Figure 1. Diagram of the digestive system**\(^\text{10}\)
II. CLINICAL

IBS, a functional gastrointestinal disorder, has such a vast number of symptoms related to the disease that it has become necessary to draw specific criteria prior to diagnosing a patient. Today gastroenterologists utilize the “Rome II” method which covers psychological as well as physiological testing which appear to both be related to dysfunction of the motor system in the intestinal tract. Prior to using the “Rome II” method to test for IBS, a patient must present with at least 12 consecutive weeks of related symptoms within the past year. Because IBS symptoms cover both psychological as well as physiological factors, it is recognized as having dual etiologies—both biological and the other psychological.

It appears that the behavior of the bowels in the digestive tract can react independently of the central nervous system (CNS) of the enteric nervous system (ENS). However, for the ENS to react there must be some type of stimulus in the lumen of the bowel, i.e., where enteroendocrine cells play a key role as enterochromaffin cells which synthesize serotonin receptors. Through further investigation it is found that serotonin (5-hydroxytryptamine, 5-HT) acts as a secondary neuronal receptor to ACh. The primary mechanism of excitatory neurotransmission in the ENS involves a network of neurons that are stimulated by some form of pathological or physiological reaction (ingestion of food). The reactive nerves for 5-HT are located only in the intestinal tract as interneurons of the myenteric plexus.

Because there are several types of 5-HT receptors, tests have been run to determine which receptor best reacts to which specific symptom allowing a better chance of prescribing an effective treatment plan. As far as IBS is concerned, the symptoms of inflammation and excessive gas provoked usually by ingestion of food cause neurotransmitters to induce a reflex mechanism. By inducing the reflex mechanism this increases the release of excess 5-HT receptors as observed in patients presented with gastric hypersensitivity. It has been discovered that 5-HT_{4} agonists have been recommended for IBS with symptoms of diarrhea whereas 5-HT_{3} agonists are best recommended for those with constipation because this one assists in hastening transit through the small bowels. As for the symptoms related to bloating and pain caused by bloating an antagonist 5-HT_{1p} or antispasmodic such as dicyclomine will much more effective.

**FIGURE 2. PATHOGENESIS OF IBS**

- **Visceral hypersensitivity**
- **Dysmotility**
- **Inflammation**
- **Symptoms**
- **Altered compliance**

CNS
III. PHARMACOLOGY

DICYCLOMINE AND PAPAIN ENZYMES

2-(Diethylamino)ethyl[bicyclohexyl]-1-carboxylate hydrochloride otherwise referred to as dicyclomine is prescribed for IBS to relieve symptoms of excessive gas. Dicyclomine is an antispasmodic therefore it reduces muscle spasms in the intestinal tract. Because dicyclomine is also an anticholinergic it also reacts at acetylcholine-receptor sites such as the serotonin (5-HT) sites located throughout the duodenum. Dicyclomine also reacts with BaCl₂ to reduce excess hydrochloric acids produced by the stomach. This drug is soluble in water, alcohol and ether. Note the NO₂ in the molecular formula (C₁₉H₃₅NO₂HCl) this is a nucleophilic point that will allow for an enzyme to attach to breakdown fatty molecules in the small intestines that cause excess gas.

FIGURE 3.
STRUCTURE OF 2-(Diethylamino)ethyl[bicyclohexyl]-1-carboxylate hydrochloride

Molecular Formula: C₁₉H₃₅NO₂·HCl
M.W. = 345.95
IV. CONCLUSION

I have determined that IBS is a menagerie of symptoms that can not be cured with one form of treatment. Although the area affected by these IBS symptoms are primarily in the intestinal tract of the digestive system, anything from psychological issues to ones chemical makeup of enzymatic functions or dysfunctions in this case have to be treated accordingly. Throughout the information collected it is unknown to one specific cause of IBS. There is evidence stating that IBS could be stress related only therefore the symptoms may subside on their own as time passes. However if the cause is strictly related to food ingestion then one must determine what types of food produce the symptoms related to IBS the most common being inflammation, bloating and excess gas among others. Because IBS is a chronic illness\(^3\) people are having to convert their lifestyles to adapt to the discomforts of IBS causing stress and anxiety for which antidepressants are now being prescribed combined with stomach relief aids. Both dicyclomine and papaya may have some qualities that assist in relieving discomfort temporarily however does one prefer taking a pill or supplement one half hour prior to each meal for the rest of their lives or until a cure is found. Whether you are surviving by synthetic means or homeopathic means at least attempt to treat yourself to an exercise regimen that will reduce stress and assist in digestive breakdown. Who knows with daily exercise you will not only boost your self esteem, as well as your figure you may just be able to eventually maintain your own digestive system without synthetics or supplements. For now I do not see any one treatment in the near future that will cure IBS.
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Acetylsalicylic Acid

Prepared for Dr. Mancini

Organic Chemistry Instructor

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By

Basma Binna

April 22, 2005
Aspirin, a very popular drug used around the world since the nineteenth century, to relieve pain and other serious problems. Acetylsalicylic acid has a very exciting way to treat pain and prevent serious cardiovascular problems. As aspirin does well to the body, it is harming it also. Reason for the fatal results of aspirin is the salicylic acid, the main ingredient.

Aspirin has been a popular drug since early 1800s. “A Greek physician wrote in the 5th century BC about a bitter powder extracted from willow bark that could ease aches and pains and reduce fevers” (2). Europeans were not the only ones who used aspirin to relieve pain. Native American Indians also used the “bitter powder” to relieve common pains such as headaches, fever, sore muscles, rheumatism, and chills. The white powder that relieved people, came from the bark of a willow, called salicin, after the Latin name for the white willow (salix alba). The active extract of the bark was isolated to its crystalline by Henri Leroux, a French pharmacist, and Raffaele Piria, an Italian Chemist in 1828. Raffaele Piria succeeded in separating out the acid in its pure state. As the acid was separated, it then was called salicylic acid, because salicin is highly acidic when placed in a saturated solution with water.

In 1839, German researchers also isolated this chemical from meadowsweet flowers, in Latin, spiraeae. The German researchers also observed the side effects that were caused by this chemical. Side effects which included irritated stomach, diarrhea, and even death when taken in high dozes. In 1897, Friedrich Bayer & CO. in Germany “derivatized one of the hydroxyl functional groups in salicylic acid with an acetyl group (forming the acetyl ester), which greatly reduced the negative effects”(2). As it was being manufactured, a name had to be given to the acetyl ester. Taking the a- from the acetyl group, the -spir- from the spiraeae flower, they created aspir- and –in was a common ending for a drug at the time. Aspirin. Since then, acetyl ester was the first artificial drug, and was the beginning of pharmacology.

The reaction that produces aspirin is one of esterification, carboxylic acids with alcohols to form ester through a condensation reaction. As shown in the figure below, salicylic acid and acetic anhydride are combined. Acetic anhydride is reacted with salicylic acid, because salicylic acid contains phenolic hydroxyl group, and that is what acetic acid requires reacting with to produce acetylsalicylic acid and acetic acid. The rates of the esterification reaction are increased by the addition of small quantities of mineral acids, such as phosphoric acid.
As mentioned earlier, one of esterification is a reaction that produces aspirin. Estrification is the reaction between a carboxylic acid and an alcohol, which is catalyzed by an acid, phosphoric acid. The proton from the acid attacks the carboxyl oxygen, which in turn pushes the two electrons in one of the bonds “down”. It removes the electrons and spreads them out. The removed electrons, in the presence of alcohol, rearrange and bond temporarily between the two reactants. The proton then from the alcohol attacks the oxygen in the original –OH portion of the acid forming a positively charged oxygen atom and a sort of water molecule still attached to the intermediate. The electrons “holding” the water to the intermediate flip down, releasing the water, leaving the delocalized intermediate. The proton then leaves and electrons left behind flip down, closing the double bond on the oxygen atom and leaving the ester product. The esterification mechanism is shown below.

Synthesis of Esterification:

(1)

(2)

(3)

(4)
When salicylic acid and acetic anhydride are reacted with each other (figure bellow), one of the lone pairs of the oxygen from the phenyl attaches to the carbon, pushing one of the bonds, and giving the oxygen a negative charge. When acid is added, in this case phosphoric acid, it donates a proton to the oxygen, and leaves. In part C, the lone pair on the oxygen flips down, creating a double bond with the carbon. At this point, the carbon contains more than four bonds, so the carbon releases the bond to the oxygen. The oxygen detaches from the acetylsalicylic acid and becomes acetic acid.

![Chemical reaction diagram]

Bellow is the aspirin IR spectra. Each peak represents the absorption of compounds contained in aspirin.

![IR spectra of aspirin]

<table>
<thead>
<tr>
<th>Peaks</th>
<th>Bond</th>
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<td>1190 cm⁻¹</td>
<td>C-O bond</td>
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<td>1693 cm⁻¹</td>
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</tr>
<tr>
<td>2859 cm⁻¹</td>
<td>Alkanes</td>
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The NMR spectrum shows the chemical shifts of the compounds contained in aspirin. The chemical structure of aspirin is C₉H₈O₄.

<table>
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<tr>
<td>7.1 ppm</td>
<td>Aromatic ring</td>
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</table>

In order to stop the pain that is caused by the prostaglandin, aspirin attacks the cyclooxygenase first. Cyclooxygenase (COX) is accountable for the change of arachidonic acid to prostaglandin G₂ (PGG₂), the first step in prostaglandin synthesis and forerunner to prostaglandins of the E and F series. “Cyclooxygenase exists in 2 isozymes: cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2). in vivo, aspirin is hydrolyzed to salicylic acid and acetate” (3). For aspirin activity, hydrolysis is not required, because it can restrain COX permanently by acetylation of a specific site moiety. During an in vivo inflammation, salicylic acid restrains prostaglandin synthesis, yet in vitro, salicylic acid has no ability to inhibit COX. Aspirin, however, is powerful
enough to inhibit COX-1 but not COX-2. Inhibition mechanism of prostaglandin, by salicylic acid is vague, yet theories include the inactivation of transcriptional regulatory proteins, such as NF-kappaB, as the potential mechanism for salicylic acid, which regulate the appearance of inflammatory proteins. “Aspirin appears to inhibit COX through two pathways and seems to have a different mechanism of action than other salicylates. Aspirin does not inhibit the peroxidase activity of COX and does not suppress leukotriene synthesis by lipoxygenase pathways” (3).

For decades, aspirin has served as one of the most effective anti-inflammatory, fever-fighting, pain-relieving drug on the market. Recently, doctors have instructed heart attack victims to take aspirin once daily to prevent heart attacks. “It was Dr. John Vane who found that aspirin worked by inhibiting the body’s production of a hormone-like substance, and received the Nobel Prize in 1982” (5). Aspirin then abridges the body’s response to a series of chemical processes that eventually leads to pain. Through the identical course of action, aspirin relieves inflammation and swelling associated with injury, or arthritis, while recent evidence indicates prostaglandin is also active in inflamed tissue. Aspirin was also used to relieve fever, and it was the best drug to diminish it. However, children who took aspirin for their fevers during chickenpox, flu, or any type of viral sickness died soon after; a rare but serious illness that can affect the blood, liver and brain of children and teenagers after a viral infection, called Reye Syndrome. In Reye's syndrome, “the level of ammonia and acidity in the blood typically rises while the level of sugar drops. At the same time, the liver may swell and develop fat deposits. Swelling also may occur in the brain and can cause emergency symptoms such as seizures or convulsions. Reye's syndrome can eventually lead to a coma and brain death” (6).

“People who take aspirin regularly can reduce the risk of colon cancer, according to the largest, most definite epidemiologic study to investigate this link” (4). According to epidemiologist, John A. Baron of Dartmouth Medical School in Hanover mentioned, “There is no study that can prove that aspirin itself help prevent colon cancer. For example, he points out the side effects of frequent aspirin use, such as intestinal bleeding may have caused members of this subgroup to seek medical attention more frequently than other volunteers, thereby increasing the likelihood that any developing colon cancer would receive early diagnosis. And early diagnosis increase the likelihood the chance that a person with colon cancer will survive” (4). However, aspirin inhibits prostaglandins, which drive body cells, including colon cells, to multiply. That suggests that widespread cell division can be prevented by aspirin by interfering with prostaglandin production.

Aspirin is mostly prescribed for patients with heart problems. “Acetylsalicylic acid prevents blood clots by preventing platelets from releasing the prostaglandin thromboxane which causes platelets to clump together in a blood clot. Aspirin's anti-coagulant action can help prevent potentially fatal circulatory problems” (5). Therefore, Cardiovascular events can be prevented, such as heart attacks and strokes, by reducing the inclination of platelets to clot and allowing blood to flow more freely, without requiring the heart to contract with force.

In spite of the good affects of aspirin, from relieving pain to preventing cardiovascular problems, acetylsalicylic acid can cause more harm than good. Taking low dose aspirin daily as a preventive measure against coronary heart disease, which is a very common practice, may actually cause more harm than good.
Besides cataracts and damage to the lining of the stomach and bleeding, aspirin side effects include Gastro Intestinal bleeding, ulcers, bruising, abnormal liver functions, and liver damage. When taken too much, the toxic effect is kidney damage, and severe metabolic derangements. It is the salicylic acid in the aspirin that is creating all the major problems to the body. Why take aspirin to prevent heart attacks and create new problems in the body because of aspirin, when there is buffered aspirin that also prevents heart attacks without the major side effects? Buffered aspirin is aspirin with magnesium. "Studies have shown that magnesium contained in buffered aspirin, has a powerful protective effect on the heart. It dilates blood vessels, aids potassium absorption into the cells (preventing heartbeat irregularities), acts a natural anti-coagulant, and keeps the blood cells from sticking together"(1). It is not the aspirin that prevents cardiovascular problems, but he salicylic acid in the aspirin is preventing the heart attacks from happening, and at the same time salicylic acid is the reason for the side effects.

Daily use of aspirin can contribute to macular degeneration, the leading cause of blindness. "New research finds that an-aspirin-a-day can slowly destroy the eyesight, resulting in blindness later in life"(7). Macular degeneration is already the leading cause of blindness in people over 55, and doctors still have no effective treatments. This can be a serious problem if blindness continues to increase without an effective treatment.

Acetylsalicylic acid does both good and harm to the body at the same time. Sometimes people cannot decide where to take or not to take aspirin daily to prevent harmful diseases. Aspirin became very popular because it can prevent heart attacks from occurring, but as mentioned earlier that it causes other problems as well. Since magnesium is also a blood coagulant, it can be used to prevent heart attacks or other cardiovascular problems, without harming the whole body with toxin that is contained in aspirin. Magnesium is also a good way to get nutrients to the body, when these nutrients are not found in regular meals.
Bibliography


The involvement of Antenolol on the sympathetic Nervous system and its side effects

Prepared for Dr. Mancini
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By
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April 22, 2005
Atenolol, a popular and successful, beta-blocking agent, used worldwide. It was discovered by a Scottish pharmacologist. Atenolol in general is a long tedious step-wise reaction involving complex reagents and cataylists. Also Atenolol mainly has an influence on the sympathetic nervous system.

"Atenolol was discovered by ICI in 1976, whilst searching for a specific Beta-1 cardioselective adrenoreceptor-blocking agent. Though ICI's research was invaluable, Atenolol may be seen as a drug evolved from the series of research being conducted into beta receptors during the late nineteen fifties. Slater, Powell and co-workers at Lilly discovered the first development of a chemical that acted to inhibit beta-receptors in 1958" (1). However the compound, 3,4-dichloro isoproterenol only acted as a partial agonist that produced marked stimulation of cardiac beta-receptors before inhibition.

"The milestone in the treatment of hypertension and angina came from a Scottish pharmacologist, Sir James Whyte Black. Atenolol is a drug used in the treatment of hypertension, Angina Pectoris and acts as an Anti-Arrhythmic to regulate the heartbeat in the prevention of myocardial infarction. Atenolol is widely referred to as a beta-adrenergetic blocking agent or a beta adrenoreceptor antagonist" (1). However, it is more commonly known as a beta-blocker. "More specifically it acts as a beta-1 (β-1) cardio selective adrenoreceptor-blocking agent, whose fundamental objective is to control the heart. Atenolol does so by restricting certain nerve impulses, thereby controlling the rate and force of contraction, consequently reducing blood pressure. In addition, its use in the treatment of Angina Pectoris ("Angina"), make it an invaluable drug in industry" (4).

"On the outset, Atenolol actively reduces the heart rate, in turn decreasing systolic and diastolic blood pressures" (2). The net effect of both the heart rate and blood pressure being controlled is the reduction in myocardial work and oxygen requirement, which reduce cardiovascular stress, thereby preventing arrhythmia and anginal attacks. Black developed the drugs propranolol and cimetidine for the treatment of angina and peptic ulcers respectively. Black studied medicine at St Andrews University, graduating in 1946 and consequently began research at ICI's pharmaceuticals division. During the 1950s and early 1960s he searched for a drug to relieve angina. He realized that a drug, which blocked beta-adrenotrophic receptors, would have the desired effect and following several years' research, was able to synthesize the drug propranolol, a beta-blocker that became a major success in the treatment of high blood pressure. Black was elected Fellow of the Royal Society in 1976, was knighted in 1981, and received the Nobel Prize for Medicine in 1988 for developing drugs to treat heart disease and stomach and duodenal ulcers.

The characteristics of any drug are crucial in the understanding of its chemical composition and the consequent effects it has on the human body. Atenolol has a diversity of attributes, which gives rise to both its physical and chemical behavior. In the table below shows the physical and its chemical names.
<table>
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<th>CHARACTERISTIC</th>
<th>ATENOLOL</th>
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<tbody>
<tr>
<td>NAME</td>
<td>(RS)-4-(2-hydroxy-3-(isopropylamino) propoxy) phenyl acetamide</td>
</tr>
<tr>
<td></td>
<td>2-4-(2-Hydroxy-3-isopropylaminopropoxy) phenyl acetamide</td>
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<tr>
<td></td>
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<tr>
<td>MOLECULAR FORMULA</td>
<td>C14H22N2O3</td>
</tr>
<tr>
<td>RELATIVE MOLECULAR MASS</td>
<td>266.3</td>
</tr>
<tr>
<td>MELTING POINT</td>
<td>152-154°C</td>
</tr>
<tr>
<td>DISSOCIATION CONSTANT pKα</td>
<td>9.6 @ 24°C</td>
</tr>
<tr>
<td>PARTITION COEFFICIENT [log P (octanol)]</td>
<td>0.23</td>
</tr>
<tr>
<td>ENANTIOMERS</td>
<td>YES R (+) and S (-)</td>
</tr>
<tr>
<td>CAS NUMBER</td>
<td>29122-68-7</td>
</tr>
<tr>
<td>APPEARANCE</td>
<td>Atenolol is an odorless white powder</td>
</tr>
</tbody>
</table>

The table below shows the different solubility of Atenolol.

<table>
<thead>
<tr>
<th>SOLVENT</th>
<th>RELATIVE SOLUBILITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>WATER</td>
<td>0.3 mg/mL</td>
</tr>
<tr>
<td>ETHANOL</td>
<td>3.4 mg/mL</td>
</tr>
<tr>
<td>DMSO</td>
<td>18 mg/mL</td>
</tr>
<tr>
<td>ETHER</td>
<td>Practically Insoluble</td>
</tr>
</tbody>
</table>
Atenolol is an enantiomers, it has two optical isomers. These mirror images are labeled the R (+) and S (-) enantiomers of Atenolol. So that gives rise to Atenolol having two optical isomers. Atenolol has a chiral center or also known as a chiral carbon as highlighted below:

By virtue of the chirality’s of the carbon, the molecule is able to exhibit optical isomerism. These are in the forms of the stereoisomers R-Atenolol and S-Atenolol

Industrially, Atenolol is produced as a racemic mixture of the two enantiomers. Conveniently both forms are bioactive in treating hypertension, angina and arrhythmia, which makes it a truly versatile drug. Full details of the production of Atenolol are given in the Synthesis section. Recent studies have shown that the S-Atenolol isomer was found to avoid the occasional side effect of an excessively lowered heart rate sometimes encountered with the racemate. In terms of how this isomeric molecule is structurally
characterized, one must explore its spectroscopy essentially defining the compound. In order for one to appreciate the spectroscopy for Atenolol, one must initially consider its full molecular structure. The simplest means to explore and trace the Atenolol’s spectroscopic characteristics is to look at its 2D arrangement as shown below:

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\begin{center}
\text{\includegraphics[width=\textwidth]{atenololStructure.png}}
\end{center}
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On the outset it is clear that Atenolol possesses a multitude of component substituents. The main "bulk" on the molecule is attached to a bulky structure itself, namely the benzene ring. Such a molecule can be described as a benzeneacetamide by virtue of the O=C-NH2 amide group extruding from a benzene ring. As well as the amide functional group, the conjugating C=C bond in the benzene ring, the methine (CH), methylene (CH2), methyl (CH3) and -OH functional group should be distinctive on the IR spectra (1650 cm\(^{-1}\); CH- 2880-2900 cm\(^{-1}\); CH2- 2916-2936 cm\(^{-1}\); CH3- 2850 cm\(^{-1}\); conjugating C=C-1640-1610; -OH-3200-3550 cm\(^{-1}\)). The mass spectra should theoretically present the molecular ion at 266, being the relative molecular mass of the drug. In relation to Atenolol’s 13-Carbon and 1-Hydrogen NMR, the splitting patterns would be vast, likely to have one pronounced broad peak due to the -OH group. The effect of the electronegative oxygen leads to neighboring hydrogen nuclei being deshielded, moving the coupling peaks downfield whilst also possibly giving rise to hydrogen bonding.

**NMR of Atenolol**

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IR SPECTRA

A Key observation, which is raised in the IR spectrum of Atenolol, is the level of hydrogen bonding. By virtue of the electronegative Nitrogen atom and the even more electronegative Oxygen atom, the IR spectra indicates that intermolecular H-bonding may be present. The IR frequency bands of the -OH and H-N groups having stretched at 3368 cm⁻¹ and 3198-3071 cm⁻¹ respectively as it is demonstrated below:

<table>
<thead>
<tr>
<th>IR FREQUENCY BAND (cm⁻¹)</th>
<th>GROUP RESPONSIBLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>3610-3645 (sharp)</td>
<td>Free -OH</td>
</tr>
<tr>
<td>3200-3550 (broad)</td>
<td>H bonded -OH</td>
</tr>
<tr>
<td>3300-3500</td>
<td>Free -NH</td>
</tr>
<tr>
<td>3070-3350</td>
<td>H bonded NH</td>
</tr>
</tbody>
</table>
The following section deals with both the chemical synthesis and its mechanisms of Atenolol:

Butyl p-hydroxyphenylacetate (5) is used as an alternate starting product. Also readily available, species (5) can be easily synthesized from the esterification of p-hydroxyphenylacetic acid with 1-butanol. Industrially Atenolol is produced as a racemic mixture of both the R and S stereoisomers. This is achieved by treating product (7) with 2-methyl-ethanamine yielding approximately 94% racemic Atenolol.

Conversion in the region of 94% is achieved by treating product (8) with 2-methyl-ethanamine. Purification by adding with ammonium hydroxide in methanol followed by a single recrystallisation in ethyl acetate raises the percentage yield to an excess of 95%. Lipase from Candida Cylindracea is utilized in the production of the R + Atenolol.

Acetic anhydride may also be used as a substitute for 1-butanol however, its inherent toxicity led to one opting for 1-butanol. Even though 1-butanol is harmful in its own right, on a relative scale is was the most suitable and effective alternative evolving an approximate 94% conversion. Yet again, greater than 95% conversion is achieved after purifying the precipitate by treating (R) 1-[[butoxy-carbonyl]methyl] phenoxy]-3-chloropropan-2-ol (10) with 2-methyl-ethanamine. This is then followed by addition of ammonium hydroxide in methanol and finally single recrystallisation in ethyl acetate.
As briefly discussed earlier, Atenolol is a beta-blocker, specifically a beta-1 (β-1) cardioselective adrenoreceptor-blocking agent. “Atenolol actively restricts certain nerve impulses, thereby controlling the rate and force of contraction, consequently reducing blood pressure” (3). The human body contains target cells, called receptors that act to receive chemicals released from glands or nerves. The transmitter hormone released by the adrenal glands is known as adrenaline (epinephrine) and for the sympathetic flight or fight response; the transmitter excreted by the nerves is called noradrenaline (norepinephrine). The complimentary receptors for these chemicals are alpha and beta-adrenergic. Sympathetic activity is communicated to tissues through involuntary nerve impulses and through the blood. The acceptor site and mechanism is demonstrated below, the hormone (adrenaline) inducing the ATP to cAMP conversion.

![Diagram of hormone receptor, adenyl cyclase, and cAMP response element]

The β-1 receptors are substantially postsynaptic and are predominately found in the heart. “Their activation causes an increase in the rate of contraction of the heart and presynaptically the receptor induces an inflation of noradrenaline production” (4). Atenolol, fundamentally inhibits such mechanisms. During activation, whether it is traced to a flight or fight or a parasympathetic transducer, the body naturally secretes various hormones to trigger the body into supplying more oxygen to muscles and cells as a response to the changing conditions. This inherently means the heart is forced to work harder in pumping oxygenated blood around the body. “The endocrine system responds to beta-adrenergic receptor stimulation by increasing blood sugar levels, inducing a faster heart rate and producing stronger heart contractions all by means of secreting adrenaline” (1). This fundamentally results in an increase of blood pressure. This is where Atenolol plays a vital importance. Essentially, Atenolol blocks the receptor targets on heart muscle cells and prevents epinephrine and norepinephrine from stimulating the cardiovascular system. These chemicals typically increase heart rate, strength, and activity leading to elevated blood pressure. Atenolol inhibits these effects.

“As with any drug, Atenolol is after all a xenobiotic for the body” (1). Despite the benefits, there are secondary interactions and bioactive pathways, which can lead to a diversity of implications. On the outset, side effects from Atenolol are rarely diverse in
their symptoms. The following is a list of possible side effects, which may ensue whilst taking Atenolol. The following is a list compiled from an actual prescription of Atenolol:

<table>
<thead>
<tr>
<th>Tiredness</th>
<th>Dizzy Spells</th>
<th>Depression</th>
<th>Fatigue</th>
<th>Confusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep Problems</td>
<td>&quot;Pins and Needles&quot;</td>
<td>Sore Throat</td>
<td>Headache</td>
<td>Dry Mouth</td>
</tr>
<tr>
<td>Nausea/Vomiting</td>
<td>Diarrhea</td>
<td>Constipation</td>
<td>Stomach Cramps</td>
<td>Fever</td>
</tr>
<tr>
<td>Hallucinations</td>
<td>Mouth Ulcers</td>
<td>Itching</td>
<td>Scaly Rash</td>
<td>Blurred Vision</td>
</tr>
<tr>
<td>Sore eyes or Conjunctivitis</td>
<td>Impotence</td>
<td>Rheumatic pain</td>
<td>Swelling of ankles</td>
<td>Temporary thinning of hair (very rare)</td>
</tr>
<tr>
<td>Peyronie's Disease</td>
<td>Weak pulse or mildly slow heart rate (heart block)</td>
<td>Coughing up blood</td>
<td>Blue lips/fingernails</td>
<td>Weakness of muscles</td>
</tr>
</tbody>
</table>

As demonstrated above, the array of side effects are indeed diverse. Despite the string of possible effects stated, it has been known that the wide majority of side effects are rarely observed. "One is unable to "rank" each side effect in terms of their implications on the patient as that is traced to their relative degrees of effect. In other words, their relative "danger" is fundamentally unique to the individual albeit some obviously posing a greater risk than others" (1). Primarily, the success of any drug is based on its ability to solve the prescribed task with the minimal implications to one's health. Essentially, this explains Atenolol's commercial success.

By the inherent nature of any drug, Atenolol may interact with various other drugs. The main groups of concern are heart, diabetes, and respiratory and gastro-digestive medication due to counter-effects, which may be encountered. For example, whilst Atenolol inhibits the adrenaline pathway thereby reducing blood pressure levels, an NSAID drug such as Ibuprofen has been suggested to increase blood pressure. This counter-effect is fundamentally hazardous to the patient. Each trade name is given in brackets:

**heart medication** such as nifedipine (Procardia, Adalat), reserpine (Serpasil), verapamil (Calan, Verelan, Isoptin), diltiazem (Cardizem, Dilacor XR), clonidine (Catapres), digoxin (Lanoxin), doxazosin (Cardura), guanadrel (Hylorel), prazosin (Minipress), or terazosin (Hytrin).

**Diabetes medication** such as insulin, glyburide (Micronase, Glynase, Diabeta), glipizide (Glucotrol), chlorpropamide (Diabinese), or metformin (Glucophage).
nonsteroidal anti-inflammatory drug (NSAID) such as ibuprofen (Motrin, Advil, others), naproxen (Aleve, Anaprox, Naprosyn, others), ketoprofen (Orudis, Orudis KT, Oruvail).  
Respiratory medication such as albuterol (Ventolin, Proventil, Volmax, others), bitolterol (Tornalate), metaproterenol (Alupent, Metaprel), pirbuterol (Maxair), terbutaline (Brethaire, Brethine, Bricanyl), or theophylline (Theo-Dur, Theochron, Theolair).  

stomach medication cimetidine (Tagamet, Tagamet HB).

Atenolol has undoubtedly fixed its position as one of the most widely prescribed drugs on a global scale. This has been traced to the diversity of factors, from its ability to solve the prescribed task to its rare occurrences of acute side effects. While Atenolol is being industrially produced as a racemate of the R and S stereoisomers, maybe the S isomer could be found to avoid the occasional side effect of an excessively lowered heart rate. Symptoms of dizziness, fatigue or tiredness can be consequently avoided by virtue of the rate of oxygen being supplied to cells being limited. Despite the racemate having slight implications, Atenolol has been known to induce acute side effects, effectively giving rise to its global success. It might be suggested that the future of Atenolol is almost certainly secure for the foreseeable future, by virtue of its current position in the market. For example, the effectiveness of only a 50mg dose of Atenolol, compared to 100mg doses of Toprol-XL and Metoprolol CT. Atenolol exceeds the potency of Toprol-XL and despite Metoprolol CT seeming to provide a slightly greater reduction in heart rate, it must be indicated that the latter had been given at twice the dosage as Atenolol.
Bibliography


Marijuana:  
A Good Medical Plant or Not?  

By  

Shadi Bishara  

22 April 2005
Marijuana
A Good Medical Plant or Not?

Abstract:
This paper is written to find out whether or not THC or marijuana has good medical usage. There has been a lot of research that had been conducted by various scientists around the globe, and most of them were experimenting on how would and if possible to have marijuana as a medical treatment.

Marijuana is a topic that we hear about very often in today’s world. We hear it in our streets, in our schools, in our homes, and even from our little brothers and sisters mouths. So it is wise to ask the questions: what is marijuana? Does it have good uses? Does it have true medical uses? How does Marijuana affect our bodies?

Marijuana is a type of plant. It is known to scientists as cannabis sativa. This plant belongs to the family cannabianacea. The desired flowers and fruits of the female plants are used as a source of drugs (Bailey, 1978). It has a large amount of chemicals in it, but its main active ingredient, which provides a good dosage of poison to the user, is tetrahydrocannabinol, or better known as THC and Cannabinoids (CBD), which will be discussed later on in this paper. Actually, two forms of this molecule are formed in marijuana plants. The Delta1-3, 4-transisomer and the delta6-3, 4-transisomers (Merck index, 1976). Both of these molecules are known to cause serious psychological disturbance in humans. However, the delta1-3, 4-transisomer is thought to be the major active ingredient.

A major concern in our society is that marijuana is that it is in the hands of our children, brothers, sisters, and friends. Marijuana is becoming little by little an easy access drug to everyone. At this time people especially teens know now how to make it or “roll it” like a professional. All a user needs is rolling papers, pipes made of wood, metal, plastic or glass, water pipes called “bongs”, scales for weighing, joints, small clips referred to as “roach clips” (used to hold the joint when it is almost at the end), toke stones (used for smoking joints). (Daily, john)

With every drug there are short-term effects and long term effects. Some of the short term effects of Marijuana are: - relaxation, altered perception, paranoia, dilated pupils, week concentration & memory, dry mouth & throat, increased heart rate, fear & anxiety, cravings for sweets or as most users would call it “munchies”. Some of the long term effects are: reduced levels of male & female hormones, damage to sperm or menstrual cycles, temporary loss of productiveness in men and women, addiction, loss of motivation also referred to as, “A motivational syndrome” (this loss of interest in motivation to work, attend school, loss of interest in sports, family, etc can also just be a symptom of drug addiction in general), lung damage, cancer, bronchitis, lowered ability to deal with frustration and other unpleasant feelings, decrease of immunity against infection, interferes with emotional growth and the personality development of
adolescents. Some statistics show that Marijuana has been increased in its percentage of THC in its contents, it says that the concentration of THC in 1960’s was about 1%, then it increased to 4% in the 1970’s, but today the concentration of THC has increased to 10% THC and that is because of all of the technology that we have in order to synthesize “better drugs”. (Daily, John)

So far the facts apply largely to Marijuana in what people call “street terms”, or daily life. However, what about Marijuana in medical Terms? Is it really a beneficial drug to society or is it a menace?

Well, as mentioned before Marijuana’s primary active ingredient is THC CBS (tetrahydrocannabinol). Cannabinoids are a group of chemicals which activate the body’s cannabinoid receptors. The term referred to a unique group of secondary metabolites found in the cannabis plant, which are responsible for the plant’s peculiar pharmacological effects. Currently, there are three general types of cannabinoids: herbal cannabinoids occur uniquely in the cannabis plant; endogenous cannabinoids are produced in the bodies of humans and other animals; and synthetic cannabinoids are similar compounds produced in the laboratory. (Wikipedia, 2005).

Cannabinoids do not react with the cell membrane, because if cannabinoids did then they would react with every cell in every organ which might cause in a large amount of cell damage. Instead, cannabinoids combine with specific receptors found only in mammals, fish, birds, and reptiles called CB1 and CB2. Furthermore, CB1 and Cb2 are receptors that are only found in certain organs. CB1 is found in the basal ganglia and the limbic system including the hippocampus, but absent in the medulla oblongata, which is a part of the brain that is responsible for respiratory and cardiovascular functions. In other words, the respiratory and cardiovascular functions are not affected by taking marijuana as a lot of people might say. As for CB2 it is found in the immune system mostly in the spleen. Moreover, it turns out that CB2 receptors are responsible for anti-inflammatory (prevents swelling). For that reason when an injury occurs and the place of the injury did not swell, then it will cause more blood pressure (force) applied on the internal organs which might cause some damage. Also considering the fact that cannabinoids are stereoselective, they would combine to certain receptors that are responsible for medical usages. (Wikipedia, 2005)

There are three types of cannabinoids; Herbal, Endogenous (which is found naturally in living organisms), and synthetic I’m only going to talk about two.

Herbal cannabinoids are nearly insoluble in water, but soluble in lipids, alcohols, and non-polar solvents. The reason why it doesn’t react with the cell membrane is because cannabinoids need special receptor to bind with first, as mentioned before. Herbal cannabinoids are produced by decarboxylation of their carboxylic acids and catalyzed by heat, light or basic ph. Herbal cannabinoids are only found in the plant cannabis sativa in the female fruit, more specifically they are found in the hair of the plant (tricorns) (Wikipedia, 2005). Terpenes are also found in the resin which causes the bad odor. Although there are more than sixty different herbal cannabinoids known only the two
which are already desired (delta1-3, 4-transisomer, and the delta6-3, 4-transisomer). Shown below are few of the herbal cannabinoid.

![Chemical structures of THC (Tetrahydrocannabinol), CBD (Cannabinol), CBN (Cannabinol), CBG (Cannabigerol), Anandamide, 2-Arachidonyl glycerol, and CP 55,940.]

Picture taken from Wikipedia, 2005

Endogenous cannabinoids are produced in the tissues and organs of various species bodies but most specifically animals. “In the early 1990s, the first such compound was identified as arachidonyl ethanolamine and named anandamide, a name derived from the Sanskrit word for bliss and amide. Anandamide is a polyunsaturated fatty acid with pharmacology similar to THC, although its chemical structure is different. Anandamide bonds primarily to the CB1 receptor, and is found in a wide range of animals. It is about half as potent as THC. Two analogs of anandamide, docosatetraenylethanolamide and homo-γ-linoleoyl ethanolamide, have similar pharmacology”. (Wikipedia, 2005).

Now after that brief explanation about what are cannabinoids are, we can talk about how Marijuana and cannabinoids are linked together to make good medical uses.

Well, according to some studies done by Herkenham and his associates says that: THC or Marijuana does not effect the brain as any of the other drugs for two reasons: the first is because there is a lack of THC receptors in the medulla oblongata to cause any permanent damage to the brain or even deaths by THC. The second reason is the lack of receptors in the mesocorticoclimbic pathway and that reduces the effect of addiction and serious physical dependencies. A number of studies have been conducted on the analgesic effect of THC in both animals and human subjects; the results have been conflicting. Recent identification of cannabinoid receptors as well as anandamide. There is some evidence that they are part of a natural pain control system distinct from the opioid system. Recognizing that some studies have demonstrated an analgesic effect of THC and related compounds in rodents, it may be useful to identify what specific kinds of pain may be relieved by marijuana or THC. (Wikipedia, Herkenham, 2005).
Animal studies on the analgesic effect of marijuana have produced inconsistent results. Whereas one study shows that marijuana is equivalent to morphine in rats, and more potent than morphine in mice. Other studies showed that THC was less potent than morphine in both mice and rats. Cannabinoids have been shown to be possibly analgesic in animal models of neuropathic pain. (Ad Hoc)

Another study was performed where scientists gave a high dosage of marijuana to mice and rats as a test to see if taking THC into their system would be cause cancer or any other evidence of toxicity. After two years of study they found out that in rats the high dosage of THC that was given to the rodents produced a higher state of survival over the non-treated ones in both male and female rats. The same thing also occurred with the mice. The study also showed that the higher dosage of THC given to both rodents the fewer tumors they started developing; as a consequence both rodents (mice and rats) it didn’t matter if it was a male or a female, they started losing weight. Although the treated animals and the non-treated animals ate the same amount of food at the same time. After a few weeks of exposure the study started showing that the mice and rats began to develop seizures and convulsions. Especially when they were dosed. The researchers decided to check the brain for any materials that would cause the mice or rats to have these seizures or uncontrollable shaking, unfortunately they found none. No evidence of cancer causing activity in the rats was found, but there was "ambiguous evidence" of one kind of thyroid tumor in the mice. No evidence of a dosage being related to addiction was found. Other tumors were less common in the treated animals than in the controls. Except in one case, which the toxicologists believed was due to the fact that the treated animals lived longer, and therefore had more opportunity to develop tumors. (James, 1997)

This is a picture of the chemical structure of THC.
THC in 3-D mode

Here is a picture of what would abusing marijuana does to a brain

As you can see in the picture this is what will happen when a person abuses marijuana or takes a high dosage of THC chronically. If the picture isn’t clear the bottom picture shows that more that 65% of the brain is under active. The bright neurons show underactive areas.(kolin)

Another study involving THC and glaucoma raised uncertainty of the treatment working 100%. Marijuana could be a cure for glaucoma; glaucoma is an eye disorder marked by
abnormally high pressure within the eyeball that leads to damage of the optic disk and, if not treated, causes impaired vision and sometimes blindness (Beaver, et al). The initial observation was that smoking marijuana lowered intraocular pressure (IOP) was made by Hepler and Frank in 1971. Hepler and Petrus (1976) which they later stated that 4 percent THC marijuana cigarettes lowered the pressure on the eye about 27 percent more than did a placebo at 30 minutes in normal volunteers, and that 20 mg of THC taken orally or by smoking marijuana lowered the IOP about 17 percent more than placebo at 30 minutes. They also reported that smoking marijuana lowered IOP much more dramatically in-patients with poorly controlled glaucoma. One patient demonstrated a reduction from 40 mm Hg to 10 mm Hg in one eye and from 35 mm Hg to 15 mm Hg in the other. Hepler and Petrus concluded that smoked marijuana or oral THC was additive in effect to these therapeutic agents, and presumably worked by an independent mechanism. In these short-term studies, lasting up to 4 hours, 2 cigarettes were as effective as 20 cigarettes, and intoxication occurred. Others confirmed that the marijuana could have a significant effect in glaucoma patients.(Ad Hoc)

Smoking marijuana or taking a good dosage of THC effects epilepsy by preventing chronic seizures stop occurring. For instance one patient called Tim Shellman. Is 29 year old had suffered from epilepsy from the age of 15. He went to many doctors who gave him various drugs like carbamazepine (Tegretol), phenytoin (Dilantin), valproic acid (Depakote), phenobarbital, primidone (Mysoline), ethosuximide (Zarontin), and clonazepam (Klonopin), which are drugs that are used today to cure epilepsy. Unfortunately, approximately 70% of all the patients with epilepsy can control their disorder by taking the drugs listed above. Of the 30% of the patient is approximately 10% can control it by combining two or more of the drugs. But not Tim. After a long and much research and testing at the age of 17, Tim started to smoke marijuana because he got into a fight where his jaw was broken so he couldn’t take his seizure medicine. So decided to smoke marijuana so that he would not feel the pain. Tim started noticing that his seizures were controlled because of the usage of marijuana. So he was seizure free for 8 months until he ran out of marijuana supplies. Later on, Tim woke up one day in the bathroom with blood all over him because apparently had another seizure presumably because of the lack of marijuana. Currently Tim is taking Phenobarbital 180 mg 3 times a day in addition to marijuana, which is because of his addiction to THC. So instead of getting rid of one disease, now he is addicted to it and he has to take two pills. (Shellman, tim and pattie)

In conclusion, although marijuana has some potential benefits for medical uses, the consequences of its use are higher. As the first experiment showed, high doses are not toxic, but can cause addiction. This is due to a lack of receptors in parts of the brain responsible for vital functions. It could make the user addicted to it to a point where that person can’t live without the drug. Also experiments with mice and rats showed that although conditioned rodents had fewer tumors and lived longer that control rats. Those same rodents started loosing weight and after a while started developing seizures and convulsions from the high dosage of marijuana. However, although it seemed that marijuana can be used as a mean to cure glaucoma and the results of the experiment were some what successful, the same researchers also stated that two cigarettes of marijuana were equal in toxicity to 20 tobacco cigarettes. In other words, toxicity occurred. Finally
research shows that the more a person uses marijuana the more the person's brain becomes under active. So as a conclusion in my opinion there is no way marijuana should be used in medical treatments because it damages more than it does well.
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Breast Cancer & Arimidex

Written by:
Jennifer Bluvas

Submitted to Dr. Mancini,
Paradise Valley Community College

22 April 2005
Abstract

Breast cancer is one of the most common cancers and is one of the leading kinds of cancer deaths found in women. After its detection there are several methods of treatment including the manipulation of hormones. One form of hormone treatment is the use of aromatase inhibitors such as anastrozole. This drug is becoming the preferred treatment of hormone receptor-positive breast cancers found in postmenopausal women.

Breast Cancer

Cancerous cells divide and grow at a rate that is out of control; normal cells do not¹. Due to this behavior cancer cells crowd out normal, healthy cells and form masses called tumors. While all cancer cells react this way, cancers in different parts of the body are different and respond to different kind of treatments.

Breast cancer occurs when malignant tumors originate in tissues of the breast¹. While men can get breast cancers it is a condition that mostly occurs in women. Breast tissues include lobules or milk glands, ducts, fatty tissue, blood vessels and lymph vessels. When a tumor develops in one of these tissues the cancerous cells are capable of spreading through the lymph vessels to nodes located under the arms. Once in the lymph nodes, cancer is more likely to metastasize to other parts of the body.

Breast Cancer Risk Factors

Breast cancer is the most common type of cancer found in women second only to skin cancer and it is the second leading cause of cancer death in women after lung cancer¹. All women are at risk for getting breast cancer but there are certain risk factors that may increase one’s risk; the risk may increase as a woman ages, if she has a family history of breast cancer, has already had breast cancer, is Caucasian or started menstruating early in her life.

All the previous risk factors a person cannot control but several others can be attributed to a woman’s lifestyle. Chances of developing breast cancer may increase if a woman does not have children, uses birth control, uses hormone replacement therapy, does not breastfeed her children, drinks excessive amounts of alcohol, is overweight or does not exercise. While all of these things may increase a woman’s chance of getting breast cancer, it does not mean that one will; often, affected women do not have any of the risk factors.

Breast Cancer Detection & Treatment

Breast cancers are often detected in one or more of the following ways: a mammogram, clinical breast exam or a breast self-exam¹. While one in seven women may get breast cancer during her lifetime only one in thirty-three will die from it. This death rate is always decreasing.
largely due to early detection of the cancer and improved methods of treatment. Common treatments for breast cancer may include one or more of the following: surgery or tumor removal, radiation, chemotherapy, hormone therapy and immunotherapy.

**Hormonal Treatment**

For those breast cancers that have hormone receptors hormone therapy would be a likely form of treatment. In these kinds of tumors estrogen can promote cell growth; the goal of hormone therapy is to stop this effect of estrogen. There are three ways in which hormone receptor-positive breast cancer cells are controlled: to block the receptors, lower hormone levels, and/or eliminate the receptors. When one attempts to block the receptors the aim is to prevent growth signals from getting to the tumor cells one is trying to eliminate. By reducing the levels of estrogen in the bloodstream one is lowering the hormone levels in the body. This means that less hormone receptors receive fewer signals for growth. The third method involves reducing the number of receptors that can receive growth signals. All three of these hormone treatment methods are based on the principle that hormone receptor-positive tumor cell growth will slow down or cease when estrogen growth signals cannot get to the cell.

**Tamoxifen vs. Arimidex**

The standard endocrine treatment for post-menopausal women with hormone receptor-positive breast cancer is five years of tamoxifen. The introduction of this hormone receptor blocker in the 1970's was a turning point in breast cancer treatment because it was effective in reducing breast cancer growth, was well tolerated by patients and fairly non-toxic. It is for these reasons that tamoxifen has remained the standard against which all new endocrine therapies tend to be compared. During the past decade, however, it has been identified that prolonged use of tamoxifen results in an increased risk for gynecological complications. The recurrence of breast cancer and its side effects have limited it efficacy as well as lead to the creation of alternative medications such as Arimidex (anastrozole).

In the ATAC (Arimidex, tamoxifen alone or in combination) trial consisting of 9,366 post-menopausal women with early hormone receptor-positive breast cancer there were many conclusions concerning the efficacy of both tamoxifen and Arimidex. It was found that treatment with anastrozole “led to significant improvements compared with tamoxifen for disease-free survival and time-to-recurrence”. The risk reduction over tamoxifen for time-to-recurrence was decreased by 26% and the absolute differences in recurrence rates increased over time between the two drugs.
Figure 1: time-to-recurrence in hormone receptor-positive patients taking tamoxifen or anastrozole during five-year treatment.

With anastrozole there was twice the number of patients eligible for breast conservation therapy and a substantially reduced incidence of contra lateral breast cancer compared with tamoxifen. Anastrozole was also associated with fewer endometrial carcinomas, less vaginal bleeding and discharge, fewer venous thromboembolic events, fewer hot flushes, and fewer ischemic cerebrovascular events. Fewer patients taking anastrozole rather than tamoxifen withdrew from treatment due to drug-related adverse effects. The reduction in recurrence rates of breast cancer in association with anastrozole suggests that a decrease in deaths from breast cancer will be seen in the future.

All of these findings exhibit that aromatase inhibitors, such as anastrozole, show an improved efficacy and lower toxicity compared with tamoxifen, an estrogen antagonist. For this reason anastrozole is a possible candidate to help enhance tamoxifen's activity against breast cancer or to replace it entirely.

Arimidex

The medication anastrozole is sold under the name Arimidex and is manufactured by AstraZeneca Pharmaceuticals L.P. It is chemically described as 1,3-Benzenediacetonitrile, alpha, alpha, alpha', alpha'-tetramethyl-5-(1H-1,2,4-triazol-1-ylmethyl). Anastrozole is an "off-white powder" with a molecular weight of 293.4 and a molecular formula of C_{17}H_{19}N_{5}. The structure of the active ingredient in Arimidex is as follows:
Arimidex is used for the adjuvant treatment (treatment following surgery with or without radiation) of postmenopausal women with hormone receptor-positive early breast cancer. The recommended dosage of Arimidex is one 1-milligram tablet taken every twenty-four hours; the optimal duration of treatment is still unknown but median duration of treatment is at thirty-one months. Further information about the synthesis and chemistry of this medication are unavailable at this time because the data is proprietary.

**Mechanism**

Aromatase inhibitors, such as anastrozole, are a form of anti-estrogen therapy. The estrogen in a young, healthy woman's body is produced by her ovaries but as a woman ages this production ceases; estrogen in post-menopausal women is converted from androgen, another hormone.

The adrenal gland produces hormones including aldosterone, cortisol, and androgens. An enzyme called aromatase is necessary to convert androgen to estrone and estradiol, the most common forms of estrogen in postmenopausal women. This enzyme catalyzes the conversion of androgens to estrogen in peripheral tissues such as fat and muscles and locally within cancerous tumors by attaching to the androgens and converting them. Aromatase inhibitors block the synthesis of estrogen in non-ovarian tissues by inhibiting aromatase, a cytochrome P450 enzyme; anastrozole prevents the enzyme's activity, which reduces the amount of estrogen in a woman's body.

By preventing androgens from being converted to estrogen, aromatase inhibitors ensure that there is less estrogen available to reach hormone-receptors and stimulate cancer cell growth and proliferation. Postmenopausal women taking aromatase inhibitors like anastrozole can have their estrogen levels reduced by more than 97%.
Figure 3: Endocrine pathway for estrogen synthesis in postmenopausal women.²

Figure 4: Blocking of the endocrine pathway for estrogen synthesis in postmenopausal women taking Arimidex (anastrozole).²
Side Effects of Arimidex

Some of the side effects that can be seen with anastrozole are chest pain, shortness of breath, peripheral swelling, weakness, loss of appetite, back and joint pain, flushing, and dizziness. Those symptoms seen less frequently can include anemia, hypertension, thromboembolism, vaginal hemorrhage, anxiety, insomnia, and flu symptoms. When compared to tamoxifen in the ATAC trial, the administration of Arimidex was associated with a greater number of musculoskeletal disorders and bone fractures. This data suggests that aromatase inhibitors have a negative impact on bone density. The increase in fractures may be a result of the estrogen deprivation caused by the aromatase inhibitors. Bone mineral densities of women on aromatase inhibitor treatments that reduce estrogen levels can be monitored throughout and after treatment.

Clinicians who opt to start patients on anastrozole should request a baseline bone density scan which can be repeated throughout treatment. These patients should also receive vitamin D and calcium supplements and they should be encouraged to maintain a workout routine that includes weight-bearing exercise.

Future of Arimidex

Breast cancer is a disease that over 200,000 women will learn that they have this year alone; of these newly diagnosed individuals, more than 40,000 will die from the disease. Over eighty percent of those women will survive, however, and this is largely due to advances made in treatment methods and medications. Tamoxifen has been the benchmark medication used to treat hormone receptor-positive breast cancer cells. But the recent development of aromatase inhibitors, such as anastrozole, show promise for the future treatment of breast cancer with fewer side effects and higher efficacy.

Anastrozole has been approved by the Food & Drug Agency as a first line drug in the therapy of breast carcinomas. It is a promising drug for the adjuvant treatment (treatment following surgery with or without radiation) of postmenopausal women with hormone receptor-positive early breast cancer. The encouraging antitumor results associated with anastrozole suggest that aromatase inhibition increases efficacy and reduces side effects that were previously seen with the administration of tamoxifen. The reduced risk of endometrial cancer seen with anastrozole could, in the long term, save unnecessary anxiety for patients and could reduce health service costs associated with treating this new condition.

Arimidex is a fairly new medication and longer follow-up studies and additional safety data are required before making a definite confirmation about the benefits of long-term aromatase inhibitor use. Several remaining issues concerning aromatase inhibitors are the optimal duration of treatment, toxicity and long-term effects. There are also questions about whether they should be used concomitantly or sequentially with other breast cancer treatments. In respect to anastrozole’s effects on bone density, there are prevention studies involving aromatase inhibitors in the active planning stage in combination with bone-preserving agents.
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A Brief Exploration of the Chemistry of Zocor (Simvastatin), a Popular Treatment for Hypercholesterolemia

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Coronary heart disease is the leading cause of death in America and it has been shown that hypercholesterolemia increases the risk of developing coronary heart disease. Statins are the drug therapy of choice to lower the blood cholesterol levels. While all statins lower cholesterol by competitively inhibiting the HMG-CoA reductase catalyzed transformation of HMG-CoA to mevalonate, their different chemical structures govern their water solubility which in turn influences their absorption, distribution, metabolism, and excretion. One of the statins, simvastatin, is synthesized from another statin, lovastatin. There are two approaches to accomplish this synthesis. Either perform a deacylation to de-esterify the 2-methylbutanoylxy side chain of lovastatin followed by reacylation/re-esterification with 2,2-dimethylbutyric acid, or, use protective reactions to protect the hydroxy group and carbonyl on the lactone ring followed by an alkylation of the methylbutanoylxy side chain with methylhalide/metal alkylamide and then perform deprotective reactions to return the hydroxy group and carbonyl to the lactone ring. An example of this second method is explored.

Introduction

The American Heart Association [AHA] (2005) estimates that in 2002 there were 70.1 million Americans with one or more forms of cardiovascular disease (CVD), 927,448 of them died as a result of it. This represents 38 percent of all deaths in America. Over 150,000 of those who died were under the age of 65.

Coronary heart disease (CHD) is one form of CVD. It is caused by atherosclerosis which is a narrowing of the coronary arteries due to fatty build ups of plaque. CHD is the leading cause of death in America with over 494,000 deaths in 2002. This compares to 557,271 deaths caused by all forms of cancer, 106,742 accidental deaths, and 14,095 HIV/AIDS related deaths. An estimated 106.9 million Americans have total blood cholesterol levels of 200mg/dL or higher (AHA, 2005). Of course CHD is not a problem unique to America. This is a problem that affects the world and since elevated cholesterol levels (hypercholesterolemia) have been shown to increase the risk of developing CHD, it is no wonder why there is such a large market for drug therapies that will lower cholesterol levels.

A lot more is known today than twenty years ago about the biological processes that take place between the consumption of food and the development of atherosclerosis. However, this is still a very active area of research and more is learned every year. What is known so far has shown that these processes are complex and provide many opportunities to disrupt the cycle that leads to CHD. Currently, statins are the preferred drug therapy to address hypercholesterolemia because of their proven effectiveness and safety profile (Schachter, 2005). This has led to continual development of the methods used to produce these medicines. This paper will focus on just one of many ways to synthesize Zocor, the Merck trade name for simvastatin, a member of the statin family.
Background – How Do Statins in General, and Simvastatin in Particular, Work?

Lovastatin was introduced into therapy in 1989 as the first drug in the statin class (Hollmann et al., 2002). Since then seven additional compounds have been introduced: simvastatin, pravastatin, fluvastatin, atorvastatin, cerivastatin, pitavastatin, and rosuvastatin) although cerivastatin was withdrawn from clinical use in 2001 (Schachter, 2005). While all statins have a common mechanism for reducing blood cholesterol levels, they differ in terms of their chemical structures, pharmacokinetic profiles, and lipid modifying effectiveness. The chemical structures of statins govern their water solubility, which in turn influences their absorption, distribution, metabolism, and excretion (Schachter, 2005) (see Figures 1 through 8).
Lovastatin, simvastatin, and pravastatin are derived from fungal metabolites while fluvastatin, atorvastatin, cerivastatin, pitavastatin, and rosuvastatin are all fully synthetic compounds. The fungal metabolite derivatives have an elimination half-life (the time it takes for half of the ingested amount to be eliminated) of 1-3 hours. The half lives of the fully synthesized compounds range from 1 hour for fluvastatin which has a structure moderately similar to pravastatin (one of the fungal metabolite derivatives), to 19 hours for rosuvastatin which is very different from the three fungal derivatives (Schachter, 2005).

Lovastatin, simvastatin, fluvastatin, atorvastatin, cerivastatin, and pitavastatin are relatively lipophilic (lipid loving, i.e. attracted to lipids and not water soluble) compounds while pravastatin and rosuvastatin are hydrophilic (i.e. water loving and water soluble). This is important because except for pitavastatin, the lipophilic statins are more susceptible to metabolism by the cytochrome P450 isoform 3A4 (CYP3A4) system (Schachter, 2005). This means that intake of anything that disrupts the CYP3A4 system will disrupt the metabolism of these drugs and could lead to toxic levels within the blood or non-target tissues. A list of the medications that affect the CYP3A4 system is provided in the product information insert for each medication. However, one common item that affects the CYP3A4 system and should be avoided while using any of the statins is grapefruit juice. A single 8 oz. serving of grapefruit juice a day will raise the blood levels of the active hydroxy acid form of simvastatin by 18 percent. Ingestion of the equivalent of 1.2 liters of grapefruit during and immediately after ingesting the simvastatin has been demonstrated to increase the blood levels for active inhibitors by 1600 percent (Lilja et al, 2004). Because compounds that lower blood lipid (and cholesterol) levels are found quite frequently, lack of toxicity is the true criterion for selecting appropriate compounds for drug development (Hollmann et al, 2002).

Statins as a class are selective for effect in the liver, largely due to efficient first pass uptake (Schachter, 2005). For example, less than 5 percent of an oral dose of simvastatin reaches the general circulation as active inhibitors. Approximately 95 percent of the simvastatin and its active β-hydroxy acid metabolite are highly bound to human plasma proteins (Merck.com). The lipophilic statins are primarily taken up by passive diffusion through the hepatocyte cell membranes while hydrophilic statins are taken up by active, carrier-mediated processes (Schachter, 2005).

Simvastatin is a prodrug (i.e. it exhibits its pharmacologic activity after biotransformation within the body). Simvastatin is given in an inactive lactone form (see Figures 9 and 11) and is
transformed by the liver to its major active form, an open ring 3,5-dihydroxy acid (see Figures 10
and 12). The other hepatic metabolites produced are the 6'-hydroxy, 6'-hydroxymethyl, and 6'-
exomethylene derivatives of the hydroxy acid (Merck.com). This method of administration
allows for greater hepatic uptake and lower circulating plasma levels, which can reduce toxicity
(Slater & MacDonald, 1988; Mantell, 1989).

Figure 9: General form of a lactone where G is an unsubstituted or
substituted alkyl, aryl, or hetero aryl.

Figure 10: General form of a dihydroxy acid where X is a proton (H), metal, or amine and G
is an unsubstituted or substituted alkyl, aryl, or hetero aryl.

Figure 11: Lactone form of simvastatin (Zocor) as administered (inactive).

Figure 12: 3,5- dihydroxy acid form of simvastatin (Zocor) after hepatic metabolism
(active)

Statins are competitive inhibitors of the enzyme 3-hydroxy-3-methylglutaryl coenzyme A
reductase (HMG-CoA reductase). The HMG-CoA reductase catalyzes the reaction that converts
HMG-CoA to mevalonate (see Figure 13). The conversion of HMG-CoA to mevalonate is an
early and rate limiting step in the biosynthesis of cholesterol. The statins, by inhibiting the
cholesterolgenesis cause an increase in the synthesis of low density lipid (LDL) receptors within
the liver. The increased number of LDL receptors on the hepatocytes results in increased
removal of LDL from the blood (Hardman et al, 2001).

Figure 13: HMG-CoA reductase catalyzed conversion of HMG-CoA to mevalonate
The Chemistry Behind Simvastatin

The chemical name for simvastatin is quoted in different forms in different references. Ullmann's Encyclopedia of Industrial Chemistry names it as 2,2-dimethylbutanoic acid (1S, 3R, 7S, 8S, 8aR)-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]-ethyl]-1-naphthalenyl ester. However, Merck, the manufacturer of Simvastatin by the brand name Zocor, names it as butanoic acid, 2,2-dimethyl-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)-ethyl]-1-naphthalenyl ester, [1S-[1α,3α,7β,8β (2S,4S)-8αβ]]. In either case, the empirical formula is C_{22}H_{38}O_5, its molecular weight is 418.57, and its melting point is 135-138°C. It is an off-white, nonhygroscopic (i.e. it does not absorb water), crystalline powder that is practically insoluble in water and is freely soluble in chloroform, methanol, and ether (Merck.com).

Simvastatin is derived synthetically from lovastatin (Figure 1) which is a fermentation product of Aspergillus terreus (Merck.com). It has been reported that lovastatin can not be converted directly to Simvastatin by an alkylation reaction because of the higher acidity of the lactone α-protons compared to the α-protons of the ester side chain. The higher acidity causes alkylation to occur preferentially in the α-position of the lactone (Dabak & Adiyaman, 2003).

The addition of one methyl group on the alkyl side chain of lovastatin results in a doubling of potency (Slater & MacDonald, 1988; Mantell, 1989; Stalenhoef et al, 1989).

Synthesis of Simvastatin

In general there are two known routes to introduce the additional methyl group to the 8-acyl side chain of lovastatin. One involves a deacetylation/reacetylation procedure, comprised of de-esterification of the 2-methylbutanoyloxy side chain of lovastatin followed by re-esterification with 2,2-dimethylbutyric acid (see Figure 14) (Dabak & Adiyaman, 2003).

The second method involves protection reactions and an alkylation of the methylbutanoyloxy side chain with methylhalide/metal alkylamide, and deprotection reactions. Dabak and Adiyaman published an example of the second method in 2003 (see Figure 15). Their synthesis procedure started by using PhCOCl and pyridine in dichloromethane (CH_2Cl_2) to convert lovastatin to its benzoate derivative (3a in Figure 15). They achieved a 95 percent yield with this step. Then the benzoate derivative was treated with ethane-1,2-diol, (EtO)_2CH, and a catalytic amount of sulfuric acid (H_2SO_4) in tetrahydrofuran (THF) to obtain the protected orthoformate (4a in Figure 15). They obtained a yield of 51 percent in this second step. The methylation of the (S)-2-methylbutanoyloxy side chain of 4a was carried out in the third step by using BuLi, pyrrolidine, and MeI in THF followed by aqueous workup to obtain the simvastatin β-hydroxyorthofomrate derivative (5 in Figure 15). Dabak and Adiyaman achieved an 85 percent yield during this third step. In their discussion of their process, Dabak and Adiyaman
emphasized that “the simultaneous removal of the OH protecting group in 4a occurred during the aqueous workup due to generation of the basic medium in each case”. During their fourth and final step, Dabak and Adiyaman treated the simvastatin β-hydroxy orthoformate derivative with dilute hydrochloric acid (HCl) in THF to remove the C=O protecting group and obtain simvastatin in its inert, lactone form. They achieved a 92 percent yield in this final step for an overall process yield of approximately 38 percent.

![Chemical Structures]

Figure 15: Reaction describing the Dabak Adiyaman synthesis of simvastatin from lovastatin.

One advantage of the Dabak and Adiyaman process above is that they do not open and close the lactone ring and therefore avoid the formation of a dimer. However, as previously stated, there are many different processes published for the synthesis of simvastatin from lovastatin. Chemists around the globe continue to experiment with new processes in an effort to reduce the cost of this synthesis by improving yield or finding a process that takes less time, uses cheaper reagents, or is performed at conditions more easily obtained or conditions that are maintained less expensively. Of course this research is not typically done solely for altruistic reasons. The production and sale of statins is a multibillion dollar a year industry where improving a process yield even a little bit can achieve a significant reduction in annual production cost. Each year new patents continue to be filed as researchers find these alternative processes.
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Celexa-
A Selective Serotonin Reuptake Inhibitor

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Abstract

The drug Celexa® (citalopram) is a fairly new drug first marketed in the United States in 1998 by Forest Laboratories. It is a drug used primarily in the treatment of major depressive disorders. Celexa® is a selective serotonin reuptake inhibitor (SSRI), one of five (5) currently available in the United States and, due to its outstanding results, has become one of the leading drugs prescribed by physicians.¹ This paper will discuss the history, chemistry, structure and synthesis of Celexa® (citalopram).

Introduction

For many years, the long periods of time that a person experienced the “blues” was simply that; however, now doctors have determined a clinical name for this feeling, depression. Depression has been clinically defined as a “feeling of profound and constant sense of hopelessness and despair”² and it is estimated that over 18 million Americans suffer from depression each year.³ Major depression is characterized by such symptoms as sadness, despair, insomnia, and sometimes suicidal behavior, along with other sometimes debilitating symptoms.

Antidepressants were developed as a part of the search for a cure for this endless feeling of hopelessness which has dated as far back as Sigmund Freud, a noted psychologist of the twentieth century. The first forms of anti-depressive treatments were based on opium and amphetamines which were mainly used as sedatives or stimulants and had no basis for helping solve the underlying problem, a lack of serotonin in the brain. The lack of a proper level of serotonin for the use by the brain is considered the trigger for the depression felt by so many. By the end of the 1950’s, huge advancements had been made and the first antipsychotic, imipramine, was used in clinical trials in America. The discovery of imipramine lead to further research for related compounds based on the tricyclic dibenzazepine structure.⁴ These advancements have lead to the numerous types of antidepressants that are prescribed today including the SSRI, Celexa®.

In 1989, a company called Lundbeck in the United Kingdom began to market a drug called Cipramil® in Denmark. It was an immediate success. Finally there was a drug on the market for individuals with depression that promised to have few side effects and could be safely taken in conjunction with other medications. Cipramil® quickly became Lundbeck’s top selling product and represented over 78% of the total sales in 1999. Since 1989 the product has been sold in 70 countries around the world.⁵

Lundbeck had the antidepressant market cornered in Europe and was looking for a new way to market their drug and turned to the United States as its new market. In September of 1998, Forest Laboratories, an American genetics lab, began to market Cipramil® under a new name called Celexa®. Forest Laboratories did not engage in the initial research on Celexa®, but promoted its development and sales within the United States. Since 1998, Celexa® has become one of the mainstream antidepressant drugs marketed in the United States today, along with other prominent drugs such as Prozac®,
Paxil®, and Zoloft®. Celexa® is now the eighth top selling antidepressant in eight other European countries.  

Celexa® (citalopram HBr) is an orally administered selective serotonin reuptake inhibiter drug (SSRI) with a chemical structure unlike that of other SSRI’s of tricyclic, tetra cyclic or other available antidepressant agents. Citalopram is a racemic bicyclic phthalane designated (+) - 1-(3-dimethylaminopropyl)-1- (4-fluorophenyl) - 1, 3-dihydrosobenzofuran-5-carbonitrile, HBr, with a molecular formula of C₂₀H₁₂BrFN₂O and the following structural formula:  

![Structural formula of citalopram](image)

Citalopram HBr occurs as a fine white to off white powder. It is somewhat soluble in water and is soluble in ethanol. Celexa® is a coated, oval shaped scored tablet containing citalopram HBr in strengths of 20 mg or 40 mg citalopram base; it is also available in an oral solution. The drug has a pKₐ of 9.5. It is recommended that citalopram HBr and its oral solution be stored at 25°C. When stored, it can be kept for three years and six months following the date of manufacture.  

**Mechanism**

Celexa® belongs to a category of drugs that are called selective serotonin reuptake inhibitors and should not be confused with monoamine oxidase inhibitors (MAOIs). SSRIs are believed to help increase the effectiveness of the neurotransmitters for serotonin in the brain. Serotonin is thought to control appetite, sleep and mood. Low levels of serotonin causes disturbances to these functions. The mechanism of citalopram hydrobromide as an antidepressant is thought to be linked to the potentiation of serotonergic activity in the central nervous system resulting in an inhibition of CNS neuronal reuptake of serotonin (5-HT). Celexa increases the serotonin levels in the brain by blocking the reuptake in the synapse; this temporarily causes an increase in serotonin levels at the receptor sites. Citalopram is a 50/50 racemic mixture, and the inhibition of 5-HT is said to be due to the (S)-enantiomer. The drug does not inhibit the 5-HT₁₅, 5-HT₂₅, dopamine D₁ and D₂, a₁, a₂, and β-adrenergic, histamine H₁, gamma aminobutyric acid (GABA), histaminergic and adrenergic receptors. Since Celexa® does not inhibit these activities like most other therapeutic drugs, it is thought that the adverse side effects
such as anticholinergic, sedation, and cardiovascular effects have been eliminated unlike the long term use of other antidepressants or MAOIs.\textsuperscript{8}

**Pharmacokinetics/Absorption/Elimination**

The pharmacokinetics of citalopram is linear (linear refers to a change in drug dose results in a proportional change in concentration) and dose proportional in the range of 10-60 mg a day. The pharmacokinetics studies done during clinical trials were not found to be different between men and women. The biotransformation of citalopram occurs mainly in the liver, with a half life of about 35 hours. Using a once a day dose in a healthy individual, approximately 75% of the dose was excreted in the urine and approximately 10% was eliminated in the feces within 17 days. The steady plasma concentration is achieved within a week. The accumulation of citalopram in the plasma based on the half life is 2.5 times the concentration found after a single dose. Both the tablet and oral solutions forms are bioequivalent.\textsuperscript{8}

After the initial dose (40mg tablet) of citalopram, peak blood levels occur at about four hours. The bioavailability of citalopram was about 80% and absorption was not found to be affected by food. In studies done on >=60 years of age compared to younger subjects and those on subjects with impaired hepatic function, the half life was increased substantially. The recommend dose was then reduced to 20 mg daily for those over 60 years of age and those with renal hepatic impairment.\textsuperscript{8}

**Side Effects**

While Celexa® does not have many of the side effects other anti-depressants have; it does have some of its own. The main side effects seen after continued use of this drug are: nausea, vomiting, lack of appetite, diarrhea, drowsiness, dizziness, trouble sleeping, dry mouth, muscle and joint pain, and fatigue. In 2% of the patients taking this drug, noticeable sexual side effects have occurred and further studies are being done to determine if this is due to the SSRI or other unknown reasons.\textsuperscript{9}

Another concern for an adverse reaction is what is referred to as the discontinuation syndrome. Of the five SSRIs available and used, four of them which include Celexa® are considered short life SSRIs and can cause this syndrome if abruptly discontinued. This syndrome must not be confused with what would be considered withdrawal syndrome which is found when an addicting drug is stopped. SSRIs are not considered addicting drugs. Tapering off the drug is recommended to discontinue and thus avoid this syndrome which would include: flu like symptoms, lightheadedness, uneasiness or restlessness, sleep problems or headache which can last three to five days.\textsuperscript{7}

The strictest warnings come with the interaction of Celexa® or SSRIs with MAOIs. Patients receiving serotonin reuptake inhibitor drugs in combination with monoamine oxidase inhibitors (MAOI) are warned of the seriousness of this combination. The combination of the two causes an elevation in blood pressure and may evoke
behavioral excitation which could lead to death. It is highly recommended that a patient under treatment with either Celexa® or an MAOI must have discontinued the MAOI or SSRI (Celexa®) for at least 14 days and never take these drugs together.7

Manufacturers are finding that they may need to be cautious with the age group seven to seventeen diagnosed with a depressive disorder and undergoing a drug therapy treatment. There is now evidence that there may be a link between suicidal thoughts and suicide attempts in pediatric patients with manic depressive disorder (MDD) taking such drugs as Prozac, Zoloft, Paxil, Luvox, Celexa®, and other like drugs. They continue to study this issue. The United Kingdom has urged its doctors not to prescribe most SSRIs when treating patients under the age of 18.10

New Developments

Since marketing the drug Celexa® in the United States, continued research has been done on this drug. Two research reports were presented at the 23rd Collegium Internationale NeuroPsychopharmacologium Congress in Montreal in June 2002; both reports indicated that isolated active isomers from this mixed isomer compound would yield a product with significant improvements in efficacy and safety.11

The first report was on the antidepressant escitalopram (Lexapro), which was developed in Europe by Lundbeck and then licensed by Forest Laboratories for marketing in the U.S. This report stated that the S-isomer of the compound Celexa® (citalopram) was more than twice as potent at increasing brain serotonin availability as Celexa®. Escitalopram is the S-isomer of citalopram, which is a compound that contains two isomers (S and R) of the same molecule.11

The second report indicated that when the S-citalopram is administered along with the R-isomer of citalopram, the ability of the S-isomer to increase the serotonin levels declines, indicating that the R-isomer may be interfering with the S’s ability to increase the serotonin availability in the brain. How this happens or occurs is not known;
however, it is suspected that the two are competing to bind and that one is not as effective at binding and blocking the reuptake transporter as the other.\textsuperscript{11}

The advantages of single enantiomer drugs are increased selectivity, reduced drug to drug interaction, less complexed pharmacokinetics (how the drug is processed in the body) and an improved response in most patients to the drug. In 1999 single-enantiomer drugs made up about one third of the drug market; in 2000 it increased in the drug market to forty percent of drug sales.\textsuperscript{3}

In August of 2002, Forest Laboratories received approval to market Lexapro (escitalopram) in the United States. It is their intention to continue providing Celexa to those patients still using this drug, but they will be focusing their marketing on this new drug, Lexapro.\textsuperscript{3}

\textbf{Synthesis}

The process used to synthesis and make Celexa\textsuperscript{®} (citalopram HBr) is a multi-step process using Grignard reagents.\textsuperscript{12}

\begin{align*}
1. \quad & \begin{array}{c}
\text{N=} \\
\text{(benzophenone)} \\
\text{O} \\
\text{O}
\end{array} + \begin{array}{c}
\text{MgBr} \\
\text{F} \\
\text{F}
\end{array} \rightarrow \begin{array}{c}
\text{N=} \\
\text{O} \\
\text{OH} \\
\text{F} \\
\text{Mg+Br} \\
\end{array}
\end{align*}

In step number one, 5-cyanophthalide is reacted with 1 equivalent Grignard reagent, p-fluorophenylmagnesium bromide to yield a 2-(hydroxymethyl) benzophenone derivative.\textsuperscript{12}

\begin{align*}
2. \quad & \begin{array}{c}
\text{N=} \\
\text{OH} \\
\text{O} \\
\text{F}
\end{array} + \begin{array}{c}
\text{ClMg} \\
\text{CH}_{2}\text{CH}_{3}\text{N}
\end{array} \rightarrow \begin{array}{c}
\text{N=} \\
\text{O} \\
\text{OH} \\
\text{F} \\
\text{Cl}^- \text{Mg}^+ \\
\text{CH}_{2}\text{CH}_{3}\text{N}
\end{array}
\end{align*}

For step number 2, the 2-(hydroxymethyl) benzophenone derivative is again reacted with another Grignard reagent, but this time 3-(dimethylamino) propylmagnesium was used for the reagent to yield a cyano-substituted phthalan.\textsuperscript{12}
In step 3, the cyano-substituted phthalan went through dehydration with $\text{H}_3\text{PO}_4$ resulting in a loss of water and ultimately closing the ring to yield the final product of citalopram. Citalopram was converted into its HBr salt by conventional methods.\textsuperscript{12}

Conclusion:

Celexa\textregistered is an SSRI that can be of benefit to some people who are suffering from the debilitating effects of clinical depression. However, like all drugs, this drug has its limitations and is not a “cure all” for ending the hopelessness and sadness that depression can bring. Only through further research on how the brain works biologically are we going to find a way to help all those who suffer from many of the depressive disorders today. The difficulty comes in determining which of the many biological variations found in humans, including their hereditary backgrounds, environment, and other lifestyle and health issues are material, and which have no effect. Where one drug (be it Celexa\textregistered or any other drug) may work for some, it may not work for another; the questions which must be researched through both the biological fields and the chemistry fields, are why a given compound is so effective in one person and ranges from mildly effective to ineffective, to toxic in another. Man is a very complicated machine. How the body works and how the drugs introduced into the body to solve a disorder affect its function is also very complicated. Hopefully, the knowledge gained in both fields of research will bring exciting and positive changes in the lives of humankind and in pharmaceutical medicine.
References


SevoFlo™ (Sevoflurane)
Inhalation Anesthetic for Use in Dogs

Prepared for Dr. Mancini
Paradise Valley Community College

Prepared by Sandra Christensen
April 21st, 2005
Abstract:

The development of fluorine substituted volatile anesthetics has revolutionized surgery in both human and veterinary medicine.\(^1\) SevoFlo\(^\text{TM}\) (sevoflurane) is the latest inhalation anesthetic agent used for the induction and maintenance of general anesthesia in dogs.\(^2\) It offers some unique benefits in regards to safety, speed, and ease of use over other anesthetics currently being used. As with any anesthetic agent, there are risks associated with the use of SevoFlo\(^\text{TM}\) which can include severe respiratory and cardiopulmonary depression.\(^3\) This paper will discuss the history, structure, and chemistry of sevoflurane; as well as explore advantages, disadvantages and comparisons to similar agents used in veterinary medicine today.

History:

History of Anesthesia:\(^7\)

1540 - Paracelsus recorded that ether anesthetized chickens
1800 - Sir Humphry Davy suggested anesthetic effect of nitrous oxide
1842 - Ether first used in human anesthesia
1862 - Nitrous oxide reintroduced in humans
1875 - Chloral hydrate introduced
1878 - Cocaine suggested for local anesthesia
1930s - Barbiturates introduced
1950 - Phenothiazine tranquilizers
1956 - Halothane introduced
1971 - Xylazine and ketamine introduced
1975 - Establishment of the American College of Veterinary Anesthesia
1985 - Isoflurane introduced
1989 - Propofol introduced
1999 - SevoFlo\(^\text{TM}\) introduced

SevoFlo\(^\text{TM}\), a trademark of Abbott Laboratories and product of Japan, has received market authorization for induction and maintenance of anesthesia in dogs. Despite the fact that SevoFlo\(^\text{TM}\) is a recently licensed product, it is not a new drug. Sevoflurane, the active ingredient in SevoFlo\(^\text{TM}\), was approved for clinical use in the United States in 1995.\(^4\) The version approved for use in humans is called Ultane\(^\text{TM}\) \(^2\) and has been used extensively in pediatrics, initially gaining popularity in Japan in the early 1990s, prior to its acceptance in Europe and the United States.\(^5\)

A patent was issued on October 19, 1999 by the United States Patent Office for a method of preparing sevoflurane which comprised of (a) providing a liquid mixture of (CF\(_3\))\(_2\)CHOCH\(_2\)Cl, hydrogen fluoride, an amine and water; and (b) reacting the mixture, to form (CF\(_3\))\(_2\)CHOCH\(_2\)F.\(^1\)

Today, SevoFlo\(^\text{TM}\) is a veterinary-approved product manufactured by Abbott Laboratories and supplied in amber colored bottles containing 250 mLs of sevoflurane.\(^6,3\) (see figure 1) Federal law restricts this drug to use by or on the order of a licensed veterinarian.\(^3\)
Structure Determination/Pharmacology:

SevoFlo™ (will be referred to as “sevoflurane” throughout the remainder of this paper) is an isopropyl ether inhalational anesthetic. Its chemical name is fluoromethyl 2,2,2-trifluoro-1-(trifluoromethyl) ethyl ether. Its structural formula is shown below in Figure 2.

![Chemical Structure of Sevoflurane]

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**Sevoflurane Physical Constants are:**

- Molecular weight: 200.05
- Boiling Point at 760 mm Hg: 58.6°C
- Specific Gravity at 20°C: 1.520-1.525 g/mL
- Vapor Pressure in mm Hg at 20°C:
  - at 25°C: 197
  - at 36°C: 317

**Distribution Partition Coefficients at 37°C:**

- Blood/Gas: 0.63-0.69
- Water/Gas: 0.36
- Olive Oil/Gas: 47-54
- Brain/Gas: 1.15

**Mean Component/Gas Partition Coefficients at 25°C for Polymers Used Commonly in Medical Applications:**

- Conductive rubber: 14.0
- Butyl rubber: 7.7
- Polyvinyl chloride: 17.4
- Polyethylene: 1.3

The exact mechanism that inhalant anesthetics exert their general anesthetic effects is not precisely known. What we do know, is that inhalant anesthetics may interfere with functioning of nerve cells in the brain by acting at the lipid matrix of the membrane. Sevoflurane has a very low blood:gas partition coefficient (0.63-0.69) allowing very rapid anesthesia induction and recovery making rapid mask induction possible. Minimal Alveolar Concentration (MAC %) is the minimum alveolar concentration of an anesthetic (in volume %) at which 50% of the patient will not respond to painful stimuli (e.g., surgery-skin incision, tail clamp, or electrical stimulation). The data here shows MAC % in oxygen reported for sevoflurane in various species: Dog = 2.09 - 2.4; Cat = 2.58; Horse = 2.31; Sheep = 3.3; Swine = 1.97-2.66; Human (adult) = 1.71 - 2.05. Several factors including acid/base status, temperature, additional Central Nervous System (CNS) depressants on board, age of recipient, and ongoing acute disease may alter MAC. MAC % will be discussed further in the comparisons section of this paper.
Chemistry:

Sevoflurane is chemically stable and no discernible degradation occurs in the presence of strong acids or heat. The only known degradation reaction in the clinical setting is through direct contact with CO₂ absorbents (soda lime and Baralyme®) producing pentafluoroisopropenyl fluoromethyl ether, (PIFE, C₄H₃F₂O), also known as Compound A; and trace amounts of pentafluoromethoxy isopropyl fluoromethyl ether, (PMFE, C₅H₆F₂O), also known as Compound B. The production of degradants in the anesthesia circuit results from the extraction of the acidic proton in the presence of a strong base (KOH and/or NaOH) forming an alkene (Compound A) from sevoflurane similar to formation of 2-bromo-2-chloro-1,1-difluoro ethylene (BCDFE) from halothane (see halothane structure in figure 5, next page). Baralyme® causes more production of Compound A than does soda lime. Laboratory simulations have shown that the concentration of these degradants is inversely correlated with the fresh gas flow rate (See Figure 3).

Sevoflurane degradation in soda lime has been shown to increase with temperature. Since the reaction of carbon dioxide with absorbents is exothermic, this temperature increase will be determined by quantities of CO₂ absorbed, which in turn will depend on fresh gas flow in the anesthesia circle system, metabolic status of the patient, and ventilation. The relationship of temperature produced by varying levels of CO₂ and Compound A production is illustrated in the following in vitro simulation where CO₂ was added to a circle absorber system.

Figure 3: Fresh Gas Flow Rate versus Compound A Levels in a Circle Absorber System

Figure 4: Carbon Dioxide Flow versus Compound A and Maximum temperature
Figure 5 below shows the chemical structures and mass spectra of compound A, sevoflurane, and 1,1,1-trifluoro-2-iodoethane. This is the result of an experiment conducted by the Department of Anesthesia, University Hospital at Ghent University, De Pintelaan in Ghent, Belgium to quantitatively determine the presence of Vapor-Phase Compound A in Sevoflurane using gas chromatography–mass spectrometry.  

![Chemical Structures](image)

\[
\begin{align*}
\text{F}_3\text{C} & \quad \text{C} \quad \text{O} \quad \text{CH}_2\text{F} \quad (1) \\
\text{F}_2\text{C} & \quad \text{CH} \quad \text{O} \quad \text{CH}_2\text{F} \quad (2) \\
\text{F}_3\text{C} & \quad \text{CH}_2\text{I} \quad (3)
\end{align*}
\]

**Figure 5.** Chemical structures and mass spectra of compound A (1), sevoflurane (2), and 1,1,1-trifluoro-2-iodoethane (3).  

\[16\]
Comparisons/contrasts to other anesthetics:

The following compounds are some of the commercially available volatile fluorinated anesthetics on the market today.\(^1\)

Halothane (Fluothane\(^5\)) (figure 6) is mainly used on large animals.\(^7\) An inhalant general anesthetic agent, halothane occurs as a colorless, nonflammable, heavy liquid. It has a characteristic odor resembling chloroform and sweet, burning taste. The pungent smell of halothane may prompt the animal to hold their breath during induction and therefore prevents the uptake of the inhalant anesthetic and slows the speed of induction.\(^7\) Halothane remains a useful general anesthetic in veterinary medicine due to its relative safety, potency, controllability, nonflammability, and comparative low cost; however, sevoflurane and isoflurane have largely supplanted it.\(^6\)

Isoflurane (IsoFlo\(^5\) Abbott Labs) (figure 7) is mainly used on small animals and is currently the leader in anesthetic use for small animal clinics. An inhalant general anesthetic agent, isoflurane occurs as a colorless, nonflammable, stable liquid. It has a characteristic mildly pungent musty, ethereal odor. Isoflurane is the primary potent inhalation anesthetic used for maintenance of anesthesia.\(^8\) Just as with halothane, it is too pungent for mask inhalation induction and is the most vasodilatory of these agents.\(^4\) Some animal studies have indicated that isoflurane may be fetotoxic so use during pregnancy is not highly recommended.\(^6\)

Sevoflurane (SevoFlo\(^\text{TM}\) Abbott Labs) (Figure 8) used on both small and large animals and is the preferred anesthetic gas for domestic pets. It is reported to have a pleasant odor and is not irritating to airways. It is the least pungent of the potent inhaled agents and is used commonly for inhalation induction.\(^8\) It is nonflammable and non-explosive. It is clear, colorless liquid that is miscible with ethanol or ether and slightly soluble in water.\(^9\) Sevoflurane, as previously discussed, is subject to degradation by the basic environment present in the carbon dioxide absorbent. The breakdown products include Compound A, a substance associated with renal injury in rats. So far, renal injury due solely to sevoflurane have not been reported. The physical properties of sevoflurane allow a smooth, rapid inhalation induction and a quick emergence from anesthesia.\(^4\)

Desflurane (Suprane\(^5\) Baxter Labs) (Figure 9) is commonly used in human medicine. It is extremely volatile but nonflammable and not explosive at clinical concentrations. Desflurane is less potent than other ethers.\(^4\) This agent is the most pungent of the inhalation anesthetics, causing breath-holding and coughing, and is not recommended for inhalation induction of general anesthesia.\(^4\) The boiling point of desflurane is near room temperature, thus necessitating a special heated vaporizer to convert the liquid to a gas. The desflurane vaporizer requires a plug-in with an electrical outlet for external heat supply to the vaporizer, a design that is not practical for most of veterinary hospitals which require anesthesia machines to be more mobile.\(^14\) This vaporizer is much more expensive than the vaporizers that deliver isoflurane, sevoflurane and halothane. This expense may also limit the usefulness of desflurane in veterinary medicine.\(^14\)
Blood/Gas solubility: Rate of induction, change in anesthetic depth, and rate of recovery are related to the blood/gas solubility of each inhalant anesthetic. The higher the blood/gas solubility, the slower the a) induction rate b) rate of change in depth of anesthesia and c) recovery rate.\textsuperscript{7} Table 1 compares the solubility, vapor pressure and metabolism of the four agents.

<table>
<thead>
<tr>
<th>Anesthetic Agent (Trade name)</th>
<th>Blood/gas solubility</th>
<th>Vapor Pressure at 20°C (mmHg)</th>
<th>% of anesthetic recovered as metabolites</th>
</tr>
</thead>
<tbody>
<tr>
<td>Halothane CBrCH2-CF3 (Fluothane®)</td>
<td>2.4</td>
<td>243</td>
<td>Up to 20-25% is metabolized by the liver and kidneys</td>
</tr>
<tr>
<td>Isoflurane CF3-CHCl-O-CF3H (Forane®, IsoFlo®)</td>
<td>1.4</td>
<td>240</td>
<td>&lt; 1% is metabolized by the liver and the kidneys</td>
</tr>
<tr>
<td>Sevoflurane CF3-H-O-(CF3)2 (Ultane®, SevoFlo®)</td>
<td>0.69</td>
<td>160</td>
<td>&lt; 3% is metabolized by the liver and the kidneys</td>
</tr>
<tr>
<td>Desflurane CF3-CF=O-CF3H (Suprane®)</td>
<td>0.42</td>
<td>664</td>
<td>No documented metabolism</td>
</tr>
</tbody>
</table>

Induction, recovery and changes in anesthetic depth are relatively slower with halothane and more rapid with desflurane and sevoflurane. Sevoflurane has a low solubility with a blood gas partition coefficient of 0.69 slightly higher than desflurane.\textsuperscript{4} Sevoflurane has an induction of two to four minutes and recovery rates of less than five minutes. Isoflurane induction requires three to five minutes, slightly longer than sevoflurane but faster than halothane which is five to eight minutes.\textsuperscript{7}

Metabolism: Due to the relatively high vapor pressures of sevoflurane, isoflurane and halothane; the use of precision vaporizers (which are out of the breathing circle) are required.\textsuperscript{7} For a patient with hepatic dysfunction, the choice of inhalation anesthetic should not be halothane due to high liver metabolism.\textsuperscript{7} Metabolism for halothane can be up to 25% which is pretty significant compared to the relatively low percentages of sevoflurane (<3%), isoflurane (<1%) and desflurane with has no documented metabolism.

| Table 2. Comparison of anesthetic potency of inhalant anesthetics using MAC (volume %)\textsuperscript{7} |
|---------------------------------------------------------------|---------------------------------------------------------------|---------------------------------------------------------------|---------------------------------------------------------------|---------------------------------------------------------------|
|                        Dogs                                  |                        Cats                                    |                        Horses                                   |                        Human                                     |
| Halothane               0.87 %                                |                        0.82 %                                  |                        0.88 %                                   |                        0.75 %                                   |
| Isoflurane              1.28 %                                |                        1.63 %                                  |                        1.31 %                                   |                        1.15 %                                   |
| Sevoflurane             2.1 - 2.36 %                            |                        2.58 %                                  |                        2.31 %                                   |                        1.7 %                                    |
| Desflurane              7.2 %                                 |                        9.8 %                                   |                        7.6 %                                    |                        6.0 %                                    |

MAC is used to compare inhalation anesthetic potency.\textsuperscript{17} Clinically, achieving a surgical plane of anesthesia usually requires 1.2 to 1.5 times MAC to ensure 99.9% of the patient that will not respond to the surgical stimulation. The lower the MAC value, the more potent the anesthetic agent. MAC values from the table above clearly show that halothane, isoflurane and sevoflurane are much more potent than desflurane.\textsuperscript{7}
Respiratory: All anesthetics in modern practice will depress respiratory function. Inhalation anesthetics do so in a dose-dependant fashion. There are no major distinctions among halothane, isoflurane, desflurane, and sevoflurane in terms of respiratory function. Halothane and sevoflurane share the characteristic of being pleasant to breathe without causing airway irritation or bronchospasm. Isoflurane and desflurane have a more pungent aroma and can elicit coughing or bronchospasm, especially in asthmatic patients.\textsuperscript{12}

Cost Considerations: The most common reason cited for veterinary hospitals not completely switching to sevoflurane is cost. As expected, the newer inhalation anesthetics carry with them a higher price.\textsuperscript{7} Table 3 below lists some of the relative costs for inhalation anesthetics at Washington State University.\textsuperscript{12} When we consider the amount of liquid used based on the potency (MAC) of the anesthetic at the same fresh gas flow rate a relative estimate of cost per hour of anesthesia can be generated.\textsuperscript{12}

<table>
<thead>
<tr>
<th></th>
<th>Halothane</th>
<th>Isoflurane</th>
<th>Desflurane</th>
<th>Sevoflurane</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost ($)/bottle</td>
<td>30</td>
<td>30</td>
<td>75</td>
<td>180</td>
</tr>
<tr>
<td>Cost ($)/ml</td>
<td>0.12</td>
<td>0.30</td>
<td>0.30</td>
<td>0.72</td>
</tr>
<tr>
<td>Cost ($)/hr @ 1.5 X MAC</td>
<td>0.49</td>
<td>1.89</td>
<td>9.72</td>
<td>7.45</td>
</tr>
</tbody>
</table>

Example: One ml of liquid anesthetic produces about 200 ml of anesthetic vapor. To provide a 2% concentration in oxygen at 1 liter/min, will require about 20 ml of vapor or 0.1 ml of liquid anesthetic per minute. Thus, to anesthetize a dog with isoflurane for 1 hour at 2% (1.5 X's the MAC value) will require about 6 ml of liquid anesthetic. Correcting for differences in MAC (potency) gives an estimate of the liquid anesthetic cost for each agent (Table 3).\textsuperscript{12}

Advantages of Sevoflurane:

The major advantage presented by sevoflurane is the speed with which it acts as well as the speed of recovery for the dog.\textsuperscript{17} Sevoflurane might arguably be considered safer than the other agents because speed gives it the ability to change anesthetic depth more rapidly. Sevoflurane allows a veterinarian to more quickly fine tune anesthetic depth to the patient’s requirements during the course of an anesthetic period, which results in less fluctuation in cardiorespiratory variable.\textsuperscript{17}

Mask induction with sevoflurane is accomplished quickly and without a significant excitatory response.\textsuperscript{12} Clinically, many veterinary hospitals use sevoflurane for mask induction because it possess several desirable properties for mask induction over other inhalant anesthetics.\textsuperscript{7} Sevoflurane has a lower blood/gas solubility; it does not irritate airway and stimulate excessive secretions; it lacks of pungency and allows animal to accept the inhalant with ease. The vaporizer of sevoflurane can be set as high as 7-8% to pressurize the inhalant into the patient’s lungs.\textsuperscript{7} No overt fetotoxicity or teratogenicity has been demonstrated in lab animal studies, but definite safety has not been established for use during pregnancy.\textsuperscript{3}
Disadvantages of Sevoflurane:

As with any new drug, the cost of switching over to a new anesthetic drug can be an issue for some hospitals. Not only is sevoflurane more expensive than the other inhalant anesthetics, there are also operational cost for equipment and training that need to be considered. Another disadvantage would be 3-5% of sevoflurane that is metabolized in the body (with a little less than 3% metabolized by the liver and kidneys), giving an inorganic fluoride by-product. Although fluoride toxicity (high-output renal failure) was a concern with this agent, it has not been seen in a clinical context. Sevoflurane is also subject to degradation by the basic environment present in the carbon dioxide absorbent. One disadvantage not previously mentioned in this paper is the pollution of the work environment during induction. Waste inhalant anesthetic gas may cause headaches and other health problems to doctors and technicians. This can be taken care of by improve the ventilation at the working place. An electrical fan can be turned on during the induction to blow away the waste gas from the handlers.

Adverse Effects/Warnings:
Adverse reactions during maintenance anesthesia are hypotension, tachypnea, muscle tenseness, excitation, apnea, muscle fasciculations and emesis. Sevoflurane is contraindicated in patients with a history or predilection towards malignant hyperthermia. It should be used with caution (benefits vs. risks) in patients with increased CSF or head injury, or renal insufficiency. Because of its rapid action, one should use caution not to overdose during the induction phase. Because of the rapid recovery associated with sevoflurane use caution (and appropriate sedation during the recovery phase), particularly with large animals. Geriatric animals may require less inhalation anesthetic. Sevoflurane does not appear to be a good inhalational anesthetic in rabbits (breath holding, struggling).

As mentioned before, sevoflurane can react with carbon dioxide absorbents to produce "compound A", a nephrotoxin. However, after extensive clinical use in humans, nephrotoxicity has not been demonstrated to be of clinical concern. Sevoflurane should be used in precision, agent-specific, out of circuit vaporizers.

Conclusion:

The desired result of general anesthesia is to achieve an ideal situation, where the patient is analgesic, unconscious and immobile throughout the course of surgery. The "perfect" anesthetic would be one that provides rapid onset and rapid recovery; produces no heart or lung depression; provides adequate analgesia; provides excellent muscle relaxation; is not metabolized by the patient; is not toxic; and is readily reversible. Unfortunately, a single drug incorporating all of these elements does not exist at this time, therefore, the practice of anesthesia involves the use of multiple drugs to achieve the endpoints of hypnosis, analgesia and lack of movement. Even though the perfect anesthetic has yet to be found, the fluorine substituted volatile anesthetic have properties which approach ideal drug behavior. The availability of sevoflurane offers a new, reliable anesthetic with advantages and disadvantages over isoflurane. Speed of induction/recovery, airway reactivity, and costs are among the issues that will help the practitioner decide which agent is best. Isoflurane is still the primary potent inhalation anesthetic used in veterinary medicine today, however, many experts agree that sevoflurane is likely to be the primary inhalant anesthetic for the future.
Glossary:
Abbott Animal Health: produces products for poultry and companion animals (pets) worldwide. Abbott is a leader in anesthesia and critical care products for the veterinary market. Abbott’s new anesthetic agent, sevoflurane, recently received U.S. approval for use in dogs.
Alveolar: of relating to, resembling, or having alveoli; especially of relating to or constituting the part of the jaws where the teeth arise, the air-containing compartments of the lungs, or glands with secretory cells about a central space.
Apnea: transient cessation of respiration
Blood Gas Solubility: The ratio of the amount of sevoflurane dissolved in blood compared to the amount of sevoflurane in the same volume of gas in contact with that blood. The partial pressure of an inhalant in the body tissues, including the brain, approaches that of the partial pressure in the body tissues, including the brain, approaches that of the partial pressure in the alveoli. Therefore, the less soluble an inhalant anesthetic, the more rapidly the alveolar concentration rises (or falls) and thus the more rapidly brain partial pressure rises (or falls), resulting in more rapid inductions (or recoveries).
Bronchodiilator: a drug that relaxes bronchial muscle resulting in expansion of the bronchial air passages.
Bradycardia: relatively slow heart action
Degradation: Physical, metabolic, or chemical change to a less complex form. Foods are physically degraded during chewing, and then chemically degraded from complete compounds, such as proteins and starches, to amino acids and sugars, respectively.
Emesis: an act or instance of vomiting
General anesthesia: anesthesia affecting the entire body and accompanied by loss of consciousness; General anesthesia is a drug-induced reversible depression of the central nervous system (CNS), used most commonly during surgical procedures. Anesthesia works by slowing body functions, relaxing muscles and blocking pain.
Halothane: a volatile, halogenated inhalation anesthetic. Blood gas solubility is (2.3) and its MAC is (0.75%)
Hypotension: Abnormally low blood pressure
IsoFlo®: Abbott Animal Health’s brand of isoflurane.
Isoflurane: a volatile, halogenated inhalation anesthetic. Blood gas solubility is (1.4), its MAC is (1.15%). Odor is pungent and can be an irritant to the throat.
Lime: Calcium oxide, CaO. A substance obtained from limestone. Calcium oxide is prepared from limestone, CaCO3, by heating it sufficiently to drive off the carbon dioxide. When lime is mixed with water, heat is produced. Lime is an ingredient of cement and mortar.
Muscle fasciculations: muscular twitching involving the simultaneous contraction of contiguous groups of muscle fibers.
MAC Minimum alveolar concentration: The end-alveolar concentration of an inhalation anesthetic at which 50% of patients do not respond to a painful stimulus (e.g., standard surgical stimulus); measure the potency of the anesthetic and is expressed as a percentage.
Surgical Anesthesia: General anesthesia that provides unconsciousness, relaxes muscles, and relieves pain to allow surgery to be performed.
SevoFlo™: Animal Health’s brand of sevoflurane. An inhalant anesthetic, which provides veterinarians rapid induction of anesthesia and excellent control during the maintenance phase of anesthesia.
Sevoflurane: A volatile, sweet smelling (non-pungent), halogenated inhalation anesthetic given to animal patients by vaporization. Blood gas solubility is (0.68) and its MAC is (2.4%).
Ultane™ (sevoflurane): inhalation anesthetic for use in humans is a trademark of Abbott Laboratories.
Vasodilatory: widens the lumen of blood vessels.
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*Note: These journal articles, abstractions were accessed via Veterinary Information Network (VIN). The Reference Center contains information from a wide range of sources. These include veterinary & human literature, Plumb's Veterinary Drug Handbook, the VIN message board archives, FAQs, etc. The Veterinary Information Network, founded in 1991 by veterinarians Dr. Duncan Ferguson and Dr. Paul D. Pion, is a division of the Veterinary Information Network, Inc. VIN is the veterinary profession’s premiere online resource, providing veterinarians, veterinary students, and the veterinary industry with the information and tools they need to address the demands of modern veterinary practice. VIN - for veterinarians, by veterinarians - unites more than 19,000 veterinarians, veterinary students and veterinary industry partners in a truly interactive worldwide online community. Among its many offerings, VIN provides its members unlimited access to a large medical database, active and expert-moderated case and professional issue discussions, practice management information, and online continuing education courses. Price of subscription is $528/year for VIN. For more information visit http://www.vin.com/
Radioimmunotherapy: The New Age of Radiation Therapy

Prepared for
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Prepared by
Tawny Cruickshank

April 18, 2005
Abstract:

This paper begins by talking about non-Hodgkin’s Lymphoma and introducing the quickly growing treatment with radioimmunotherapy. The history of radioimmunotherapy is talked about followed by an explanation of just what radioimmunotherapy is and how it works and is administered. The general audience is then informed of a safer form of radioimmunotherapy that used the molecules Avidin and Biotin. The two most well known radiolabeled antibodies, Zevalin and Bexxar, are discussed. Their characteristics are compared and contrasted. The experience a woman has with non-Hodgkin’s Lymphoma and radioimmunotherapy with the use of Zevalin is shared followed by a short discussion of the safety measures a patient, health care provider, and a patient’s contacts should take during and after the delivery of radioimmunotherapy. The paper is concluded with addressing a few of the major tasks that are still remaining in the process of making radioimmunotherapy an even safer and more attractive form of therapy for cancer patients.

Introduction:

With non-Hodgkin’s Lymphoma (NHL) having the second fastest growing mortality rate, radioimmunotherapy seems to offer a brighter future for the cancer patients. Radioimmunotherapy (RIT) is a form of radiation therapy that uses a mixture of antibodies, like those produced by the immune system to fight off disease, and radiation. The patient receives this mixture through an IV allowing the radiolabeled mixture to run through the blood stream and travel through the body until it finds the specific tumor cell it is labeled for.

Background:

The idea of using radioimmunotherapy to treat cancer patients who had exhausted all other options began in 1948 at the California Institute of Technology. Two men by the names of David Pressman and Geoffrey Keighley were the first researchers to discover that radioactive isotopes could be linked to antibodies and used to target specific parts of the body. The researchers were able to direct iodine-131 to the kidneys of rats. Between 1948 and the present, there have been numerous researchers who have made contributions to and have expanded the understanding and knowledge people have on radioimmunotherapy. Tumor-targeting done in rats, dogs, and humans showed “tumor-specific uptake” in approximately two-thirds of the patients. The experiments were carried out at the University of Rochester School of Medicine and Dentistry by William Bale and Irving Spar. Over the next several years and by 1966, it was shown that patients treated with an antibody that had Iodine-131 linked to it reacted positively with the regression of their tumors. This was reported by Robert Craeld from the University of Colorado Medical Center. Byron Ballou began the modern era of radioimmunotherapy with his work done at the University of Pittsburgh in the late 1970s. Ballou’s work has led to the development of hundreds of different cloned antibodies. Although not all of them have been successful, the radiolabeled antibodies have been used to treat various different cancers and have been able to target different tumors.
Body:

The antibodies that are produced by the body, as well as those cloned for RIT, are y-shaped proteins. The purpose for cloning an antibody is to cause it to bind to specific proteins, known as antigens, on the cancerous cell. The cloned antibody is then labeled with a radioactive isotope and used to carry the isotope to the tumor where it destroys the abnormal cells. Although this form of radiation treatment is extremely effective, it can only be applied to localized cancer in comparison to cancer that has spread to the other parts of the body.

In order to destroy as many cancerous cells as possible and do minimal damage to the surrounding healthy tissues, it is important that the radiolabeled antibody reach its target as quickly as possible and then be eliminated from the body as quickly as possible so that the radiation does not spread. Researchers have been exploring a new area of RIT that uses the Avidin and Biotin molecules to deliver the treatment more quickly and safely.

There are three steps to RIT treatment with Avidin-Biotin. In STEP 1 of treatment, the patient receives an endovenous injection of the cloned antibody. This antibody, which has been previously linked to the Biotin molecule, reaches its target site in approximately 24-48 hours. In STEP 2 of treatment, approximately 24-48 hours after the first injection, the patient receives another injection of Avidin. Because there is a strong attraction between the Avidin and Biotin molecules, the Avidin will bind to the Biotin that is already present on the tumor. The patient’s liver will metabolize any extra Avidin not used or needed. In STEP 3, the last step of treatment, after the previously dispersed antibodies have been eliminated, the patient receives a final injection. It is a dose of Biotin that has been labeled with a radioactive isotope. Since there is Avidin located on the tumor, the radioactive Biotin is attracted to it and reaches its target site within minutes of being injected. The Biotin molecules are extremely small making it easy for the kidneys to eliminate them quickly from the body. Aside from allowing the rapid excretion of the radioactive antibody from the body, the highly stable bond that is formed between Avidin and Biotin also prevents the antibody from radiating through the body.

Although there are numerous RIT drugs that are currently being developed, there are two major ones that have already been approved and are currently being used: Zevalin and Bexxar. In February of 2002, Zevalin became the first RIT drug approved by the FDA for use in treatment for B-cell NHL. It consists of a cloned antibody called ibritumomab tiuxetan (see Figure 1 for the chemical structure), which is connected to the radioisotope, yttrium-90. Treatment with Zevalin is a two-step process in which the patient first receives a dose of rituximab. The purpose for that dose is to prepare the target sites. The patient is then given a test dose of Zevalin that is attached to a low dose of radiation. Once the test dose shows that the tumors are successfully targeted, the patient receives a second dose of rituximab. Approximately one week later, another dose of Zevalin is given, linked to Yttrium-90, which destroys the tumors.
Ibritumomab tiuxetan
Structure

Figure 1-Structure of Ibritumomab tiuxetan

Many times, the radioisotope needs help from a chelating agent in order to properly attach to the antibody. The chelating agent that helps attach Y-90 in Zevalin is Mx-DTPA. The structure of this is illustrated in Figure 2. The chelating agents also help keep the bone-seeking yttrium-90 from collecting in the bone and spreading radiation through the marrow.

Figure 2-Chelating Agent (Diethylenetriaminepentaacetic acid)

Because there is less radiation traveling through the patient's body, they experience minimal side effects from the effective RIT treatment with Zevalin with the most serious being a significant decrease in the number of white blood cells and platelets in their body. It only takes 2-3 weeks to recover from this. Unlike chemotherapy, the patient does not experience any hair loss, fatigue, nausea, or vomiting, and this can be done on an outpatient basis.
Before a patient is treated with Zevalin, some recommendations should be followed. There should be pretreatment tests and evaluations done to determine whether the patient has an adequate white blood cell and platelet count as well as confirm that the body is not immune to the antibodies that are derived from mice. Women who will be receiving the treatment should also take a pregnancy test to make sure that they are not pregnant. Patients do not need to make any changes to their eating habits or daily activities prior to receiving radioimmunotherapy with Zevalin.

A patient who is eligible for treatment with Zevalin must have no problem with their bone marrow reserve and a platelet count of more than 100,000 cells/mm\(^3\). The patient cannot have ever failed the collection of bone marrow or stem cells. It is tolerable if the patient is taking other medications because there have been no drug interaction studies done to show that there could be harmful reactions. A patient on any medication that might affect the white blood cell or platelet count should be monitored more than normal.

The effectiveness of the use of Zevalin has been showed through a series of clinical trials. While only 56% of patients responded positively to an alternative drug, 80% of the patients responded positively to Zevalin. A positive response means that the follow-up CT scans and images showed that the tumor has shrunk. Thirty percent of patients achieved complete remission, meaning there was no trace of cancer left as compared to only 16% of patients who used an alternative drug. With Zevalin yielding as good results as it is, the interest that the biotech companies have in the radioisotope yttrium-90 is on the rise.

The second major drug that is being used in radioimmunotherapy is Bexxar. It is made up of the cloned antibody tositumomab, which has the ability to target the cancerous cells, and the radioisotope Iodine-131, which has the ability to destroy these cells. Bexxar is administered to the patient in the same fashion as Zevalin; it is injected into the bloodstream using an IV. Also like Zevalin, the most severe side effect that a patient will experience is the loss of white blood cells and platelets. However, they will, more than likely, also experience "fever, chills, sweating, nausea, low blood pressure, shortness of breath, labored breathing, weakness, increased cough, infection, pain, rash, or headaches." A very small percentage of patients have also suffered from hair loss or have developed "severe nausea, vomiting, or mucositis." Mucositis is the development of sores in the mouth or gastrointestinal tract. Aside from all of the minor side effects, Bexxar has another unattractive characteristic. Because it contains Iodine-131, patients must stay in the hospital longer than when other isotopes are used, and they must also be isolated and lead shielded during administration. Iodine-131 emits extremely high levels of gamma radiation and also has the tendency to detach from the antibody and accumulate in the body.

There are some additional differences between the radioimmunotherapy drugs Zevalin and Bexxar. Treatment that is given with Zevalin can cost as much as $30,000 while treatment with Bexxar is slightly cheaper. Determining the dosage amount of Zevalin is based on the body weight and baseline platelet count of the patient. When treated with Bexxar, the dosage is determined by a process called dosimetry. Dosimetry is a process in which "imaging of gamma is used to determine the uptake and clearance of the drug from patient-specific dosing." During treatment, radiation is spread throughout the body. With the use of Zevalin, the excess radiation is absorbed by the
liver. With the use of Bexxar, the excess radiation is absorbed by the thyroid. The radiation given off by yttrium-90 in Zevalin has a longer path length of approximately 5mm compared to the shorter path length of radiation emitted by the Iodine-131 in Bexxar which radiates anywhere from 0.8mm to 2.4mm. Yttrium-90 only emits beta radiation while Iodine-131 emits gamma and beta radiation. Because Bexxar emits both kinds of radiation, doctors have the ability to monitor the amount of radiation that is actually reaching the target sites in the patient. Although the radioisotope clearance is faster using Iodine-131, Yttrium-90 has a shorter half-life of approximately 2.7 days while the half-life of Bexxar is closer to 8 days.\textsuperscript{14}

Although Zevalin has more appealing characteristics, Bexxar, even with its minor side effects, is still effective enough to be used in radioimmunotherapy. During clinical studies, 56% of patients had an overall response and 30% of patients had a complete response.\textsuperscript{15}

One woman's experience with radioimmunotherapy has proven to be a positive and effective option for patients who have relapsed after chemotherapy or the use of other radioimmunotherapy antibodies. Eileen Merle-Rao is a 37-year old singer who has been diagnosed with non-Hodgkin’s Lymphoma. The first treatment that Eileen had received was with the therapeutic antibody, Rituxan. Rituxan travels though the body via the bloodstream and attacks all foreign substances including cancerous cells. The only side effects that Eileen suffered from the antibody were flu-like symptoms that she would get in half hour increments. When Eileen’s treatment was combined with chemotherapy, she began to experience the more severe side effects. Knowing that she would have to deal with her hair falling out, Eileen cut her hair extremely short. She said that she would be calmer when she woke up in the morning with only two inches of hair on her pillow rather than two feet. Aside from losing her hair, Eileen also developed a severe case of bronchitis, which left her speechless for several weeks and had to deal with emotional side effects. After being in remission for two and a half years, Eileen was at the point of being able to get pregnant but a visit to the doctor’s office showed that the cancer had come back. Eileen received a second round of the Rituxan treatment with chemotherapy, and it only eliminated the cancer for eight months. Because these treatments continued to fail, Eileen’s doctor suggested that she turn to the new radioimmunotherapy with Zevalin. The radiation particles that Zevalin contains are a lot more effective in destroying the cancerous cells. Even though this new treatment scared Eileen, she knew her options were becoming extremely narrow. With the treatments of chemotherapy taking several months to complete, Eileen could not believe that her treatment with Zevalin was completed in just a week and a half. The only side effect that she experienced with the use of Zevalin was the normal reduction of white blood cells, which she recovered from in approximately six weeks. Unlike the treatment with chemotherapy, Eileen was able to go about her normal daily activities during her treatment with Zevalin. Although there is no guarantee that the cancer will not return, Eileen is now cancer free and is hopeful to start a family in the near future as well as get her singing career back together.\textsuperscript{16}

Radioimmunotherapy is an, overall, safe treatment for the patients and the people around them. However, there are some actions that can be taken to make the therapy even less harmful. There are different safety actions that a patient should take after being treated. For the first three days after treatment, the patient should be sure to clean any spilled urine and body fluids and wash hands thoroughly after using the toilet or if their
hands come in contact with any bodily fluids. For the first week after treatment, patients should be sure to use condoms during sexual intercourse, and they should be sure to avoid pregnancy for the first year. If a patient happens to be breastfeeding during treatment, it should stopped immediately because it can be extremely harmful to the baby. Patients who receive radioimmunotherapy will be able to return to their normal daily activities shortly after completing the treatment.

The beta-radiation that is emitted by some of the radioimmunotherapy drugs does not escape the patient's body, therefore posing little radiation hazards to the caregivers, healthcare providers, or the patient's contacts. The key safety areas that healthcare providers focus on are: using the appropriate shielding (normally lead shielding) during administration, minimizing the exposure time to the radioactive elements, and maximizing their distance from the source of radiation.

There are some major tasks that are still remaining to improve radioimmunotherapy and its effects on the patient's body. Doctors want to be able to "correlate the estimated radiation doses with biological responses in tumors and healthy tissues." They also want to "define more clearly how radioisotope radiation affects healthy and diseased tissue."

Conclusion:

Although there are still some improvements that can be made on how effective radioimmunotherapy and its antibodies are, it is still a promising advancement in medical technology for cancer patients who have tried other methods of treatment and were faced with the problem of relapsing. Once researchers and doctors are closer to perfecting this treatment and as more radiolabeled antibodies are made available, it will not be surprising if radioimmunotherapy completely replaces the use of chemotherapy as well as other more destructive forms of radiation therapy.
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Progesterone vs. Synthetic Progestins

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Abstract: There is a world of difference between synthetic progesterone and natural bio identical progesterone spanning from not only the chemical make up, but also the metabolic pathways that ensues from the use of each. Synthetic progesterone, or progestins, or dangerous and can potentially lead to the formation of fibroids and cysts. Natural Bio-Identical progesterone, on the other hand, has many beneficial and healthy side effects. The synthetic progestin is a foreign chemical not naturally found or produced in the human body, whereas bio-identical progesterone is chemically identical to the progesterone in all human bodies.

I. Introduction

We live in an era when more and more emphasis is being placed on the importance of natural substances. Natural food supplements and herbal formulations are in demand. Homeopathic physicians and caregivers are gaining popularity. Everyone seems to be asking, "What can we do to help the body repair itself in a more natural fashion?" Thrown in the midst of all this hype, be it a trend or just a new generation of persons trying to find to fountain of youth is hormone replacement therapy. It is difficult, especially recently to distinguish between what is safe and/or natural and what is not safe and/or synthetic or not natural. When referring to hormone replacement therapy usually we consider the sex hormones, which are those secreted from the reproductive organs, the ovaries in a female and the testis in a male. There are several different sex hormones but most commonly studied and subsequently most commonly prescribes and used are progesterone, estrogens, and testosterone. Many woman are placed on these drugs or what they think to the natural hormones unbeknownst to them that they could potentially be being exposed to synthetic hormones that could have a detrimental effect on there lives.

II. What are Hormones?

Inside every human body there are over one-hundred hormones, and they are all chemically identical. If one were to take a molecule of progesterone from a nineteen year-old boy and a molecule of progesterone from a ninety year old woman, the molecules would be 99.99% identical, so close that it would be impossible to determine which hormone came from which subject. The primary scope of this paper will focus on a particular hormone that recently has become the topic of many debates among the medical world and also the world of almost every woman in menopause or perimenopause: Progesterone. In order to understand the importance of this hormone and why it is the target of such scrutiny we must understand what hormones are and how they work.

Steroid hormones are essential for the growth, differentiation and function of many tissues in both animals and humans. It has been established by animal experimentation that modification of the hormonal environment by surgical removal of endocrine glands, by pregnancy or by exogenous administration of steroids can increase
or decrease the spontaneous occurrence of tumors or the induction of tumors by applied carcinogenic agents. In humans, endogenous hormones are important in the initiation and progression of tumors. The incidence of tumors in humans could be altered by exposure to various exogenous hormones, singly or in combination.

Hormones are chemical substances that are secreted into the body by glands. Once secreted into the body they are transported to tissues through the blood stream bound up in a substance called sex hormone binding globulin. The sex hormone binding globulin releases the hormones at specific tissues throughout the body. Once at the tissue the hormones begin to perform a modern biological miracle. They bind to there specific receptor site where there signal is magnified and they begin to change the DNA of the cell in the tissue. The hormones are responsible for rebuilding your body and telling your DNA to replicate and ultimately your survival.

Progesterone is the oldest steroid hormone—some 500 million years old on the evolutionary scale. All vertebrates produce progesterone, although it is only in higher vertebrates that this hormone is instrumental in the reproductive cycle. In lower vertebrates progesterone functions in relation to glucose metabolism, the development of intelligence and bone formation.

All the different molecules that end up as steroid hormones start out as a single molecule of cholesterol. As shown below in the hormonal cascade the cholesterol molecule goes down a metabolic pathway and is converted many times over to form our body’s primary sex hormones, including progesterone:

![Hormonal Cascade Diagram]

III. Progestin vs. Progesterone

The process of producing natural progesterone, which is made from yams and soybeans, was discovered by Russell Marker, a Pennsylvania State College chemistry professor. While experimenting with sapogenins, a group of plant steroids, in the jungles of Mexico in the 1930s, Marker realized that progesterone could be transformed by chemical process from the sapogenin, diosgenin, which is found naturally, in yams.
Synthetic progestins however, were developed with the advent of the birth control pill. The half life of natural progesterone was very short and researchers were looking for an agent that would give a longer half life and yet produce or mimic the effects of progesterone. Birth control pills contain, in most cases, a synthetic progestin and a synthetic estrogen. The very potent synthetic progestins prevent ovulation in a very low dose and, therefore, accomplish their function of birth control.\(^5\)

There is a world differences between synthetic progesterone, commonly called progestins, or medroxyprogesterone prescribed also as Provera, and the micronized natural bio-identical progesterone. The biggest difference, and what sets the stage for the major differences in function and metabolic pathways, is the chemical structures. As you can see from figures 1a and 1b the chemical make up of medroxyprogesterone acetate (progestins) and the natural progesterone differs in several ways. A few major differences are the locations and number of methyl groups and the number of oxygen atoms, also the progestin has an ester functionality that the natural progesterone does not have.

The most astounding difference between the two is that medroxyprogesterone is an analog, a "look alike", of progesterone, not truly a molecule of progesterone at all, but rather a progestin. The chemical structure of medroxyprogesterone closely resembles the chemical structure of progesterone as it is produced naturally in the human body. But, even a slight difference in the molecular configuration of a compound can produce a totally different response from its natural counterpart.\(^5\)

The other differences in the two chemicals all stem from the structural differences. The human body has specific hormone receptor sites on certain cells. These highly specialized and unique receptor sites are specifically designed for the hormone designated to fit in that receptor site. Comparatively almost like a key fitting into a lock, whereas only the right key will open the lock. The synthetic progestins are designed to fit into these receptor sites but at the same time cannot function as the natural hormone progesterone would in the same receptor site. Dr Uzzi Reiss MD/O.B.-GYN. sums up his opinions on the use of progestins in one sentence “These substances [progestins] have some of the actions of the natural progesterone your body makes but a lot of disturbing side effects.”\(^3\)

Progesterone and progestins differ in function in three primary areas of the body, the heart, the breasts, and the brain. In the heart synthetic progestins act as coronary
constrictor. "The drug [Provera] is a coronary constrictive. That means that it reduces the diameter of the arteries leading to the heart." Dr. Uzzi Reiss.  

IV. The National Institute of Health Study Halted

In July 2002, the National Institute of Health halted a study on natural hormone replacement of estrogen in combination with progestins. In this study women taking estrogen plus progestin had 8 more strokes per year for every 10,000 women than those taking the placebo The National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health (NIH) stopped early a major clinical trial of the risks and benefits of combined estrogen and progestin in healthy menopausal women due to an increased risk of invasive breast cancer. The large multi-center trial, a component of the Women's Health Initiative (WHI), also found increases in coronary heart disease, stroke, and pulmonary embolism in study participants on estrogen plus progestin compared to women taking placebo pills. There were noteworthy benefits of estrogen plus progestin, including fewer cases of hip fractures and colon cancer, but on balance the harm was greater than the benefit. The study, which was scheduled to run until 2005, was stopped after an average follow-up of 5.2 years.  

When the monitoring board of the Women's Health Initiative (WHI) canceled the estrogen-progestin arm of the study in July 2002, the effect was immediate and dramatic, as several million postmenopausal women with the full agreement of their physicians ceased taking combined hormone therapy. Soon thereafter the manufacturers of conjugated equine estrogens felt compel to publicize a drastic restriction of the indications for their product. Little notice, except in the medical literature, was given to the continuation of the other treatment arms of the Women’s Health Initiative, nor did the rather small (however significant) increases in risk of cardiovascular disease and breast cancer resulting from combined therapy receive widespread serious analysis.

V. Effects of Progesterone and Progestins

Progesterone has many effects on the human body including maintaining the lining of the uterus. It also promotes the survival of the embryo and fetus during gestation, which is why in pregnant woman progesterone levels can go as high as tripling or even quadrupling. Progesterone converts through a chemical process into allopregnenolone which acts a neurotransmitter in the brain and thus is an anti-depressant. Progesterone promotes fat burning and energy a process called thermogenesis. Progesterone stimulates osteo-blats to create new bone cells and thus causes and increase in bone density, and prevents against osteoporosis. All of these positive effects are countered by synthetic progestins due the chemical structure similarities in progestins and progesterone.
Progestins actively bind to receptor sites designed for progesterone and thus block the correct chemical from attaching and sending its signal to the DNA. Though progestins are similar in structure to progesterone they differ vastly in side effects. A few side effects of medroxyprogesterone (another word for progestin) are Acne, anaphylaxis (life-threatening allergic reaction), blood clot in a vein, lungs, or brain, breakthrough bleeding (between menstrual periods), breast tenderness or sudden or excessive flow of milk, cervical erosion or changes in secretions, depression, excessive growth of hair, fever, fluid retention, hair loss, headache, hives, insomnia, itching, lack of menstruation, menstrual flow changes, spotting, nausea, rash, skin discoloration, sleepiness, weight gain or loss, yellowed eyes and skin.

Progesterone is known to have a profound effect on the tissues of the breasts. This means that progesterone has a quintessential role in the development and prevention of breast cancer. Breast tissue is of several different types. Epithelial tissue divides during the progesterone-dominant phase of the menstrual cycle. Ductile tissue grows and branches during pregnancy as a result of estrogen. The lobule-alveolar systems of the breast also develop during pregnancy as a result of the effect of progesterone, which causes the growth of the lobules, the building of alveoli, and an increase in the secretory capacity of the alveolar cells. That process, which is termed ‘differentiation’, is the reason for which full-term pregnancy in early life provides protection against carcinogen-induced breast cancer. Cancers often develop in epithelial cells. All cells have a finite life span, and there is a balance between cell division and cell death. When stimulated by estrogen, the BCL2 gene causes breast cells to grow rapidly and prevents cell death. In ovarian carcinoma cell lines and in breast epithelial cells, progesterone induces apoptosis (cell death) and unregulated the P53 gene. In a study by Formby and Wiley progesterone was demonstrated to at a concentration similar to that seen in the third trimester of pregnancy exhibited a strong anti-proliferation effect on at least two breast cancer cell lines. Apoptosis was induced in the progesterone receptor expressing T47-D breast cancer cells.

Sex hormones, such as progesterone, have been and are used extensively in human therapy. When they are used for the treatment of disseminated cancer, such as that of the breast, prostate and endometrial, their effect on tumor growth and the severity of their side-effects are the major considerations. The use of sex hormones in therapy for other conditions (for example, menstrual disorders, climacteric syndrome, pregnancy maintenance, osteoporosis, abnormal protein metabolism, gonadal deficiency) makes the question of carcinogenic hazard more pertinent. With the continuing development of steroid use for the control of conception, the question of possible carcinogenic hazards has become of major importance.

Progesterone has been shown in many studies to reduce the size and possibility of developing fibrocystic lumps in the breasts. One study by Dr. John Lee took women who had fibroids in their breasts and told half of them to apply progesterone directly onto the site of the breasts where the lumps were, while directing the other half to do nothing and monitor the lumps. After a short period of time with continual use of the progesterone the half of the subjects reported a ‘noticeable decrease in size’ of the lumps. The other
half had little or no change in the lumps. According to these test results it would appear that progesterone actively inhibits and reverses certain types of breast cancers.

According to Dr. Jonathon V. Wright MD, “Women who take natural progesterone in physiological doses (i.e. doses that reproduce normal levels in the body) reported virtually no unwanted effects.” On the other hand synthetic progestins had a plethora of unwanted side effects including; birth defects when taken during pregnancy, breast cancer, formation of blood clots (especially in the lungs, and brain), fluid retention/swelling, breakthrough bleeding or other menstrual irregularities, impaired glucose intolerance, breast tenderness and milk production, skin rash, acne, hair loss or unwanted facial hair growth, and finally weight gain.6

VI. Conclusion

Natural Bio-Identical progesterone is far safer then synthetic progestins. There is overwhelming evidence that not only does progesterone protect the heart and body from certain cancers and diseases, but it is also the same exact hormone found in every single human body. Synthetic progestins are foreign substances that are chemically altered to mimic and impersonate progesterone. The bottom line is that progestins not only have different, often worse side effects then progesterone, but they also bind to the same receptor sights that progesterone would, therefore progestins also actively block the receptor sights from allowing progesterone, the hormone that is supposed to be there, from attaching and performing its functions.

Registered pharmacist Pete Hueseman concludes his comparison and contrast of progestins and progesterones in this simple sentence, “Natural progesterone duplicates the body’s progesterone exactly, causes fewer side effects and can be more consistently utilized by the body. In the case of natural progesterone versus synthetic progestins in hormone replacement, natural does appear to be better.”5
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Medical Uses of Snake Venom: Heart Attacks

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Organic Chemistry Research Paper
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Abstract

Snakes: most people see them as a danger and a threat. Today, however, snakes, or their venom, are used to save lives. In the last decade it has come to light that snake venom blocks fibrin and prohibits platelet aggregation, which prevents the blood from clotting. A new drug has been produced from the venom to prevent heart attacks, which are caused when a clot stops flow to the heart.

History

Throughout human history, snakes have been a symbol of power, magic, knowledge, sex, death, and medicine. In India, the deadly king cobra was worshipped. In Greece, the God of Healing transformed himself into a snake to heal people and give advice (figure 1). In the American colonies, the snake was put on the flag as a sign of power. In the Judo-Christian religion, the snake is viewed as the devil. And it is an anaconda that pulls the canoe of life underwater in a Tukanoan Indian legend.

Because of the magical properties of snakes, their venom has been used for many medical purposes. In the 12th century, doctors believed that because the snake could heal after it shed its skin, the venom could transfer those properties to heal leprosy. People used rattlesnake venom to treat over 50 diseases even though most treatments proved to be unsuccessful. Cottonmouth venom was used until the 1940’s to treat bloody noses and bleeding after pulling teeth.

Figure 1: Greek God’s Single-snake staff

Snake venom was even used to make war. In the second Punic War between Rome and Carthage, the Carthage general Hannibal would throw venomous snakes onto Roman war ships. Cobra venom was used to make biological weapons until the 1972 Biological Weapons Convention that banned such weapons and ordered the destruction of all biological weapons.

Snakes have been seen in many different ways in history. Their have played healers and killers and been good and evil. Their venom has been used for torture, murders, and war, but it has also been used to heal and treat many diseases. They have fascinated us and terrified us and now they are being used to help save us.

Saw-Scaled Viper

Saw-scaled, or carpet, vipers are small, dangerous snakes from Africa and the Middle East. They are a distinct group of snakes with pearl-shaped heads, small eyes, and keeled scales (figure 2). Most are reddish or brown in color with varying patterns. Originally all carpet vipers were put into two species: Echis carinatus and Echis coloratus.
Venom is produced in venom glands that evolved from salivary glands. The venom is injected into the victim through hollow fangs that are connected to the venom glands by venom ducts. Snakes usually use venom to kill prey, but they also use it as a defensive measure\textsuperscript{18}. Venom can be milked from snakes when they are agitated by getting them to bite a membrane stretched over a jar or vial.

The venom of the Northeast African carpet viper, \textit{Echis} saw-scaled viper, \textit{pyramidum}, is a slow-acting anti-coagulant. The bite area is painful and will swell. Because it is an anti-coagulant, the blood will not clot around the wound and spontaneous systemic bleeding occurs\textsuperscript{19}. It is because of these properties, scientist began to study the venom of \textit{Echis pyramidum}.

\section*{Heart Attacks}

A heart attack is defined as “the death of heart muscle due to the loss of blood supply”\textsuperscript{3}. The blood supply is usually cut off by a blood clot in the coronary artery. These clots form on the cholesterol plaque located on the inner wall of the artery. The plaque builds up due to cholesterol deposits, and continues to build up as the human body ages (figure 3). The plaque can become sticky, which causes the blood to clot\textsuperscript{3}.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{heartattack.png}
\caption{Cholesterol build up in a human heart}
\end{figure}

Blood clots when platelets stick to each other and to vessel walls by forming noncovalent bonds between a cells surface receptor and Arg-Gly-Asp (RGD) sequence and adhesive proteins in the platelets. The receptors are called integrins and the principal integrin on platelets is the glycoprotein IIb/IIIa complex. The most important adhesive protein is fibrinogen because of its abundance in the human body\textsuperscript{5,9}. RGD binds to the IIb/IIIa complex\textsuperscript{5}, which in turn is a receptor for the fibrinogen\textsuperscript{1}. This base provides a material for fibrin, an insoluble protein, to form a clot\textsuperscript{12} by trapping
Many snake venoms have platelet aggregators and aggregation inhibitors. Both were extracted from a saw-scaled viper\textsuperscript{11}.

**Disintegrins**

Disintegrins are defined as a family of polypeptides purified from snake venom, which contain the agrinine-glycine-aspartic acid (RGD) sequence\textsuperscript{4}. Experiments show that many types of venom that contain this protein cause local hemorrhage and inhibit platelet aggregation in vitro\textsuperscript{10}.

The first disintegrin was isolated from the venom of *Trimeresurus gramineus* and was characterized by its ability to inhibit fibrinogen binding to the \(\alpha_{IIb}\beta_3\) integrin without activation of the integrin (figure 4). The disintegrin can do this because of a unique RGD-sequence loop that can express the proper ligand-induced binding site to the \(\beta_3\) subunit. Because they bind to the \(\alpha_{IIb}\beta_3\) integrin on the platelet, they impair the platelet aggregation and those clotting. The aggregation response is lost because the integrin that stimulates binding is occupied by the disintegrin\textsuperscript{10}.

Disintegrins are divided into four different groups based on the length of their polypeptide and the number of disulfide bonds their contain. The four groups are short (49-51 residues and 4 disulfide bonds), medium (about 70 amino acids and 6 disulfide bonds), and long (84 polypeptides cross-linked by 7 disulfide bonds). These first three groups are all single chains. The fourth group is dimeric disintegrins, which contain about 67 residues, including 10 cysteines with the formation of 4 intrachain disulfide bonds and 2 interchain cystine links\textsuperscript{13}.

**Echistatin**

Echistatin is a protein containing 49 amino acids found the venom of *Echis pyramidum*. It has 2000-fold potency over the acyclic peptide arg-gly-asp-ser sequence. Echistatin is one of the key venom proteins that bind to platelets to inhibit clotting. To better understand the way natural disintegrins bind to \(\text{IIb/IIIa}\) complex receptor, scientists are now studying the structure of natural occurring proteins that strongly bind to the receptor sites\textsuperscript{5}.

Samples of echistatin were synthetically prepared by solid-phase synthesis and refolded to the biologically active structure. An NMR was taken of two samples, each between 1.5 and 2.5 mM. The first sample was dissolved in 90% H\(_2\)O/10% D\(_2\)O to display the
amide proton resonances. The second sample was dissolved to D$_2$O to show the exchanging amide proton resonances$^5$.

Double-quantum-filtered correlation spectroscopy (DQF-COSY), total correlation spectroscopy (TOCSY) (figure 5) with a mixing time of 55 ms, single-relayed coherence transfer spectroscopy (RELAY with relay times of 18, 20, and 25 ms, and nuclear Overhauser effect experiments (NOESY) with mixing times are 50, 100, 150, 175, 200, 300, and 350 ms were recorded. A “precess” pulse sequence with an isotropic mixing time of 20 ms was integrating into the RELAY and NOESY experiments for the samples in H$_2$O in order to remove α-proton resonance that would otherwise be bleached by preirradiation of the H$_2$O resonance$^5$.

Figure 5: NH-aliphatic region of the TOCSY Spectrum of echistatin dissolved in 90% H$_2$O/10% D$_2$O$^5$.

Echistatin solutions were also made by dissolving lyophilized protein in 5 mM sodium phosphate buffer at a final pH of 3.4 and 7.3. The concentration of echistatin in the solutions was determined from ultraviolet absorption spectra using a molar extinction coefficient of 1780 M$^{-1}$ cm$^{-1}$ at 280 nm. Concentrations ranged from 35 to 45 µM. Far-UV CD spectra in the wavelength range of 184-260 nm were analyzed for the secondary structure (figure 6). The fractional contributions of different secondary structures were estimated by an unconstrained analysis, followed by selection of fits that yielded values between 0.9 and 1.1 for the sum of fractions and less than 0.2 for root mean squared errors$^5$.

The flexible nature of the echistatin chain is most likely what gives it the ability to bind with RGD receptors in the human body$^5$. However, if straight was injected into the human body, the other components of the molecule can cause harm to the body. So scientist had to find a way to replicate echistatin without doing harm to humans$^{17}$. 
Figure 6: A) Secondary structure of echistatin. B) Global fold of echistatin for two possible disulfide pairings.

**Aggrastat® (Tirofiban Hydrochloride)**

Robert Gould, Ph.D. noticed that certain venoms including toxins and enzymes that digested blood vessel walls. As the executive director of pharmacology at Merck and Co., Inc. he chose to study that of the Kenyan saw-scaled viper because "the chemical sequence was simple and thus easily replicated in the lab". Working with scientist at Temple University, they were able to isolate echistatin and study the specific regions in the molecule that preventing blood from clotting. After 10 years, they were able to develop a drug that blocked certain blood platelet receptors but that was not harmful to humans as the venom was. The drug, called Aggrastat®, does not actually contain any snake venom, but instead mimics the anti-clotting factor in the venom.

![Chemical structure of Aggrastat®](image)

Figure 7: Structure of Aggrastat®.
clots in heart attack patients. Platelet aggregation is down 90% thirty minutes after Aggrastat® is admitted. The advantages of this drug include, but are not limited to: three times as many heart patients can receive platelet blocking medication, treatment is reversible and can be turned off is a patient needs to be operated on, and it gives patients time to lower cholesterol intake before a heart attack occurs. Risks include increase risk of bleeding, especially in patients in need of operation

Aggrastat® works much like the venom it mimics. It binds to the IIb/IIIa receptors on a platelet preventing fibrin from binding to those receptors and forming clots. It is injected with a sterile needle through veins and reduces platelet aggregation in a dose- and concentration-dependent manner.

Aggrastat® was tested over three large-scale clinical trials. The first patients to receive Aggrastat® were people with Acute Coronary Syndrome (unstable angina/non-Q wave myocardial infarction). Acute Coronary Syndrome is characterized by long or repetitive symptoms of cardiac ischemia that occurs when resting or with minimal action. These studies looked at the effects of Aggrastat® alone, with heparin and before and after angioplasty.

In the studies, patients with unstable angina/non-Q-wave myocardial infarction were randomized to receive either Aggrastat® alone, Aggrastat® with heparin, and or heparin alone for 48 hours. For some patients who underwent surgery, their dosage continued for longer than 48 hours to on average 71.3 hours. One average, patients using Aggrastat® combined with heparin had a 30% risk reduction of a myocardial infarction at 30 days (figure 8). In the studies, there were no adverse effect of Aggrastat® on mortality at 7 or 30 days was detected.

At the end of the study, proper dosages based on age, gender, and weight were calculated for general use and Aggrastat® was approved for use by the FDA in May 1998.
Future uses for venom

With the discovery of disintegrins came a realization that Mother Nature might have already supplied us with many of the solutions to modern diseases. Today, the venoms of many animals, not just snakes, are being studied to find cures and medications for other diseases. For example, the venom from the Cameron red tarantula might one day be used to treat neurological disorders and the venom from an Israelia scorpion binds to brain cancer cells and keeps it from spreading\textsuperscript{17}.

Animals are also being studied for other extraordinary things they can do. Dolphins are being studied to develop better sonar. Snakes are being studied to develop better infrared mapping devices. And apes are being studied to better understand the social order of humans. By studying and learning about the animals on this planet, we are discovering that we do not know much about how nature develops and evolves such wonderful creatures.

Conclusion

I believe that will all the studying of venoms and toxins, it would not be unlikely to see a boom in products based on natural toxins in the next decade or so. I also believe that the revelations that toxins in snakes, insects, and arachnids with help build awareness for saving rainforests and natural landscapes and to begin a more complete study of animals that inhabit rainforests to better understand if they offer medical purposes.
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Adderall®
(Dextroamphetamine Salt Combo)

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April 22, 2005
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Abstract

Adderall, the brand name for D-Amphetamine Salt Combo, is a drug that is widely used to mainly treat Attention Deficit Disorder with Hyperactivity (ADHD). This report will first give some background information on ADHD disorder. Then it will get into details of what Adderall is made up of and how it helps children and adults with ADHD, its chemistry; including the chemical structure(s), biological reactions, and one method of synthesis.
I. Introduction

Adderall, also known under the generic name drug D-Amphetamine salt combo, is used mainly to treat children and adults with attention deficit hyperactive disorder (ADHD).

ADHD, formerly called hyperkinesis or minimal brain dysfunction is the most common chronic neurobehavioral disorder of childhood. It is characterized by two distinct sets of symptoms; inattention and/or hyperactivity/impulsivity. These sets of symptoms typically occur together, however one may be present without the other. The absence of hyperactivity/impulsivity would be identified as attention deficit disorder (ADD). These symptoms are maladaptive and inconsistent with developmental level; hence children do not generally outgrow these conditions. ADHD persist into adolescence in 60% to 80% of children and into adulthood in about 66% of cases. Inattention tends to carry on into adulthood, but motor hyperactivity/impulsivity tend to decline with age. With improperly diagnosed and treated ADHD, symptoms can lead to poor academic performance, low self-esteem, and conflicts with parents, teachers and peers, and co-workers.

The etiology of ADHD is not known, however, genetics, neurotransmitter deficits and prenatal complications have been implicated, out of which the genetic and neurobiological etiologies appear to be the most plausible.

To explain the neurobiological etiology, one must understand the function of neurons as illustrated (Fig. 1). It is believed that irregularities of the neurotransmitter dopamine in pathways of the brain play significant roles in ADHD. This hypothesis is accepted by majority of mental health professionals as the dopamine hypothesis. The dopamine hypothesis postulates that ADHD is due, in large part, to inadequate dopamine in key areas of the brain. Therefore the effectiveness of Central Nervous System (CNS) stimulant drugs such as in the management of ADHD supports the dopamine hypothesis as these CNS stimulants increase the release of dopamine and norepinephrine from presynaptic neurons in the central nervous system and inhibit their reuptake, thereby increasing the amount of these chemicals in neuronal systems.

![Diagram of a neuron showing electrical activity generation and transmission](image)

Figure 1. Electrical activity is generated within the neuron cell body and transmitted down the axon to the axon terminals. From here, a chemical substance known as the neurotransmitter does transmission of signals to the target tissue across the synaptic gap.
Adderall is a mixture of salts of a single entity amphetamine. Amphetamines are non-catecholamine sympathomimetic amines with CNS stimulant activity. Amphetamines support the dopamine hypothesis as stated earlier, by blocking the reuptake of norepinephrine and dopamine into the presynaptic neuron and increase the release of these monoamines into the extra-neuronal space.⁶

II. Chemistry

a) Structure Determination

Adderall is a combination of the neutral sulfate salts of dextroamphetamine and amphetamine, with the dextro isomer of amphetamine saccharate and d, l-amphetamine asparate, hence the generic name is D-Amphetamine salt combo. The chemical formulas for each salt is depicted below in (Fig. 2⁶) as well as a detailed table indicating the amount of each salt contained in various dosages. Note that one tablet of any dosage, would contain an equal amount of each salt.

![Chemical structure of D-Amphetamine Salt Combo. (Adderall)](image)

Amphetamine has a chemical structure similar to the neurotransmitters noradrenaline (norepinephrine) and dopamine, and the hormone adrenaline (epinephrine), as Illustrated in Fig 3.⁷

![Chemical structures of dopamine, epinephrine, and noradrenaline](image)

Figure 3. Dopamine, Epinephrine(adrenaline), and Noradrenaline respectively from left to right. Note the similarity of these structures to the D-Amphetamine Salts in Fig. 2.
b) Biological Reactions

When amphetamine is ingested, many of the biological reactions normally controlled by neurotransmitters noradrenaline, dopamine are elicited. Amphetamine is not metabolized as rapidly as adrenaline, noradrenaline, and dopamine. As a result, it remains active in the body longer and effects can still be felt four to six hours after oral ingestion of a relatively small dose.

When amphetamine is synthesized, two mirror image molecules are formed, a “d” form and an “l” form. The “d” form (dextroamphetamine) acts more on the brain while the “l” (levoamphetamine) form acts more on the cardiovascular system. Since amphetamines are usually used for their actions on the brain; the “d” form is most commonly used, although mixtures of the “l” and “d” form do exist.5

Dextroamphetamine being a stereoisomer of amphetamine, is an indirect-acting stimulant that releases norepinephrine from nerve terminals, thus promoting nerve impulse transmission. It increases motor activity and mental alertness, and reduces drowsiness and a sense of fatigue, decreasing motor restlessness and improves one’s ability to pay attention.

Finally, amphetamine can act inside the nerve terminal as well as outside to inhibit the action of monoamine oxidase (MAO), an enzyme normally involved in the breakdown of noradrenaline and dopamine. Inhibition of this enzyme allows released transmitters to remain active longer, to further exaggerate the actions of these transmitters.4

c) Synthesis 8

The reactions explained here are steps to the synthesis of dextroamphetamine sulfate, from the starting material D-phenylalanine (compound I in Fig. 4). Note that the experimental numbers (weights of reactants) were not mentioned by the source, only the sequences of reactions.

D-phenylalanine is reduced by refluxing with lithium aluminum chloride (LAH), and using tetrahydrofuran (THF) as the solvent. After reflux, the excess reagent is decomposed by dropwise addition of 2N aqueous Sodium Hydroxide, and water. The white solids are collected by filtration and washed with THF. The filtrate and washings are then combined and concentrated under reduced pressure. The residual clear oil slowly crystallizes and is recrystallized from ethyl acetate-hexane.

The product obtained is (R)-(−)-2-Amino-3-Phenylpropanol (Compound II in Fig. 4).

![Figure 4. D-phenylalanine reduced to (R)-(−)-2-Amino-3-Phenylpropanol](image)

Now a mixture of compound (II) is prepared and added to sodium carbonate a 50/50 mixture of acetone and water is stirred at room temperature, and benzyl-
chloroformate is added. The reaction mixture is stirred for 3 hours, diluted with water, and acidified to pH = 2, with concentrated hydrochloric acid. The mixture is shaken with ethyl acetate, and the organic layer is washed with saturated aqueous sodium chloride. After drying using magnesium sulfate, the filtered organic solution is concentrated in vacuo (Kugelrohr Apparatus). The product is crystallized from ethyl acetate-hexane. This is (R)-(+-)N-(Benzyloxy carbonyl)-2-amino-3-phenylpropanol (compound III).

Now, (R)-(+-)N-(Benzyloxy carbonyl)-2-amino-3-phenylpropanol (compound III), and p-toluenesulfonyl chloride are dissolved in pyridine. The solution is stored at room temperature with the exclusion of moisture for 4 days.

After 4 days, water is added; and left to sit for 30 minutes; the solvent is distilled under reduced pressure. The residue is then extracted between ethyl acetate and saturated aqueous sodium bicarbonate, and the organic layer is dried using magnesium sulfate. After filtration of the drying agent and concentration of the filtrate, the residual wet solid is recrystallized from ethyl acetate-hexane. Resulting compound is: (R)-(+-)N-(Benzyloxy carbonyl)-2-amino-3-phenylpropanol p-Toluenesulfonate (IV)

\[
\begin{align*}
\text{Figure 5. From (R)-(+-)2-Amino-3-Phenylpropanol (II) to (R)-(+-)N-} \\
\text{(Benzyloxy carbonyl)-2-amino-3-phenylpropanol (III), then to (R)-(+-)N-} \\
\text{(Benzyloxy carbonyl)-2-amino-3-phenylpropanol p-Toluenesulfonate (IV)}
\end{align*}
\]

The final steps for the synthesis of dextroamphetamine are as follows. Compound IV and 10% Pd/C are mixed in absolute ethanol, and the reaction is shaken under 50 psi of hydrogen for one hour. The catalyst is removed by filtration using celite, and the filtrate is concentrated in vacuo. The residue is then extracted between aqueous sodium hydroxide and ethyl acetate. The organic solution was washed with water. The solution is then concentrated under reduced pressure water bath temperature of 25°C, and the oily residue was distilled in vacuo at 0.05 mm and 40-60°. The clear distillate was dissolved in ether and carefully acidified to pH of 4 by addition of H2SO4 in ethanol. The white solid is collected by filtration, washed with ether, and dried in vacuo to yield Dextroamphetamine [(S)-(+-)-α-Methylphenethylamine] Sulfate (Compound V Fig. 6)

\[
\begin{align*}
\text{Figure 6. Final synthesis of Dextroamphetamine Sulfate (V) from (R)-(+-)N-} \\
\text{(Benzyloxy carbonyl)-2-amino-3-phenylpropanol p-Toluenesulfonate (IV)}
\end{align*}
\]
Conclusion:

Adderall is a very powerful medicine for people with ADHD, as it has 70% success rate in children, adolescence, and adults. The response rate to this medication as well as other CNS stimulant drugs such as Ritalin®, and Concerta® results in a dramatic and consistent improvement of the core symptoms of inattention, hyperactivity, and impulsivity. The downside of this medication is its high potential for abuse. Amphetamines administered for long periods of time, along with high dosage will cause dependency. However, when administered properly, it will allow the child or even an adult to be able to improve learning skills at school or work, and efficiently battle everyday challenges of life.
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Fuzeon

Danny Franco
March 14th
Abstract

A short introduction is given about a new product for HIV patients called Fuzeon. Fuzeon is a fusion inhibitor, it was approved by the U.S. Food and Drug Administration in March 2003. Fuzeon is approved for HIV-positive people who have tried other anti-HIV drugs in the past and their viral loads undetectable using drugs that are currently available. It has not yet been approved for HIV-positive people who are starting anti-HIV drug treatment for the first time. I will be discussing the history, description, administration, absorption, clinical studies, and cost of the medication.

History

As of the end of 2001, more than 816,000 people in the United States and 40 million people worldwide were infected with HIV. A number of agents used to treat vital infections grew substantially during the 1990’s. A great deal of development has been improved in the area of antiretrovirals. Anti-retroviral Protease Inhibitors, Anti-retroviral Nucleoside Reverse Transcriptase Inhibitors and Anti-Retroviral Non-nucleoside Reverse Transcriptase Inhibitors, fortunately new important therapies for non-HIV infections have been developed as well.


Cidofovir 1994 is the first member of a group of antivirals known as acyclic phosphonate nucleotide analogs. Cidofovir is structurally similar to acyclovir and ganciclovir. Lamivudine (Epivir), which was organically approved as an antiretroviral agent in 1995, has been approved in a lower dosage strength for the treatment of hepatitis B in 1998. A new class of antiviral agents was introduced in 1999 the neuraminidase inhibitors. The new two agents in this class is oseltamivir and zanamivir.

There are several immunoglobulin products available that provide passive immunity against specific viral infections. Palivizumab 1998, which is a monoclonal antibody, and respiratory syncytial virus immune globulin 1996, a polyclonal immunoglobulin preparation are used in high risk pediatric patients to prevent infection with respiratory syncytial virus. Cytomegalovirus immune globulin, hepatitis B immune globulin, rabies immune globulin and varicella-zoster immune globulin are used in the treatment of hepatitis B and C also on venereal warts. Other biologic approaches to the treatment of viral include vaccines and the use of colony-stimulating factors to stimulate immunity.
A new class of antiviral agents called fusion inhibitors Enfuvirtide (Fuzeon) is the 17th antiretroviral agent to become available in the United States and the first member of a unique class known as HIV fusion inhibitors. Enfuvirtide has been shown to block the entry of HIV into cells, which may keep the virus from reproducing. At least one compound of the new class T-20 has been shown in early clinical trials to reduce viral load in patients with drug-resistant disease.

**Description**

Enfuvirtide, also known as T-20 is the first of the newest class of anti-HIV drugs called fusion inhibitors. The first new class of drugs developed and approved for the treatment of HIV since 1996. It is a synthetic 36-amino-acid peptide derived from the HIV-1 envelope glycoprotein gp41 and it interferes with the entry of HIV-1 into the cells by inhibiting the fusion of viral and cellular membranes. The use of Enfuvirtide should be reserved as a salvage therapy for individuals who have advanced HIV, are treatment experienced and continue to show evidence of ongoing viral replication. For example if the patient shows resistance to current HIV treatments. Enfuvirtide is a synthetic peptide and cannot be administered orally. Enfuirtide should be used in combination with an individualized antiretroviral regimen. Enfuirtide remains active against HIV strains in patients who have previously received and developed resistance to other classes of antiretroviral agents. In clinical trials, patients receiving Enfuirtide in addition to an individualized antiretroviral regimen were less likely to experience virologic failure or relapse compared to those receiving an individualized antiretroviral regimen alone. Patients whose virus was sensitive to a greater number of antiretroviral drugs did not demonstrate a greater sensitivity of enfuvirtide. At least 98% of patients who use enfuvirtide will develop injection site reactions to varying degrees, with almost 85% of patients the reactions within the first week of use. Patients should be appropriately counseled regarding injection site reactions before enfuvirtide therapy is started. Enfuirtide was granted FDA approval on March 13, 2003 and received traditional approval by the FDA on October 15, 2004.

**Mechanism of Action**

Enfuvirtide interferes with the entry of HIV-1 into host cells by inhibiting the fusion of the virus and cell membranes. In order for HIV-1 to enter and infect a human cell, the viral surface glycoprotein gp120 binds to the host CD4+ cell receptor, along with a chemokine co-receptor (CXCR4 or CCR5) both expressed on lymphocytes and mononuclear cells. Then the viral transmembrane glycoprotein gp41 undergoes a conformational change facilitating the fusion of cellular and viral membranes. Enfuirtide binds to the first heptad-repeat (HR1) in the gp41 subunit of the viral envelope glycoprotein and prevents the conformational change required for membrane fusion and subsequent viral entry into target cells. This mechanism results in a lack of cross resistance to fuzeon for viral isolates resistant to one or more antiretrovirals.
Structure

Enfuvirtide is an inhibitor of the fusion of HIV-1 with CD4+ cells. Enfuvirtide is a linear 36-amino acid synthetic peptide with the N-terminus acetylated and the C-terminus is a carboxamide. It is composed of naturally occurring L-amino acid residues.

Enfuvirtide is a white to off-white lyophilized powder. It has negligible solubility in pure water and the solubility increases in aqueous buffers (pH 7.5) to 85-142 g/100 mL. The empirical formula of enfuvirtide is C_{204}H_{301}N_{51}O_{64}, and the molecular weight is 4492. It has the following primary amino acid sequence: CH_{3}CO-Tyr-Thr-Ser-Leu-Ile-His-Ser-Leu-Ile-Glu-Glu-Ser-Gln-Asn-Gln-Glu-Lys- Asn-Glu-Gln-Glu-Leu-Leu-Glu-Leu-Leu- Asp-Lys-Trp-Ala-Ser-Leu-Trp-Asn-Trp-Phe-NH_{2}.

![Structure of Enfuvirtide](image)

Each single-use vial contains 108mg of enfuvirtide for the delivery of 90mg. The contents of the vial are reconstituted on 1.1ml of sterile water for injection giving a volume of 1.2mls to provide delivery of 1ml if the solution. Each vial of the reconstituted solution contains 90mg of enfuvirtide with the amounts of the following: 22.55mg of mannitol, 2.39mg of sodium carbonate (anhydrous), sodium hydroxide and hydrochloric acid for PH adjustment as needed. The reconstituted solution has an approximate pH of 9.0.
Drug Resistance

HIV-1 isolates with reduced susceptibility to enfuvirtide have been selected in vitro. Genotypic analysis in vitro-selected resistant isolates showed mutations that resulted in amino acid substitutions at the enfuvirtide binding HR1 domain positions 36 to 38 of the HIV-1 envelope glycoprotein gp41. Phenotypic analysis of site-directed mutants in positions 36-28 in a HIV-1 molecular clone showed a 5-fold to 684-fold decrease in susceptibility to enfuvirtide. In clinical trails HIV-1 isolates with reduced susceptibility to enfuvirtide have been recovered from subjects failing a enfuvirtide regimen.  

Posttreatment HIV-1 virus from 277 subjects experiencing protocol defined virological failure at 48 weeks exhibited a median decrease in susceptibility to enfuvirtide of 33.4 fold (range 0.4-6318 fold) relative to their respective baseline virus, results were 249 patients had decreases on susceptibility to enfuvirtide of greater tht 4-fold and all but 3 exhibited genotypic changes in the codons encoding gp41. HR1 domain amino acids 36-45, substitutions in this region were observed with decreasing frequency at amino acid positions 38,43,36,40,42and 45.  

Cross-resistance

HIV-1 clinical isolates resistant to nucleoside analogue reverse transcriptase inhibitors (NRTI), non-nucleoside analogue reverse transcriptase inhibitors (NNRTI), and protease inhibitors (PI) were susceptible to enfuvirtide in cell culture.

Pharmacokinetics

The pharmacokinetic properties of enfuvirtide were evaluated in HIV-1 infected adult and pediatric patients.

Absorption

Following a 90-mg single subcutaneous of Fuzeon in to abdomen in 12 HIV-1 infected subjects the mean (±SD) C max was 4.59 ± 1.5ug/ml, AUC was 55.8(± 12.1 ug*hr/ml and the median T max was 8 hours (ranged from 3to 12 hours). The absolute bioavailability (using a 90-mg twice a day dosing of Fuzeion subcutaneously in combination with other antiretroviral agents in 11 HIV-1 infected patients. The mean (±SD) steady state Cmax was ±1.7 ug/ml. C through was 3.3 ± 1.6ug/ml, AUC 0-12hrs was 48 ± 19.1 ug*h/ml and the median T max was 4 hours ranged from 4-8 hours. Absorption of the 90-mg dose was comparable when injected into the subcutaneous tissue of the abdomen, thigh or arm.

Distribution

The mean (±SD) steady state volume of distribution after intravenous administration of a 90-mg dose of Enfuvirtide. Enfuivrtide is approximately 92% bound to plasma over a
concentration range of 2-10 ug/ml. It is bound predominantly to albumin and to a lower extent α-1 acid glycoprotein.

**Metabolism/Elimination**
As a peptide enfuzirtide is expected to undergo catabolism to its constituent amino acids with subsequent recycling of the amino acids on the body pool. In viral studies with human microsomes and hepatocytes indicate that enfuzirtide undergoes hydrolysis to form a deamidated metabolite at the C-terminal phenylalanine residue called (M3). The hydrolysis reaction is not NADPH dependent. The M3 metabolite is detected in human plasma following administration of enfuzirtide with an AUC ranging from 24%-15%.
Following a 90-mg single dose of enfuzirtide the elimination half-life is 3.88±0.6 h and the mean ±SD clearance was 24.8 ± 4.1 ml/h/kg. In combination with other antiretroviral agents in 11 HIV-1 infected patients the mean ±SD apparent clearance was 30.6 ± 10.6 ml/h/kg.

**Special Populations**

**Gender**
Analysis of plasma concentration data from subjects in clinical trials indicated that the clearance of enfuzirtide is 20% lower in females than males after adjusting for body weight.

**Race**
Analysis of plasma concentration data from subjects in clinical trials indicated that the clearance of enfuzirtide was not different in Blacks compared to Caucasians. Other test studies show that no difference between Asians and Caucasians after adjusting for body weight.

**Weight**
Enfuviirtide clearance decreases with decreased body weight irrespective of gender. Relative to the clearance of a 70-kg male and a 40-kg male will have a 20% lower clearance and a 110-kg male will have a 26% higher clearance. Relative to a 70-kg male a 40-kg female will have a 36% lower clearance and a 110-kg female will have the same clearance. No dose adjustment is recommended for weight or gender.

**Pediatric Patients**
The pharmacokinetics of enfuzirtide have been studied in twenty-three pediatric subjects aged 6-16 years at a dose of 2mg/kg. Enfuviirtide pharmacokinetics were determined in the presence of concomitant medications including antiretroviral agents. A dose of 2mg/kg twice a day with a max dose of 90mg twice a day provided enfuvirtide plasma concentrations similar to those obtained in adult patients receiving 90mg twice a day.
Drug Interactions

Influence of Concomitant Drugs on the Metabolism of enfuvirtide. As indicated in Table 1. Studies were conducted with enfuvirtide and the following drugs: ritonavir, saquinavir/ritonavir and rifampin.

Effect of Ritonavir, Saquinavir/Ritonavir and Rifampin on a steady state pharmacokinetics of Enfuvirtide 90mg bid. 9

Table 1

<table>
<thead>
<tr>
<th>Coadministered Drug</th>
<th>Dose of Coadministered Drug</th>
<th>N</th>
<th>% Change of Enfuvirtide Pharmocokinetic Parameters (90% CI)</th>
</tr>
</thead>
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<tr>
<td></td>
<td></td>
<td></td>
<td>$C_{\text{max}}$</td>
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<tr>
<td>Ritonavir</td>
<td>200mg, q12h, 4 days</td>
<td>12</td>
<td>↑24 (↑9 to ↑41)</td>
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<td>Saquinavir/Ritonavir</td>
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<td>12</td>
<td>↔</td>
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<tr>
<td>Rifampin</td>
<td>600 mg, qd, 10 days</td>
<td>12</td>
<td>↔</td>
</tr>
</tbody>
</table>

All studies were performed in HIV-1 subjects using a sequential crossover design.  
↑ = Increase; ↓ = Decrease; ↔ = No Effect (↑ or ↓ <10%)

Indications And Usage
Fuzon in combinations with other antiretroviral agents is indicated for the treatment of HIV-1 infection in treatment experienced patients with evidence for HIV-1 replication despite ongoing antiretroviral therapy.  
This indication is based on results from two controlled studies of 48 weeks duration.  
Subjects enrolled were treatment experienced adults; many had advanced disease.
Description of Clinical Studies

Studies T20-301 and T20-302 were randomized, controlled, open label, multicenter trials in HIV-1 infected subjects. Subjects were required to have either (1) viremia despite 3 to 6 months prior therapy with a nucleoside reverse transcriptase inhibitor (NRTI), nonnucleoside reverse transcriptase inhibitor (NNRTI), and protease inhibitor (PI) or (2) viremia and documented resistance or intolerance to at least one member in each of the NRTI, NNRTI, and PI classes.

All subjects received an individualized background regimen consisting of 3 to 5 antiretroviral agents selected on the basis of the subjects prior treatment history and baseline genotypic and phenotypic viral resistance measurements. Subjects were then randomized at a 2:1 ratio to Fuzeon 90mg bid with background regimen or background regimen alone.

After week 8 patients on either treatment arm who met protocol defined criteria for virological failure were permitted to revise their background regimens. Those on background regimen alone were also permitted to add Fuzeon.

Demographic characteristics for studies T20-301 and T20-302 are shown in Table 2. Subjects had prior exposure to a median of 12 antiretrovirals for a median of 7 years.9

Table 2

<table>
<thead>
<tr>
<th>T20-301 and T20-302 Polled subject demographics</th>
<th>FUZEON+Background Regimen</th>
<th>Background Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td>N=334</td>
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<tr>
<td>Mean Age (yr) (range)</td>
<td>42 (16-67)</td>
<td>43 (24-82)</td>
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<tr>
<td>Median Baseline HIV-1 RNA (log10 copies/ml)</td>
<td>5.2 (3.5-6.7)</td>
<td>5.1 (3.7-7.1)</td>
</tr>
<tr>
<td>Median Baseline CD4 Cell Count (cells/mm³) (range)</td>
<td>89 (1-994)</td>
<td>97 (1-847)</td>
</tr>
</tbody>
</table>
The disposition and efficacy outcomes of studies T-20-301 and T20-302 are shown in Table 3.

**Table 3**

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>FUZEON+Background Regimen 90mg/bid N=663</th>
<th>Background Regimen N=334</th>
</tr>
</thead>
<tbody>
<tr>
<td>Virological Responder (at least 1 log₁₀ below baseline)</td>
<td>304 (46%)</td>
<td>61 (18%)</td>
</tr>
<tr>
<td>Virological Non-responder: Switch: Completed 48 weeks randomized regimen*</td>
<td>0</td>
<td>220 (66%)</td>
</tr>
<tr>
<td></td>
<td>191 (29%)</td>
<td>12 (4%)</td>
</tr>
<tr>
<td></td>
<td>Continued Background Regimen (N=112)</td>
<td></td>
</tr>
<tr>
<td>Discontinued due to insufficient treatment response#</td>
<td>37 (5%)</td>
<td>13 (12%)</td>
</tr>
<tr>
<td>Discontinued due to adverse reactions/intercurrent illness/labs</td>
<td>46 (7%)</td>
<td>9 (8%)</td>
</tr>
<tr>
<td></td>
<td>12 (6%)</td>
<td></td>
</tr>
<tr>
<td>Deaths</td>
<td>15 (2%)</td>
<td>5 (4%)</td>
</tr>
<tr>
<td>Discontinued due to injection: Injection site reactions: Difficulty with injecting FUZEON##:</td>
<td>27 (4%)</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>18 (3%)</td>
<td>NA</td>
</tr>
<tr>
<td>Discontinued due to other reasons†</td>
<td>25 (4%)</td>
<td>14 (13%)</td>
</tr>
<tr>
<td></td>
<td>6 (3%)</td>
<td></td>
</tr>
<tr>
<td>Continued Background Regimen (N=220)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>switched toFUZEON</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Includes never responded, rebound, and, missing RNA data.

# Includes study discontinuation for virological failure and insufficient response as per the judgment of the investigator.
### Includes difficulties with injection, such as injection fatigue and inconvenience.
† Includes lost to follow up, treatment refusal, and non-compliance.³

At 48 weeks, 154 (23%) of subjects in the FUZEON+background regimen and 27 (8%) in the background regimen alone had HIV RNA levels <50 copies/ml, and 225 (34%) of subjects receiving FUZEON+background regimen had HIV RNA levels < 400 copies/ml compared to 44 (13%) in the background regimen alone. Subjects achieving HIV RNA levels < 50 copies/ml were included in the < 400 copies/ml category and both categories were incorporated in the overall virologic category of achieving HIV RNA at least 1 log₁₀ below baseline.

The mean log change in HIV-1 RNA from baseline was −1.4 log₁₀ copies/ml in subjects receiving FUZEON+background and −0.5 in those receiving background alone, The mean change in CD⁴⁺ cell count from baseline to week 48 was +91 cell/mm³ in the FUZEON+background arm and +45 cell/mm³ in the background alone arm.

Subjects on the FUZEON+background arm achieved a better virologic and immunologic outcome than subjects in the background alone arm across all subgroups based on baseline CD⁴⁺ cell count, baseline HIV-1 RNA, number of prior ARV’s or number of active ARV’s in the background regimen.

**Contraindications**

Fuzeon is contraindicated in patients with known hypersensitivity of Fuzeon or any of its components

**WARNINGS**

**Local Injection Site Reactions**

Local injection site reactions were the most frequent adverse events associated with the use of Fuzeon. In Phase 3 studies (T20-301 and T20-302), 98% of subjects had at least one local injection site reaction (ISR). A total of 7% of subjects discontinued treatment with Fuzeon because of ISRs (4%) or difficulties with injecting Fuzeon (3%) such as injection fatigue and inconvenience, (85%) of subjects experiences their first ISR during the initial week of treatment; ISRs continued to occur throughout treatment with Fuzeon. For most subjects the severity of signs and symptoms associated with erythema, induration, the presence of nodules or cysts, and mild to moderate pain at the injection site. In addition, the average duration of individual ISRs was between three and seven days in 41% of subjects and more than seven days in 24% of subjects. Also, the numbers of ISRs per subject at any one time was between six to fourteen ISRs in 26% of subjects and more than 14 ISRs in 1.3 of subjects. Infections at the injections site was reported in 107% of subjects. See Table 4
Table 4
Summary of Individual Signs/Symptoms Characterizing Local Injection Site Reactions to Enfuvirtide in Studies T20-301 and T20-302 Combined (% of Subjects) Through 48 Weeks

<table>
<thead>
<tr>
<th>Event Category</th>
<th>Any Severity Grade</th>
<th>% of Patients with Grade 3 Reactions</th>
<th>% of Patients with Grade 4 Reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain/Discomfort</td>
<td>96%</td>
<td>11%</td>
<td>0%</td>
</tr>
<tr>
<td>Induration</td>
<td>90%</td>
<td>39%</td>
<td>18%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;25 but &lt;50mm</td>
<td>&gt;50mm</td>
</tr>
<tr>
<td>Erythema</td>
<td>91%</td>
<td>22%</td>
<td>10%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;50 but &lt;85mm</td>
<td>&gt;85mm</td>
</tr>
<tr>
<td>Nodules and Cysts</td>
<td>80%</td>
<td>23%</td>
<td>0.2%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;3 cm average diameter</td>
<td>draining</td>
</tr>
<tr>
<td>Pruritus</td>
<td>65%</td>
<td>3%</td>
<td>NA</td>
</tr>
<tr>
<td>Ecchymosis</td>
<td>52%</td>
<td>5%</td>
<td>2%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;3 but ≤5cm</td>
<td>&gt;5cm</td>
</tr>
</tbody>
</table>

a Grade 3 = severe pain requiring prescription non-topical analgesics or limiting usual activities.
Grade 4 = severe pain requiring hospitalization or prolongation of hospitalization, resulting in death, or persistent or significant disability/incapacity, or life-threatening, or medically significant.
b Grade 3 = refractory to topical treatment or requiring oral or parenteral treatment; Grade 4 = not applicable.

Costs

Actual acquisition cost for Fuzeon is currently unavailable; however, it is predicted the twice-daily injection regimen is likely to cost approximately $20,570 per patient per year, making it the most expensive antiretroviral marketed in the United States. Below is application for a reimbursement assistance program.

Summary

In closing, Fuzeon has great potential for patients that are not getting results with their current therapy, the only downfall is cost. Fortunately the manufacturer offers a reimbursement assistance program. Fuzeon is not a cure but with patient compliance life can be prolonged. With research a cure could be around the corner.
<table>
<thead>
<tr>
<th>Pharmaceutical Company</th>
<th>Roche Pharmaceuticals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Program Name</td>
<td>Fuzeon Reimbursement Assistance Program</td>
</tr>
<tr>
<td>Program Address</td>
<td>PO Box 221769</td>
</tr>
<tr>
<td></td>
<td>Charlotte NC, 28222</td>
</tr>
<tr>
<td>Medicines On Program</td>
<td>Fuzeon T-20</td>
</tr>
<tr>
<td>Phone Number</td>
<td>866-487-8591</td>
</tr>
<tr>
<td>Fax Number</td>
<td>866-487-8592</td>
</tr>
<tr>
<td>Application</td>
<td>Contact program for application</td>
</tr>
<tr>
<td>Guidelines and Notes</td>
<td>The patient must be a US citizen with no prescription coverage. The patient must also meet financial guidelines that are not disclosed. This program is for outpatient use only.</td>
</tr>
<tr>
<td>Initiating Enrollment</td>
<td>The patient or doctor calls to get an application faxed to the doctor's office. The application is patient specific and cannot be copied. The completed application can be faxed back to the company.</td>
</tr>
<tr>
<td>Health Provider's Role</td>
<td>Fills out and signs a section of the application.</td>
</tr>
<tr>
<td>Patient's Role</td>
<td>Fills out and signs a section of the application and attaches proof of income. (see application for accepted documents.)</td>
</tr>
<tr>
<td>How Dispensed</td>
<td>The medication is sent either to the patient's home or doctor's office.</td>
</tr>
<tr>
<td>Amount Dispensed</td>
<td>Up to a one month supply at one time</td>
</tr>
<tr>
<td>Refills</td>
<td>The patient must contact the company to arrange for refills.</td>
</tr>
<tr>
<td>Reapplication</td>
<td>Every six months a new application is needed.</td>
</tr>
</tbody>
</table>

12/29/2004
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Topiramate, More Than an Anti-epileptic Drug

Prepared for
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Prepared By
Nichole Frazier

April 22, 2005
Abstract

This review describes the history, uses and side effects of Topiramate also known as Topamax. Describing Topamax thru the structure, mechanism and pharmacokinetics provides a thorough understanding of this drug. This medication is currently an anti-epileptic and migraine preventive medication with future possibilities of treating other disorders.

Introduction

Topiramate, also known as the trade name Topamax, is one of the newly approved anti-epileptic drugs (AED) approved by the Federal Drug Administration (FDA) in the last 10 years. Topamax, being a broad spectrum AED, works to prevent both the mild attacks known as partial seizures and the severe tonic-clonic convulsions known as grand mal seizures. Further studies have shown that Topamax, an antiseizure medication, is effective for the prevention of migraine headaches, and for the treatment of other disorders. This review of Topamax will include the background of Topamax, the chemical structure, mechanism, and pharmacokinetics. It will also review the multiple uses of Topamax, the side effects, cautions, and special considerations.

Background

The discovery and development of Topamax was by the R.W. Johnson Pharmaceutical Research Institute. Topamax was officially the first “newer generation” anti-epileptic drug, which means, it prevents seizures. Roughly, 25% of people diagnosed with seizures become resistant to the traditional anti-epileptic drugs. Typically, the use of Topamax is highly effective against seizures when added to other antiseizure medications. In December of 1996, the FDA approved Topamax Tablets, which became available in the United States in 1997, followed by the approval of a sprinkle-capsule formulation in 1999. Since the approval of this drug in 1997, the use increases every year. Doctors recommend Topamax to help reach the patients goal of fewer seizures with the least amount of side effects. Figure 1 shows the comparisons of usage to earlier anti-epileptic drugs.

![Percent Change in New Prescriptions per Product Over the Last 3 Years]

**Figure 1.**

1 IMS National Prescription Audit, 1997, 1999, 1999, and 2000. Among AEDs with ≥50,000 new retail prescriptions in each of the last 3 years. Specific indications and dosage vary by product.
Ortho-McNeil Pharmaceutical and Johnson & Johnson companies market Topamax in the United States. Marketing for Topamax is also in 80 other countries including the United Kingdom, France, Sweden, Australia, Hong Kong and Canada. Topamax Tablets are available in 25mg, 50mg, 100mg, and 200mg round tablets for oral administration. Topamax Sprinkle Capsules are available in 15mg, and 25mg capsules. Depending on the dose, one tablet can range from approximately $1.50 to $5.00.

**Structure**

Topamax is a white crystalline powder with a bitter taste and derived from the naturally occurring monosaccharide D-fructose. It is a sulfamate-substituted monosaccharide with a pH of 9 to 10. Topamax is mainly in alkaline solutions containing sodium hydroxide or sodium phosphate. It is freely soluble in acetone, chloroform, dimethylsulfoxide, and ethanol. In addition, Topamax has solubility in water of 9.8mg/mL, along with a saturated solution pH of 6.3. The molecular formula of Topamax is C12H24NO7S and has a molecular weight of 339.37. The chemical name for Topamax is 2, 3: 4, 5-Di-O-isopropylidene-β-D-fructopyranose sulfate. The structural formula is as follows:

![Chemical Structure of Topamax]

**Mechanism**

Topamax is an anti-epileptic medication that blocks the spread of a seizure unlike other AEDs, which raise the seizure threshold. Although the precise mechanism of Topamax is unknown, laboratory studies have revealed five properties that contribute to Topamax's effectiveness to calm the activity of nerve cells and reduce seizure frequency. One mechanism of Topamax reduces the nerve cell excitation by blocking certain neurotransmitters from binding to amino acid (glutamate) receptors in the brain. Second, it enhances the activity of GABA (gamma-aminobutyric acid), a neurotransmitter that inhibits nerve cell excitation in the brain. At GABA-A receptors increase the frequency at which GABA activates GABA-A receptors. Third, Topamax blocks sodium channels, which also decrease excessive nerve cell firing. The fourth mechanism property antagonizes the kainate / AMPA (alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid) subtype of the amino acid (glutamate) receptor. The fifth mechanism inhibits the L-type high-voltage calcium ion channels. These five mechanisms are important but unique to Topamax since other AEDs do not share these functions.
Pharmacokinetics

The pharmacokinetics of Topamax is linear with dose proportional increases in plasma concentration over the dose range studied (200 to 800mg a day).\textsuperscript{1} The mean plasma half-life elimination is 21 hours after a single or multiple doses. Topamax is 15-41\% bound to human plasma proteins over the blood concentration range of 0.5-250\mu g/mL. The fraction bound decreases as blood concentration increases. Taking Topamax orally, the absorption is rapid with peak plasma concentrations occurring approximately two to four hours after a 400mg dose. The bioavailability from the tablets is about 80\% compared to solution. In addition, the bioavailability has no affect by co-administration with food. Sprinkle formulation is bioequivalent to the immediate release tablet formulation and, therefore, maybe substituted as a therapeutic equivalent.\textsuperscript{1} Topamax’s pharmacokinetics may also be affected by age, hepatic function, and renal impairment. The metabolism of Topamax is by the process of hydroxylation, hydrolysis, and glucuronidation.\textsuperscript{1} Topamax is excreted in the urine.\textsuperscript{6}

Uses

The FDA first approved Topamax for seizure prevention. Epilepsy is a disorder of seizures, which currently has no cure. Epileptic seizures are categorized into two areas; generalized which begin on the both sides of the brain and partial, which begin on one side of the brain.\textsuperscript{3} Topamax is used frequently as a “add on” medication to a single antiseizure medication due continuation of seizures.\textsuperscript{7} Figure 3 shows the reduction of partial seizures with using Topamax as an additional treatment.

![Partial-Onset Seizures in Adults](image)

\textbf{Figure 3}\textsuperscript{3}
FDA has recently approved Topamax for the prevention of migraines. Approximately 13% of Americans suffer from migraines. After careful testing by Ortho-McNeil Pharmaceutical, Topamax received approval from the FDA for the prevention of migraines in 2004. There is no cure for migraines, but studies have shown Topamax will prevent migraines. Significant decrease in the frequency of migraines occurred after starting Topamax. (See Figure 3 below). The usefulness of Topamax during a migraine has not been studied. Studies are ongoing for other uses such as, eating disorders, bipolar disorder, and neuropathy pain.

![Graph: Significant Reduction in Migraine Frequency From Baseline](image)

**Figure 4.**

**Future Indications**

Although the primary use of Topamax is for seizure treatment and migraine prevention, recent studies show there may be multiple uses for this drug in the near future. Eating disorders, including bulimia and anorexia, are complex and challenging psychological conditions, which cause life-threatening consequences. One randomized study, using the drug Topamax, showed a decrease in the amount of binges. The study was inconclusive due to the large amount of participants that did not complete the study. One side effect of Topamax is mood elevation and weight loss, which has started the interest of studying Topamax as a medication treatment for bipolar disorders and obesity. Since the treatment of neuropathy pain is provided by other AEDs, Topamax is also being studied for this purpose.
Side Effects

More than 500,000 people worldwide have used Topamax and is generally well tolerated. This newer anti-epileptic drug has fewer side effects than older AED medications. For instance, the older AEDs side effects included problems with bone marrow and an extremely small incidence of liver abnormalities in those with prior liver abnormalities. Other side effects include a change in taste, predominantly in carbonated drinks, tingling in the extremities, and at times interference with mental function. For women taking a combination of oral contraceptives and Topamax have a significant decrease in estrogen exposure. The efficacy of the oral contraceptive decreases. When adding Topamax to other antiseizure medications, the common side effects are sleepiness, dizziness, coordination problems, speech disorders, psychomotor slowing (a delay between thought and action), abnormal vision, difficulty with memory and double vision. In addition, some serious risks associated with Topamax include increased eye pressure (glaucoma), decreased sweating, increased body temperature and kidney stones. To prevent kidney stones, take this medication with plenty of fluids. Topamax is also one of three AEDs that have statistically proven susceptibility to lose weight. The following chart summarizes the overall most common side effects.

<table>
<thead>
<tr>
<th>Most Common Adverse Events</th>
<th>Percent of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (n=92)</td>
</tr>
<tr>
<td>Somnolence</td>
<td>9</td>
</tr>
<tr>
<td>Anorexia</td>
<td>7</td>
</tr>
<tr>
<td>Fatigue</td>
<td>4</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>2</td>
</tr>
<tr>
<td>Nervousness</td>
<td>2</td>
</tr>
<tr>
<td>Weight decrease</td>
<td>4</td>
</tr>
<tr>
<td>Dizziness</td>
<td>4</td>
</tr>
</tbody>
</table>

Figure 5

Cautions and Recent Warnings

One primary caution of Topamax is not to stop the drug abruptly. If withdrawing from this drug quickly, seizures may occur, even when normally not experiencing seizures. Common advisement while taking Topamax is not to drive or operate heavy machinery until the patient has gained enough experience on Topamax.
In March of 2004, McNeil Pharmaceuticals, the marketing company for Topamax, revised the prescribing information for this anti-epileptic drug to include a warning that the drug causes hyperchloremic, non-anion gap metabolic acidosis. Metabolic acidosis can result in hyperventilation, non-specific symptoms such as fatigue and anorexia, or severe cardiac arrhythmias or stupor. If left untreated, metabolic acidosis can lead to kidney stones, skeletal problems with an increased risk of fractures. A common sign of metabolic acidosis is decreasing serum bicarbonate. Decreases in serum bicarbonate occur soon after starting the treatment, but they can also occur at any time during treatment. New labeling recommends measuring serum bicarbonate levels at baseline, and serum bicarbonate periodically during Topamax’s treatment. If metabolic acidosis develops and continues, reduce the dose or gradually discontinue the drug.

Special Considerations

The following are the special considerations when using Topamax:

- Adjusting the dose of Topamax with special consideration to age, renal and hepatic function is imperative.
- Topamax depresses the central nervous system (CNS) which emphasizes the precaution of using alcohol, sedatives tranquilizers and other CNS depressants.
- Due to the intolerance of the side effects, follow the recommended dosing schedule. This will increase compliance of taking the medication.

Conclusion

Topamax originally designed as an adjunct medication to prevent seizures, recently gained approval from the FDA as a prevention to migraines. Since the age of Topamax is young, research continues to explore new uses for it. Current research has described the various side effects such as weight loss and mood elevation. This has triggered researchers to utilize the side effects from Topamax to help treat other disorders, for example, mood elevation for bipolar disease and weight loss for obesity. The multi use of Topamax is in its’ beginning stages. Be assured the future research will develop more uses for Topamax that will prevent or alleviate disturbing disorders.
Pharmacology and Therapeutics of Selective Serotonin Reuptake Inhibitors (SSRIs) versus Tricyclic Antidepressants (TCAs)

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April 18, 2005
ABSTRACT

Tricyclic Antidepressants (TCAs) and Selective Serotonin Reuptake Inhibitors (SSRIs) are two classes of antidepressants with similar mechanisms of actions. TCAs predate SSRIs, and have a lower market cost, although much clinical data does not discern a therapeutic difference between the two. This paper will define the differences between the drug classes on the basis of comparative pharmacology, safety and therapeutic value between TCAs and SSRIs to see if one class of medicine is superior to the other. A brief look at the stereochemistry and differences between the drugs within each class of medicine, specifically chemical structure, will also be explored.

1. INTRODUCTION TO DEPRESSION AND KEY NEUROCHEMICALS

The foremost medical theory on depression, the Monoamine Hypothesis of Depression, proposes that “depression results from a CNS [Central Nervous System] deficiency of monoamine (noradrenergic and/or serotonergic, 5-HT) function” which explains why most (though not all) antidepressants work through roughly the same mechanisms. This paper will examine two classes of anti-depressants solely, Tricyclic Antidepressants (TCAs) and Selective Serotonin Reuptake Inhibitors (SSRIs), which work by preventing the reuptake of monoamines. Various other antidepressant pharmaceuticals or supplements, such as Monoamine Oxidase Inhibitors (MAOI), which both work by preventing the breakdown of monoamines, are beyond the scope of this paper. L-Tryptophan, a supplement often used to lessen depression, is discussed only in its mechanism and relationship to serotonin and the SSRI class.

The monoamines mentioned above (serotonin, noradrenaline, and 5-hydroxy tryptophan) are the key chemicals when it comes to neurochemistry and depression. To understand how the TCA and SSRI drugs attach to receptor sites in the brain, we logically need to understand the structure of the molecules the receptors are designed to attach to. Fundamentally, if we expect the drugs to attach to highly unique receptors in the brain, then they must bear some similarity, especially in the amine functionality, to the brain chemicals that govern depression.

Serotonin (C10H12N2O), probably the most integral of the chemicals, is a bicyclic compound with three notable functional groups, a terminal (primary) amine, a secondary amine within the 5 membered ring placed one carbon away from the bridgehead carbons, and an alcohol (hydroxy) functionality attached two carbons away from the bridgehead carbons of the bicyclic carbon.

5-hydroxy tryptophan (C11H12N2O3) is a precursor of serotonin and is naturally converted into the body to serotonin. The structure of 5-HTP is the same as serotonin when it comes to the cyclic portion and the alcohol is at the 5th position on the six-membered aromatic ring, hence, the “5-hydroxy” in the common name. The difference between the two is the carbon chain attached to the 5 carbon membered ring, 5-HTP has a carboxylic acid replacing a hydrogen atom on the primary carbon of the chain.

A practical application to the interchangeability of the two molecules is found, surprisingly, in the relationship between eating turkey and sleepiness. As is commonly reported around the Thanksgiving holiday, turkey contains L-tryptophan, which is reported to cause sleepiness. That is technically incorrect, however, as the L-tryptophan
is not the culprit; it is reacted in the body, naturally catalyzed to put an alcohol on the 5th position of the aromatic ring, making 5-hydroxy tryptophan. This natural reaction is made possible by an enzyme appropriately titled “human tryptophan hydroxylase (hTrpOH).” Following that reaction, the newly made 5-HTP molecule is reacted by the body to eliminate the carboxylic acid, putting a hydrogen on in its place, making serotonin.\(^3\) Serotonin, not tryptophan, is the real cause of the sleepiness and feeling of ease after the turkey dinner. The detailed reaction and structures of three molecules are shown in Fig. 1. This briefly explains why people may choose to supplement with L-Tryptophan for depression. However, if the patient lacks the natural enzymes to convert the L-Tryptophan molecule into serotonin, the therapy will be ineffective.

Noradrenalin (norepinephrine) is a key neurotransmitter relating to depression and depression-indicated drugs. It is involved in a lengthy chemical process in the body responsible for such chemicals such as adrenalin and dopamine. Thus, a lack of available noradrenalin in the cells, due to either a lack of production or excessive reuptake, can inhibit this natural biochemistry reaction. The interruption of this process can be related to what happens to frequent users of the illegal drug MDMA (ecstasy) or cocaine experience over time when the dopamine receptors are damaged inhibiting the intake of dopamine to the cells and also affecting the production of noradrenalin. Dopamine is a precursor to noradrenalin and is naturally catalyzed to noradrenalin in the body, making it harder for the user to experience happiness and energy when not taking the drug, thus increasing their need for the addictive drug.\(^4\)

II. BACKGROUND OF TCA AND SSRI DRUGS / SUMMARY OF PURPOSE

With the aforementioned knowledge of depression, we can understand at a basic level of how psychotropic pharmaceutical drugs work to correct depression-inducing chemical imbalances. Tricyclic Antidepressants (TCAs) and Selective Serotonin Reuptake Inhibitors (SSRIs) are now the two leading classes of depression drugs on the market. Several factors may influence a doctor’s decision on which class to prescribe. A minor concern to the prescriber might be the cost of the drug to the patient. TCAs predate SSRIs by many years and are off-patent in the United States. With TCAs established in generic brands, the consumer saves a considerable amount of money in comparison to the cost of brand-name drugs. The earliest SSRIs are now beginning to come off patent but, in general, TCA-class drugs are much cheaper than SSRI drugs.\(^5\) However, as we attempt to look at these drugs purely in a chemical sense, we must disregard money as a criterion for superiority. The true tests for the viability of a drug are its efficacy, effectiveness and safety. To define these terms by a clinical definition, efficacy is defined as the drug’s efficiency in lab settings, effectiveness is defined as the drug’s effectiveness in real-world practice and safety is the drug’s potential for adverse effects and toxicity.\(^5\) TCAs are unselective molecules which go after the norepinephrine and 5-HT reuptake receptors as well as serotonin reuptake inhibitors, while SSRIs, obviously, focus solely on preventing serotonin reuptake.\(^6\) TCAs have a danger of high toxicity, while SSRIs have been linked to unique side effects causing paradoxical reactions which worsen depression, the worst-case scenario being the patient having suicidal tendencies.\(^7\) Also, a trend has been noted with SSRIs causing sexual side effects even after the drug is discontinued.\(^8\) It is the attempt of this paper to review the current evidence on both the pharmacology of these
drugs (of which we still have limited knowledge, even though they are in very widespread use) and the current studies of therapeutic value of these drugs to determine if there is a greater benefit of SSRIs to justify their greater cost and whether these drugs are safe for widespread use, in general.

III. DISCOVERY / MECHANISM OF SSRI vs. TCAs

In terms of scientific discovery, SSRIs have a more glamorous history than TCAs. The discovery of the TCA class of drugs was by all means an accident, "the result of an unsuccessful attempt to improve on the antipsychotic effectiveness of phenothiazines." TCAs were introduced into broad practice in the 1950s. When TCAs (as well as MAOIs) were revealed to have benefits against major depression, it opened the door for more in-depth research by scientists to attempt to create molecules that would specifically latch on to just one type of receptor (molecular targeting). For example, amitriptyline, a tertiary amine TCA, can attach up to 9 different neuroreceptor sites which could potentially give the effect of up to 9 separate drugs. This could cause the drug’s effectiveness to vary greatly based on the patient’s body type; some drugs work/don’t work in an individual’s biochemistry for reasons that cannot be determined with science at this time. Since scientists had the knowledge of where the TCAs attached and knew of their effects on depression, it was only a matter of conducting research studies and refining their test molecules until they could make a class of drugs to have a more selective MOA (“Mechanism of Action”) and, hopefully, more effective on depression with less side effects.

The general structure of the Tricyclic antidepressants is, appropriately, three cyclic rings with a chain attached to the middle ring. Both the left and right rings are aromatic while the center is not. The chain is almost always an alkyl group with an amine functionality. The structures of the SSRIs are much more diverse (as seen in Appendix A); however, they all include halides, which are not present in the three basic neurochemicals mentioned earlier, as well as the amine functionality that TCAs have. The amine functionality is the key to the drugs binding to their appropriate receptor sites, but the exact mechanism of how this happens is unknown for both classes of drugs.

The essence of antidepressant drugs is to block the "reuptake receptor" sites of a certain molecule. Reuptake pumps/receptors must be differentiated from receptors. Receptors take the molecule when it is in plasma circulation and bind to it, making the effects of the drug (such as the anti-depressant qualities of serotonin) available and felt by the body’s central nervous system (CNS). Reuptake receptors take the molecule out of plasma circulation. For example, a serotonin reuptake pump takes serotonin out of circulation and binds it so it cannot reach the receptor and its effects cannot be felt. Sequentially, if we inhibit the reuptake pump, we give a higher quantity of serotonin molecules left in circulation to be bound to receptors, increasing the useable serotonin levels in the body and relieving depression. It should be noted that "reuptake inhibition causes an initial increase in serotonin only at the cell body and the dendrites, not at axon terminals. The immediate consequence is to inhibit the rate of firing of serotonin neurons (and the release of serotonin) by an action at 5HT 1A somatodendritic autoreceptors." In other words, the blocking of the reuptake inhibitor also causes the firing of the neurons to
slow down, consequently making the body more efficiently use the serotonin it has access to.

The TCA drugs MOA suggests an affinity for mostly “5-HT” (5-Hyroxy Tryptophan) and “NE” (norepinephrine) reuptake inhibition, but they also, to a degree, bind to the serotonin reuptake site. A problem with TCAs is that they bind to H-1 and H-2 histamine receptors which causes a high occurrence of side effects. TCAs were an important breakthrough in depression science because it solidified that depression was a matter related more to biochemistry than mood, and the scientific community was able to ascertain that depression was mostly related to three chemicals discussed earlier in the paper. SSRIs were designed to target just the serotonin receptors since they were believed to have the greatest affect not only on the fundamental causes of depression but on a series of bodily systems such as “pain perception, sleep, thermal regulation, appetite, gut regulation, balance, reproductive function, motor function, cognitive function, [and] sensory interpretation.” Since serotonin is involved with so many bodily functions, there is still potential for side-effects but the greater selectivity avoids the consequences of binding to H-1, H-2 and acetylcholine receptors which cause the bulk of the mild-to-moderate side effects in TCA drugs. TCAs and SSRIs have varying tendencies within their respective classes. For the TCAs, molecules that have tertiary amines (e.g. amitriptyline, doxepin) have a greater natural inclination for the serotonin reuptake inhibitor than TCAs that have secondary amines, which naturally seem to boost norepinephrine more. The prescriber can use these differences to discern within the drugs of the TCA class when it comes to prescribing: “The tertiary amines... are more useful where depression is accompanied by sleep disturbance, agitation and restlessness; whereas the secondary amines may be preferable where the depressed patient is fatigued, withdrawn, apathetic and inert.”

For SSRIs, in-depth data, beyond the scope of the paper, is available detailing the selectivity of the SSRI drugs and which receptors certain molecules tend to bind to aside from the targeted serotonin reuptake receptor. This gives physicians information about which SSRI drugs are more likely to react for certain side-effects or drug-drug interactions. This is not an exact science but another tool for doctors to use in an attempt to get the diagnosis and medication order as accurate as possible on the first try. It is very difficult to create a dichotomy of the SSRIs as we did based on the amine classification for the TCAs.

One of the more difficult things to understand when it comes to comparing SSRIs vs. TCAs is that binding to more types of receptors is not beneficial based on the medical community’s hypothesis that serotonin is the most influential chemical on depression. A useful analogy would be to imagine a TCA and SSRI given in stoichometrically equal amounts and binding to the same amount of receptors. With the SSRI a much higher percentage of serotonin reuptake inhibitors would be covered, since it is much more selective of a molecule, leaving more serotonin available to the receptors. However, our knowledge about the mechanisms of how TCAs and SSRIs bind to the receptors is incomplete as is the scientific community’s data about serotonin being more effective than 5-HTP and norepinephrine when it comes to relieving depression. Hence, we need to look further to see if SSRIs are truly superior to TCAs as most doctors and scientists would suggest based on existing evidence. We need to look at comparative testing, which
should show that SSRIs have a higher success rate in practice, and real-world safety data, which should show a lower trend of side effects and better safety profile.

IV. CLINICAL TRIALS

For a new drug to be prescribed in place of an existing drug on the marketplace it must show some combination of "greater effectiveness, fewer side effects, or significantly reduced costs to the purchaser."7 The cost considerations for the patient have been addressed earlier in this paper. Now we will investigate therapeutic value of the drugs as assessed in comparative clinical research. Surprisingly, although SSRIs seem to have a superior mechanism of action, this has not translated to more effectiveness in drug trials. Numerous sources list that SSRIs seem to be equally effective in trials, but not greater.5,8,11 Two types of research have been done on the differences between the drug classes: studies that administer drugs to test groups of patients and monitor their progress, and studies which analyze aggregate data from real world patient case files. A test group study of a managed care facility showed a dramatic difference between compliance on the two classes of medicines. The study has two equal groups of test subjects start on antidepressants, one starting on fluoxetine (SSRI) and one starting on desipramine (TCA). The results were rather remarkable, with 60% of the SSRI group remaining on their medications compared to only 30% of the TCA group staying on their medication.5 The study tests two variables because the patients were managed by a group of primary care practitioners. Thus, the study shows patients had greater resolve to continue their medications on SSRIs and also that the doctors had more confidence in the SSRIs, which trickled down to their patients. One study, which examined 13,000 patient case studies, showed that doctors were more likely to discontinue using TCAs than they were SSRIs.5 The reason the doctors discontinued TCAs more often was because of adverse side effects, not the effectiveness of the therapy. Another study, simply monitoring patients compliance on prescribed antidepressants through a series of clinical trials, showed that the patient-initiated dropout rate of SSRIs had a median of 15% where TCAs had a median of 21%.7 A 6% degree of compliance is a huge issue in pharmaceutical studies when extrapolated to account for the massive number of patients who receive treatment with psychotropic drugs. Another experiment, monitoring antidepressant therapy in a sample of elderly patients, also reported higher compliance and less side effects with SSRIs.12 There is an argument that SSRI compliance evens out in the real world when consumers pay for their prescriptions due to the cost of SSRIs being 20 to 30 times higher in some cases.7 The opposing viewpoint is that SSRIs have roughly equal total costs to TCAs when considering the costs of failed treatment or hospitalization due to adverse effects.5,12 The group of studies surveyed for this paper suggests, in general, that SSRIs prevail when cost is taken out of the equation showing a real world application of SSRIs improved MOA (Mechanism of Action) as opposed to TCAs.

V. SAFETY / COMPLIANCE

Clinical trials show that SSRIs are available to avoid the muscarinic effects often seen in the TCAs. These effects occur in TCAs due to the tendency of those drugs to bind
to H-1 and H-2 receptors. SSRIs are better at targeting the right receptors and thus avoid the histamine systems, which govern mucus production. Users of both drugs in controlled settings seemed to experience less dry mouth, constipation and blurred vision with SSRIs.\(^1\) Weight gain, one of the biggest concerns listed by patients, was also reduced with SSRIs.\(^1\) Side effects can also lead to more serious medical conditions through indirect causes. SSRIs are better than TCAs in this way because “less ataxia and incoordination in elderly people [on SSRIs compared to TCAs] reduce the risk of falls, and postural hypotension [with SSRIs] is uncommon because of the absence of (alpha)1 receptor blockade.”\(^7\) The most serious problem associated with TCAs is their toxicity even in relatively low doses and is much more likely to cause a problem in the body with drug clearance than SSRIs.\(^1\) This can become an issue with patients with other psychiatric disorders who are at constant risk of suicide or have problems managing their medications. An accidental or intentional overdose is much easier on TCAs than SSRIs. SSRIs, however, also have serious proprietary side effects, one of which being that they seem to cause sexual dysfunction to a much greater degree than TCAs.\(^9\) This seems to be linked to their greater effect on serotonin levels which govern the sexual cycles in the body. An increase of too much serotonin can often cause inorgasmia in patients as well as problems with arousal. One other serious and unique side effect does exist with SSRIs. In limited cases, SSRIs can actually worsen depression. The mechanism has only been speculated on and the discovering of the phenomenon is relatively recent.\(^13\) The FDA only began requiring a warning to be put on SSRI drug bottles about the possible side effects in late 2004.\(^13\) The FDA in the past has required the pharmacist to dispense a package insert with drugs that have potential serious health consequences, such as estrogenic drugs. There is not yet a requirement requiring pharmacists to dispense the package insert with either SSRIs or TCAs. Another common issue with SSRI drugs is that serotonin receptors can decrease after taking the drug for an extended period of time making the therapy continually less effective.\(^14\) Sometimes the correction for this syndrome can be an increased dosage but eventually a patient may only respond to a new drug, or in the worst case, not respond at all to antidepressant drug therapy.

VI. STEROEOCHEMISTRY

There are a good number of psychototropic drugs that are achiral so they have no stereochemistry concerns. For the drugs that have a chiral carbon, there is no distinct trend towards either racemic mixtures or single enantiomer release even within a certain class of antidepressant drugs. For example, Paxil (paroxetine) is marketed as a single enantiomer version based on efficacy research while another SSRIs like Prozac (fluoxetine) are made as racemates and show no marked benefit in single enantiomer versions\(^15\). Some drugs are released in both versions. A current example in the SSRI class on the United States market is Celexa in relation to Lexapro. Celexa is the racemic mixture (R,S) of citalopram, while, Lexapro is strictly the (S) enantiomer, called “escitalopram”. Lab studies suggest the R enantiomer is “30% less potent” but both scored around evenly when compared with a placebo in trials.\(^15\) So although lab research shows a higher efficacy for the (S) enantiomer, clinical trials have yet to show a marked benefit. It should be noted than one of the advantages of making a single enantiomer version of a drug after a racemic version has been released is that the drug manufacturer
gets a new patent. Celexa had recently gone off patent when Lexapro was released and the sales of Lexapro have dwarfed the sales of brand name Celexa since its induction. Another common tactic, which also extends the life of a drug patent, is to develop an “extended release” or different dosing mechanism for the drug in an attempt to create a greater effectiveness of the drug.

Still, the ability to isolate enantiomers, as well as control the release of an active ingredient within a drug, gives drug chemists the chance to experiment further with the drug and possibly isolate an enantiomer or new dosage medium that metabolizes better in the body allowing the serious probability of side effects to be reduced.

VII. SUMMARY

Antidepressant drugs have become a large sector of American pharmaceutical sales and the two classes discussed are the foremost classes of antidepressants. TCAs are the old guard, having been the most prescribed class from the beginning of their clinical use in the 1950s until the mid-90s. While they were discovered until humble circumstances, the knowledge of their structure coupled with the observations of how they affected depression provided some of the key primary chemical knowledge on depression and neurochemistry. While we still do not know the exact mechanisms of either class of drugs, what we do know has helped solidify the important viewpoint that depression spawns from biochemistry related matters as much, if not more, as it does from someone’s societal upbringing, though the two can be interrelated. The scientific community’s knowledge of TCAs facilitated the preliminary laboratory work that led to the synthesis of the SSRI drugs. The advantage of SSRI drugs, chemically, is that they are more selective chemically in binding to receptor sites, being targeted to prevent the reuptake of strictly serotonin. While logically one would assume this would cause a greater effectiveness, clinical trials seem to equate the positive benefits of TCAs and SSRIs around equal.

The real benefit of SSRIs, many drug companies argue, is not increased positive effects over TCAs but rather diminished negative effects (i.e. increased safety and tolerability of SSRIs in comparison to TCAs). This seems generally true, although some instances of sexual dysfunction, due to bonding of the serotonin receptor, and paradoxical reactions causing suicidal tendencies, by an unknown mechanism, have been reported with SSRI use. Regardless, SSRIs are more tolerated and have less minor-to-moderate side effects to their superior mechanism, which affects fewer systems in the body. An important factor to note is that money is often a concern for the consumer when filling a prescription, and the doctor might take this into consideration when prescribing. Market trends indicate, however, that SSRI prescriptions are rising and TCA prescriptions are declining at a rate in which SSRIs will control a large market advantage. The reason for this is twofold. First, physicians are more likely to prescribe a medication with a better safety profile, even if it merely has the same effectiveness of an older drug, since their concerns about the monetary amount of a drug for the consumer are generally minimal and their concerns about malpractice insurance are generally great. Second, physicians receive a sizeable amount of their informal continuing education from drug representatives who are more willing to talk about a newer drug, especially if the drug company has a patent for exclusivity on the drug. Some of the first SSRIs are off patent,
such as Paxil and Prozac, but in general SSRIs are of a significantly higher cost than TCAs. Also, many drugs that are off patent have been modified into a new dosage form. Celexa, off patent, has been re-released as Lexapro, a single enantiomer version of the drug as compared to the racemic mixture. Paxil, previously mentioned as off patent, is available in an extended release version as Paxil CR, on patent.

Monetary concerns aside, the evidence contained in this paper supports the theory that SSRIs seem to be the chemically superior drug, although the difference between the two classes is closer than expected. Maybe the most shocking finding in the research for this paper was the high prevalence of serious side effects with both classes of drugs and the overall uncertainty regarding the safety of these drugs. While these medications have done a lot of good in the population, and there is little to no alternative at this time, it is my opinion that either class of drugs should be used with caution under close supervision of a physician and that further research is needed to fully ascertain the safety consequences of these medications and improvements.
References


10) Freeman, M.S. Tricyclic Antidepressants, <http://cypress.mcsr.olemiss.edu/~ecmsf/index.html>


Appendix A: Structures of Neurochemicals and Antidepressant Drugs

While it is not currently known how the TCA or SSRI drugs bind to the receptors in the brain, we do know that the key is the amine functionality. This chart shows the structure of the three neurochemicals mentioned in the text and also some examples of each class of drug to show structures tendencies.

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Fig. 1: Reaction of L-Tryptophan into 5-HTP into Serotonin.
DRUGS USED TO TREAT PARKINSON'S DISEASE

PREPARED BY
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APRIL 22, 2005
Abstract

This paper describes the primary drugs used to treat Parkinson's Disease, beginning with the most commonly used. It explains how the drugs interact with the human body and what side effects they may cause. Also discussed is the treatment of Parkinson's Disease, synthesis of levodopa, the functional groups associated with these drugs. Problems associated with levodopa therapy and the prospects for drug therapy.

Introduction

Since drugs are currently the most effective treatment for relieving the symptoms of Parkinson's Disease, so that the people with this disease can continue to function in their lives. As I consider these medications, it's important to keep in mind the motor control system of the brain is enormously complex and adding drugs to the system affected by Parkinson's Disease can only approximate the way the system normally works. Nonetheless, these drugs represent a significant improvement to what was available even ten years ago.  

Treating the Disease

No drug can cure Parkinson's Disease or stop its progression, but many drugs can make movement easier and enable people to function effectively for many years. Approved in 1970, levodopa is most effective in reducing tremor and muscle rigidity and improving movement. Treatment with levodopa can produce dramatic improvement in people with Parkinson's Disease. The drug, levodopa, is what doctors call the "gold standard" of Parkinson's therapy, because it is often the first-line treatment for the disease.

To prevent rapid breakdown of levodopa in the body, the drug is combined with either carbidopa or benserazide. Carbidopa/levodopa (Fig. 1) is marketed throughout North America while benserazide/levodopa (Fig. 2) is marketed throughout Europe. When the two drugs are given together, a lower dose of levodopa can be used, and the side effects of levodopa are reduced. Sinemet is the mainstay of the treatment of Parkinson's Disease.
The full chemical name of final building block "assembly line" for dopamine manufacturers is extremely cumbersome: Levodihydroxyphenylalanine. Scientists abbreviate it to either L-dopa or levodopa. The final chemical reaction that transforms levodopa into dopamine strips away a specific cluster of atoms, known as carboxyl group from levodopa molecule. This chemical reaction is therefore appropriately called decarboxylation. The reaction takes place only in presence of a specific enzyme. The enzyme that makes possible this final transformation of levodopa to dopamine bears a logical name decarboxylase. Decarboxylase is in abundant supply throughout the body, including substantial nigra, even in Parkinson's patients.

So, in theory, there was at last available a method whereby the concentration of dopamine in the brain could be increased despite the barrier to its direct entry there - a way of getting around the blood - brain barrier. The main problem with levodopa was only a very small proportion (1% or less) of the administered levodopa, could find its way first to the brain and thence, as dopamine, to the striatum. What happens to the rest of the dose? Unfortunately, most of it is quickly transformed in the body into dopamine. And it is in the body (that is, outside brain and spinal cord) that dopamine functions as a hormone. Too much dopamine acting as a hormone, at least, cause episodes of rapid, forceful heartbeats.

Clearly a need existed for some drug that would prevent conversion of levodopa to dopamine in the body. A drug that would, at some time, avoid interfering with conversion of levodopa to dopamine in the brain. Scientists found the drug they were looking for; carbidopa, a remarkable chemical with too highly desirable properties. First, it is peripheral dopadecarboxylase and hence, prevents transformation of levodopa into dopamine in body. Second, it is unable to penetrate blood - brain barrier and therefore interfere with the conversion of levodopa to dopamine in the brain.

To determine the best dose of levodopa for a particular person, doctors must balance control of the disease with the development of certain side effects, which may limit the amount of levodopa a person can tolerate. Many experts believe that the development of involuntary movement can be delayed by using a drug that mimics the action of dopamine (a dopamine agonist) with or instead of levodopa during early years of treatment.

SYNTHESIS OF SINEMET (carbidopa/levodopa)

The synthesis involves a rhodium hydrogenation catalyst containing a chiral phosphorus ligand called (R,R)-DiPAMP, (R,R)-1,2-bis[(2-methoxy phenyl) phenyl phosphino] ethane, shown below, reacting with an enamide. The hydrogenation product is obtained in 95% enantiomeric excess. The removal of the protecting groups leads to levodopa.
Levodopa is the "gold standard" for the treatment and management of Parkinson's disease worldwide. However, following prolonged use of the drug, the "honey-moon" which was once enjoyed by patients on levodopa begins to wane. The clinical as well as the socio-economic costs associated with such failure in response to levodopa is enormous. Various approaches in the management of Parkinson's disease patients experiencing motor fluctuations with levodopa treatment have been suggested and include both pharmacologic and non-pharmacologic strategies involving invasive surgical intervention. Currently, the non-pharmacological approach, which is invasive, remains to be fully perfected and is associated with high morbidity and mortality. The use of the non-invasive, pharmacological approach is currently the most widely accepted approach but would require a review of all possible drug regimens used. This entails evaluating the pharmacokinetics and pharmacodynamic actions of the drug regimens used and possibly, dosage form and route of administration of the drugs. The use of levodopa formulated for transdermal or intranasal administration might help improve the ease of use and compliance.

However, it is worthy of mention that an integrated optimal pharmacological approach involving the peripheral, and central pharmacokinetics of levodopa as well as its central pharmacodynamics would ensure better treatment and management of this disease. In addition, the choice of alternate formulations and routes of administration will not only improve on the bioavailability and overall pharmacokinetics of levodopa, but also increase compliance. Furthermore, monitoring of both plasma and central concentrations of levodopa and its metabolites might play a major role in individualization of pharmacotherapy in special Parkinsonian patients experiencing motor fluctuations with levodopa.

Problems Associated with Prolonged Levodopa Therapy in Parkinson's Disease

Motor fluctuation associated with levodopa therapy is a major problem encountered in the treatment of Parkinson's disease. Following prolonged use of levodopa (usually greater than 5 years), especially in advanced stages of the disease, the efficacy and benefits derived from levodopa begin to wane and motor complications occur regularly.

Loss of therapeutic effectiveness of Levodopa following long-term administration is a serious problem. After initial benefit from Levodopa, many Parkinson's disease patients develop (1) progressive, global loss of drug effectiveness; (2) the "wearing-off" phenomenon, in which daily periods of benefits after individual doses of levodopa become shorter; and (3) "on-off" phenomenon, which refers to abrupt and unpredictable fluctuations in responsiveness and which is thought to be unrelated to dosage schedule. A study to determine the continued benefit and pattern of motor complications sequel to long term levodopa reported dyskinesia as the most common occurring and earliest noticeable effect of prolonged levodopa use, followed by wearing-off and on-off phenomenon.
Like most capacity limited or saturable systems, upon prolonged use of levodopa, the "law of diminishing returns" begins to set in. The usual "honeymoon" once enjoyed upon initial introduction of therapy gradually disappears. Mechanisms of motor fluctuations associated with prolonged use of Levodopa are not fully understood. Various authors have suggested that it could be due to one or combination of the following factors: (a) modulation of central pharmacokinetics (delivery of L-dopa from pre-synaptic to post-synaptic receptors), (b) peripheral pharmacokinetics or delivery of levodopa from an exogenous source to the brain across the blood brain barrier (c) pharmacodynamics -alteration in the interaction between dopamine and striatal receptors.\(^5,7\)

The loss of benefit from levodopa therapy is usually associated with problems such as end-of-dose deterioration and dyskinesias. The mechanisms involving changes in levodopa pharmacokinetics and pharmacodynamics including changes in responsiveness of dopamine receptors in the CNS have been supported by others.\(^9\) Hyperkinetic movement disorders, such as chorea, dystonia and myoclonus develop in most Parkinson's disease patients following prolonged use of levodopa.\(^4\) Most often, the dyskinesia may occur from an overshoot of the therapeutic concentration of L-dopa, thus calling for a careful monitoring of the therapeutic optimum of this drug in advanced Parkinson's disease patients.

A reduction in the capacity of dopaminergic cells to synthesize, take up, and store dopamine leads to a dependence on the bioavailability of externally administered levodopa. Thus, delivery of levodopa to the brain from the peripheral pool remains a major strategy to ensuring adequate availability of dopamine to the brain. Hence, it is expected that factors that modulate the peripheral concentrations as well as the central levels of dopamine will in turn affect the amount of drug available for delivery to the brain. Some studies aimed at ensuring adequate peripheral levels of Levodopa have demonstrated improvement in motor function in Parkinson's disease patients with increasing plasma concentration of levodopa.\(^8,9\)

A good understanding of the reasons for the occurrence of motor dyskinesias and delineation of the pharmacokinetics and pharmacodynamics of levodopa in these subjects may provide clues to solving the problem. However, an ideal approach would be to determine central pharmacokinetics of levodopa.\(^9\) Currently, this is a tedious process with existing technology and is not plausible. However, a good monitoring of peripheral pharmacokinetics of levodopa would be much easier and may be helpful in the pharmacotherapy of patients experiencing motor fluctuations. The relationship between plasma concentrations of levodopa and its clinical response remains to be categorically defined.
Dopamine Agonist

Class of medications that are not converted to dopamine in the brain as levodopa is, instead, they bind directly to the dopamine receptors on the walls of the brain cells, like a key fitting into a lock. There are currently four different dopamine agonists available to treat Parkinson's Disease in the United States and Canada. Two "old" ones Bromocriptine (Fig. 3)\textsuperscript{13} and Pergolide (Fig. 4)\textsuperscript{13} and two "new" ones, Lisuride (Fig. 5)\textsuperscript{13} and Pramipexol (Fig. 6).\textsuperscript{13} All have been shown to be effective and all can be used in place of levodopa in the early stages of disease, but most patients will eventually need levodopa in later stages of Parkinson's. The dopamine agonist can improve motor fluctuation and reduce "off" time and they are less likely to cause dyskinesias than levodopa.\textsuperscript{11}
Anticholinergics

When brain level of dopamine is depleted by Parkinson's Disease, this upsets the balance between dopamine and a chemical messenger called acetyl choline. Anticholinergics block the action of acetyl choline, and this improves the balance between acetyl choline and dopamine. It is now accepted that not all problems people have from Parkinson's Disease are related to the loss of dopamine cells in substantia nigra.\textsuperscript{10} Defects in other chemical systems such as serotonin systems plays a major role in depression, and problems with thinking and sleeping. Some of levodopa complications including fluctuating and dyskinesias, result from excessive activity of brain's glutamate receptors. This excess may cause neurons to die, and may contribute to the progression of the disease. Amantadine, benztrpine, biperiden and trihexyphenidyl hydrochloride (Fig. 7,8)\textsuperscript{13} appear to work as glutamate antagonists blocking the receptors and diminishing this excessive activity.\textsuperscript{2,10} Amantadine is frequently initial treatment for Parkinson's Disease, especially if the slowness of movement or rigidity are principal symptoms. It is generally well-tolerated and acts clinically like a weak form of levodopa. The visual hallucinations are a disturbing side effect of amantadine.

![Amantadine](image)

Amantadine
Tricyclo [3.3.1.1(3,7)] Decane-1-amine

![Benztrpine](image)

Benztrpine
1alphaH,5alphaH-tropane

Fig. 7

Fig. 8
Monoamine Oxidase Inhibitor (M.A.O)

The monoamine Oxidase is an enzyme that breaks down dopamine. It exists in two forms, M.A.O type A. It is found adrenal glands, heart and liver. M.A. O. type B is present in the brain, a substance that inhibits the action of M.A.O. type A, prevents the breakdown of the dopamine, as well as adrenalin and nonadrenalain. M.A.O. type A inhibitors "amitriptyline" (Fig. 9)13 are used as an antidepressant2. Selegiline hydrochloride (Fig. 10)13 is a M.A.O. type B inhibitor, which has a unique feature of selectively blocking the action of M.A.O. type B, thereby preventing the breakdown of dopamine in the brain, while allowing degradation of other monoamine, such as nonadrenaline, and adrenaline.10

Fig. 9

Fig. 10

Prospects for Drug Therapy

We seem to live in a world of scientific and technological miracles. Every nook and cranny of planet earth and of outer space is being explored and studied. Nothing seems impossible. Our expectations are essentially unlimited, especially in the field of medicine. Drugs have been developed within the last few decades that combat most serious infectious diseases, thus freeing mankind from periodic worldwide epidemics that formerly took the lives of a third or more of entire populations. Intensive medical research is being pursued by universities, industries and governments. Surely, we have good reasons to be optimistic that a cure for Parkinson's Disease will be found relatively soon.

Researchers are just starting to identify signals that tell a stem cell to become a brain cell. We need to do more work to understand how to coax those brain cells into becoming specific dopamine producing cells we want them to be.10 As well, there is evidence that even the adult human brain still has some capacity to grow new cells. In the future, we may be able to regulate these "stem" cells that are already in the brain, and manipulate them into becoming a dopamine producing cell.
Yet we must strive to be realistic. How formidable a challenge is the understanding of the human brain. The most complex apparatus of our entire observable universe! And so difficult to study, too. Differences between the human brain and an animal's are, for the most part, too great to permit us to apply directly to humans the information gained from animal studies. Furthermore, the cutting or probing into the living human brain cannot be justified for research purposes alone. Given such obstacles, we shouldn't be over confident that even the cleverest investigators can soon accomplish another major breakthrough in the understanding of this disease.

Reality also forces us to acknowledge once again that the present approaches to therapy of Parkinson's Disease are all palliative. No current treatment attacks the root cause of the problem, because the root cause is unknown. Present treatments are only attempts to patch up some of the disturbing effects of a causative agent or process. History discloses abundant evidence that until the true cause of a disease is understood, a preventive or curative treatment will remain elusive. When the cause is discovered, the cure usually soon follows.

Drugs and Their Functional Groups:

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<td>Amine Aromatic sulfur</td>
<td>Amine</td>
<td>Amine tricyclic</td>
</tr>
</tbody>
</table>
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LSD: An Altered State of Reality

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Abstract:

The body of this paper entails information pertaining to the history, synthesis, use, chemistry, and effects of the illegal narcotic, LSD (Lysergic Acid Diethylamide). Each of these subjects will be addressed in detail, and the similarities of LSD and Serotonin will be compared. LSD is as prevalent now as it was when it was discovered. Spreading awareness of the drug will help educate those unfamiliar with LSD, and therefore, help control the problem.

Introduction:

It is a well-known fact that LSD was a major part of the 1960’s “hippie” generation. During this time period, drug usage was a normal everyday occurrence. Society did not think about the consequences of their actions, but they lived for the moment. As threats of the harm of LSD spread throughout the years, usage decreased but did not disappear. It is estimated that over 12 million people ages 12 or older have tried LSD at least once. A study also determined that white males are more likely to use LSD than any other demographic group. White males make up 57% of LSD users, white females represent 35%, and the remaining 18% is made up of other racial and ethnic minorities. Since LSD use is concentrated in high school and college age people, it is almost certain that every person, female or male, will be approached to try LSD at some point in life. Helping educate the younger population about this drug may prevent young people from becoming a statistic.

Background:

LSD (Lysergic Acid Diethylamide)

In 1938 a Swiss scientist named Dr. Albert Hofmann accidentally developed a new chemical, which he named Lysergic Acid Diethylamide, while investigating new medications to alleviate headache pain. However, after much investigation, it was found that LSD was not useful in combating any ailments, and it was set aside. It was not until 1943 that Hofmann decided to begin testing the drug he had discovered many years earlier. Shortly after testing began, Hofmann accidentally ingested LSD. He immediately reported a strange, confused, intoxicated state. He described the experience as the following:

"I suddenly became strangely inebriated. The external world became changed as in a dream. Objects appeared to gain irrelief; they assumed unusual dimensions; and colors became more glowing. Even self-perception and the sense of time were changed. When the eyes were closed, colored pictures flashed past in a quickly changing kaleidoscope."
After a few hours, the not unpleasant inebriation, which had been experienced whilst I was fully conscious, disappeared. What had caused this condition?"³

Amazed by the potent reaction of LSD, Hofmann began further research into the drug. Reports of the drug spread quickly around the world. Scientists believed that LSD would prove effective at curing many mental illnesses, as well as become a useful tool for psychotherapy. In 1949 LSD hit the United States at the Boston Psychopathic Hospital.⁴ Although experts in the United States were excited and open to the benefits of LSD, the Food, Drug, and Cosmetic Act of 1938 declared that new drugs must be tested on animals and humans before they could be sold. In 1953 the Food and Drug Administration (FDA) allowed the distribution of LSD to eligible psychiatrists for research purposes.² LSD was tested on thousands of people for a multitude of reasons. It was used to treat alcoholism, relieve autistic symptoms in withdrawn children, ease the stress of terminally ill patients, as well as relieve the effects of many other mental illnesses.¹ The CIA even began testing the effects of the psychedelic drug for use in chemical warfare. It was believed that LSD could be used for brainwashing or mind control. However, the CIA conducted tests on people without their knowledge or consent. This resulted in the irreversible illness of many participants of the experiment.² CIA investigation into the drug continued despite its adverse effects. It was thought that LSD could be used on prisoners of war as an interrogation tool. Testing on their own operatives continued, and the information retrieved was deemed unreliable due to the induced anxiety and loss of contact with reality. This did not discourage CIA officials. Instead of using the drug as a truth serum, they believed that it would prevent U.S. soldiers from releasing information to enemies after their capture.¹

As the effects of the psychedelic drug became known outside the scientific community, recreational use ran ramped. The abuse of LSD as well as other narcotics became such a problem that new drug-testing laws were passed in 1963. By this time the drug had become a key part of 1960’s cultural youth rebellion.¹ The ability to sell, give away, or distribute LSD was taken away by the Drug Abuse Control Amendments of 1965.² By this time the synthesis of Lysergic Acid Diethylamide was known by amateur chemists and researchers, making it impossible to control.

Synthesis

The preparation of LSD is an uncomplicated procedure that can be carried out by anyone with limited lab experience, and access to the necessary chemicals. The following will detail two different methods of preparing lysergic acid diethylamide. The experiments require the presence of photographic yellow and red safety lights to prevent the decomposition of lysergic acid derivatives. Rubber gloves are recommended to protect against the poisonous effects of ergot alkaloids, and a hair dryer will assist in evaporation.
Method #1

Step 1 (Requires the use of Yellow light)

In a small round bottom flask place one volume of powdered ergot alkaloid material and add two volumes of anhydrous hydrazine. Boil for 15 minutes after adding 1.5 volumes of water. The solution should be cooled in the refrigerator to generate isolysergic acid hydrazide crystals.

Step 2 (Requires the use of Red light)

All reagents should be chilled prior to use, and a cup of ice should be close at hand. Dissolve 2.82 g hydrazine quickly in 100 ml 0.1 N ice-cold HCl. The reaction tube should maintain a temperature of 0 C. Next, 100 ml ice-cold N NaNO2 is added to the mixture. After briskly stirring for 2 to 3 minutes, another 130 ml of HCl should be added dropwise. The mixture should be placed in an ice bath and the stirring should continue. After approximately 5 minutes, the solution should be neutralized using a saturated solution of NaHCO3. An extraction should be completed using ether. Remove the aqueous solution and dissolve the gummy substance in ether. For every 300 ml of ether extract, add 3 g diethylamine. Over the next 24 hours, the solution should steadily warm to 20C while standing in the dark. After the 24 hours, evaporate in a vacuum and purify the product to convert the isolysergic amides to lysergic acid amides.

Method #2

Step 1 (Requires the use of Yellow light)

Suspend 5.36 g of d-lysergic acid in 125 ml of acetonitrile and cool to about -20 C in a bath of acetone cooled with dry ice. Add a cold solution of 8.82 g of trifluoroacetic anhydride in 75 ml of acetonitrile to the suspension. Let solution stand at -20 C for an hour and a half. During this time the suspended material will dissolve, and the d-lysergic acid is converted to the mixed anhydride of lysergic and trifluoroacetic acids.

Step 2 (Requires the use of Red light)

Add the anhydrides in acetonitrile to a 150 ml solution of acetonitrile containing 7.6 g of diethylamine. In a dark room, let the mixture stand at room temperature for 2 hours. Using a vacuo, the acetonitrile is evaporated leaving a residue of LSD-25 and other impurities. Using a mixture of 150 ml of chloroform and 20 ml ice water, dissolve the LSD residue. The chloroform layer should be removed and the aqueous layer is extracted with several portions of chloroform. Combine the chloroform portions and wash four times with 50 ml of ice-cold water. The chloroform solution should be dried using anhydrous Na2SO4 and evaporated yielding LSD.
After either of these methods have been completed, it is necessary to purify the product to limit the presence of isolysergic acid amides. The following procedure should be carried out to reduce the unpleasant effects of the isolysergic acid amides.

Step 1

Dissolve the obtained product in a 3:1 mixture of benzene and chloroform. Pack the chromatography column with a basic alumina in benzene so that a 1 inch column is six inches long. After draining the solvent to the top of the alumina column, add a portion of the LSD-solvent solution containing 50 ml of solvent and 1g LSD. Run through the column, and track the quickest moving fluorescent band. After it has been collected, use MeOH to wash the remaining material from the column. Evaporate the second portion and set aside. The pure LSD is concentrated using a vacuum causing a syrup to slowly crystallize.

Step 2

Take the portion saved from the prior step and dissolve it in a small amount of alcohol. Add twice the volume of 4N Alcoholic KOH solution. The mixture should sit at room temperature for several hours. Add HCl to neutralize the solution. Add a small amount of NH4OH to make the solution slightly basic, and extract with chloroform. Evaporate and chromatograph as in the previous step.

Since the lysergic acid compounds are unstable to heat, light, and oxygen, the storage container should be tightly closed and stored in the refrigerator.

Usage

LSD comes in many different forms that allow it to be easily ingested. Since it is not smoked, sniffed, or injected, it is incorrectly thought of as much safer than other drugs such as heroin, cocaine, or crack. The most common means of ingestion of the drug is orally. LSD is most often seen on a form of super absorbent paper called blotter paper. The paper is perforated into 1/4 squares, which are often called tabs. The sheets are soaked in a liquid solution of lysergic acid diethylamide, which often varies from chemist to chemist. Due to the inconsistency of absorbency, each tab may contain a different dosage of the drug. Since the nature of the chemicals is so potent, a single tab provides enough drug to induce a high.

The second most common form of LSD is liquid. The chemical is usually diluted in water and may be prepared in many different ways. The liquid may be added to a bottle of eye drops, and dripped directly into the eyes. Users will also saturate sugar cubes with the liquid LSD and consume the sugar. Since the potency depends on the volume of solvent used to dissolve the chemical, this form is very dangerous. A single drop of liquid may be up to 50 times as strong as a tab.
The third most common form of LSD is called a windowpane. A windowpane is formed when the liquid LSD is mixed with gelatin and formed into thin squares. In this form less of the chemical is exposed to sun and air preventing its decomposition.\(^3\)

The following is a table outlining the Oral Dosages of LSD:

<table>
<thead>
<tr>
<th>Oral LSD Dosages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Threshold</td>
</tr>
<tr>
<td>Light</td>
</tr>
<tr>
<td>Common</td>
</tr>
<tr>
<td>Strong</td>
</tr>
<tr>
<td>Heavy</td>
</tr>
<tr>
<td>LD50 (Lethal Dose*)</td>
</tr>
</tbody>
</table>

Erowid

**Chemistry**

Once the user has ingested the drug, it begins through the normal digestive process. First it is absorbed through the gastrointestinal tract and mucous membranes. The kidneys and liver absorb the majority of the drug; however, the small amount sent through the bloodstream to the brain is enough for the user to become high.\(^2\) Once the drug has entered the brain, it begins a process that triggers the mind to hallucinate.

The first step in understanding how hallucinogens work in the brain is understanding how neurotransmitters work. Neurotransmitters are messengers that transfer nerve impulses. The body possesses somewhere between 50-100 neurotransmitters, of which five, acetylcholine, norepinephrine, dopamine, and serotonin, affect psychoactive drugs.\(^7\) Even though much research has been done to understand the workings of hallucinogens in the brain, the process is not understood 100%. It is believed that LSD looks and acts like the neurotransmitter serotonin, so that it easily fits into the serotonin receptors within the brain. Serotonin is chemically known as 5-hydroxytryptamine (5-HT). Within the brain it regulates sleep, memory, learning, body temperature, mood, behavior, and cardiovascular function.\(^4\) Each neurotransmitter has its own receptor that only recognizes the shape of that particular neurotransmitter or a molecule that looks very similar. Recent research has determined that the majority of 5-HT receptors are concentrated in the neocortex region of the cerebral cortex. The neocortex processes sensory informations, and incorporates it with pre-existing associations.\(^4\) Hallucinogens stimulate the receptors in this area, which in turn links the effects of LSD with the functions of the neocortex. Since hallucinogens so closely mimic the structure of neurotransmitters, they are easily received into the receptors within the brain.

The structures of LSD and Serotonin appear below as the following:
Lysergic Acid Dimethylamide

Serotonin (5-hydroxytryptamine)

Obviously LSD is a much more complex molecule than serotonin, but the basic structure and components are very similar. The chemical formula for LSD is C₂₀H₂₅N₃O, which is very similar to the chemical formula for serotonin C₁₀H₁₄N₂O₆. LSD has also been found to have a melting point of 198-200 °C and a molecular of 398.485. Research into the connection between LSD and serotonin continues, in order to explain the astonishing effects hallucinogens have on the human brain.

Effect:

The effect that hallucinogens have on the human brain is complicated and difficult to explain because of how unbelievable it sounds. Physical and psychic effects begin to appear 30 minutes to an hour after the drug has been consumed and may continue for up to 12 hours more. The pupils will dilate, blood pressure and heart rate may increase, and the sensory-perceptual changes start to occur. This may include the intensification of color, the movement of stable objects, or the flashing of shapes. The most amazing effect of LSD is called synesthesia. Although hard to comprehend, the senses begin to cross boundaries. For example, a user can taste color or see sounds. This usually prompts uncontrollable laughter and grinning. These effects may seem harmless and fun, but in many cases the effects may be frightening.

Along with the effects mentioned above, LSD also promotes the feeling of anxiety and paranoia. This leads to what many call a “bad trip.” Just as pleasurable events are intensified in a “good trip,” bad feelings are exaggerated during a “bad trip.” Reports of users jumping off buildings, becoming withdrawn, causing irreversible harm to themselves are all fueled by “bad trips.” Frequent users may also end up permanently fried, meaning that they cannot snap out of their hallucinogenic state. Although LSD does not typically cause death by overdose like many other narcotics, it may cause a state of psychosis in which a person loses touch with reality. During this time knowingly or unknowingly abusers commit suicide. Predicting the effect of an LSD trip is almost impossible. In some cases the trip goes well, and in others it causes permanent damage. After the effects have worn off, users may suffer from permanent personality changes, chronic depression, flashbacks, and confusion.
This makes it difficult to excel and lead prosperous, healthy, and normal life. However, most users are living for the moment, not for the future.

Conclusion:

The youth of today must learn from the past and realize that using LSD is like gambling with their life. Although the majority of hallucinogenic episodes are not harmful, it is not worth risking the life long effects of a bad experience. One bad choice can change a person’s life forever. For this reason any risk cannot be justified. By educating young people about the adverse effects of LSD, the youth of the world will feel confident in turning it down.
References:


   *http://leda.lycaeum.org/*.

Clopidogrel and Antiplatelet Therapy

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April 22, 2005
Abstract

A number of studies and clinical trials have demonstrated the benefit of antiplatelet agents. Aspirin is a relatively weak antiplatelet agent, but it has been used successfully over the years in the treatment and prevention of cerebrovascular and cardiovascular events. Recently, more potent platelet inhibitors, like clopidogrel, have shown promising better patient outcomes. This paper will introduce this relatively new drug, describe its chemical structure, mechanism of action, side effects, indications, stereochemistry, synthesis, metabolism, pharmacokinetics, drug interactions, and the growing uses of clopidogrel.

Introduction

An arterial thrombi is mainly composed of platelets. Antiplatelet agents are used primarily for the treatment and prevention of arterial thrombosis. Arterial thrombi occur at sites of elevated shear stress in blood vessels where there is atherosclerotic vascular injury and disturbed blood flow. This event is irreversible and often leads to complications such as peripheral arterial disease, myocardial infarction, stroke, transient ischemic attack, and unstable angina among others. The key to reducing the incidence of an arterial thrombotic event is to inhibit platelet aggregation. Ticlodipine and clopidogrel are two medications specifically used for this purpose.

Chemical Structure

Ticlodipine is an earlier antiplatelet agent that has a similar chemical structure to clopidogrel. Both are derivatives of thienopyridine. Clopidogrel differs structurally from ticlopidine by the addition of a carboxymethyl side group.

![Chemical structures of ticlodipine (top) and clopidogrel (bottom).]
The drug clopidogrel bisulfate is otherwise known as the generic name, Plavix. The chemical name is: methyl(+)-(S)-α-(2-chloroprene)-6,7-dihydrothieno[3,2-c]pyridine-5(4H)-acetate sulfate.

Mechanism of Action

When vascular endothelial cell damage occurs, natural platelet inactivators and smooth vessel wall relaxers are disrupted. This injury allows collagen exposure to blood, and platelets attach at the site via glycoprotein (GP) Ib/IX receptors connected to von Willebrand factor. The activated platelets release numerous substances including, adenosine 5'-monophosphate (AMP), and adenosine 5'-diphosphate (ADP). The released ADP can bind to a low-affinity type 2 purinergic receptor (P2Y12) or to a high-affinity purinergic receptor (P2Y1). Ticlopidine and clopidogrel selectively inhibits the binding of ADP to the type 2 purinergic platelet receptor (P2Y12), and prevents the activation of the GP IIb/IIIa receptor complex which results in platelet aggregation.
Side Effects

The following table lists side effects of clopidogrel and ticlopidine.²,⁴

<table>
<thead>
<tr>
<th>Gastrointestinal</th>
<th>Dermatologic</th>
<th>Hematologic</th>
<th>Miscellaneous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>Rash</td>
<td>Aplastic anemia</td>
<td>Severe cholestasis</td>
</tr>
<tr>
<td>Nausea</td>
<td>Pruritis</td>
<td>Bleeding</td>
<td>Intracranial hemorrhage</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>Urticaria</td>
<td>Neutropenia**</td>
<td>Hepatitis</td>
</tr>
<tr>
<td>Anorexia</td>
<td>Ecchymoses</td>
<td>Thrombotic</td>
<td>Acute interstitial nephritis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>thrombocytopenic purpura</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Thrombocytopenia**</td>
<td>Acute renal insufficiency</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bone marrow toxicity**</td>
<td></td>
</tr>
</tbody>
</table>

** Less common with clopidogrel.²,⁴

Indications

Ticlopidine was launched in 1979.⁵ Clopidogrel was approved for use in the reduction of thrombotic events by the FDA on November 17, 1997.⁶ Today, clopidogrel has almost completely replaced its predecessor, ticlopidine. It has a wider therapeutic index, a lesser side effect profile, and is more effective at doses used clinically. Indications accepted for use are recent stroke (excluding transient ischemic attacks), recent MI, established peripheral arterial disease, and acute coronary syndrome (ACS). ACS (unstable angina/non-Q-wave MI) includes medical management of patients with percutaneous coronary intervention (with or without stent) or coronary artery bypass graft.⁵,⁶
Stereochemistry

Clopidogrel is an enantiopure carboxylic ester of (S)-configuration. This is a chiral drug that is inactive in vitro. Optical purity is 98.9. A chiral inversion of a drug can occur in the body with no side effects. Ibuprofen is an example of a safe, inactive (R)-enantiomer that undergoes conversion to the therapeutically desired profen (S)-form. The (R)-enantiomer of clopidogrel does not have antithrombotic activity, but it can provoke convulsions at high doses in animals.  

Since it is known that chiral inversions can occur, safety evaluations looked for the possibility of the chiral inversion of clopidogrel in animals. Rats were fed clopidogrel at varying doses for four weeks. After clopidogrel metabolism, the main circulating metabolite is a carboxylic derivative with either (R) or (S)-acid configuration. This metabolite was measured from blood samples and separated with a stereoselective assay. Enzymatic inversions were investigated in rat hepatocyte suspensions. Nonenzymatic chiral inversions were measured by H NMR (Proton Nuclear Magnetic Resonance) and HPLC (High Performance Liquid Chromatography).²

Clopidogrel has a carboxymethyl side group.² It has been shown that a nonenzymatic chiral inversion of the S-acid would be unlikely because "a carboxy group is known to stabilize chiral carbon atoms of the type R''R'RC-H." However, it was found that after administration of pure (S)-acid isomer clopidogrel, 4-8% of it became (R)-acid.² The chiral inversion was found to take place very slowly, and in humans, plasma levels of the (R)-acid was undetectable with an oral dose of clopidogrel up to 150mg.² The following figure is a proposed reaction of chiral inversion in this experiment.

\[ \text{Clopidogrel} \xrightarrow{a} \text{Enantiomer of clopidogrel} \]

\[ \text{(S)-acid} \xrightarrow{a} \text{(R)-acid} \]

Potential reactions of chiral inversions (a) and hydrolysis (b) of clopidogrel investigated in this study."
Synthesis

Clopidogrel is made by Sanofi – Synthelabo. The racemic clopidogrel synthesis starts with commercially available [benzene-U-C]-benzoic acid. This multi-step synthesis gives [benzene-U-C]-(+,-)-clopidogrel with an overall yield of 7\%.\(^5\) It is illustrated in eight steps.

1. SOCl\(_2\)
2. H\(_2\)NC(CH\(_3\))\(_2\)CH\(_2\)OH
3. SOCl\(_2\)

\[ \text{1. } \text{SOCl}_2 \text{, toluene, } -78 \degree C \text{ then C}_2\text{Cl}_6, -40 \degree C \text{ to rt, 60\%} \]

1. Mel, rt
2. NaBH\(_4\), EtOH, rt

\[ \text{1. } \text{Mel, rt} \text{ then C}_2\text{Cl}_6, -40 \degree C \text{ to rt, 60\%} \]

1. 2 N HCl, rt

\[ \text{2 N HCl, rt} \]

HCl, MeOH, rt

quant.

HCl, MeOH, rt

quant.

1. 2 eq. H\(_2\)SO\(_4\), MeOH, reflux
2. H\(_2\)SO\(_4\), Et\(_2\)O, rt

\[ \text{(±)-2} \]
Soon, more efficient ways to make clopidogrel were developed. They also gave a much higher yield. A two-step method starts with 2-chlorobenzaldehyde (1). This is treated with tribromomethane in dioxane with an aqueous solution of potassium hydroxide to give α-bromo-(2-chlorophenyl)acetic acid (2). A methyl ester (3) is formed after refluxing. An SN2 displacement with the nucleophile, thieno[3,2-c]pyridine and (3) produces racemic clopidogrel (4) with an 88% yield.\(^5\)

Another manufacturer, RPG Life Sciences discovered a one pot synthesis of (+,-)-clopidogrel. This proved to be cheaper and it gave a 90% yield.\(^5\)
The stereochemistry portion of this report pointed out that only the enantiomerically pure (+)-(S)-acid of clopidogrel inhibits platelet aggregation. The other isomer has adverse side effects. Therefore, a resolution of racemic clopidogrel was needed to isolate (+)-clopidogrel. The resolving agent shown below is levorotatory camphor-10-sulfonic acid. The resulting salt is recrystallized from acetone to create enantiomerically pure (+)-clopidogrel.  

\[
\text{(±)-2} \quad \xrightarrow{\text{HO} \text{SO}_3 \text{O}} \quad \left[ \begin{array}{c}
\text{[Structure]} \\
\end{array} \right] \quad \xrightarrow{\text{acetone}} \quad \text{[Structure]} \\
\]

\[
\text{recrystallization} \quad \xrightarrow{\text{acetone}} \quad \text{[Structure]} \quad \text{H}_2\text{SO}_4 \\
\]

(+)-2, clopidogrel
Metabolism

Clopidogrel is not active in vitro. It is a prodrug, which needs to be metabolized in the liver to active metabolites. Clopidogrel requires oxidation by hepatic cytochrome P450. Interestingly, this fact was not known until 1999; two years after the drug was FDA approved. The P450 human isoenzymes that have been found to metabolize clopidogrel faster than any other human P450 isoenzyme are CYP3A4 and 3A5. They are predominantly responsible for the activation of clopidogrel in vivo into a short-lived active platelet inhibitor.

The main systemic metabolite of clopidogrel is the carboxylic acid derivative SR 26334, which has no platelet inhibiting effect. Peak plasma levels of the inactive derivative occur one hour after a repeated dose of 75mg of clopidogrel. This demonstrates that this drug is rapidly absorbed and extensively metabolized. The plasma elimination half-life of SR 26334 is 8 hours. The following illustration demonstrates the in vivo metabolism of clopidogrel.
Pharmacokinetics

The recommended daily dose of clopidogrel is 75mg, or a 300mg loading dose followed by the 75mg daily dose in patients with ACS.\textsuperscript{5} Length of administration can vary depending on the clinician and the circumstances of the thrombic event. Dose adjustments are not needed for elderly, renally impaired, gender or with food.\textsuperscript{3} Antiplatelet aggregation of clopidogrel is concentration-dependant.\textsuperscript{4} This is because it takes time to metabolize and activate the drug.\textsuperscript{5} A 75mg dose shows inhibition of platelet activity occurring two hours after drug administration.\textsuperscript{9} Repeated doses of 75mg has significant inhibition in 2-3 days, followed by maximal inhibition at 4-7 days.\textsuperscript{2} The antiplatelet action is irreversible, and it occurs for 7-10 days. This corresponds to the life-span of a platelet. One source reported that achievement of a steady state with 50% inhibition of platelet aggregation occurs six hours after a loading dose of 300mg or after 4-5 doses.\textsuperscript{9} Loading doses up to 600mg can be seen in clinical practice today.\textsuperscript{4}

This evolving trend of loading doses followed by a daily 75mg maintenance dose has been done in response to numerous studies that have shown beneficial outcomes of reduced complications and treatment of atherothrombotic events. It demonstrates the need to get clopidogrel in the system quickly.

Two studies conducted in 1999 looked at the pharmacodynamics of clopidogrel when administered in different amounts to healthy subjects in order to find a recommended loading dose. The loading doses ranged from 75mg to 600mg. In both studies it was found that the doses of 375mg or 400mg achieved the fastest and most effective platelet inhibition. Antiplatelet aggregation reached a plateau at 400mg.\textsuperscript{10,11}

These tests were conducted on healthy volunteers. The patients who receive clopidogrel usually have existing health problems and are already on drugs that can interfere with the activity of clopidogrel.

Drug Interactions

The major catalyst of clopidogrel, CYP3A4 also metabolizes many drugs. It is likely that these drugs will modify the bioavailability of clopidogrel and decrease or increase its effectiveness.\textsuperscript{4} For example, HMG-CoA reductase inhibitors like atorvastatin and simvastatin bind to CYP3A4 and impair the effect of clopidogrel.\textsuperscript{6,12} A recent clinical study challenges this finding by showing that in the treatment of 1651 patients with acute coronary syndrome, there was no significant difference between clopidogrel combined with a CYP3A4-statin and a non-CYP3A4-statin.\textsuperscript{13} Additional studies on HMG-CoA reductase inhibitors (CYP34A-statin) with clopidogrel had comparable amounts of outcomes for or against co-administration of the two drugs. The package insert of Plavix\textsuperscript{®} reports no “evidence of clinically significant adverse reactions” with cholesterol lowering agents.

Other CYP3A4 inhibitors are erythromycin and celecoxib.\textsuperscript{6,12} Conversely, rifamycins are inducers of CYP3A4 and can increase clopidogrel activity.\textsuperscript{6} Clopidogrel may interfere with the metabolism of phenytoin, tamoxifen, tolbutamide, warfarin, torsemide, and fluvasitatin. Caution should be used when using nonsteriodal anti-inflammatory drugs and warfarin.\textsuperscript{3}
Future Uses

The two landmark studies championed by the makers of clopidogrel are CURE\textsuperscript{14} and CAPRIE\textsuperscript{15}, Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators and Clopidogrel versus Aspirin in Patients, and Risk for Ischaemic Events, respectively. Both of these studies were referenced in virtually all clopidogrel research. Briefly, the CURE study showed that in 12,562 patients given clopidogrel, the percentages of patients with in-hospital refractory or severe ischemia, heart failure, and revascularization procedures were significantly reduced.\textsuperscript{14} In 19,185 patients, CAPRIE found that “long-term administration of clopidogrel to patients with atherosclerotic vascular disease is more effective than aspirin in reducing the combined risk of ischaemic stroke, myocardial infarction, or vascular death.”\textsuperscript{15}

Since these two examples show how effective the antiplatelet property of clopidogrel is, it was questioned why it could not be used in patients with mechanical aortic valves. Serious complications occur if these patients are not properly anticoagulated long-term. Warfarin, a fibrin inhibitor, is the anticoagulant used for mechanical valve patients. It does not prevent platelet aggregation. It is thought that mechanical heart valves stimulate platelet activation.\textsuperscript{16} Warfarin requires close, frequent monitoring and testing to maintain therapeutic levels. It is also hard to achieve a steady state in the body because it is easily influenced by many factors, including diet. Clopidogrel does not require this rigorous routine, making it a better choice for patients.

High doses of clopidogrel with aspirin was found to be equivalent to warfarin, with mechanical heart valves in rabbits.\textsuperscript{16} The same authors of this study conducted a pilot study with 200 aortic valve replacement patients. The pilot study was terminated early because a patient on clopidogrel had an aortic valve thrombosis after just two months. It was hypothesized that in comparison to a high flow stented cardiac artery used successfully in the CAPRIE study, the aorta does not have sufficient flow for clopidogrel to be effective.\textsuperscript{16} A second pilot study had success because it only used patients who received a more modern aortic prosthesis and a larger loading dose of clopidogrel.\textsuperscript{17}

Another investigated use for clopidogrel is in patients with congestive heart failure (CHF). The Plavix Use for Treatment Of Congestive Heart Failure (PLUTO-CHF) trial showed that clopidogrel and aspirin had greater antiplatelet effects than aspirin alone. "Patients with CHF with heightened platelet activity represent a potential target population in which addition of clopidogrel may decrease mortality rates by reducing the incidence of thrombotic vascular events.”\textsuperscript{18}

The investigations of clopidogrel in CHF and mechanical aortic valves were small pilot studies. Larger, randomized trials will prove to be more effective to make the use of clopidogrel a standard treatment in these health problems. Clopidogrel will be accepted sooner in CHF versus aortic valve treatment because it is using two antiplatelet agents synergistically. Aspirin and clopidogrel are currently used together for this reason in other diseases. Mechanical aortic heart valve studies are comparing two anticoagulants that work in different ways, antiplatelet (clopidogrel) and antihrombin (warfarin). This will be more difficult to evaluate, and it will take more time to achieve. However, the latter will greatly improve patient satisfaction in the prevention of aortic valve thrombus.
Discussion

It was interesting to discover how this drug evolved since its FDA approval in 1997. In the beginning, exact mechanism of metabolism and activation was not known, but the drug was still approved for use. Today, debate still exists on the intricacies of clopidogrel. I could see discoveries about clopidogrel with each new study that I read. Text books were not a useful tool to me because data was ever-changing. Many laboratory and clinical studies overlapped so much that I had to be careful in choosing the most accurate, up to date, and appropriate information for my paper. This was further complicated by conflicting data. When a laboratory study showed the behavior of the drug, clinical trials would dispel or perhaps disregard it. So, it became clear to me that the package insert of Plavix® merely serves as a guideline for clinicians and consumers.

The chiral inversion study cited in the stereochemistry portion of this paper shows why a racemic mixture of clopidogrel will in all probability not be seen on the market. It is unclear to me how rat metabolism and human metabolism correlate; especially if higher doses were given to humans. According to the study, a 150mg dose was undetected in humans, but today people are taking up to 600mg. Would there be a higher percent of (S)-acid inversion to the harmful (R)-acid?

I contacted sanofi-synthelabo, a French partner of Bristol-Myers Squibb Company which is the distributor of the drug. After a few calls and e-mails, I found no workers in the complex matrix could help me find out the synthesis of clopidogrel. It was not a confidentiality issue; people reported that they just did not know. I was consistently redirected to the Plavix® website, the avenue that I had initially looked to. A pharmacist in the drug information department helped me locate a few studies on the future use of clopidogrel on mechanical valve patients. She told me that no studies have been done on this topic by her employer. It became clear to me that once a drug becomes FDA approved, follow-up, monitoring and public relations is not a primary concern of the distributor and maker of the drug. Rather, future studies will continue to shape and define clopidogrel.

In conclusion, there is a significant population that is affected by atherothrombosis. One study revealed a statistic of 50%.

Whether this is over or underrated, it can be argued that the approved uses for clopidogrel make this drug a powerful and widely used tool.
References

(3) Plavix Package Insert, 2003. Bristol-Meyers Squibb/Sanofi Pharmaceuticals Partnership,