7th Annual Science Symposium
May 15, 2001
Paradise Valley Community College
Foreword

The 7th Annual Science Symposium was held on May 15, 2001. Students enrolled in General Organic Chemistry II, CHM 236, participated in the event.

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

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

I would also like to dedicate this symposium to my friend and colleague, Mr. Steven M. Platte, Physics and Astronomy Faculty. He has served his campus as Faculty President and his Division as Division Chair. His leadership and vision have been essential in the growth of the faculty and the Science/Math Division. He is and will always be regarded as a dedicated faculty member and my dear friend.

William L. “Hank” Mancini, PhD
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Current and Proposed Pharmacological Treatments for Parkinson’s Disease

Amy A. Allen

April 27, 2001
The treatment options for Parkinson's disease patients have been, since the 60's, administration of levodopa with few alterations for the increased adsorption of the drug. The degenerative neurological disease is characterized by a loss of the dopaminergic cells that result in the loss of function associated with the disease. Introduction of drugs that compensate for the dopamine neurotransmitter depletion taken along with the dopamine precursor levodopa show greater understanding and treatment options than current therapy.

Parkinson's disease (PD) is a disabling neurological condition marked by tremor, starting in the extremities, and gross motor dysfunction. The muscles become stiff, resulting in slow movement, postural instability and the characteristic "mask" like appearance due to unexpressive facial tone. Development of mood disorders, memory loss and verbal processing errors follow the general cognitive decline. (1,2,3) Although juvenile and brain trauma induced forms of the disease occur, onset of the disease usually begins after age 40 and affects approximately 1 million people in the United States.

The pathology of the disease results in the degenerative loss of dopaminergic neurons, specifically in the substantia nigra area of the midbrain that is closely associated with the basal ganglia. (4) The basal ganglia are associated with motor control and diseases that affect this area cause movement disturbances. Symptom onset occurs with a greater than 30% reduction in these dopaminergic neurons, due to disease progression independent of aging. (5) Neurons that contain high levels of dopamine are prominent in the mid brain regions of the substantia nigra and ventral tegmentum with many of the axons of these neurons terminating in the corpus striatum where they participate in controlling complex movements. Degeneration of dopaminergic synapses in the corpus striatum occurs in Parkinson's disease.

The decline of dopamine producing neurons in the substantia nigra results in the increased activity of neurons in the subthalamic nucleus, presumably to compensate for the loss. The resulting over activity inhibits the activity of the areas of the brain associated with motor control. The rate of progression is measured as the degree of dopamine production loss and for Parkinson's disease is shown to be a 5% loss per year following the onset of symptoms.

Dopamine is one of the neurotransmitter end products of the catecholamine synthesis of tyrosine, an amino acid. Tyrosine is converted to dopa with the enzyme tyrosine hydroxylase (TH). Levodopa is converted to dopamine with the aromatic L-amino anid decarboxylase enzyme. This reaction requires Pyridoxal Phosphate (PLP), the co-enzyme form of pyridoxine or vitamin B6.
Levodopa (L-dihydroxyphenglalanine) or L-dopa is the immediate precursor to dopamine and its ability to cross the blood brain barrier allows for the administration of oral medication of levodopa to replace the dopamine loss associated with Parkinson's disease. This has been the standard treatment since the 60's with only slight modification.

Most Parkinson's disease patients are on Sinemet (registered trademark of DuPont pharmaceuticals) (fig 1), a combination of levodopa and carbidopa. Carbidopa [(−)-L-alpha-methyl-beta-(3,4-dihydroxybenzene)] inhibits aromatic acid decarboxylation of circulating levodopa, permitting it to cross over into the brain. (8) Lower doses of levodopa are needed in order to affect treatment and adverse side affects of dopamine formed in extra cerebral tissue are lessened. The carbidopa does not cross the blood brain barrier and does not interfere with catecholamine synthesis in the central neurons system. Vitamin B6 is also prevented from increasing the rate of aromatic amino acid decarboxylation by carbidopa.

Carbidopa, an inhibitor of aromatic amino acid decarboxylation, is a white, crystalline compound, slightly soluble in water, with a molecular weight of 244.3. It is designated chemically as (−)-L-alpha-hydrazino-alpha-methyl-beta-(3,4-dihydroxybenzene)propanoic acid monohydrate. Its empirical formula is C10H14N2O4H2O, and its structural formula is:

```
CH3
HO
\[\text{NH}_2\text{NH}_2\]
\[\text{CH}_2\text{CHCOOH} \cdot \text{H}_2\text{O}\]
```

Tablet content is expressed in terms of anhydrous carbidopa which has a molecular weight of 226.3.

Levodopa, an aromatic amino acid, is a white, crystalline compound, slightly soluble in water, with a molecular weight of 197.2. It is designated chemically as (−)-L-alpha-amino-beta-(3,4-dihydroxybenzene)propanoic acid. Its empirical formula is C9H11NO4, and its structural formula is:

```
\[\text{NH}_2\]
\[\text{HO-CH}_2\text{CHCOOH}\]
```

Fig 1
Levodopa relieves many of the motor disturbances of Parkinson’s disease but chronic use causes fluctuations in motor control ("on-off" syndrome) and choreic and dystonic involuntary movements while not significantly altering disease progression. In addition, the problems associated with cognitive decline are unaffected. Levodopa administration does improve overall quality of life in Parkinson’s disease patients and the many proposed treatment options include levodopa usage with modification that may lesson its’ detriment.

The most severe indications of levodopa usage are the proposition that it may accelerate the disease by inducing neurotoxicity in its metabolism. The proposed mechanism of its toxicity has been the production of free radicals resulting in cell death. (9) Hydrogen peroxide formation and other reactive oxygen species resulting from the oxidative metabolism of dopamine causes a cascade of reactions leading to oxidative stress in the substantia nigra. Increased dopamine turnover results in excess peroxide formation [fig. 2 (a)(b)] glutathione (GSH) becomes deficient, therefore diminishing the ability of the brain to clear hydrogen peroxide [fig. 2 (c)] which in turn reacts with ferrous iron promoting the highly reactive cytotoxic hydroxyl radical. Iron levels are found to be increased in the substantia nigra of PD patients. Deficiencies in glutathione are also found in the substantia nigra and are exclusive to PD.

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(a) \( \text{DA} + \text{O}_2 + \text{H}_2\text{O} \rightarrow \text{MAO} \rightarrow 3,4 \text{DHPA} + \text{NH}_3 + \text{H}_2\text{O} \)

(b) \( \text{DA} + \text{O}_2 + \text{H}_2\text{O} \rightarrow \text{SQ}^* + \text{*O}_2^- + \text{H}^+ \)

\( \text{DA} + \text{*O}_2 + 2\text{H}^+ \rightarrow \text{SQ}^* + \text{H}_2\text{O} \)

(c) \( \text{H}_2\text{O}_2 + 2\text{GSH} \rightarrow \text{GSSG} + \)

(d) \( \text{H}_2\text{O}_2 + \text{Fe}^{+2} \rightarrow \text{OH}^* + \text{OH}^- + \text{Fe}^{+3} \)

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Fig 2 Both the enzymatic and the chemical metabolism of dopamine result in the formation of hydrogen peroxide (H2O2) (a & b) that is normally cleared by reduced glutathione (GSH) (c) However, a increase in the concentration of H2O2 leads to the reaction with ferrous iron (Fe+2) that generates the highly reactive and cytotoxic hydroxyl radical (OH*) (d)
The oxidative damage found in the substantia nigra of PD patients is extensive. The action of dopamine as an endogenous toxin accounts for the selective cell loss that occurs in PD. In addition to dopamine cells in the substantia nigra, dopamine neurons in the ventral tegmental area show considerable involvement. Additional factors such as the amount of dopamine produced and its turnover may explain the selective vulnerability of large midbrain neurons with extensive projections. Norepinephrine and Serotonin oxidize less readily than dopamine and produce less toxicity in culture, presumably accounting for the less extensive involvement of neurons releasing these transmitters in PD patients. (10) Levodopa has been shown to destroy cultured dopamine neurons and although postmortem oxidative damage is found in PD brains the wide spread use of levodopa makes it difficult to isolate as the cause.

Although current treatment is more advanced than the simple administration of levodopa, pharmacological advances beyond Sinemet (carbidopa/levodopa) have been proven to be difficult.

Uses of alternative medications, which decrease dopamine turnover, have been shown to have limited success. The direct dopamine agonists work by activating the dopamine receptors. Some of the proposed agonists are Parlodel, Pergolid, Pramipexole, Ropinirole, Cabergoline, Bromocriptine & Lisuride. Advantages to direct dopamine agonists are the direct stimulation of post-synaptic dopamine receptors without the metabolism of precursor molecules. The reduced need for L-dopa can increase its effectiveness later in the treatment.

Usually the treatment of agonists is considered only for early-diagnosed Parkinson's disease patients due to the lessened effectiveness of the drugs. More often it is used in combination therapy with lowered doses of levodopa usage. (11)(12) Many adverse side effects such as nausea/vomiting, postural hypertension, hallucinations and edema may induce patients to discontinue their therapy. The findings of studies determining the effectiveness of monotherapy report that only a few years of therapy without L-dopa can be considered effective.

The choice between the many possible agonists available is often dependent on patient reactions and no single agonist has been found to have a greater effectiveness in every Parkinson's disease patient. Some benefit may be gained by switching when one therapy becomes less effective.

Another promising drug involved in decreasing the turnover of dopamine is the drug Deprenyl. The drug works by inhibiting a dopamine degrading enzyme monoamine oxidase at the synaptic cleft thereby slowing the metabolic break down of dopamine.

The antioxidant effects of dyrenyl as a MAO inhibitor give it neuroprotective properties. The reported inefficiency of the drug toward the primary motor disturbances in PD has caused a three-fold drop out rate over other agonist monotherapy.
The benefit gained through using deprenyl is the absence of motor complications but the results were negated when add on therapy of levodopa began. (13)

The therapeutic difficulties of managing the dopamine combination and/or monotherapy of agonists may prove to be less advantageous because of the limited benefits received and the uncomfortable side effects produced.

The nigrostriatal dopamine depletion also affects the glutamatergic pathways from the subthalamic nucleus to the basal ganglia output nuclei with the overactivation of the N-methyl-D-aspartate (NMDA) glutamatergic receptors. The introduction of NMDA receptor antagonists in the treatment of PD has been promising. Glutamate receptor antagonists such as LY235959 or amantadine reduced the dyskinesias associated with PD treatment with levodopa.

This result shows strong evidence for a link between NMDA receptor stimulation and levodopa induced motor complications. Changes in the distribution and/or coupling function of NMDA receptors may represent adaptive mechanisms associated with levodopa exposure, which may ultimately contribute to the development of motor complications. The possible synergistic interactions of these antagonists with levodopa allow for the reduction of levodopa doses. (14) (15)

Different NMDA antagonists may prove to cause symptoms ranging from sedation to behavioral disturbances that are not associated with levodopa use. CP-101, 606 showed the lowest incidence of side effects. CP-101, 606 is structurally related to ifenprodil and part of a class of compounds that inhibit the NMDA receptor by activity-dependent mechanism involving the potentiation of proton inhibition. The results suggest that the activity dependent mechanism of inhibition may contribute to the lowered complications in this compound. The NMDA antagonists must be used in combination therapy to prove effective. The neuroprotective qualities afforded by NMDA antagonists may give greater life expectancies for PD patients as well as improved symptoms associated with PD.

The development in the progression of understanding the underlying causes and affects of Parkinson’s disease and treatment with levodopa have gone through dramatic changes in recent years. The introduction of carbidopa to inhibit the decarboxylation of peripheral levodopa to dopamine greatly improved the efficiency of levodopa administration as well as lessening the adverse side effects.

Introduction of the therapeutic affects of direct dopamine agonists in the late 70’s added to the understanding of progression of the disease and the consequences of the treatment with levodopa. Agonists are still being studied and the development of greater delivery to more specific receptors that are primarily affected by the levodopa treatment are still on the horizon.
The mechanisms of the MAO-inhibitors in the degeneration of dopaminergic neurons are promising but further progress is needed to develop better abilities at prevention of the initial loss. The PD patient has already gone so far down the path of degenerative neuron loss by the onset of symptoms that improving the further loss may be difficult to accomplish given the severe oxidative stress in the substantia nigra.

The most promising insights involve the connection to the glutamatergic pathways of the levodopa therapy. The reduction of the dosage and the symptoms associated with the standard and most effective therapy, levodopa, may prove to greatly enhance the lives of PD patients.

The introduction of neural transplantation of neurons to replace the loss associated with PD as well as surgical techniques to lesson overactive tissue or stimulate under active tissue remains a viable alternative to pharmacological therapy. But the invasion with surgical instruments is often seen as a last resort to the inevitable decline associated with PD. (16)(17)

There remains hope that further understanding will enable the development of better drugs that counteract the progression and ultimate destruction of the remaining function of PD sufferers.


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Nitroglycerin

By Billy Anderson
April 27, 2001
Abstract:
Nitroglycerin is one of sciences most famous discoveries. Nitroglycerin has an interesting past and standing future. It has and interesting composition, and has been employed as an explosive for many years. Also, Nitroglycerin has a wonderful biological application that has elongated many peoples lives, including Alfred Nobel. Nitroglycerin has been a blessing and also a burden.

History:
The first noted preparation was in 1846 by the Italian chemist Ascanio Sobrero. However, Nitroglycerin became more famous in 1866. Alfred Nobel had success in making nitroglycerin into a stable explosive, almost intently becoming wealthy. Although, his brother was killed in 1864 by an explosion, Nobel established factories 90 factories in 20 countries. The chemical properties makes its implications profound. Such as demolition and a weapon for war. The prospect of its use as a weapon is the reason Alfred Nobel decided to set up the noble peace prize, for anyone who has an invention / discovery that is good for the World. Nitroglycerin itself has a peaceful side as well, since 1864 it has been taken as a drug. However, little literature was available at the time on the exact mechanism.

Properties and Structure:
The Nitro groups are what make Nitroglycerin so interesting. The molecular weight of the compound is 227.087g, has three carbon backbone with 1, 2, and 3 nitro groups.

\[ \text{C}_3\text{H}_4\text{(NO}_3\text{)}_3 \]

Nitroglycerin is a clear yellow substance that has a sweet, burning taste. The chemical is very sensitive to shock. The freezing point occurs at 13°C, interestingly the solid form is more sensitive to shock then the liquid. Contrary to the solid and liquid form, the dissolved form is much more stable. Nitroglycerin is slightly soluble in water, and is soluble in methanol, alcohol, acetone, carbon disulfide, ethyl ether, ethyl acetate, glacial acetic acid, toluene, phenol, chloroform, and in methylene chloride. Nitroglycerin starts to decompose at 50-60°C and will explode at 218°C. The formula for decomposition is as follows:

\[ 2 \text{C}_3\text{H}_4\text{(NO}_3\text{)}_3 \rightarrow 3\text{CO} + 2\text{CO}_2 + 6\text{NO} + \text{H}_2\text{O} + \text{H}_2\text{CO} \]

Nitroglycerin's form can be analyzed using UV absorption bands as one major test. Nitroglycerin has UV absorption around 2000 to 5000 angstrums. This can be attributed to the NO\textsubscript{2} groups. A graph shows the UV absorption ban.
Explosive:

The explosion that is produced from nitroglycerin is amazingly massive when put into retrospect with its original form. The volume of the gases is 1200 times the volume of the reactant during standard conditions. The heat that is generated is 5000°C, an immense exothermic effect. The pressure momentously rises to 20,000 atmospheres. Due to the rise in pressure a wave moves at 7700 meters per second. Nobel’s discovery of the blasting gel led to the discover of Ballistite, used as a propellant. Nitroglycerin produces a lot of power efficiently.

Synthesis:

Nitroglycerin is a simple reaction when monitored and kept under control. Nitroglycerin is made from pure glycerol and 90% nitric acid.\(^7\) The formula is as follows:

$$C_3H_5(OH)_3 + 3HNO_3 \rightarrow H_2SO_4 \quad C_3H_5(NO_3)_3 + 3H_2O$$

The sulfuric acid is a catalyst, acid in / acid out. The proton sulfuric acid will attack the OH group of the glycerol. Meanwhile, the nitric acid will attack the carbon. The water is protonated and the proton from the nitric acid is liberated in a concerted reaction. This action happens to each subsequent hydroxyl group. The acids are kept 20 to 22°C, while glycerol is being added to prevent explosion. The purity of glycerol is important to the stability of the final product. The theoretical yield of nitroglycerin is 2.467 to 1; however, the actual yield is closer to 2.36 to 1 in 90% nitric acid solution. The diagram shows the specific mechanism:
Biological:

As long as it has been used as an explosive it has been used as a vasodialting drug. Vasodilatation is the relaxation of a muscle. Nitroglycerin has been used to treat angina specifically. Angina is a heart affliction which causes pain that can range from dull aches to crushing pains. The attacks can rage from several times a day to once a year. Angina is caused by the influx of calcium into the vascular smooth muscle, causing it to contract. The flow sometimes binds which make it harder for the heart to relax. Nitroglycerin rapidly metabolizes to dinitrates and to mononitrates at about 1 to 4 minutes. The medicine is usually in tablet form under the tongue readily taken into the blood stream. When nitroglycerin enters into the smooth muscle it undergoes biotransformation in the endothalamus to nitric oxide. The nitric oxide then activates the guanylate cyclase catalyzing production of cyclic GMP and initiates relaxation. The extracellular nitric oxide also reduces cysteine. Nitrates promote the production of cyclic AMP which promotes vascular relaxation. The figure below is a visual representation of the process that nitroglycerin undergoes.
Interaction and Side effects:

When taking any drug care must be reserved to know potential side effects or drug interactions. Headache which may be severe and persistent can occur after immediate application of the drug. Occasionally, Vertigo, weakness and palpation will afflict dependent patient, more often to those stuck in immobile up right positions. The same treatment has been reported to cause nausea, vomiting, weakness, diaphoresis, pallor and collapse in clinical doses. Patients reported flushing, drug rash and exfoliate dermatitis. Overdose can result in severe hypotension, tachycardia, heart blockage, palpation, death due to cerebral collapse, coma followed by convulsions, and many previously stated. Alcohol may cause hypotension. People taking antihypertensive have the possibility additive effects of hypotension. Aspirin may decrease the clearance and enhance the hemodynamic effects of sublingual nitroglycerin. Expectant mothers should not take the medicine unless absolutely necessary; however pediatric data has not been collected. Decisions must be made to prevent possible disaster when taking nitroglycerin.

Environmental Concerns:

Nitroglycerin gone un-checked can pollute water and the air. Some process during the production of nitroglycerin produce soda ash, and the wash water can contain glycerin, nitrates and sulfates. Acidic water can be neutralized by passing through lime beds. Some investigated methods include biodegradation, reverse osmosis absorption by
polymeric resins, and oxidation with ozone and permanganate. The decomposition of nitroglycerin into Carbon monoxide would aid in the decomposition of the ozone, H2CO is carcinogen which is highly toxic. However, moderation and attention to detail will limit these hazards.

Conclusion:

With the advancement in biomedical technologies nitroglycerin my be put out to rest. Organisms may be invented by genetic alteration that would facilitate vascular relaxation during cardiac distress. As an explosive it seems highly pollutant, and many other technologies may take its place as a tool for demolition and weapons. Such as, high powered lasers, cold fission and engineered toxins. Nitroglycerin had a good and jolting life.

Anyone must concede that nitroglycerin will still have a place in the future. People will be stuck on the past and will not easily move on to new technologies. Ethic will play a major role in the use of many other drugs production; therefore, not permitting them to take the place of pre-existing drugs. Nitroglycerin my be kept up by stature alone.
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Information About a Chemical Compound Called Flonase:
Fluticasone Propionate

Benjamin M. Bouillon

July 27, 2001
Abstract

Fluticasone Propionate is the active ingredient in the commercially available nasal spray called Flonase. Flonase is a preferred treatment for the management of the nasal symptoms associated with seasonal and perennial allergic and non-allergic rhinitis in adults and pediatrics four years of age and older. The physical properties, preparation, side effects, uses of, and case studies of this compound will be presented and discussed.

Physical Properties

Fluticasone Propionate is a synthetic trifluoronated corticosteroid that is synthesized from a 19-carbon androsterone nucleus rather than a 21-carbon pregnane nucleus. Halogenation at positions 6 and 9 and a double bond at the 1,2 position of the androsterone molecule increases the anti-inflammatory activity of fluticasone propionate. Esterification of the oxygen at position 17 of the androsterone nucleus and addition of a second group, the fluoromethyl carbothioate group at position 17 also enhances the anti-inflammatory effect as well. Fluticasone Propionate has the organic chemical name of S-fluoromethyl 6α,9α-difluoro-11β-hydroxy 16α-methyl 3-oxo-17α-propionyloxyandrosta-1,4-diene-17β-carbothioate, and sells under the trade name Flonase. It has the following structure:1

![Chemical Structure](image)

Fluticasone Propionate is a white to off-white powder with a molecular weight of 500.6 amu. It is insoluble in water, soluble in dimethyl sulfoxide, and slightly soluble in methanol and 95% ethanol.2 Flonase nasal spray is an aqueous suspension of microfine fluticasone propionate for topical administration to the nasal mucosa via a metering, atomizing spray pump.
Synthesis

The basic structure of the class of compounds that have good anti-inflammatory activity are represented in the following figure:

![Chemical Structure](image)

**Fig. 2**

The compound shown in fig. 1 is a pharmaceutical composition containing the formula represented in figure 2 and can be prepared by a variety of different processes. One particular one is the esterification of the androstane compound containing either a free 17β - carbothioic acid group (or functionally equivalent group) or a free 17α - hydroxy group. Then the molecule is halogenated, reduced, deprotected, and reacted at a 9,11 double bond to form a 9α - halo - 11β - hydroxy grouping. The reaction is best carried out in an organic solvent such as benzene, methylene chloride, or an excess of carboxylic acid. The reaction is best run at a temperature of between 20° - 100° C. The preparation of fluticasone propionate is prepared using various starting materials of which could not be found or determined. These starting materials are placed in a solution of methanol (2ml) and kept at room temperature for 3 hours. The mixture is then evaporated to dryness to produce an 11β - alcohol (25mg) and thus the S - fluoromethyl 6α,9α - difluoro - 11β - hydroxy - 16α - methyl - 3 - oxo - 17α - propionyloxyandrost-1,4 - diene - 17β - carbothioate. The foregoing molecule can then be formulated into very useful preparations suitable for topical administration with the aid of a vehicle and specifically inhalation but may also include ointments, lotions, creams, powders, drops (eye or ear), sprays (for nose throat, lung or skin), suppositories, retention enemas, and aerosols for use in inhalers.
Pharmacology

The chemical is intended for administration on a prophylactic basis to humans suffering from allergic and or inflammatory conditions of the nose, throat or lungs such as asthma and rhinitis, including hay fever. The aerosol vehicle is presented in such a way that with each shot, metered dose, or “puff”, roughly 50μg - 100μg of the compound. Administration of the medicine may be several times a day with 1,2 or 3 doses each time.6

Fluticasone Propionate is a highly selective against at the human glucocorticoid receptor with negligible activity at androgen, estrogen, or mineralcorticoid receptors. Following topical application to the nasal mucosa, fluticasone propionate produces anti-inflammatory and vasoconstrictor effects. The exact mechanism or mechanisms action of corticosteroids in allergic rhinitis is not quite clear at this time, but may involve reductions in the following: mediator cells (basophils, eosinophils, helper – inducer [CD4+, T4+] T-cells, mast cells, and neutrophils) in the nasal mucosa, nasal reactivity to allergens, and release of inflammatory mediators and proteolytic enzymes.2

There have also been other theories of mechanisms of action by which corticosteroids may act by to improve symptoms of allergic rhinitis that include the following: Inhibition of post capillary venule dilation and permeability and facilitation of nasomucociliary clearance of nasal secretions. Flonase nasal spray, like other corticosteroids, is a medicine that does not have an immediate effect on allergic symptoms. The maximum benefit of this drug may not be reached for several days and upon discontinued use, symptoms may return in a few days.

Absorption

Because plasma levels after three weeks of intranasal treatment were only detectable when the dosage was well above the recommended dose (50 pg/ml), an indirect route was needed to measure the absolute bioavailability. The most common method was that of oral administration with radio labeling. This method has demonstrated that fluticasone propionate is highly extracted from plasma and absorption is low. Fluticasone propionate is poorly absorbed from the respiratory and GI tracts following nasal inhalation of the drug as an aqueous spray and according to the author of the AHFS Drug Information® book, a major portion of an intranasal dose of corticosteroids is swallowed and undergoes extensive first – pass metabolism in the liver. Current data suggests that the benefits of intranasal Fluticasone propionate can be attributed to the topical effects of the drug on the nasal mucosa.
Excretion

Following intravenous dosing, fluticasone propionate had an elimination half-life of 7.8 hours and less than 5% of a radio labeled oral dose was excreted in the urine, with the remainder excreted in the feces as parent drug and metabolites.5

Clinical Trials

A total of thirteen randomized, double blind, parallel, multi center, vehicle-controlled clinical trials were conducted in the United States of America in adults and pediatrics (aged four years and older) with seasonal or perennial allergic rhinitis.3 The trials included 2633 adults, 440 adolescents, and 500 children. The trials evaluated the total nasal symptom score (TNSS) that included rhinorrhea, nasal obstruction, sneezing, and nasal itching in known allergic patients who were treated for two to twenty four weeks. And according to the product information guide, subjects treated with flonase nasal spray exhibited significantly greater decreases in TNSS than patients receiving a placebo. However, on rare occasion, the development of localized infections of the nose and pharynx with Candida albicans has occurred. It is recommended that if such an infection should occur or develop, it may require treatment with appropriate local therapy and the discontinuance of treatment with flonase.

There were no significant differences between Fluticasone propionate regimens whether administered as a single daily dose of 200mcg (two 50 mcg sprays in each nostril) or as 100 mcg (one 50 mcg spray in each nostril) twice a day. Maximum total daily dose should not exceed two sprays in each nostril (total dose, 200 mcg/day). There has not been any evidence that a higher dose would be beneficial.

Adverse Reactions:

In general, reactions in clinical studies have been primarily associated with irritation of the nasal mucous membranes. However, the following events occurred in clinical practice and have been included either do to their seriousness, frequency of reporting, causal connection to fluticasone propionate, occurrence during clinical trials, or a combination of these factors. Hypersensitivity reactions, alteration or loss of sense of taste and or smell and, rarely, nasal septal separation, nasal ulcer, sore throat, throat irritation and dryness, cough, hoarseness and voice changes. And those associated with the eyes are as follows: dryness and irritation, conjunctivitis, blurred vision, glaucoma, increased intraocular pressure, and cataracts.
The following is a chart that includes the most common adverse reactions:

<table>
<thead>
<tr>
<th></th>
<th>Vehicle Placebo (n = 758) %</th>
<th>FLONASE 100 mcg Once Daily (n = 167) %</th>
<th>FLONASE 200 mcg Once Daily (n = 782) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>14.6</td>
<td>6.6</td>
<td>16.1</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>7.2</td>
<td>6.0</td>
<td>7.8</td>
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<tr>
<td>Epistaxis</td>
<td>5.4</td>
<td>6.0</td>
<td>6.9</td>
</tr>
<tr>
<td>Nasal burning/nasal irritation</td>
<td>2.6</td>
<td>2.4</td>
<td>3.2</td>
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<tr>
<td>Nausea/vomiting</td>
<td>2.0</td>
<td>4.8</td>
<td>2.6</td>
</tr>
<tr>
<td>Asthma symptoms</td>
<td>2.9</td>
<td>7.2</td>
<td>3.3</td>
</tr>
<tr>
<td>Cough</td>
<td>2.8</td>
<td>3.6</td>
<td>3.8</td>
</tr>
</tbody>
</table>

Other effects included suppression of the Hypothalamic – Pituitary – Adrenal (HPA) axis. Evidence of HPA – axis suppression has been observed with oral fluticasone propionate therapy (20 mg daily) in several patients with distal ulcerative colitis or celiac disease. It is suggested that the recommended dose not be exceeded because hypercorticism and suppression of HPA function may occur.

Fluticasone propionate nasal spray has not been evaluated for geriatric patients to date. Also, this nasal spray should only be used in pregnant women if the benefit of the treatment outweighs the possible risk to the fetus.

No evidence of mutagenicity was observed in vitro in prokaryotic and eukaryotic cells when fluticasone propionate was tested in in vitro studies including the Ames microbial (Salmonella typhimurium) mutagen test, Escherichia coli fluctuation test, and Saccharomyces cerevisiae gene conversion test. Furthermore, no evidence of adverse chromosomal effects was observed in an in vivo micronucleus test. And finally, there is limited information pertaining to the acute toxicity of fluticasone propionate.

We live in an age of biotechnology and chemical engineering where pharmaceutical companies are capable of mass producing drugs that help humans to either combat diseases and ailments or simply keep them under control. As one reads through this researched information, it is recommended to keep in mind the uncertainty that is associated with the chemical compounds that are synthetically produced in the laboratory then mass produced for human consumption by pharmaceutical companies. A question that one should ponder is whether one feels the benefits of taking the medicine are far greater than the risks associated with them.
Just a few of the side effects of this particular anti-inflammatory agent called fluticasone propionate are headache, pharyngitis, and possible interference with hypothalamus, pituitary, and adrenal function. Also are the effects to the eyes, ears, and throat.

There is not a claim or prediction to be made here just simply an observation that medicine is being manufactured for the purpose of combating one set of conditions, ailments, or diseases and “possibly” producing another set of problems, ailments, or diseases. The information contained in the foregoing paragraph states that the risk of fetal damage should be weighed to determine if the benefit that the mother might experience would be greater that the possible damage that might be done to the fetus. It is clear at this point in time that medicine cannot be synonymous with panacea.
1 flonase Product Information Insert #410822
2 AHFS Drug Information 2000 pg. 3241
3 Physicians Desk Reference 2000 pg. 1184
4 United States Patent #4,335,121 Phillips et al
5 Flonase.com
6 chemweb.com
THE MYSTERIES OF BOTULISM

By
Gwendolyn Marie Collier

April 27, 2001
Abstract

This report summarizes the disease known as botulism, which is caused by the release of a neurotoxin by the bacteria *Clostridium botulinum*. It gives background material, such as the history of botulism. The structure and toxin types are defined. The harmful effects of the toxin are reviewed. The therapeutic uses of drugs derived from the botulinum toxin are explored. Finally, the future of botulism and botulism drugs is predicted.

Introduction

One of the most recent cases of botulism to be published happened at Aker University Hospital in Oslo, Norway. In February 2000, a 27-year-old heroin addict was checked into the hospital with the complaint of “muscle weakness”. The most obvious difficulty in which he had was he could not hold his head up under his own power. Eventually, doctors diagnosed him as suffering from wound botulism. ¹

Botulism is a type of poisoning caused by neurotoxins released by the *Clostridium botulinum* bacteria. Since botulism was first discovered by studying sausages, the name comes from the Latin word for sausages, *botulus*. ² Botulism is caused by one of the world’s most lethal neurotoxins, but this substance can be purified and transformed into one of the world’s most effective drugs for the treatment of various ailments.

History

The first scientist to publish information about botulism was the German doctor and health officer, Justinus Kerner. In 1817, he described foodborne botulism; however, Kerner believed the toxin was caused by a “fatty acid” instead of a bacteria. ³ He wrote about case studies and made predictions on the future use of his “fatty acid” as a drug to cure hypercontractions, hyperhidrosis, and hypersalivation. During this time Kerner’s contemporaries in Russia discovered “fish poisoning”, later identified as type E botulism, a condition with many of the same symptoms Kerner described. The *C. botulinum* bacteria and its toxins were first mentioned in print by van Ermengen in 1897; he actually discovered what would later be known as type A botulism. Type B botulism was not isolated until 1904. Then in 1943, wound botulism was first described. The public became aware of infant botulism in 1976.

War has played a key role in the expansion of botulism knowledge. Interest in the toxin hit a high point during W.W.II, because for the first time biowarfare became a realistic threat. The US army’s interest in botulism slowed down in 1972, after the signing of the Biological and Toxin Weapons Convention Agreement. ⁴ However, the Department of Defense continued to search for a way to prevent death from botulism. In 1978, Colonel George Lewis and a team of scientists at the US Army Medical Research Institute of Infectious Diseases (USAMRIID) began investigating the possibility of an equine derived botulinum antitoxin. He injected a horse, named First Flight, with a modified non-lethal form of the toxins called toxiods. When First Flight’s immune system adapted to the toxiods, he was injected with gradually increasing amounts of
unmodified toxins. After his immune system was built up with antibodies for the toxins, his blood was taken. The antibody enriched plasma was extracted and stored, while the red blood cells (in a saline solution) were injected back into the horse. Researchers at the University of Minnesota Medical School, noted for its experience in the equine serums, continued to produce antitoxin from First Flight. During the Persian Gulf war, in 1991, antitoxin was stockpiled by U.S. Armed Forces stationed in Saudi Arabia because of potential biological warfare. Fortunately, there was no need to use the antitoxin in the Gulf war, but it did not go to waste. The antitoxin has been used to save the lives of adults and children throughout the world. First Flight died on May 17, 1999 from natural causes, at the age of 31 (in horse years).5

Structure

The *C. botulinum* bacteria is a rod shaped, gram-positive bacteria native to soil. Gram-positive means when the bacteria is stained, it traps more of the violet dye used. This happens because the bacteria has a cell wall made of peptidoglycan, a group of polypeptides made from modified sugars.6 The bacteria is anaerobic, meaning it can not survive in an oxygen enriched environment. The bacteria reproduces by releasing spores, which then grow into more bacteria.

According to Eric A. Johnson, a microbiologist at the University of Wisconsin-Madison’s Food Research Institute, the toxin is expelled when “...the organisms [bacteria] commit “mass suicide” by dissolving their own cell walls...”.7 *C. botulinum* produces a neurotoxin, one of the world’s deadliest poisons by molecular weight. Depending upon the toxin type, it can weigh between 150 to 165 kDa. The toxin starts off as a single-chain polypeptide. Then bacteria proteases nick the polypeptide to form a two-chained, one heavy chain and one light chain, molecule. The two chains are attached with a disulfide bond. The toxin is a zinc-dependent metalloprotease, meaning zinc is an essential component of the poison. In 1998, scientists at the University of Dartmouth in Massachusetts and the University of Nebraska at Omaha, proposed zinc may serve three functions: catalyst, maintenance, and structure. By removing the zinc, researchers discovered the potency of the toxin was destroyed and structural damage to the secondary and tertiary levels was inevitable. In some of the experiments, the damage caused by the removal of the zinc was irreversible. Their results were based on complicated IR readings, UV (near and far) analysis, and mass spectrometer tests.8 The zinc binding site is located in a central region of the light chain.

The third component of the toxin is the amino acid belt. A group of scientists at the University of Wisconsin-Madison with the help of Lawrence Berkley (California) National Laboratory discovered the belt using X-ray crystallography. They found the light chain, which is responsible for opening the cell, loops around the toxic part of the protein; therefore, hiding the poison until it is inside the cell.9

Types

There are seven types of the toxin A, B, C, D, E, F, and G. Type A is most commonly used in therapeutic treatments. Types C and D only infect animals, usually
Prevention

Botulism can be prevented by taking certain precautions. To prevent foodborne botulism, make sure home canned foods are cooked for a long enough time at a high enough temperature. Most professional chefs suggest cooking filled jars for a full 10-15 minutes at a full boil. Caution needs to be taken when cooking potatoes in foil, either serve immediately after cooking or refrigerate immediately. The same standard applies for oils infused with garlic or herbs. Keep such items refrigerated at all times when not in use. Throw away any dented or bulging cans of food; the bulging is a sign the can most likely contains botulinum toxin. To prevent infant botulism, do not feed babies 12 months or younger honey. To avoid wound botulism, have large open wounds treated immediately by a medical professional and avoid injecting street drugs such as black tar heroin.

Statistics

According to the Center for Disease Control, CDC, as of April 5th 2000, there have been 110 cases of botulism reported last year. Approximately 25% (about 28 cases) were foodborne botulism, 72% (about 79 cases) were infant botulism, and the other 3% (about 3 cases) were wound botulism. The amount of food borne and infant cases have remained consistent; while the number of wound cases have increased, especially among heroin addicts in California. Through medical advancements during the last 50 years, like the development of antitoxin, the number of botulism related fatalities have decreased from 50% to 8%. However, this only reflects the cases actually reported to health officials. No one is sure how many cases go unreported or misdiagnosed each year.

Therapeutic Uses

The dreaded stigma of botulism is slowly dissipating, as it is becoming a healing compound instead of a harmful one. The first approved medical use of type A toxin was in 1976 by Alan B. Scott at the Smith Kettlewell Eye Research Institute in San Francisco. It was used to treat people suffering from Strabimus, a condition in which double vision and other problems are caused by crossed eyes. Botulinum toxin can be used to treat dystonias, spasmodic dysphonia, adductor spasmodic dysphonia, which are muscle spasms of the head, throat and face. It can be used to treat speech problems caused by vocal cord trouble and prevent blindness caused by blepharospasm. The toxin is being investigated as a possible treatment for chronic pain, migraines and cerebral palsy. One unique experimental use for botulism is to cure severe sweating problems. It works by paralyzing the nerves which control the sweat glands. This could replace the current treatment of surgically removing the sweat glands under the arm or severing the nerves controlling the sweat glands. 13

Botulism is sold in two forms Botox and Dysport. Botox was first produced in 1979 by Allergan; in 1998, the formula for Botox was modified to be more efficient. Dysport is manufactured by Speywood in Wales. Doctors need to use caution when
administering these drugs, because each vial can have different potencies. It is important to remember Botulism effects are temporary; therefore, Botox and Dysport only alleviate symptoms, so far they are not permanent cures for anything.

The most popular commercial use of Botox is to reverse the signs of aging. The theory is by deadening the nerves that cause facial lines, clients can avoid getting wrinkles. Patients still face serious side effects; for example, the Botox should not be injected near or around sensitive areas like the mouth. Also the dosages have to be carefully calculated.

According to the article “Toxin to the Rescue”, experiments are being done by Lance Simpson, a toxicologist at Jefferson Medical College in Philadelphia, which would create a stronger toxin to destroy overactive nerves completely. To do this, he is replacing the botulism toxin in the amino acid belt with a stronger poison, from South America, called ricin.

Predications

When Dr. Kerner first discovered his “fatty acid”, botulism, in 1817 he knew someday it would have beneficial effects in the field of medicine. He summed up his predictions as “…belongs to the realm of hypothesis and may be confirmed or disposed by observations in the future.” So here are some predictions for the future use of botulism and its drug derivatives:

1) The use of Botox and/or Dysport to alleviate the tremors related with Parkinson’s disease, but not to cure it.
2) The study of botulism will improve understanding of certain biological processes such as endocystosis, and will lead to the discovery of other compounds with amino acid belts.
3) The increased manipulation of botulism into biological warfare.
4) The experimentation of botulism in gene therapy to cure other diseases, through the substitution of genes for toxin in the amino acid belt.
5) The realization some cases of Sudden Infant Death Syndrome (SIDS) may have actually been misdiagnosed cases of infant botulism.

Conclusion

It is amazing one of the world’s deadliest neurotoxins can be altered into drugs which can alleviate the symptoms of incurable diseases. As for the case of the heroin addict who could not hold up his head described in the beginning of this paper, doctors aggressively treated him for wound botulism with antitoxin and he survived.
birds. There are four clinical forms of the disease: foodborne botulism, wound botulism, infant botulism, and botulism of undetermined etiology.

Foodborne botulism, usually caused by type A toxin, is the form of botulism most familiar to people. It results from adults eating foods in which the toxin has already developed. The bacteria develops toxin in foods which are not cooked long enough, at a high enough temperature. Home canning is a leading cause of foodborne botulism. Because the canning process involves some heat and a lack of oxygen, it can create the perfect breeding ground for *C. botulinum* bacteria to reproduce and release their toxins. Fermented foods can also cause intoxication. For example, kim chee, fermented cabbage common in the Vietnamese culture, and fish head soup, an ancestral favorite among some native Americans in the Alaska area. Vacuum sealed bags, due to the lack of oxygen inside the bag, are another potential cause of foodborne botulism. A new danger of foodborne botulism exists in potatoes baked in foil. The cooked potatoes can become lethal if left to sit at room temperature for an extended amount of time. Recently, it has been discovered that peyote, a drug used in native American religious ceremonics, can also lead to foodborne botulism.

The other types of botulism are caused by the actual spores of *C. botulinum* bacteria compared to just the toxin. Wound botulism results from spores settling into open wounds, then growing and releasing toxins, usually caused by types A or B toxin. This has become an increasing problem among heroin addicts who practice skin-popping, a technique in which an addict will inject Black Tar heroin subcutaneously and intramuscularly. There is some debate among researchers on whether the spores injected are from the person’s own skin or if the spores come from the black tar heroin. Studies are showing more support towards the contaminated heroin theory. Infant botulism, usually a result of types A, B, or F toxins, affects babies under the age of 12 months. It is caused by an infant breathing in the spores from dust in the air or by ingesting honey containing the spores. This is why parents, after 1976, were cautioned against feeding their babies honey. There are two schools of thought as to why adults do not acquire the infant form of botulism. The first idea is adult’s immune systems have built up a tolerance to the spores. The other notion is adult intestinal tracts contain a larger amount of a stronger bacteria, which is capable of killing the spores before they have the chance to do any damage. The last clinical type, botulism through undetermined etiology, is still a mystery to researchers. This category has become a sort of catch all for reported incidents not falling neatly into one of the other more documented categories of botulism. Scientists believe it is caused by types A, B, or F and by the digestion of spores.

**Mechanism**

In order for muscles to move, they must first be stimulated by nerve cells. The nerve cell does this by releasing Acetylcholine (Ach), a neurotransmitter, into an area called the neuron synapse in the neuromuscular junction. The Ach binds to special receptors, thus activating the muscle. Botulinum toxin attacks the neuromuscular junction at the motor and autonomic nerve endings, prohibiting the release of Ach.
First, the toxin travels through the circulatory system until it reaches the neuromuscular junction. Then the heavy chain attaches to the presynaptic cleft and makes a hole into the cell. Next the light chain, containing the amino acid belt, pushes into the cell through receptor-mediated endocytosis and releases the poison. Receptor-mediated endocytosis is a process in which something (toxin in this case) attaches to a receptor and then is engulfed by the cell. By not allowing the nerve cell to release Ach into the cleft, the muscle can not be stimulated; thereby, resulting in paralysis. Different botulism toxins vary in the exact position where they attack the nerve. If Acetylcholine is already attached to a receptor, the toxin can not bind at that particular site.

Symptoms and Diagnosis

The symptoms include the following: double or blurred vision, droopy eyelids, slurred speech, difficulty swallowing, dry mouth, and muscle weakness. Signs of botulism usually start to appear between 12 to 36 hours after initial contact with the spores or toxin. Eventually, the botulism will cause paralysis of the extremities. Finally, the paralysis will reach muscles controlling the lungs, thus possibly resulting in death. Infant botulism symptoms include a poor appetite, constipation, weak cry, and deficient muscle tone. Babies suffering from infant botulism have been referred to as “floppy babies”; these infants resemble rag dolls.

These symptoms mirror the symptoms of other neurological disorders; for example, myasthenia gravis, Fishcher Miller variety of Guillain-Barre syndrome, magnesium intoxication, and poliomyelitis. Since botulism is a rare disorder, a lot of doctors are not looking for it when a patient, with these symptoms, is presented to them. This can cause delays in a situation where sometimes time is a commodity.

The best way to diagnose botulism is through toxin assay, or bio assay. A bioassay is a test in which a stool or serum sample from a patient is injected into a mouse. If the mouse develops botulism, then the test is positive and the patient has some form of the disorder. This test is not the most accurate, because it does not tell scientists what specific type of toxin has infected the patient. Now researchers have developed other more humane and accurate diagnostic methods; such as, gel hydrolysis, or enzyme immunoabsorbent assay and electrophysiological investigation.

Treatments

Treatments depend upon which type of botulism has infected someone. If foodborne botulism is suspected, treatment may start with the removal of contaminated food from the patient’s body. Wound botulism may include surgery to remove the infection from the open or healing wounds. Most occurrences, excluding the majority of infant botulism cases, involve giving the patient antitoxin derived from an equine serum. If the person suffers from severe botulism, the treatment may include ventilation. The most effective treatment for botulism is time, for rehabilitation and physical therapy. In some cases, it may take years for a patient to fully recover all muscle strength.
Prevention

Botulism can be prevented by taking certain precautions. To prevent foodborne botulism, make sure home canned foods are cooked for a long enough time at a high enough temperature. Most professional chefs suggest cooking filled jars for a full 10-15 minutes at a full boil. Caution needs to be taken when cooking potatoes in foil, either serve immediately after cooking or refrigerate immediately. The same standard applies for oils infused with garlic or herbs. Keep such items refrigerated at all times when not in use. Throw away any dented or bulging cans of food; the bulging is a sign the can most likely contains botulinum toxin. To prevent infant botulism, do not feed babies 12 months or younger honey. To avoid wound botulism, have large open wounds treated immediately by a medical professional and avoid injecting street drugs such as black tar heroin.

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Phenylpropanolamine Hydrochloride
The Secret Stroke

Jessica Day
CHM 236
Dr. Mancini
Abstract
Many people are wondering what phenylpropanolamine actually is and why scientists just figured out that it is related in hemorrhagic strokes in young women. PPA was used in certain cold and cough medications along with certain diet pills. These were being sold to people without a prescription due to past observations that the product seemed harmless. During time, more and more women were being diagnosed with this rare stroke. A Yale University study proved that PPA was associated to these fatal strokes. The FDA on November 6, 2000 pulled the products from the shelves.

Introduction
The ingestion of Phenylpropanolamine poses a health risk in the form of a heightened chance of hemorrhagic stroke. PPA is a vaso constrictor, which causes a narrowing of the blood vessels so that less blood is able to flow through at a time. Less blood flow through the body heightens pressure in the blood vessels. For certain individuals, this can cause the vessel to rupture and bleeding uncontrollably. In the brain, this would cause a hemorrhagic stroke, which is essentially a “bleeding in the brain(1).”

What exactly is a stroke? A stroke is a lack of blood flow to the brain that causes damage to brain tissue. The cause of this is most likely a blood clot in an artery that has been narrowed by atherosclerosis. The resulting damage to the brain and the effects to the individual are determined by the length of time the brain is without proper blood flow, the affected area of the brain and how prompt the medical treatment.

A cerebral hemorrhage can begin quite suddenly and can evolve for several hours. Symptoms often include headache, nausea and vomiting and altered mental status. When the hemorrhage is a subarachnoid type, warning signs can occur from the leaky blood vessel a few days to a month before the aneurysm fully develops and ruptures. When the aneurysm actually ruptures the stroke victim’s eyes may become fixed in a single direction or lose vision completely. There is a possibility of a general stupor, body rigidity and in some cases, a coma may occur.

High blood pressure contributes to nearly 70% of all strokes. Two numbers are used to denote blood pressure: the systolic pressure is measures as the heart contacts to pump out the blood; the diastolic pressure is measures as the heart relaxes it allow blood refill the heart between beats. High diastolic pressure appears to pose a particular risk.

Background/Historical Information
Phenylpropanolamine has been marketed for many years. During the early 1970’s, the FDA initiated a scientific review of over-the-counter drug products to determine the safety and the effectiveness of products marketed in the United States. That review included phenylpropanolamine(2). In 1976, one expert panel recommended that PPA be generally recognized as safe and effective as a nasal decongestant, and in 1982 another expert panel recommended that PPA be generally recognized as safe effective for weight control. FDA did not finalize a safe and effective status for phenylpropanolamine because of concerns about occasional reports of hemorrhagic stroke associated with using this drug. Because of continued reports of hemorrhagic stroke potential associated with phenylpropanolamine, FDA asked the pharmaceutical industry to conduct a study that evaluated the risk of hemorrhagic stroke from taking PPA. The drug allowed to be
marketed while this study was being preformed because of the previous results by the expert panels.

Phenylpropanolamine is a synthetic sympathomimetic amine structurally similar to pressor amines (epinephrine) and central nervous system stimulants (amphetamine). It is a common ingredient in cough-cold remedies and appetite suppressants. It is one of the most commonly used non-prescription drugs in the United States (3).

![Image of phenylpropanolamine molecule]

PPA is a white or almost crystalline powder with a slight aromatic odor. It is soluble in water and insoluble in ether. Its molecular formula is C_{17}H_{21}ClNO. Its molecular weight is 187.67. It is composed of 57.60% C, 7.52% H, 18.89% Cl, 7.46% N, and 8.53% O. It also has a melting point of 101-101.5 °C (4).

PPA interacts with the sympathetic nervous system, which is involved in the homeostatic regulation of a wide variety of functions. These functions include heart rate, force of cardiac contraction, blood pressure, bronchial airway tone and carbohydrate and fatty acid metabolism. Stimulation of the sympathetic nervous system normally occurs in response to physical activity, psychological stress and generalized allergic reactions. The sympathomimetic amines are basically naturally occurring catecholamines and drugs that mimic their actions.

Most of the actions can be classified into seven broad types:

1. A peripheral excitatory action on certain types of smooth muscle, such as those in blood vessels supplying skin and on gland cells.
2. A peripheral inhibitory action on the wall of the gut or in blood vessels supplying skeletal muscle.
3. A cardiac excitatory action, which increases heart rate.
4. Metabolic Actions
5. Endocrine actions
6. CNS actions, such as appetite or respiratory regulation
7. Presynaptic actions, which result in the release of neurotransmitter norepinephrine.

Most of the reactions that take place are very closely associated to the adrenergic receptors(5).

Case Studies

Case reports have linked exposure to phenylpropanolamine to the occurrence of hemorrhagic stroke. Many of the affected patients have been young women using PPA as
an appetite suppressant. To further examine the association between PPA and hemorrhagic stroke, the research team designed a case-control study involving men and women ages 18 to 49 years that were hospitalized with a subarachnoid hemorrhage or intracerebral hemorrhage. Eligible case subjects had no prior history of stroke and were able to participate in an interview within 30 days of their event.

The final study comprised 702 case subjects and 1376 control subjects. Age matching occurred for 1367 controls and ethnicity matching occurred for 1321 controls. Subjects were classified as exposed to PPA if they reported use of this drug within three days of the stroke event for case subjects, or a corresponding date for control subjects. Scientists watched them carefully(6).

The study reported an association between PPA use and hemorrhagic stroke in women. The increase in risk of hemorrhagic stroke was found mostly in women using PPA for weight control in the 3 days after starting use of the drug and women using the drug as a nasal decongestant product in the first day of use. Although the study showed that the risk of hemorrhagic stroke was found mostly in women, men may also be at risk.

After this discovery the FDA Public Health sent this advisory notice out:

On November 6, 2000, the Food and Drug Administration announced a ban on the sale of phenylpropanolamine in products that are sold over the counter. In addition, the agency requested that all drug companies discontinue marketing products containing PPA. This chemical is found in many over-the-counter and prescription cold and cough medications, nasal decongestants and OTC appetite suppressant and weight-loss products. PPA is one of the most commonly used non-prescription medications in the country, with literally billions of doses consumed each year.

PPA has been linked to a heightened risk of hemorrhagic stroke, a serious health condition marked by bleeding in the brain or into the tissue surrounding the brain. Real concern followed the release of a scientific study from Yale University that found that women between the ages of 18-49 were nearly 16 times more likely to experience a stroke within the first three days of taking appetite suppressants containing PPA than those whom did not take PPA.

The Yale study suggests that of all hemorrhagic stroke victims, those that ingested PPA within the 3 days prior to the stroke were 50% more likely to hemorrhage than the control subjects. This was particularly true of women who ingested appetite suppressants containing PPA or who consumed other drugs containing PPA while taking the appetite suppressants.

Since 1979, there have been nearly 30 published case reports of brain hemorrhaging after the ingestion of PPA. Many of these reports involved the PPA found within diet pills. Victims of this hemorrhaging were often women between the ages of 17 and 45 years. At least five reports involved PPA in cough and cold medications.

The following are some of the most popular OTC products that contain PPA (as listed by the American Pharmaceutical Association) and may pose health risks:

1. Acutrim Diet Gum Appetite Suppressant Plus Dietary Supplements
2. Acutrim Maximum Strength Appetite Control
3. Alka-Seltzer Plus Children's Cold Medicine Effervescent
4. Alka-Seltzer Plus Cold Medicine Original
5. Alka-Seltzer Plus Cold & Cough Medicine Effervescent
6. Alka-Seltzer Plus Cold & Flu Medicine Effervescent
7. Alka-Seltzer Plus Flu and Body Aches
8. Alka-Seltzer Plus Night-Time Cold Medicine Effervescent
9. Aler-Releaf
10. Allerest Maximum Strength 12 Hour Caplets
11. A.R.M. Caplets
12. BC Allergy Sinus Cold Powder
13. BC Sinus Cold Powder
14. Bromelain Elixir
15. Bromonate Elixir
16. Chericol Plus Liquid
17. Children's Allerest Tablets
18. Chlor-Rest Tablets
19. Cloro-Trimeton Allergy Sinus Headache Caplets
20. Cold-Gest Cold Capsules
21. Coldmax
22. All of the Comtrex Products
23. Conex Syrup
24. Congestant D Tablets
25. Contac 12 hour cold and sinus
26. Coricidin D Tablets
27. All Dextran Products
28. Dimaphen
29. Dimetapp Products
30. Geiprin-CCF tablets
31. Genamin Cold syrup
32. Goldline Products
33. Gulacough CF liquid
34. Gulafencex Liquid
35. Gulatuss CF liquid
36. Ipsatol Cough Formula liquid
37. Histosal tablets
38. Kophane Cough
39. Myminic Expectorant Liquid
40. Nalecon Products
41. Orthoxiol Cough Syrup
42. Pediacon EX Pediatric Drops
43. Pedituss DE Drops
44. Pedituss Liquid
45. Permathene Mega 16
46. Phanadex Cough
47. Phedex Cough
48. ProMetic Cold and Allergy
49. ProMetic Cold and Allergy DM
50. Priminicol COUgh
51. Propagest
Conclusion

In conclusion, PPA is still being researched to find out why this fatal stroke hits young women. How does it effect the body biochemically?, What happens in the brain?, are actually questions that scientists are still trying to find an answer to. They have an idea that it interacts with adrenergic receptors but they are still looking at all other possibilities. Currently there is not a single product on the shelves that contains PPA. Like I said earlier, the FDA demanded that the items be pulled from the shelves. The FDA gave a direct quote, “We suggest you stop taking the product immediately and use an alternative use.” Robitussin Cough Syrup did contain PPA, but now is being manufactured without PPA.
Works Cited


The Treatment of Migraine Headaches
with Imitrex (Sumatriptan Succinate)

Allison Dell
April 27, 2001
Abstract

The beginning of this paper is focused on explaining what a migraine headache is and how Imitrex (sumatriptan succinate) came about. The structure, properties, and synthesis will be discussed and followed by an explanation of how sumatriptan succinate works. This paper will also discuss the absorption, distribution, and elimination of the drug. The end of the paper will discuss the common dosage, side effects, and toxicity of the medication. The paper will conclude with a personal prediction.

Definition of Migraine

Migraine headaches are considered a neurovascular disorder. A migraine headache is characterized by painful attacks of severe headache. The pain of migraine headache can last from four to seventy-two hours.

The pain is characterized as moderate to severe, throbbing, and usually located on one side of the head. However, the pain can spread to the other side or cover both sides of the head. Other symptoms of a migraine headache include an upset stomach with nausea and vomiting. Sensitivity to light, sounds, and odors is also present.

Migraines can be classified as with or without an aura. An aura occurs before the headache begins and can last anywhere from five minutes to one hour. An aura is a neurological disturbance that has visual affects such as seeing flashes or experiencing small blind spots. An aura also includes sensory symptoms and can even stretch to include symptoms that affect motor skills.

To be considered a migraine patient a person must have had at least two migraines with aura or at least five migraines without aura. It is estimated that 6% of all men and 18% of all women in the United States suffer from migraine headaches. This is equal to almost 11 million people.

Despite this high number, researchers are still uncertain of the exact mechanism of a migraine headache. Many theories exist, but the current theory involves the trigeminal nerve. The trigeminal nerve is located in the pons region of the brain stem between the midbrain and medulla oblongata. It is believed that unknown triggers in the central nervous system stimulate the trigeminal nerve. The trigeminal nerve has sensory axons which are connected to the cranial blood vessels and the nucleus trigeminalis in the brain stem. The blood vessel receptors combine with secretion of neurotransmitters at the distal axon terminal. This causes inflammation and dilatation to the affected cranial blood vessels. The impulses are sent up
the axon to the brain stem and then to the thalamus and cortex where they are interpreted as pain and a throbbing headache. Basically, blood vessels in the membrane that surround the brain dilate.

Evidence shows that serotonin (5-hydroxytryptamine or 5-HT) is related to migraines. Serotonin levels in platelets in the vascular system increase before a migraine attack and decrease rapidly during the attack. In addition, a major metabolite of serotonin, 5-hydroxyindoleacetic acid, increases in urinary excretion in patients with migraines. This evidence suggests that serotonin is rapidly depleted during migraine attacks.

History of sumatriptan succinate

The search for a new anti-migraine drug was launched in 1972 by a pharmaceutical executive looking for an effective treatment for his daughter. This search led to the discovery of a new class of drugs that bind to serotonin receptors. These new drugs were called the triptans. Sumatriptan succinate under the brand name of Imitrex was the first triptan drug to be approved by the FDA.

Sumatriptan succinate is filed under United States Patent number 4,816,470. The inventors listed on the patent are Michael D Dowle and Ian H. Coates.

GlaxoWellcome released sumatriptan succinate in the United States in 1993 in the form of an injection. It was later released as a tablet and then as a nasal spray. Sumatriptan succinate continues to be a widely used medication.

Structure and Properties

The molecular formula for sumatriptan succinate is C<sub>14</sub>H<sub>21</sub>N<sub>3</sub>O<sub>2</sub>S·C<sub>4</sub>H<sub>6</sub>O<sub>4</sub> and the molecular weight is 413.5. The IUPAC name for this drug is 3-[2-(dimethylamino)ethyl]-N-methyl-indole-5-methanesulfonamide succinate(1:1).

Sumatriptan succinate is a heterocyclic compound. This means that the compound has a ring which contains an element other than carbon. This compound has two rings. A benzene ring is connected to a pyrrole ring. A pyrrole ring is a ring that has a nitrogen replacing one of the carbons. This entire ring system is called an indole system. The structure of sumatriptan succinate appears on the next page.
The structure of sumatriptan succinate is similar to the structure of serotonin. The major difference is the substitution of methane sulfonamide for the alcohol group on the indole ring of serotonin. The structure of serotonin appears below so that the comparison can be seen.\textsuperscript{11}

Sumatriptan succinate is a white to off-white powder that is soluble in both water and saline. The melting point is 165-166\degree C.

The drug is available by prescription only and comes in three forms: an injection, tablet, and nasal spray. The subcutaneous injection is a clear, colorless to pale yellow, sterile, nonpyrogenic solution. Every 0.5ml of the injection is made of 6mg of sumatriptan and 3.5mg of sodium chloride. The injection has a pH of about 4.2 to 5.3. Most people are more comfortable with taking the oral tablet. The tablet comes in three strengths: 25mg, 50mg, and 100mg. There is 35mg of sumatriptan succinate in the 25mg tablets, 70mg of sumatriptan succinate in the 50mg tablets, and 140mg of sumatriptan succinate in the 100mg tablets. The 25 and 50mg tablets are white and film-coated. The 100mg tablet is light pink and film coated. The
drug is also made in the form of a nasal spray, but not much information on it is available.

To ensure the stability, the injection and tablets should be stored away from light and kept at a temperature between 2-30°C.

**Synthesis**

Unfortunately, the exact synthesis of sumatriptan succinate cannot be released because the drug is still under the brand patent. The reactions mentioned in the patent are very general and refer to a wide possibility of products. However, the patent did say that the Fisher-Indole Synthesis is involved in the making of this compound. The general reaction for the Fisher-Indole Synthesis is as follows:

\[
\begin{align*}
\text{R} & \quad \text{ZnCl}_2 \quad \text{R'} \\
\text{(aryl) hydrazone} & \quad \text{ZnCl}_2 \quad \text{R'} \\
\text{indole} & + \text{NH}_3
\end{align*}
\]

The indole is formed by heating an aryl hydrazone of an aldehyde or ketone in the presence of a Lewis acid.

**Mechanism of reaction**

There are many different serotonin receptors located throughout the brain, brainstem, and central nervous system. These serotonin receptors can be classified as one of the seven subtypes (5-HT\(_1\) to 5-HT\(_7\)).\(^{12}\) The 5-HT\(_1\) receptors can be further divided into 5-HT\(_{1A}\), 5-HT\(_{1B}\), 5-HT\(_{1D}\), 5-HT\(_{1E}\), and 5-HT\(_{1F}\).

Sumatriptan binds to the 5-HT\(_{1B}\) and 5-HT\(_{1D}\) receptor subtypes located on trigeminal sensory neurons innervating dural blood vessels. When the drug binds to these receptors it inhibits adenylate cyclase activity and increases intracellular calcium. The binding also affects other intracellular events that cause vasoconstriction.

Sumatriptan has a weak effect on the 5-HT\(_{1A}\), 5-HT\(_{5A}\), and 5-HT\(_{7}\) receptors. The binding to these receptors is responsible for the side
effects. Sumatriptan shows no significant activity at the 5-HT₂, 5-HT₃, or 5-HT₄ receptors.

Absorption:

Sumatriptan is absorbed quickly after administration. When the drug is taken orally, absorption occurs in the small intestine. The bioavailability of the oral tablets is only 15%. The low bioavailability occurs because there is incomplete absorption and metabolism in the gut wall and liver. The onset of pain relief occurs within 10 to 34 minutes and it at a maximum at one to two hours if taken subcutaneously.

When taken subcutaneously the bioavailability is almost 97%. Pain relief usually begins within 10 to 34 minutes after administration and reaches the maximum relief after one to two hours.

Distribution

When sumatriptan is injected subcutaneously it is rapidly distributed into the body tissues. An experiment on rats showed radiolabeled sumatriptan in the liver, small intestines, and kidneys after ten minutes of IV administration.

Sumatriptan does not cross the blood barrier in significant amounts and only small amounts have shown to cross the placenta. Sumatriptan is distributed into milk, but the recovery in breast milk is 0.24% of the 6mg subcutaneous dose. Another study on rats showed sumatriptan and its metabolites bind to the melanin in the eye.

Elimination

The half-life of a 6mg subcutaneous or 50-100mg oral dose of sumatriptan is 1.5-2.6 hours. Most of the sumatriptan is excreted within 10 to 24 hours.

The major role of elimination is through metabolism. Sumatriptan is metabolized in the liver and possibly the GI tract. Studies also show that sumatriptan is metabolized by the A-isoenzyme of monoamine oxidase. It is then eliminated in urine and feces.

The primary metabolite of sumatriptan is the inactive indole acetic acid. This is formed by oxidative N-deamination of the N-dimethyl side chain. Other metabolites of sumatriptan that have been identified include an ester glucuronide of the indole acetic acid derivative and an indole ethyl alcohol derivative.
Sumatriptan is excreted in urine by glomerular filtration and tubular secretion. After a subcutaneous dose of 6mg, about 22% of the dose is excreted in urine as the unchanged drug and 38-55% of the dose is excreted as the indole acetic acid metabolite. About 0.6% of the dose is excreted in the feces as the unchanged drug and 3.3% of the dose as the indole acetic acid metabolite. When a 200mg dose is taken orally, 57-60% of the dose is excreted in urine. Only 3% of the dose remains as unchanged sumatriptan and 46% of the dose is excreted as metabolites. Approximately 37-40% of the dose is excreted in the feces with 9% of the dose excreted as the unchanged drug and 11% excreted as metabolites.

Side effects

Side effects occur in 41% of patients taking sumatriptan in the subcutaneous form and 66% of patients taking the drug orally. The side effects usually start within one hour after administration and go away within ten to thirty minutes if the dose is given subcutaneously and one hour if the dose is given orally.

The most common side effect reported with the subcutaneous injection is a reaction at the injection site. Patients report of minor pain, tingling, and burning at the injection site. The most common side effects reported with the oral tablets are fatigue, nausea or vomiting, dizziness, tingling, and nasal discomfort. However, these are also symptoms that are associated with migraines therefore it is difficult to tell what is caused by the drug and what is caused by the migraine.

Although sumatriptan is distributed poorly into the central nervous system, side effects associated with the central nervous system have been reported. Atypical sensations were the most common side effect (occurring in 42% of patients that receive a subcutaneous dose and up to 8% of patients that receive sumatriptan orally). Tingling, numbness, strange feelings, feelings of heaviness or tightness, sensations of warmth, heat, burning, cold and pressure were also experienced with both the subcutaneous and orally sumatriptan succinate.

The most common side effects relating to the cardiovascular system were palpitation, syncope, and either decreased or increased blood pressure.

Sumatriptan succinate also produces side effects associated with the gastrointestinal tract such as abdominal discomfort. Other frequent side effects include diarrhea and gastric symptoms.
Other frequent side effects include muscle pain, phonophobia, photophobia, difficulty breathing, sweating, and hypersensitivity.

Dosage

Sumatriptan is effective at any time during a migraine, but it is recommended that the dose be taken as close to the onset as possible. The dose of oral sumatriptan can be 25, 50, or 100mg. If the initial dose is ineffective a second dose can be repeated after two hours. It is not recommended to take more than 200mg per day.

The dose of subcutaneous sumatriptan is 6mg. If the headache is not relieved by the first dose, a second dose (oral or subcutaneously) will probably not help. The maximum daily subcutaneous dose is 12mg, with the injections being at least one hour apart.

Toxicity

There is not much information on possible overdoses of the medication. Studies have given patients a single dose of 140 to 300mg orally or 8 to 12mg subcutaneously without experiencing any important adverse effects.

However, studies performed on animals have lead to death. The overdose of this drug is expected to cause seizures, tremor inactivity, reduced respiratory rate, and paralysis.

Conclusion

A combination of research and personal accounts has led me to a conclusion about the future of sumatriptan succinate. My personal experience with this medication led to a temporary enlargement and hardening of my liver. In addition, I work in a pharmacy so I happen to know that many people are taking more than the recommended amount of the drug. Since most of drug is metabolized in the liver, this overuse cannot be good. These reasons lead me to believe that Sumatriptan succinate will produce, in the long run, adverse effects to the liver.
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Sarah Flowers
4/27/01

Medoproyxprogesterone Acetate
(Depo Provera)
Abstract: Medroxyprogesterone acetate is a "progestin" contraceptive. It is used not only for contraceptive benefits but also for several therapeutic uses. Like any synthetic drug there are side effects, however the benefits exceed these effects.

Depo Provera is an injectable contraception that has been used for the last thirty years. The injection is a synthetic analog, called a "progestin," which has many important clinical uses, such as regulation of the menstrual cycle, prevention of endometrial hyperplasia, treatment of abnormal uterine bleeding and contraception. It is used in over ninety countries, by more than 3.5 million women. It was approved in the U.S. by the FDA in 1992, making it an established method of birth control. This birth control method is 99% effective, which makes it one of the most reliable contraceptives available. Below is a table comparing Depo Provera effectiveness with other contraceptives.

![Effectiveness Chart]

Depo Provera contains Medroxyprogesterone acetate, a chemical similar to the hormone progesterone, which is produced by ovaries in the second half of a menstrual cycle. It is a white to off-white, odorless crystalline powder. It is soluble in chloroform, acetone, dioxane, sparingly soluble in alcohol and methanol, slightly soluble in ether, and insoluble in water. The melting point is between 200° C and 210° C. The chemical name for medroxyprogesterone acetate is pregn-4-ene-3,20-dione,17(acetyloxy)-6-methyl. The structural formula is:
The injection must be given every 3 months to avoid pregnancy. When given in the recommended dose of 150 mg, the injection prevents the secretion of gonadotropins, which stops follicular maturation and ovulation and results in endometrial thinning. This is what gives Depo Provera its contraceptive effect. In each ml of the 150 mg/mL injection contains 150 mg of medroxyprogesterone acetate, 28.9 mg of polyethylene glycol 3350, 2.41 mg of polysorbate 80, 8.68 mg of sodium chloride, 1.37 mg of methylparaben, and 0.150 mg of propylparaben. When necessary the pH is adjusted with sodium hydroxide or hydrochloric acid, or both.

Depo Provera has many side effects that need to be considered before using as a contraceptive. The most common side effects are, irregular menstrual bleeding, amenorrhea, weight gain, headache, nervousness, stomach pains or cramps, dizziness, weakness or fatigue, and decreased sex drive. A study in New Zealand was done to determine discontinuation of Depo Provera. It was found the most common reasons were menstrual disturbances, and weight gain\(^4\). Knowledge about side effects leads to better counseling and information. This should help women select a contraceptive that is appropriate to their needs, which should improve continuation rates.

A major concern of Depo Provera is it may be associated with a decrease in the amount of mineral stored in bones. The loss of bone mineral if the greatest in the early use of the contraception. This can increase the risk of osteoporosis. To help prevent osteoporosis from occurring, it is important to eat high calcium foods, do cardiovascular exercise, and avoid caffeine, smoking, and alcohol. Two other risks of Depo Provera are risk of blood clots and stroke. Also, if a contraceptive fails, there is a possibility of ectopic pregnancy. However, these risks are not common and rarely take place. A study done by WHO evaluated the risks of cardiovascular disease associated with injectable progestin-only contraceptives. The contraceptive had no association with increase in overall CVD risk. There was also no increased risk of stroke, acute myocardial infarction, or venous thromboembolism among patients\(^5\).

Depression may also by an adverse effect of Depo Provera. Two published studies were done by Westhoff and colleagues, which
determined a relationship between Provera users and depression. Neither study found an association between the two. The article “Depressive Symptoms in Users and Non-users of Depot Medroxyprogesterone Acetate” is based on a study that did find a correlation between the depressive symptoms and Depo Provera users. Discontinuers of Depo Provera had higher risks of depressive symptoms than non-users. Also, users who continuously used the contraception were 40% more likely to have depressive symptoms, and women who discontinued were 60% more likely to report depressive symptoms compared to non-users. An explanation for the association could be that the drug has a pharmacological effect that causes an increase in depression among Depo Provera users. Several more studies would need to be done to make a direct correlation between depression and Provera use.

There are many benefits for using Depo Provera. It does not contain estrogen, which is found in many oral contraceptives. It also is a long lasting form of contraceptive, it can’t be expelled from the body, it offers convenience and privacy, it is reversible, and nursing mothers can use it.

Some other unique noncontraceptive benefits of Depo Provera are prevention of endometrial cancer, iron deficiency anemia, pelvic inflammatory disease, ectopic pregnancy, and hysterectomy in women with uterine leiomyomas. A case study done by WHO in 1991 found an 80% reduction of endometrial cancer, in women who used the contraception for 1 year before diagnosis. It also has been successfully used in treatment of a variety of gynecologic, menopausal, and oncologic conditions. Clinical experience suggests that it reduces premenstrual syndrome symptoms. Since Depo Provera may cause amenorrhea, it may be appropriate choice of contraceptive for women with monorrhagia, dysmenorrhea, and iron deficiency anemia. Progestins such as medroxyprogesterone acetate have been used in the management of endometriosis for decades, and a clinical study confirmed its effectiveness in treating pain related to the disease. Depo Provera has many uses and may be appropriate for a diverse group of women.

A study performed at the Department of Obstetrics and Gynecology, Universidade Estadual de Campinas showed that injection of Provera between the 8th and 13th days of the menstrual cycle did not inhibit ovulation in 30% of the patients. This was in agreement with earlier studies on the capacity of Provera to suppress ovulation when injected after day 7 of the menstrual cycle. The suppression of ovulation was related to the stage of follicle development at the time of the injection. Ovulation did not occur when given on days 8 and 9 of the cycle. The study concluded that a back up contraceptive should be used when the contraceptive is given after the 7th day of the cycle.
Medroxyprogesterone is a member of the steroid family. Steroids and their derivatives are of great importance in biology, medicine, and chemistry. The steroid group includes all sex hormones, adrenal cortical hormones, bile acids, and sterols of vertebrates. Synthetic steroids have therapeutic value, such as anti-inflammatory agents, anabolic agents, and contraceptives.

All steroids are related to a characteristic molecular structure composed of 17 carbon atoms bonded to 28 hydrogen atoms. The parent structure is called a gonane and is often referred to as the steroid nucleus.

It may be modified in several different ways by removal, replacement, or addition of a few atoms at a time. The steroid nucleus is a three-dimensional structure, and atoms or groups are attached to it by spatially directed bonds. Many stereoisomers of the nucleus are possible; the saturated nuclear structures of most classes of natural steroids are alike, except for at the junction of the first two rings. Androstane is common to many natural and synthetic steroids, and exists in two forms called cis and trans.

In the cis isomer, bonds to the methyl group and to the hydrogen atom, both face upward, in the trans isomer the methyl groups face up and the hydrogen face down.

Synthesis of steroids is a precise technical challenge. In most syntheses of steroids, a monocyclic starting material such as quinone provides one ring upon which the other rings of the nucleus are built on to.
Condensation reactions with smaller molecules give the desired stereochemistry for successive ring fusion. Each new ring closure also provides functional groups that can be used in building the next ring.

Chromatography is an important technique in steroid chemistry. The behavior of a steroid in selected chromatographic systems identifies it with a high degree of probability. Data for the behavior of steroids in paper chromatography, thin-layer chromatography, liquid and gas-liquid chromatography show that individual features of molecular structure determine the chromatographic properties of steroids in a predictable manner.

Medroxyprogesterone acetate is a steroid contraception with several different uses. Millions of women choose Depot Provera because of its convenience and effectiveness. However there is discontinuation due to the side effects, such as irregular menstrual bleeding and weight gain. In the future if a steroid derivative can be synthesized with less side effects and the convenience of Provera there is a possibility it will be the number 1 choice of women.
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CAPSAICIN

BESIDES BURNING YOUR MOUTH, IS IT BURNING FAT?

By:
Valerie D. Gallardo
April 27, 2001
Abstract

There are many types of dietary supplements in the market today. This report looks at the specific uses and claims for capsaicin to be used as an ingredient. Several types of studies have been examined to discover if there was any actual scientific proof to the allegations that were made in favor of capsaicin as a diet aid.
Today scientists, doctors and nutritionists are looking back to Mother Nature for answers to health related issues. Many ancient remedies are being chosen over prescription drugs to help treat human ailments. Now alongside pharmaceutical drugs, there are vitamins and herbal supplements which claim to solve the same types of concerns. The proportionment of the human body has long been a top concern of the general public. Diets, surgery, workouts, cosmetic surgery (liposuction), herbal body wraps and fitness centers with their different arrays of devices are just some of the many solutions to the public demand for the perfect form. Today, more and more studies have come forth calling the population obese. Due to this, plus medical and aesthetic reasons the general public wants to be healthy and with this in mind, diet aids have been created.

One of the natural-pathic options is the herbal supplement CAPSAICIN. "Capsaicin is the major pungent ingredients of hot peppers which are derived from the berries of the plant genus Capsicum. Owing to the diverse and peculiar biological effects of these fruits in humans, hot peppers have been used since antiquity as food additives and preservatives, as ingredients for social rituals and practices and as herbal medicines for maladies ranging from itch and pain to constipation." There are twenty wild and five domesticated species of the Capsicum genus. The following table demonstrates the genotypes and the range of distribution of the capsaicin and its derivatives. These Capsicum families contain the well known peppers of -listed in order potency- bell & sweet peppers, New Mexican Chili peppers, Espanola, Ancho & Pasilla, Cascabel (cherry) peppers, jalapenos and mirasol, Serrano, de Arbol, Cayenne and Tobasco, chilepin, Scotchbonnet and Thai and the hottest - Habaneros. The above listed peppers are also listed inversely by amount of capsaicin present. Habaneros have the greatest percentage of capsaicin.

Table 1: The capsaicinoid profiles for representative genotypes and the range of the relative distribution of the nonomordihydrocapsaicin (3-ND), normordihydrocapsaicin (2-ND), nordihydrocapsaicin (NDH), capsaicin (CAP), dihydrocapsaicin (DH), isomer of dihydrocapsaicin (ISO), and homodihydrocapsaicin (HD) for each species in percent.

<table>
<thead>
<tr>
<th>Capsicum species</th>
<th>Genotype</th>
<th>3-ND</th>
<th>2-ND</th>
<th>ND</th>
<th>CAP</th>
<th>DH</th>
<th>ISO</th>
<th>HD</th>
</tr>
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<tbody>
<tr>
<td>baccatum</td>
<td>0.00</td>
<td>0.00</td>
<td>6.88</td>
<td>60.46</td>
<td>30.80</td>
<td>0.02</td>
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<tr>
<td>chinense</td>
<td>0.00</td>
<td>0.00</td>
<td>6.88</td>
<td>60.46</td>
<td>30.80</td>
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<td>annuum</td>
<td>0.00</td>
<td>0.00</td>
<td>6.88</td>
<td>60.46</td>
<td>30.80</td>
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<tr>
<td>frutescens</td>
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<td>0.00</td>
<td>6.88</td>
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<td>30.80</td>
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<tr>
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<tr>
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<td>6.88</td>
<td>60.46</td>
<td>30.80</td>
<td>0.02</td>
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</table>

Capsaicin is only slightly soluble water, but it is very soluble in fats, oils and alcohols. This is due to chemical make up of capsaicin, which is not very polar. The formal chemical name of is N-vanillyl-β-methyl-6-(E)-noneamide. Some derivatives which are also found in the Capsicum genus are Dihydrocapsaicin - Dihydrocapsaicin lacks the double bond between the sixth and seventh carbon groups, Nordihydrocapsaicin - Nordihydrocapsaicin has one less carbon group on it's chain and also lacks the double bond, Homcapsaicin -
Homocapsaicin has the double bond between the sixth and seventh carbons, but it also has an extra alkyl group, and finally Homodihydrocapsaicin - Homodihydrocapsaicin is similar to Homocapsaicin in that it has the tenth alkyl group but it also lacks the alkene. The actual structures are as follows.

Due to properties and chemical make-up many claims are made concerning the prowess of the powers attributed to capsaicin. Online, there are many web sites concerning homeopathy, natural vitamins and herbal supplement sites which sell capsaicin, in chili, capsule or pure liquid forms. These sites have wonderful claims as well as testimonials from pleased consumers. One site claims "Cayenne alone or in mixtures can be used as a remedy for problems like: Angina, Arthritis, Asthma, Clogged arteries, Bruises and Sprains, Colds and Flu, Coughs, Diabetes, Headaches, Neuralgia, Body Pain, Pleurisy, Sinusitis, Sore throat, Toothaches, Ulcers, Menstrual Cramps, High Cholesterol, Fatigue (capsaicin will give tired blood a boost of energy), Obesity (researchers in England discovered Cayenne can burn calories virtually as fast as exercise)." An online health article which was linked to the sales sites, also made claims for capsaicin and went so far as to advise "Cayenne fights fatigues because the increased circulation will lower the blood pressure and increase the distribution of oxygen. Cayenne lowers cholesterol by thinning the blood. It also lowers the amount of bile acids in the intestines. As a result, the body can secrete more cholesterol. Cayenne increases the metabolism by increasing the intestinal temperture. Cayenne stimulates the vital organs of the body, thereby promoting the cardiovascular efficiency, while lowering the blood pressure." With these types of claims, it's no wonder that the same "non-profit" article ended with "Keep cayenne on the dinner table, and sprinkle it on all your food. Even small amounts are beneficial!" With this type of propaganda it is easily understood why capsaicin is being promoted as a dietary aid.
However, there are many types of dietary aids on the market. Each has its own claim. Some claim to be the miracle drug with which you'll never have to exercise again or diet - why watch fat and count calories? Some will kill the hunger cravings and give you supplements so the body's nutrition won't suffer - hey who needs food? Some claim to trap the fat and other claim to help it. There are pills for extra energy and some that will kill the fat while you sleep. There are pills for the gym, which will make an exercise session more productive while doing less. Each is the miracle, which will solve the obesity dilemma. Yet, few have similar ingredients in the market. Depending on the specific claim the pills are to be accomplished: weight loss - no exercise, weight loss and toning up, and increasing muscle through exercise: there are a wide array to choose from regardless of any category. Over thirty different brands and types of over-the-counter diet aids were examined. See the attached appendix for additional information.

The most popular type of category is the miracle slimmers. These miracles in a bottle offer the best type of weight loss - no effort. Among those examined were Exercise in a Bottle and Fat Trapper, which are sold together as the miracle pair. They promise to create muscle, burn fat and show amazing weight loss results. All this occurs suddenly while requiring little to no effort from the dieter. Other well known pills in this category were Fat Binder, Fat Burners and the Original Celebrity Diet. The Original Celebrity Diet promises to show the immediate results in just two days. Appetite suppressors were also examined. Some of the more popular or well known were Diet Slim, Slim Fast, Dexatrim, Dexatrim Naturals, Metabolife and it's knock off Metaboless. The Dr. Atkin's Diet was also included in this category due to the fact that there is a line of supplements, food, energy bars, drinks and books sold for this diet. Surprisingly, not one of the above mentioned miracle-workers contain capsaicin, quite possibly because none of them require any sort of physical exertion.

But, don't be discouraged, there are more realistic aids and supplements out there. These require a decent diet and regular exercise. They are an aid to achieve the goal of a slim muscular body. They make no claims to do it automatically. Through the exercise and a proper diet the metabolism is increased as well as more energy is created. Diet Fuel, Herbal Metabolic Supreme, Thermogenics Plus, and Phen-Free are all diet counterparts which are used in conjunction with exercise. All of the above contain capsaicin and have the instructions to consume at least a half hour before working out and/or exercising. Phen-Free by BAS contained the largest listed amount of capsaicin. It contained 30 mg per tablet. Since local GNC and Hi-Health stores were perused for their supplies, the representatives working at each location had the same information concerning why capsaicin was present in so many of the diet drugs. The general answer was that capsaicin was used because it helps to increase the body's metabolism due to an intestinal rise of temperature. This results in the burning of more fat to create muscle.

Even for body builders, who have fit bodies and healthy diets, there are supplements. They help to build more muscle and sculpt bodies faster. In this field there is an even larger array to choose from. Some of the most popular were HMB, Chroma Plus Slim, Creatine Powder, L-Carnitine, Thermacore, High Energy, Max Ripper Plus Benefits System and a Krebs Cycle Chelates. All these supplies target specific jobs and each had special ingredients to accomplish them. Yet, none contained capsaicin on their lists. As stated earlier, there is a large market for work out supplies. So, there were many other aids which did contain capsaicin. Among those were: 50+ Energy Blend, Uptime, Energy Fuel,
Ripped Fuel, Thermogenic Diet Energizer, Metabolift, and Metabolic Accelerated Formula. All of which are designed to enhance the workout's potency and the energy levels. The directions on the bottle also state to take approximately on half hour before the workout for maximum potential.

The raves for capsaicin, which were listed via the internet and well as the claims from the manufacturers of the aids are not regulated by the Food and Drug Administration since capsaicin is technically a herbal supplement. However, many different types of experiments have been preformed to test and possibly promote the claims. Each study was done to test different factors in both humans and animals. The main factors taken into consideration were body type, diet types, amount of food and capsaicin consumption, subject history and gender. Some experiments consisted of human subjects while others occurred on animals ranging from dogs to hamsters and rats. The results from these studies were as followed.

A test which featured a yellow curry sauce additive was created to test the effectiveness of capsaicin on lean and obese women of similar heights and ages. "There was no significant difference was found in physical characteristics or clinical features between the lean and obese groups except for body weight and body fat content." Another main part of this experiment was the effect on the Sympathetic Nervous System (SNS) and energy metabolism. The SNS is part of system which modulates the energy metabolism. It was found that the capsaicin affected the SNS activity predominately in the leaner women, while the obese subjects remained unchanged. The results demonstrated that "obese women possess much reduced sympathetic responsiveness to capsaicin containing spicy food as well as a lower capacity to enhance energy metabolism after food ingestion... Thus these findings including our data confirm that capsaicin has a strong sympa-ho-thermogenic effect on non-obese individuals." These types of results were only favorable in the leaner women, but had no effect/or adverse effects on the obese women.

The types of diets for the subjects were also main factors in the studies. Many of the diets were varied between High and Low Protein, High and Low Fat (HF/LF) and High and Low Carbohydrate (HC/LC) systems for both human and animal subjects. A study on the intake of red pepper and energy intake had specific sets of diets which consisted of "HF diet of: 15% Protein, 45% Fat, and 40% carbohydrate... and a HC diet of: 15% Protein, 25% Fat and 60% Carbohydrate." In another study the time the capsaicin was consumed was studied. The Red pepper was added to the breakfast of both diets and the results displayed that regardless of the diet, HC or HF, capsaicin induced a positive response. A study done on rats produced results that determined that the food intake on a LP diet mixed with capsaicin had a significant increase than the diet of HP fed rats. It was important to note that "an increase in the fat content of the diet has been shown to be associated with increases in daily energy intake and body fatness in human subjects. In rodents, HF diets have been shown to produce obesity independently of total energy intake."

Be the subject, human or animal, the effect of capsaicin mixed with different types of diets had a startling effect on the post-consumption eating patterns. The palatability of the meal in one experiment was determined that "the addition of red pepper to a LF meal might be an alternative way to increase perceived oiliness of a diet without increasing fat intake." This result was due to the observations that many of the subjects found the meals to be high in perceived oiliness. Another study concerning the relationship between salt...
intake and capsaicin had results that the salt intake level was reduced due to the addition of capsaicin in the diet of rats. "These results suggest that capsaicin may also reduce taste preference for salt and may stimulate the taste buds physiologically." Along with taste preference the actual amount of food consumed as well as the type of food consumed after a ingesting capsaicin has been studied. "The addition of red pepper to breakfast significantly decreased the protein intake and fat intake at lunch time." The amount of food eaten as a snack before the meal was also diminished. A second part of this experiment consisted of an appetizer laced with capsaicin served before lunch to measure the actual lunch consumed. The appetizer decreased the carbohydrate and energy intake significantly. The results of these factors in experiments are helpful in the determining of the relationship between capsaicin and energy.

Metabolic change is a large portion of how and why capsaicin affects the internal body. An important system in the body is the SNS. The SNS and the adrenal medulla combine to form the sympathoadrenal system which is an important regulators of energy. This activity is widely believed to be culprit of obesity. An increase of the SNS can lower food intake behavior. Another factor is the adipose tissue. Adipose tissue has two principle functions. The first is to store excess energy as fat and the second is to release fatty acids on demand. Brown adipose tissue is of major importance in the regulation of body tempetures and energy balance. Even the energy metabolism is controlled by the catecholamine secretion from the adrenal medulla though sympathetic activation via the central nervous system. These important factors are affected directly by capsaicin.

Capsaicin increases the thermogenic sympathetic nerve activities. Capsaicin stimulates primary afferent neurons which are transferred to the spinal cord adrenal sympathetic efferent nerve activities then enhanced through the excitation of the central nervous system. The cardiac SNS activity could precisely reflect autonomic events that affect energy metabolism elsewhere in the body. In lean women, the thermogenic component of SNS activity significantly increased immediately after the capsaicin diet. The underlying physiological mechanism of SNS were directly affected by the Capsaicin diet through thermogenesis which increases the internal body tempeture. Capsaicin also excites the adrenal nerves. "There is a potent direct effect of capsaicin of the adrenal epinephrine secretion and a minor indirect effect on secretion through the activation of the SNS." Capsaicin supplementation also tended to reduce the epidymal adipose tissue weight and significantly reduce perirenal adipose tissue weight. There is a significant correlation between perirenal adipose tissue weight and the dosage of capsaicin." This experiment also found that the stimulation of lipid metabolism by capsaicin is also caused by fat mobilization from adipose tissue. Capsaicin has a thermogenic action in brown adipose tissue which causes the ingested energy to be dissipated in the tissue. This suggests that capsaicin may cause the use of stored energy in the adipose tissue. Thus forcing the body to consume more energy or to release stored energy by breaking down fat cells.

As the internal tempeture rises and the body begins breaking down fat cells the body's metabolism rises. "Since the observation that brown adipose tissue may be a major site for diet induced thermogenesis several compounds have been shown to stimulate thermogenesis." It is established that the metabolism and adiposity are directly affected by capsaicin. "Serum free fatty acids and glycerols concentrations in the capsaicin diet were not significantly different from the control groups, however, the prepondrial value of free fatty acid was significantly different higher." An important experiment found that
the overall average increase in the metabolic rate in all the subjects ingesting capsaicin. The overall increase difference from the on the control diet was 25%. The preprandial value of free fatty acids is directly related to the response of the liver to the addition of capsaicin. This reaction stems from Acetyl-Co-A carboxylase, the controlling enzyme for fatty acid synthesis.

Due to the internal responses to capsaicin, body fat has been directly attributed to the influence of capsaicin. "Abdominal fat was decreased which results from the exposure to capsaicin." In rodents, a weight difference was found for the final body weight as well as the weight of the soleus muscle. The capsaicin diet subjects were found to weigh less. The actual effect of capsaicin was largely dependent on the dietary protein levels of the respective diets. Another contributing factor was the pre-existing body fat. The addition of capsaicin to a diet made little positive change in lowering the fat build up of pre-obese subjects. "Red pepper seems to have a beneficial effect on body weight (body fat) control by increasing energy expenditure via a stimulation of the sympathoadrenal system and also by decreasing the energy intake. These effects occur in addition to what may be induced by exercise training."3

Capsaicin helps to increase the energy level also. This occurs regardless of whether the subjects are at rest or during an exercise session. This factor is called the "Energy Expenditure (EE) and is determined from the Oxygen (O2) consumption and Respiratory Quotient (RQ) calculated as the ratio of Carbon Dioxide (CO2) produced to O2 consumed by using the formula: \[ EE (\text{kcal/min}^\text{-1}) = \frac{4.686 + ([\text{RQ}-0.707] \times 0.293) 	imes 0.361 \times V\text{O}_2}{V\text{O}_2} \] where 4.686 kcal l\text{-1} is the energy value of 1 liter of O2 at a non protein RQ of 0.707; 0.707 is also the RQ when only fat is oxidized; 0.293 is the difference between RQ for carbohydrate and fat oxidation; 0.361 is the difference in the energy value of a liter of O2 between an RQ of 1 and that of 0.707; and V\text{O}_2 (L\text{-min}^\text{-1}) is the rate that O2 is consumed at STPD conditions."5 In the experiment concerning lean and obese women it was determined that the O2 consumption began to increase almost immediately and the EE in lean women was also enhanced after 30 minutes of eating. A study done on long distance runners also showed very significant results concerning energy use. "The oxygen consumption was increased in just 30 minutes. The initial rise of the RQ was significantly higher in those who had the capsaicin meal. The RQ was maintained during 60 minutes of exercise. These results suggest that hot red pepper ingestion promotes carbohydrate oxidation by enhancing plasma epinephrine concentration without increasing energy expenditure."14 Even at rest the athletes had a 13% raise in the O2 consumption and the EE was by 25%. This occurs by increasing the temperture. During exercise, the results had an even larger spread. Consumption of capsaicin before exercise mainly increases carbohydrate oxidation for exercise energy fuel. In a separate experiment which consisted of eight males at rest, it was found that "an increase of in the EE after the meal containing the red pepper and during the period following changes in the substrate oxidation were observed with out affecting EE."15 So, even without any physical activity capsaicin increases the overall amount of energy provided in the body. Three charts from the last experiment have been included to display the listed information."14
Capsaicin induced reactions in the body can help to maintain an already healthy body. However, for excessive weight loss another form of assistance is necessary. Pre-obese or inactive dieters will not receive substantial assistance in weight loss from chili peppers. In agreement with the claims that capsaicin can help many to lose weight, capsaicin has not been shown to have beneficial or any type of results on already large or obese people. As a weight loss aid, capsaicin had shown some benefits for appetite inhibition, as well as the lowering of salt intake. But, there are other supplements that can be taken for the same results. As for energy levels and metabolic changes, capsaicin has shown some dynamic results. Yet, the experiments were done on already healthy people. Physically fit people can use the extra kick that capsaicin gives to step their workouts out up a bit, but I would suggest that capsaicin be used specifically in an exercise regimen.

After reading all the studies and experiments done on capsaicin and outside factors I can understand why so many workout aids include capsaicin to their lists of ingredients. It helps to raise energy levels and increase the metabolism rate. However, I feel that some of the internet sites made incomplete claims regarding weight loss and the ability of capsaicin to help solve these problems. I believe that further research is necessary. The long-term effects of capsaicin use as a dietary aid in the body has not been fully studied, but I believe that continuously super charging the body will eventually breakdown the system and later could build up a resistance level that would require more capsaicin to effectively stimulate the body. All of the subjects in the previous studies, were given small amounts of capsaicin. So, a study would need to be established to find the results of the high amounts of capsaicin in the body over longer periods of time. I believe that one of the results would be a detrimental effect to the metabolic system by causing it to become dependent on capsaicin.
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Appendix 1: Various types of over-the-counter diet aids
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A Mental Illness Disruption Disrupted: The Impact of Olanzapine on Schizophrenia

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ABSTRACT
In the venture to cure and treat mental illness many antipsychotics have been made. Olanzapine (Zyprexa) is very different from typical antipsychotics and is one of the newest agents developed for and leading treatment of schizophrenia. Many particulars must be implicated when formulating a treatment for schizophrenia, and the effectiveness of this drug illustrates the parameters of neurotransmitter affinity and compounding have been followed by proving itself noteworthy, since its FDA approval in October 1996. The exploration of the disastrous disease schizophrenia and the factors of success of olanzapine will be exploited and explained further.

INTRODUCTION

Background & Implications of Antipsychotics
For hundreds of years, humans in many different societies have used psychotropic drugs or substances that act on the central nervous system (CNS). These drugs affect peoples’ mood, thinking, and behavior. There are three main classifications for psychotropic drugs. They are depressants (alcohol, opium, Valium), stimulants (caffeine, cocaine, Ritalin) and hallucinogens (LSD). These drugs main functions are to tranquilize, sedate, awaken, stimulate, or impair perception. In the last half-century the compounding and making of chemicals to treat human disorders, mental complication, and emotional and behavioral problems, has been increasing exponentially. These drugs that have been invented are called “psychiatric drugs”. Today, about 85 psychiatric drugs are on the U.S. market, and over 70 other substances are in various phases of development as future psychiatric drugs. These drugs are revolutionary medications that are used for indications which range from calming anxiety, to relieving depression, to controlling mania. Antipsychotic drugs, in particular, are used to control symptoms of psychosis or ones loss of contact with reality, which is common in schizophrenics. Antipsychotics also help with bipolar disorder and brief reactive psychosis. Antipsychotics are commonly effective in calming the majority of positive symptoms, which are agitation or delusion and psychomotor agitation or emotional outburst. However, the effectiveness of the negative symptoms, social withdraw, are most often worsened by antipsychotics. The majority of patients who receive antipsychotics find them to result in a zombie affect or chemical straightjacket. Antipsychotics affect the body as a whole, in every aspect, from organs to cell. The most detrimental outcome of antipsychotics are abnormal movements which are known as extrapyramidal symptoms (EPS). These EPS can effect 40%-90% of patients and can range from parkinsonism (rigid muscles, loss of facial expression, unsteady gait, drooling); akathisia (inner distress, rocking, pacing, agitation); dystonia (sudden, bizarre muscle spasms); dyskinesia (rhythmic movements of face, mouth and tongue, sometimes extremities). These EPS may initiate in early (acute) or late (tardive) stages of treatment with antipsychotics.

History of Antipsychotics
Antipsychotic drugs were introduced in 1953. The development of antipsychotic drugs, during the beginning of the century, focused on calming the patient. The first antipsychotic medication chlorpromazine was initially developed to be given before anesthetic to calm patients who were weary of surgery. It was then used for the treatment of schizophrenics and found to be quite successful in diminishing the positive symptoms of the illness schizophrenia. By 1955, the psychiatric inpatients in the country decreased from 500,000 to 145,000. This was caused by the pharmacological revolution in mental health drugs. The mid 1960s were influenced to use the compound by large, blind, multicenter experiments that demonstrated the effectiveness of the
drug. Over the next 20 years, new antipsychotic medications were developed and used for treatment. Clozapine, one of the new medications on the forefront of schizophrenic treatment, was tested in the 1970s but not used in the U.S. until the 1980s. With the use of clozapine, it was understood that movement disorder side effects and the antipsychotic properties through dopamine blockade were definitely linked. Soon investigations of newer and more improved medications were initiated in efforts to capitalize on the beneficial properties of clozapine while ridding the side effects. The basis for investigation was to find a compound, like clozapine, which had the same effects on neurotransmitter receptors, blockade ratio of the receptors, and effected areas of the brain. This investigation was done by examining the clozapine molecule to find a drug that maximizes the positive effects while ceasing the negative side effects. The idea of the effort was to design a compound with serotonin blockade at strengths substantially greater than dopamine blockade. In the past decade new and improved drugs have come to light. The new medications, clozapine, risperidone, olanzapine, and quetiapine are the majority of antipsychotic prescriptions. These antipsychotic drugs are implemented to control the array of symptoms associated with schizophrenia, and they offer a new hope for improved treatment of schizophrenia. These new drugs seem to show lower rates of early onset EPS and are becoming more popular and acceptable in antipsychotic prescriptions.

**Background of Olanzapine**
The compound found after ample investigation and small manipulation of the clozapine molecule was an effective and safe drug called olanzapine. Olanzapine has many of the receptor-blocking characteristics of clozapine, being a receptor-blocking agent with affinity for serotonin, dopamine, muscarinic, and other receptors. Olanzapine was shown to be statistically superior in terms of having more patients respond to the drug, as far as reduction of psychotic symptoms, and indicated less movement disorder side effects than other antipsychotics. This drug qualifies as an atypical or new antipsychotic used in the U.S. with slightly over one-quarter of antipsychotic medication prescriptions being written for the drug.

Olanzapine is a highly accepted antipsychotic medication. Overall side effects are minimal in doses of 10-20 mg. Patients may notice sedation in the early stages of medication and weight gain (5-6 lbs.) in the first couple of weeks of use, with greater weight gain after longer use. As far as the more severe and detrimental side effects, EPS, dystonia, and parkinsonian, are uncommon with this medication at regular doses not exceeding 30 mg/day. Early use clinical studies indicate that tardive dyskinesia is 20% less apparent than that of traditional antipsychotics and overall the medication is relatively safe and effective in comparison to other antipsychotics.

**SCHIZOPHRENIA**

**Definition & Terms**
Schizophrenia is a chronic disabling brain disease which is one of the most debilitating of all of the mental disorders, that severely impairs a person’s ability to function normally. The impairment of this illness involves the disruption of one's capability to accurately interpret the world around him or her. It makes all experiences, whether real or unreal, to seem real and genuine. This mental illness causes withdraw from activities and people in the world around them, which leaves them in a world of their delusion and fantasies. This disorder seriously effects thinking, judgment, and the brain's ability to reason logically, as well as organize and
communicate thoughts. Schizophrenia is a disease that impairs and makes one incapable of having normal emotional responses to others, as well as, behaving normally in social situations. People with this horrific mental disease have obscure, convoluted, and perplexing difficulty in remembering, talking, and reacting properly. All of these attributes of the disease overwhelmingly diminish one's quality of life.

**Causes & Acquisition**

It appears likely that inherited multiple genetic components are the core cause of schizophrenia. The components create a disposition for the disease and could be considered to be a “tendency for schizophrenia.” Since the illness is genetic, family members with schizophrenia are more likely to get the disease. The disorder is known to “run” through the family. The disease is not directly passed on like eye or hair color because it would be developed in all cases with same heredity, like identical twins. Other conditions and factors must be present to initiate or spark the disease. Scientists believe the environment and stimulant drugs can trigger schizophrenia, if the genetic trait is existent. Some environmental stresses, like improper nutrition, viral infections, or pregnancy complications, in the mother’s second trimester of pregnancy can start or influence the development of this illness. Researchers believe that a complex combination of gene and environmental factors essentially cause the disease.

The inherited genetic component derived from adoption and twin studies show the percent chance of acquiring the disease.\(^4\)

- General population 1%
- Brother or sister has schizophrenia 8%
- One parent has schizophrenia 14%
- Fraternal twin has schizophrenia 39%
- Both parents have schizophrenia 39%
- Identical twin has schizophrenia 47%

**Brain Effect**

Specific genes are involved in the development of schizophrenia and evidence leads to the 6, 13 and 22 chromosomes. Structural and chemical abnormalities, in the brain of a schizophrenic, are the result of the chromosomal imperfections. The mistakes in the chromosomes cause chemical defects, as well as developmental disorders resulting in inappropriate connections during fetal development. The connection errors lay dormant until puberty, and when the brain cell reorganization and chemical changes occur normally, in this stage of maturation, faulty connections and neurotransmitter imbalance occur. The sole cause of this chronic disabling illness is the imbalance and abnormal amounts of chemicals in the brain. These chemicals are called neurotransmitters. Neurotransmitters control the communication between nerve cells and basically impact the thought processes and emotions of a person.\(^5\)

**Symptoms**

People with schizophrenia, are left with a high degree of disability, often from the suffering of severe, long lasting, and terrifying symptoms.\(^6\) Initially the signs of schizophrenia often appear as confusing or even shocking changes in behavior. The symptoms or signs can develop slowly or suddenly and may be confused or mistaken with other mental conditions. The symptoms of schizophrenia usually fall into two large categories: positive and negative symptoms. Positive
symptoms include paranoia, auditory hallucinations and visual hallucinations, and bizarre behavior. Negative symptoms include ether lack of initiative and inability to relate to others that often result in a person's withdrawing from society. The categorization and description of the positive symptoms include:

- **Disordered thinking** - thoughts that “jump”, or come and go rapidly, between completely unrelated topics or may be “blocked” causing the inability to concentrate pay attention or think straight.

- **Distorted perceptions of reality** - strikingly different perceptions of reality different from the reality seen and shared by others.

- **Delusions** - false personal beliefs or fixed ideas that have no basis in reality and are not subject to reason or contradictory evidence and are not explained by usual concepts.

- **Hallucinations and Illusions** - hearing seeing or feeling things that are not there and cause disturbances in perception without connection to an appropriate source.

The distorted perceptions of reality and disordered thinking make schizophrenics behave shockingly different. Sometimes leaving them very distant, detached, or preoccupied. They may even sit as rigid as a stone, not moving or speaking a word for hours. On the other hand they may appear to be occupied, wide-awake, vigilant and even alert. People with this disease also show difficulty organizing and collecting their thoughts along with planning ideas. In addition to not having a clear mind and they also experience memory deficits. They are also unable to sort out what is relevant and what is not relevant to a situation.

Delusions effect schizophrenics by making them suffer. These bizarre ideas and beliefs make them paranoid or irrational. Often the majority of schizophrenics believe they are being persecuted, cheated, harassed, poisoned, or conspired against. The delusions may make them feel like someone close to them is the focus of the persecution or that someone is trying to control or broadcast aloud their thoughts and feelings. Some delusions may be as eccentric as people on television are directing certain and special messages to them, or magnetic waves may be controlling their behavior.

Hallucinations and illusions effect schizophrenics by inflicting them with ludicrous images or voices that may tell them what to do or how to act. The voices most commonly comment on their behavior, carry on conversations, or tell them to kill themselves, while the illusions are truly misinterpretations and faulty mental image processing of actual stimulus.

The negative symptoms of schizophrenia are:

- **Emotional expression** - a severe reduction in emotional expressiveness

- **Avolition** - lacking of energy, spontaneity, initiative

- **Anhedonia** - lacking of pleasure or interest in activities that were once enjoyable

- **Attention deficit** - difficulty in concentrating.

The negative symptoms have an overall snowballing and compounding effect that accent each other. A person with schizophrenia will have a severe reduction in emotional expressiveness and lacks awareness of other people’s feelings. The signs of normal vocal, facial, and physical expression diminish to monotone, blank, dead gestures that make the person seem very apathetic. Schizophrenics show decreased motivation in life, which is essentially a lack of interest and
quite different from being to depressed to be interested. Also the portrayal of no enjoyment in life, personal neglect, perceived laziness, and attention deficit are the effects of the negative symptoms.

Schizophrenics live in a world distorted by hallucinations and delusions; individuals with schizophrenia may feel frightened, anxious, and confused. The symptoms they experience leave schizophrenics fearful and withdrawn. Their behavior and speech are so disorganized they may be incomprehensible, insensible, confusing and frightening to others. This will make them be left alone, isolated, and feel uncomfortable.

**Diagnosis**
Diagnosing schizophrenia is based on a clinical interview assessing the symptomatological profile and a careful psychiatric history assessing the course and development of the illness. These procedures allow for the clinician to eliminate other possible psychiatric and medical illnesses. A physical examination and laboratory testing are required to rule out disorders that might mimic the symptoms of schizophrenia, because commonly abused drugs may cause symptoms resembling schizophrenia. Some other more specific test, such as MRI, PET, and SPET scanning techniques can be observed especially at the first onset of the illness. At times it is difficult to tell one mental disorder from another. Certain symptoms like depressed mood and mania can be shared among many disorders. Essentially the combination of physical examination, laboratory tests, and clinical history are the only efficient ways a physician can confirm the diagnosis of the disease.

**Brief Facts**
Schizophrenia may affect up to 1 percent of the population worldwide, including more than 2.7 million Americans. It occurs equally in men and women. There is no cure for the illness. Only one in five affected recover completely. 5 of every 10 people with schizophrenia commits suicide. Schizophrenia costs the nation $32.5 billion annually. The most common treatment medications are clozapine (Clozaril), risperidone (Risperdal), quetiapine (Seroquel), and olanzapine (Zyprexa).

**OLANZAPINE (ZYPREXA)**
**Classification and Structure**
Zyprexa (olanzapine) is an antipsychotic agent that belongs to the thienobenzodiazepine class. Olanzapine is a yellow crystalline solid, which is practically insoluble in water. The chemical designation is:
2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine.
The molecular formula is C_{17}H_{20}N_{4}S, which corresponds to the molecular weight 312.44. The chemical structure is:
**Pharmacodynamic Properties**

Olanzapine is a selective monoaminergic antagonist displaying high receptor affinity binding in vitro at serotonin 5-HT₂A/C (Ki = 4 and 11 nM, respectively), dopamine D₁,4 (Ki = 11-31 nM), muscarinic M₁,5 (Ki = 1.9-25 nM) adrenergic alpha₁ (Ki = 19 nM) and histamine H₁ (Ki = 7 nM) receptors.¹⁰ Olanzapine binds weakly to GABAₐ, BZD, and beta adrenergic receptors (Ki > 10 μM). It binds potently to both the 5-HT₂A as well as the D₂ receptors, but more potently to the 5-HT₂A receptor by a factor of approximately 3:1.¹¹ In a single dose (10 mg) PET study in healthy subjects, olanzapine produced higher 5-HT₂A than dopamine D₂ receptor occupancy. The percent of D₂ occupancy was less than the threshold value predictive of extrapyramidal events.

**Pharmacokinetic Properties**

There are many conditions which contribute to the effect and response of olanzapine. A variety of factors have been proposed. Variable such as age, race, gender, age of onset, severity of illness, number of psychotic episodes, prior drug treatment or drug use, comorbidity and hormonal state, drug dose and absorption, metabolism, biological distribution, globulin/protein binding, excretion and rate of titration.¹² These factors all contribute to different drug response. Receptor site kinetics and sensitivity of the later receptor linked responses also determine the drug effectiveness.

Olanzapine is well absorbed after oral administration reaching peak plasma concentrations within 5 to 8 hours. The absorption is not affected by food. Plasma concentrations of orally administered olanzapine were linear and dose proportional in trials studying doses from 1 to 15 mg. The maximum plasma concentrations (Cmax) of olanzapine after single oral doses of 5,10 and 15 mg averaged 7, 14, and 21 ng/mL, respectively (20 ng/mL = 0.064 μM). In young healthy volunteers, after once-a-day repeated dosing, steady state Cmax was approximately twice that achieved after a single dose (eg 23 ng/mL versus 12 ng/mL for a 10-mg dose). In the elderly, the steady state plasma concentration was approximately 3-fold higher than that achieved after a single dose (e.g. 16 ng/mL versus 5 ng/mL for a 5-mg dose). In both young and elderly, steady-state concentrations of olanzapine were obtained after seven days of once daily dosing.

Over time and dosage range pharmacokinetic parameters within an individual are very consistent. However, plasma concentrations, half-life and clearance of olanzapine may vary between individuals on the basis of smoking status gender and age. Data pooled from, single dose pharmacokinetic studies showed the half-life of olanzapine to range from 21 to 54 hours (5th to 95th percentile), and the apparent plasma clearance to range from 12 to 47 L/hr (5th to 95th percentile).
1. Mean plasma concentrations of OLZ and radioactivity after a single oral dose of [14C]OLZ to six normal subjects.\textsuperscript{13}

The plasma protein binding of olanzapine was about 93% over the concentration range of about 7 to about 1000 ng/mL. Olanzapine is bound predominantly to albumin and alpha1-acid glycoprotein. Olanzapine is metabolized in the liver by conjugative and oxidative pathways. A mass balance study showed that approximately 57% of radiolabeled olanzapine appeared in urine, principally as metabolites. The major circulating metabolite is the 10-N-glucuronide, which is pharmacologically inactive and does not pass the blood brain barrier. Cytochromes P450-CYP1A2 and P450-CYP2D6 contribute to the formation of the N-desmethyl and 2-hydroxymethyl metabolites, respectively.

**MECHANISMS**

**General Principles**

Interaction of the antipsychotic drugs with dopamine receptors of the D2, D3, or D4 is thought to be important for their mechanisms of action.\textsuperscript{14} Consideration of carefully defined affinities of the drugs for these three receptors suggests that occupancy of the D4 is not mandatory for achieving antipsychotic effects, but actions at D2 or D3 receptors may be important. A major difference between typical and atypical antipsychotic drugs is in the production of extrapyramidal side effects by the typical drugs. Production of extrapyramidal side effects by typical drugs seems to be due to the use of the drugs at doses where striatal D2 receptor occupancy exceeds \( \sim 80\% \). Use of these drugs at doses that do not produce this level of receptor blockade enables them to be used therapeutically without producing these side effects. The antipsychotic drugs have been shown to act as inverse agonists at D2 and D3 dopamine receptors, and this property may be important for the antipsychotic effects of the drugs.

Dopamine regulates many normal body functions, including movement, emotions, behavior, and appetite. Some researchers think that the positive symptoms of schizophrenia - delusions, hallucinations, and confusion - may be caused by too much dopamine the brain or very sensitive dopamine receptors.

Currently most and all effective antipsychotic medications seem to block dopamine 2 receptors from taking up the information carried by dopamine. Blockade of the D2 receptor appears to be
a necessary and sufficient condition for antipsychotic response. Blockade of another brain receptor, the serotonin 2 receptor, explains some of the action of antipsychotic drugs and works only on the part of the brain that causes the psychotic symptoms but not on the part that controls normal muscle movement may also explain. Antipsychotics also do alterations of other brain chemicals and receptors such as GABA, glutamate and neurotensin.

**Affinity & Antagonism**
The mechanism of action of olanzapine, as with other drugs having efficacy in schizophrenia, is unknown. However, it has been proposed that this drug's efficacy in schizophrenia is mediated through a combination of dopamine and serotonin 2 (5HT2) antagonism. Antagonism at receptors other than dopamine and 5HT2 with similar receptor affinities may explain some of the other therapeutic and side effects of olanzapine. Olanzapine’s antagonism of muscarinic M1-5 receptors may explain its anticholinergic effects. Olanzapine’s antagonism of histamine H1 receptors may explain the somnolence observed with this drug. Olanzapine’s antagonism of adrenergic alpha 1 receptors may explain the orthostatic hypotension observed with this drug.

Olanzapine (0.3-20 mg/kg, p.o.) antagonizes 5HT2- induced head twitches in mice at doses much lower than those required to block the climbing response, confirming that in vivo, the compound is a more potent 5HT2 antagonist than dopamine antagonist. Olanzapine (2.5-10 mg/kg, p.o.) also antagonized oxotremorine-induced tremor in mice. In a conditioned avoidance paradigm in rats, olanzapine inhibits the avoidance response with an ED50 of 4.7 mg/kg p.o; however, unlike other antipsychotic agents, catalepsy is only observed at much higher doses (ED50 39.4 mg/kg, p.o.). These data would suggest that the compound would be less likely to produce undesirable extrapyramidal symptoms. On the basis of these results, it would therefore be predicted that olanzapine will have an atypical profile and will be less likely to induce undesirable extrapyramidal symptoms than currently available drugs.

**Reason For Effectiveness of Drug**
Olanzapine (Eli Lilly and Co.) is similar to clozapine. It is effective against both positive and negative symptoms and causes very little EPS. Because, like clozapine, olanzapine blocks many more receptors in the brain than just dopamine and serotonin receptors, olanzapine can cause some sedation and anticholinergic effects.

Special attention is paid to the role of predominant 5HT2 receptor blockade over D2 blockade. Whereas D2 receptor blockade seems to be essential for the treatment of positive symptoms of schizophrenia, it also underlies the induction of extrapyramidal side effects (EPS). Predominant 5HT2 receptor blockade may reduce the EPS liability and can improve negative symptoms of schizophrenia. It is suggested that olanzapine relieves depression in schizophrenic patients because, unlike traditional antipsychotic drug, it does not act mainly on dopamine D2 nerve receptors. Instead, it affects other dopamine neurons and receptors for serotonin, acetylcholine, and glutamate. It may have fewer side effects than traditional drugs because it does not inhibit dopamine activity in the corpus striatum, a brain region that controls body movement.
METABOLISM AND ELIMINATION
Following a single oral dose of ^14C labeled olanzapine, 7% of the dose of olanzapine was recovered in the urine as unchanged drug, indicating that olanzapine is highly metabolized. Approximately 57% and 30% of the dose was recovered in the urine and feces, respectively. In the plasma, olanzapine accounted for only 12% of the AUC for total radioactivity, indicating significant exposure to metabolites. After multiple dosing, the major circulating metabolites were the 10-N-glucuronide, present at steady state at 44% of the concentration of olanzapine, and 4'-N-desmethyl olanzapine, present at steady state at 31% of the concentration of olanzapine. Both metabolites lack pharmacological activity at the concentrations observed. Direct glucuronidation and cytochrome P450 (CYP) mediated oxidation are the primary metabolic pathways for olanzapine. In vitro studies suggest that CYPs 1A2 and 2D6, and the flavin-containing monoxygenase systems are involved in olanzapine oxidation. CYP2D6 mediated oxidation appears to be a minor metabolic pathway in vivo, because the clearance of olanzapine is not reduced in subjects who are deficient in this enzyme.

1. Recovery of radioactivity in urine and feces. Samples were collected for 21 days after a single dose of [^14C]OLZ.
2. Metabolic pathways of OLZ in humans. Compound in brackets has not been identified. Gluc, glucuronic acid; bold arrow, a major pathway.

CLINICAL DATA & STUDIES
The efficacy of olanzapine in the treatment of schizophrenia was established in 2 short-term (6week) controlled trials of inpatients that met DSM III-R criteria for schizophrenia. A single haloperidol arm was included as a comparative treatment in one of the two trials, but this trial did not compare these two drugs on the full range of clinically relevant doses for both.
Several instruments were used for assessing psychiatric signs and symptoms in these studies, among them the Brief Psychiatric Rating Scale (BPRS), a multi-item inventory of general psychopathology traditionally used to evaluate the effects of drug treatment in schizophrenia. The BPRS psychosis cluster (conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content) is considered a particularly useful subset for assessing actively psychotic schizophrenic patients. A second traditional assessment, the Clinical Global Impression (CGI), reflects the impression of a skilled observer, fully familiar with the manifestations of schizophrenia, about the overall clinical state of the patient. In addition, two more recently developed but less well evaluated scales were employed; these included the 30-item Positive and Negative Symptoms Scale (PANSS), in which is embedded the 18 items of the BPRS, and the Scale for Assessing Negative Symptoms (SANS). The trial summaries below focus on the following outcomes: PANSS total and/or BPRS total; BPRS psychosis cluster; PANSS negative subscale or SANS; and CGI Severity. The results of the trials follow:

(1) In a 6-week, placebo-controlled trial (n=149) involving two fixed olanzapine doses of 1 and 10 mg/day (once daily schedule), olanzapine, at 10 mg/day (but not at 1 mg/day), was superior to placebo on the PANSS total score (also on the extracted BPRS total), on the BPRS psychosis cluster, on the PANSS Negative subscale, and on CGI Severity.

(2) In a 6-week, placebo-controlled trial (n=253) involving 3 fixed dose ranges of olanzapine (5 ± 2.5 mg/day, 10 ± 2.5 mg/day, and 15 ± 2.5 mg/day) on a once daily schedule, the two highest olanzapine dose groups (actual mean doses of 12 and 16 mg/day, respectively) were superior to placebo on BPRS total score, BPRS psychosis cluster, and CGI severity score; the highest olanzapine dose group was superior to placebo on the SANS. There was no clear advantage for the high dose group over the medium dose group. Examination of population subsets (race and gender) did not reveal any differential responsiveness on the basis of these subgroupings.

In a longer-term trial, adult outpatients (n=326) who predominantly met DSM-IV criteria for schizophrenia and who remained stable on olanzapine during open label treatment for at least 8 weeks were randomized to continuation on their current olanzapine doses (ranging from 10 to 20 mg/day) or to placebo. The follow-up period to observe patients for relapse, defined in terms of increases in BPRS positive symptoms or hospitalization, was planned for 12 months. However, criteria were met for stopping the trial early due to an excess of placebo relapses compared to olanzapine relapses, and olanzapine was superior to placebo on time to relapse, the primary outcome for this study. Thus, olanzapine was more effective than placebo at maintaining efficacy in patients stabilized for approximately 8 weeks and followed for an observation period of up to 8 months.

An early open-label study suggests that olanzapine at doses between 5 and 20 mg/day had significant antipsychotic against both positive and negative symptoms of schizophrenia. Minimal extrapyramidal symptoms were observed. The 6-week acute phase of double blind, placebo and haloperidol-controlled trial found two dosage ranges of olanzapine, 10 ± 2.5 mg/day and 15 ± 2.5 mg/day, to be statistically significantly superior to placebo and comparable to one dosage of haloperidol, 15 ± 5.0 mg/day, in the treatment of overall psychopathology and positive symptoms. Furthermore olanzapine in the dosage range of 15 ± 2.5 mg/day was statistically significantly superior to both placebo and haloperidol in the treatment of negative symptoms.
Extrapyramidal symptoms had decreased from the baseline by the end of the study in olanzapine-treated patients but had increased in haloperidol treated patients.

**WARNINGS**

Neuroleptic Malignant Syndrome (NMS)—a potentially fatal symptom complex which has been reported in association with antipsychotic drugs, including olanzapine. This syndrome includes hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia).

Tardive Dyskinesia—a syndrome that is potentially irreversible and includes, involuntary, dyskinetic movements and may develop in patients treated with antipsychotic drugs. Increased duration and dosage of the drug may influence the development of the syndrome, however at brief treatment at low doses make the syndrome less likely to appear.

**PRECAUTIONS**

Orthostatic Hypotension—Olanzapine may induce orthostatic hypotension associated with dizziness, tachycardia, and in some patients, syncope, especially during the initial dose-titration period, probably reflecting its alpha 1-adrenergic antagonistic properties. Syncope was reported in 0.6% (15/2500) of olanzapine-treated patients in phase 2-3 studies. The risk of orthostatic Initiating therapy with 5 mg QD may minimize risk of hypotension and syncope.

Seizures—during pre-marketing testing procedures, seizures occurred in 0.9% (22/2500) of olanzapine treated patients.

Hyperprolactinemia—as with other drugs that antagonize dopamine D2 receptors, olanzapine elevates prolactin levels, and a modest elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent in vitro, a factor of potential importance if the prescription of these drugs is contemplated in a patient with previously detected breast cancer of this type.

Potential for Cognitive and Motor Impairment—Somnolence was a commonly reported adverse event associated with olanzapine treatment, occurring at an incidence of 26% in olanzapine patients compared to 15% in placebo patients. This adverse event was also dose related. Somnolence led to discontinuation in 0.4% (9/2500) of patients in the pre-marketing database.

Uric Acid—In the pre-marketing clinical trial database. Olanzapine was associated with mild elevations of uric acid in some patients. However only 1 olanzapine-treated patient experienced treatment-emergent gout, and the baseline uric acid concentration for this patient was at least as large as all concentrations observed while the patient was receiving olanzapine.

Weight Gain—Olanzapine was associated with weight gain during clinical trials. Patients treated at higher doses (15 ± 2.5 mg/day) had the greatest mean weight gain. However, a categorization of patients at baseline on the basis of body mass index (BMI) revealed a significantly greater effect in patients with low BMI compared to normal or overweight patients. Using pooled data from patients treated with olanzapine over the dosage range of 5 mg to 20 mg per day, weight gain tended to level of at 6 to 8 months of treatment with a mean gain of 5.4 kg.
Body Temperature Regulation--Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing olanzapine for patients who will be experiencing conditions which may contribute to an elevation of core temperature, eg exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration.

Drug Interactions--Given the primary CNS effects of olanzapine caution should be used when it is taken in combination with other centrally acting drugs and alcohol. As it exhibits in vitro dopamine antagonism, olanzapine may antagonize the effects of levodopa and dopamine agonists. Because of its potential for inducing hypotension, olanzapine may enhance the effects of certain antihypertensive agents.

CONCLUSION & DISCUSSION
Olanzapine is a new drug with properties similar to clozapine. Overall it has been shown to be better than haloperidol and risperidone on all symptoms of schizophrenia and have improved effects in regards to EPS, and cognitive awareness.

The dopamine basis of schizophrenia implies that hyperactivity of central dopaminergic systems is responsible for the psychiatric state observed. This could be due to increased synthesis or release of dopamine, decreased degradation of dopamine cell levels or supersensitive post synaptic dopamine receptors. This idea is supported by the observing that antipsychotic drugs block dopamine receptors and improve the overall state of schizophrenics. The implication of dopamine receptors to schizophrenia has been greatly studied. Since dopamine receptors seem to be the primary targets in the treatment of schizophrenia then drugs that are specific to the particular dopamine receptors, D2, will yield much greater results in the aspect of the positive symptoms. The trend of typical and previous antipsychotics where to effect the dopamine receptors associated with the cognitive and emotional aspects of function inside the brain. The newer antipsychotics seem to decrease the positive symptoms, yet improve the cognitive effects of a schizophrenic. The insights gathered from the research suggest newer antipsychotics can be formed, and be effective, if the correct dopamine receptors are attacked while keeping the various dopamine receptors for cognitive function unaffected. By acquiring the correct balance and of dopamine (D1-5) reception, and focusing on particular locations in the brain, the most effective and appropriate outcome may be obtained. This can only be done by ample manipulation and adjustment of the drugs already used. Antispsychotics of this nature will be the most effective in treating the positive, negative, and cognitive deficits of schizophrenia.
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"Lecithin: An Old Nutrient Resurfaces"

compiled by,
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April 27, 2001
Lecithin is a multifunctional, flexible and versatile surfactant composed of a number of compounds, which are predominantly phospholipid. By virtue of the functionalities that can be exhibited by its various components, lecithin can be utilized in a diverse variety of applications. Lecithin can be found in many animal and vegetable sources including beef liver, steak, eggs, peanuts, oatmeal, wheat germ, cauliflower, and oranges. Commercial sources for lecithin can come from soybeans, egg yolk, or brain tissue.\(^{(1)}\) Maurice Gobley, a French scientist, first discovered lecithin in 1850. Gobley named it “lekithos”, which is the Greek term for egg yolk. Lecithin is a common compound found in cells of all living organisms, its presence being required for proper biological functions. The scientific name of lecithin is:

\[
1,2\text{-diacyl-sn-glycero-3-phosphatidylcholine}
\]

Some of the common names of lecithin are lecithol, vitelmin, ketecin, and granulestine. About 13\% by weight of the lecithin molecule is choline.\(^{(2)}\) Most choline in the diet is derived from lecithin. Lecithin is purified phosphatidylcholine (PC) and denotes a particular family of compounds\(^{(3)}\) that are named under the umbrella of phosphatidylcholine (PC):

\[
\begin{align*}
\text{CH}_2\text{OR} \\
\text{R'O} - \text{C} - \text{H} & \quad \text{O} \\
\text{CH}_2\text{O} - \text{P} & \quad \text{OCH}_2\text{CH}_2\text{N}^+\text{CH}_3 \\
\text{O}^- \\
\end{align*}
\]

(R-form)

\(R, R' = \text{acyl groups}\)
Lecithin is a special type of fatty acid called a phospholipid; its chemical name is phosphatidylcholine (PC). Fatty acids are a carboxylic acid derived from or contained in an animal or vegetable fat or oil by the equivalent of oxidation of a methyl group to an alcohol, aldehyde, and then an acid:

\[ R \rightarrow CH_3 \rightarrow RCH_2OH \rightarrow RCHO \rightarrow RCOOH \]

All fatty acids are composed of a chain of alkyl groups containing from 4 to 22 carbon atoms, usually an even number, and characterized by a terminal carboxyl group --COOH. Fatty acids may be saturated or unsaturated, and solid, semisolid, or liquid. Phospholipids are cells that form a protective sheath around cells and providing for their framework. The cell membranes in the body are composed greatly of lecithin. These membranes handle the flow of nutrients in and out of the cell. The protective sheaths around your brain are also made of lecithin. Lecithin is needed by every cell in the body and is a key building block of cell membranes. Without it, the cell membranes would harden. Although lecithin is a fatty substance, it is also a fat emulsifier and supports the circulatory system.

Purified lecithin is a white, paraffin-like substance, which on exposure to air turns dark brown, acquiring a disagreeable odor and taste. It is soluble in alcohol, benzene, ether, petroleum, ether, chloroform, carbon tetrachloride, acetic acid, pyridine, glycerol, and many other organic solvents. One of the outstanding characteristics of lecithin is the insolubility in acetone. When mixed with water, lecithin becomes an opaque, colloidal suspension.

Lecithin is manufactured in the body by every healthy liver and found in varying quantities in body cells and organs. Lecithin is high in phosphorous and unites with iron, iodine, and calcium to give power and vigor to the brain. There is an especially high concentration of lecithin in the brain and around nerve sheaths. Lecithin helps to emulsify fats and contains the B vitamins choline, from which the body manufactures one of several nerve transmitters.

Lecithin is composed of phosphoric acid, choline and inositol. In the brain, the choline in lecithin is transformed into acetylcholine, a chemical compound that relays information from one nerve cell to another. Lecithin metabolizes fat in the liver. In the bloodstream, lecithin prevents fats from accumulating on the walls of the arteries. The absorption of vitamins A, D, and possibly E and K are enhanced by lecithin in the intestinal tract.

Physiologically, lecithin is an integral part of all organs and glands. The brain itself contains twenty-five percent phospholipids on a dry weight basis. Vital organs such as the liver, reproductive tract, and muscles, contain high concentration of phospholipids. Phospholipids are also among the primary building blocks of all cellular membranes. Membrane functions include cellular transport of nutrients and wastes, internal cellular pressure regulation, and ion exchange.

Due to the choline make-up of lecithin, it has been touted as a memory enhancer by improving cognitive function. Research shows a link between depleted acetylcholine
levels in the brain and Alzheimer’s disease. Although it has not been shown to have the ability to cure the degenerative disease, lecithin may slow its onset. Lecithin also has a value as a fat synthesizer and may be beneficial to a diet high in saturated fat and cholesterol because it would increase their breakdown and utilization by cells. To date, there is mounting accumulation of scientific studies, which suggest some of the diverse benefits of lecithin. Some of the multi-faceted uses of lecithin are as follows: preventing arteriosclerosis, protect against cardiovascular disease, improve brain function, increase energy levels, repair damage from alcoholism, help in digestion of fats, aging, immune disorders, AIDS, increasing the gamma globulin in the blood, herpes, and chronic fatigue syndrome.

There have been many studies done that are convincing nutritionists that lecithin is important. The following are a few case examples of lecithin studies:

Thirty-two people with high blood lipids were given 10.5g of lecithin for thirty days. Their average total cholesterol and triglycerides decreased by one-third, LDLS decreased by 38% and HDLs increased by 46%. The lecithin appears to reduce the risk of cardiovascular disease (CVD) in several ways by contributing cholesterol-lowering polyunsaturated fats, inhibiting intestinal absorption of cholesterol, increasing the excretion of cholesterol and bile acids, and favorably affecting lipoprotein profiles. The choline portion of lecithin may also reduce CVD risk by helping to metabolize homocysteine, an amino acid strongly linked with increased CVD risk. Researcher Dr. Charles S. Lieber and associates at the Alcohol Research and Treatment Center, V.A. Medical Center, in Bronx, NY suggests lecithin may protect the liver in other way besides proving choline. Lieber and associates began feeding three tablespoons of lecithin daily to twelve baboons. Six of the baboons also consumed a diet comparable to that of a chronic alcoholic, with half of the calories derived from alcohol, in this case, equivalent to eight cans of beer. A different group of eighteen baboons received the same diets without the lecithin. The tests showed that the seven of the nine baboons on the lecithin-free diet produced severe liver scars. Two of these seven had fully developed cirrhosis. The lecithin group, however, showed little scarring for the six consuming alcohol.

The researchers have two theories on how lecithin may protect against cirrhosis. The fact is based on the fact that lecithin is in the group of chemicals of phospholipids. Preliminary European research has indicated that phospholipid supplements can lower cholesterol and treat hepatitis. The scientists have noted that alcohol-induced cirrhosis in humans correlates with low phospholipid levels. However, pathologist Emanuel Rubin contends that a second mode of action for the protective effect may be due to the breakdown of fibrous tissue formed when alcohol causes the liver’s lipocytes to produce scar tissue instead of their normal function of storing vitamin A. Lieber feels the issue needs more study and is planning some human clinical trials to determine whether lecithin can actually prevent alcohol-induced cirrhosis or possibly even reverse the early stages of the disease.

Numerous animal studies show a choline-deficient diet promotes liver cancer. The disease begins with early signs of fat buildup in the liver because lecithin is required to make very-low-density lipoproteins (VLDLs), the liver’s major fat exporter. If choline
deficiency continues, a fatty liver is followed by cell death, collagen buildup (fibrosis), cirrhosis and cancer. Extra choline is shown to protect against liver cancer in mice exposed to a cancer-causing substance. A number of lecithin-like compounds are being studied in humans as potential cancer therapies.

A good deal of evidence from animal studies shows lecithin and choline improve memory and learning. When choline was fed to pregnant rats, their offspring showed significantly better memory in maze tests than rats whose mothers were not fed choline. The improved memory was maintained at a level comparable to that of much younger rats even after the rats grew old. The beneficial effect probably relates to lecithin's function in nerve membranes and to the need for choline to make the neurotransmitter acetylcholine, which enables signals to go from nerve to nerve.

Human studies suggest lecithin and choline may also benefit memory. In one study, investigators gave sixty-one healthy older adults, (aged fifty to eighty years) either two tablespoons of lecithin or a placebo for five weeks. By the end of the study, memory test scores of the lecithin group improved significantly, exceeding those of the placebo group. The lecithin group also reported a 48% decrease in memory lapses.

Because nerves also carry signals to muscle fibers, it is not surprising that studies show lecithin and choline supplements improve the performance of some physical activities. In one study, researchers found plasma choline levels of Boston Marathon runners dropped by about 40% during the race. In one double-blind crossover study, long-distance runners ran a twenty-mile race in an average of 158.9 minutes after taking a placebo; they improved their average time to 153.7 minutes after taking 2.8g of choline chloride. Given that races can be won or lost by seconds, five minutes is a large improvement. The choline supplementation prior to activity appears to prevent the decline of plasma choline and, in many cases, to improve performance. However, short-duration, less-intense activities do not appear to reduce blood choline levels or to benefit from supplementation.

Lecithin is abundant in nerve-cell membranes and is required for nerve growth and function. Additionally, choline helps generate methyl groups, which are important in activating DNA. Because of these and other functions, choline is widely recognized as important in brain and mental development of both fetus and infant. Choline in the mother's bloodstream has been concentrated 14-fold by the time it reaches the fetus and is concentrated more than 100-fold in mother's milk. Thus, the requirement for choline appears to be especially high in women during pregnancy and lactation. Infant formulas approved by the FDA are required to contain levels of choline comparable to those in human milk.

Lecithin and choline serve other functions in reproduction and development. Another choline phospholipid, platelet-activating factor, is involved in implanting the egg in the uterine wall, fetal maturation and inducing labor. In test-tube studies, lecithin restored normal structure and movement to abnormal sperm cells and nearly doubled the ability of sperm to enter and fertilize an egg.

Adverse effects generally have not been associated with lecithin as a nutritional supplement. Some studies had no observable side effects. Gastrointestinal side effects and hepatitis were experienced from a study in Alzheimer's patients taking tacrine, a
medication used for Alzheimer's, and lecithin. One report in rats observes biochemical alterations and impaired sensorimotor development in offspring of rats fed a diet including five percent lecithin, suggesting its consumption is inadvisable during pregnancy. Eliminating an egg from the average daily diet reduces the day's total lecithin intake by one-third. Dr. Richard Wurtman, a neuroscientist at the Massachusetts Institute of Technology, in Cambridge, Mass., and other experts say many people are not getting enough choline. How does one know the proper amount of lecithin to take? A reasonable amount of lecithin an individual may take as a supplement is one or two tablespoons of granular lecithin daily. This would supply 1,725mg to 3,450mg of phosphatidylcholine and 250mg to 500mg of choline. The commercial lecithin in most lecithin supplements is a mixture of phosphatidylcholine and other phospholipids extracted from soybeans. Commercial lecithin in granular form contains about twenty-three percent phosphatidylcholine; lecithin capsules provide about fifteen percent. One capsule of lecithin provides about 180mg of phosphatidylcholine and 25mg of choline. Ten to twelve capsules would match the amount of lecithin and choline in a tablespoon of granules or in one egg.

Supplemental choline also can be taken in the form of choline salts, choline bitartrate and choline chloride. However, lecithin appears to provide a more bioavailable, timed-release source. When equal amounts of choline are consumed in lecithin or in choline salts, the lecithin sustains plasma choline at a higher level for a longer time, and lecithin may be more effective than choline chloride as a therapeutic agent. Granular lecithin has a mild, nutty flavor and can be sprinkled on cereal and combined with other foods. Because it is an emulsifier, lecithin can make gravies and sauces smoother. Lecithin can partly be substituted for fats and oils in baked goods, and is the main ingredient in antistick cooking sprays. Lecithin supplements are preferred over choline salts not only because of a longer-lasting timed-release source of choline but also does not have the offensive, fishy odor like choline salts.

Lecithin has many significant uses for different ailments. Lecithin can help to prevent against arteriosclerosis and protect against heart disease, repair damage from alcoholism, and improve brain function. A lack of lecithin can cause forget-fullness, digestive problems, intolerance to fats, nausea, hypertension, and joint and muscle problems, such as bursitis, cramps, and soreness.

I chose lecithin for my topic to find out any information regarding the use of lecithin for acne treatment. In all my efforts of gathering and collecting data, I was not able to come across any studies shown that lecithin helps in the treatment of acne. I did, however, learn of the many vast uses of lecithin.

I stumbled across the use of lecithin for acne problems at the beginning of this year to help clear up my problems with adult acne. A Hi-Health representative advised me of the use of lecithin for acne. She told me of a learning session she attended and one of the topics spoken about was how lecithin can help in the treatment of acne. I asked her if she knew of how the lecithin worked in the body against acne or had any typed information on the topic. Unfortunately, she did not know or have charted facts. I figured that it could not hurt to try using the lecithin since I had tried just about everything known to mankind. The lecithin has done wonders for my skin. The
treatment is not an instantaneous ordeal. It did take about a month and a half before I did notice any type of improvement. However, for myself, I am very pleased with the results since I do not have to worry about scrubbing my face a couple times a day or worry about my skin reacting to different topical creams or ointments. Also, there are certain oral antibiotics that are used for acne treatment that can cause extra sensitivity to the sun and some that can cause birth defects.

Using lecithin is a very simple routine; take two to three capsules twice daily, and that is the end of it. Also, lecithin is a very inexpensive therapy. One bottle of lecithin costs about $10.00, and will last for about one month. I have not had any type of side effects since I have been taking lecithin. I have noticed a slight improvement of my memory, which for me, being a college student and cramming for tests, has been an added bonus to my therapy.

Lecithin is a multifunctional, flexible and versatile surfactant that can be utilized in a diverse variety of applications. A few of the multi-uses of lecithin extend from preventing against arteriosclerosis and protect against heart disease, repair damage from alcoholism, and improve brain function. Only ten years ago, nutritionists considered lecithin and choline “health food supplements” with no clear nutritional purpose because no deficiency disease was associated with them. Today, however, health and nutrition experts recognize that nutrients do more than prevent deficiency diseases; they also reduce the risk of chronic disease and optimize health.
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All material contained has been located in a minimum of three sources, and has been compiled for educational purposes only.
FDA Approved Concerta for Attention Deficit Hyperactivity Disorder

By: Katibeh Raisdana
Spring 2001
ABSTRACT
Methylphenidate has been found to be the leading pharmacotherapy for the treatment of Attention Deficit Hyperactivity Disorder. Now the FDA has approved Concerta, an extended-release formulation of methylphenidate, to be used as a more convenient method of doctoring ADD/ADHD. This psychostimulant employs an advanced form of ALZA Corporation’s OROS technology, which uses osmotic pressure to deliver medication at a controlled rate. Neurobiological and pharmacological data provides compelling support for a noradrenergic hypothesis of ADHD, and suggest that drugs with noradrenergic activity may play an important role in the therapeutics of this disorder. Both noradrenergic and dopaminergic neuroreceptor systems have been implicated in the development of ADHD. It is believed that the dopamine system acts in the brain in areas that are largely responsible for specific functions including regulation of motor output. The noradrenergic system acts more broadly, controlling the state of arousal, selective attention, and orientation, as well as the response to sensory stimulation. Once-daily Concerta can be a significant benefit for patients by providing controlled symptom relief and reducing the number of daily doses compared to conventional therapies.

WHAT IS ADD/ADHD?
Attention deficit-hyperactive disorder (ADHD) is a neurobehavioral disorder that affects 3-5% of American school children.[1] The term “attention deficit disorder” (ADD), also known as “attention deficit hyperactivity disorder” (ADHD), had been used traditionally to describe the hyperactivity in children. Hyperactivity observed in children was mainly thought to be the increase in physical activity. Recently, the term ADD/ADHD has been used by the medical community to describe both physical hyperactivity, as well as lack of focused attention that children afflicted with this syndrome display.

The diagnosis of ADHD can be made reliably by using well-tested diagnostic interview methods. However, as of yet, there is no independent valid test for ADHD. A prominent neurologist states, “The more you study hyperactivity or ADD, the less certain you are as to what it is, or whether it is a thousand different situations all called by the same name. No single cause can yet be identified of ADHD. In fact, ADHD will probably one day prove to be an umbrella term for a number of associated disorders”.[2] Uncertainty is not unique to ADHD, but applies as well to most psychiatric disorder, including disabling diseases such as schizophrenia. Until recently, all formal diagnostic criteria for ADHD were designed for diagnosing young children and had not been adjusted for older children and adults. But now for adults, newly designed tests are available to identify individuals who suffer from ADD, and were previously undiagnosed. Research has identified adults who have never outgrown this disorder.

There are two classifications of ADHD: a predominantly inattentive subtype, and a predominantly hyperactive-impulsive subtype. The American Psychiatric Association has made a list of symptoms, of which at least six must be present for a child to be officially classified as ADD.[3]
Inattention symptoms
- Often forgetting things necessary for tasks or activities
- Being easily distracted by extraneous stimuli
- Loses things necessary for tasks or activities
- Avoids, dislikes, or is reluctant to do tasks requiring sustained mental effort
- Has difficulty organizing tasks and activities
- Having difficulty in following instructions
- Often not listening to what is being said, and when spoken to directly
- Having difficulty sustaining attention in tasks or play activities
- Does not pay close attention to details or makes careless mistakes

Hyperactivity or impulsiveness symptoms
- Often fidgeting with hands or feet, or squirming while seated
- Having difficulty remaining seated when required doing so
- Inappropriately runs about, acts restless
- Having difficulty playing quietly
- Often shifting from one uncompleted task to another
- Often talking excessively
- Often blurtling out answers before questions are completed
- Having difficulty awaiting turn in games or group activities
- Often interrupting or intruding on others

In order for medication to be prescribed, symptoms must continue for six months and be more frequent and severe than normal. Evidence must show significant damage to social, academic or work functioning. Some damaging symptoms must have occurred before the age of 7, even in later diagnosis.

ADD is exhibited more frequently in boys than girls, and has been estimated to affect between 5-10% of all children around the world. Most children with ADD exhibit symptoms between the ages of 4 and 7 years of age. The exact cause of ADD is unknown, although the tendency for its running in the family is common. ADD is a syndrome that occurs early in life and continues throughout a lifetime. Although symptoms may change from childhood to adulthood, the basic inability for an individual to concentrate remains present. Attention deficit hyperactivity disorder represents a costly major public health problem. Children with ADHD pronounced impairments and can experience long-term adverse effects on academic performance, vocational success, and social-emotional development, which have a profound impact on individuals, families, schools, and society. If left untreated, ADD may result in poor academic performance, low self-esteem, poor social skills and an undesirable quality of life.

TREATMENTS
A wide variety of treatments have been used for ADHD including, but not limited to, various psychotropic medications, psychosocial treatments, dietary management, herbal and homeopathic treatments, biofeedback, medication, and perceptual stimulation/training. Of these treatments strategies, stimulant medication and psychosocial interventions have been the major foci of research. The FDA has approved several stimulant medications for treating ADHD: methylphenidate (Ritalin), dextroamphetamine (Dexedrine), methamphetamine, and a
combination of dextroamphetamine and methamphetamine (Adderall). FDA recently restricted another approved stimulant, pemoline (Cylert), to secondary use, as it can cause liver failure. The drugs stimulate the central nervous system, which decrease impulsiveness and hyperactivity, and increase attention. The drug, methylphenidate, in combination with psychotherapy had been proven to enhance attention and improve quality of life for individuals afflicted with attention deficit disorder.

DIAGNOSIS
There has been a large number of studies done, but to this day, the mechanism by which psychostimulants act as calming agents in humans with ADHD is currently unknown. Dysregulation of the central noradrenergic networks may underlie the pathophysiology of ADHD. The pertinent neurobiological and pharmacological literature on ADHD has been reviewed. The noradrenergic system has been intimately associated with the modulation of higher cortical (outer, or covering layer of brain) functions including attention, alertness, vigilance (alert for avoiding danger) and executive (decision making) function. Noradrenergic activation is known to profoundly affect the performance of attention, especially the maintenance of arousal, a cognitive function known to be deficient in ADHD. Data from family, adoption, twin, and segregation analysis strongly support a genetic hypothesis for this disorder.

Although molecular genetic studies of ADHD are relatively new and far from definitive, several replicated reports have found association between ADHD with dopamine transporter (DAT) and dopamine (D4) receptor genes. Mice lacking the gene encoding the plasma membrane DAT have elevated dopaminergic tone and are hyperactive. Additionally, these mice were impaired in spatial cognitive function, and they showed a decrease in locomotion in response to psychostimulants. This calming effect of psychostimulants depended on serotonergic neurotransmission. A wealth of pharmacological data provides strong evidence for selective clinical activities in ADHD for drugs with noradrenergic and dopaminergic pharmacological profiles. Available research provides compelling theoretic, basic biologic and clinical support for the notion that ADHD is a brain disorder of likely genetic etiology with etiologic and pathophysioligic heterogeneity. Studies have been done that support facts contrary to results found previously. Unlike cocaine and amphetamines, methylphenidate does not increase the extracellular serotonin concentration in the brain. The affinity of methylphenidate for the serotonin transporter is very low, and if augmentation of serotonin did play an important role in the therapeutic effects of psychostimulants, one would expect serotonin transporter inhibitors to be beneficial in the treatment of ADHD, which they are not.

EFFECTS OF PSYCHOSTIMULANTS
Ritalin is 40 years old, but the number of prescriptions for legal uses such as treatments of ADD has increased substantially in recent years. According to the Drug Enforcement Agency, during the last five years, the number of written prescription for psychostimulating drugs has increased by 600%. In the Journal of the American Medical Association (JAMA), reports on the alarming increase in the use of psychiatric drugs for preschoolers was documented for the first time. Study revealed that the number of preschoolers on these drugs risen 200% from 1991 to 1995. Despite progress in the assessment, diagnosis, and treatment of ADHD, this disorder and its
treatments have remained controversial, especially the use of psychostimulants for both short and long-term treatment.

Until recently, most randomized clinical trials have been short term, up to approximately 3 months. Overall, these studies support the efficacy of stimulants and psychosocial treatments for ADHD and the superiority of stimulants relative to psychosocial treatments. However, there are no long-term studies testing stimulants or psychosocial treatments lasting several years. There is no information on the long-term outcomes of medication-treated ADHD individuals in terms of educational and occupational achievements, involvement with areas of social functioning. Short-term trials of stimulants have supported the efficacy of methylphenidate dextroamphetamine and pemoline in children. These short-term trials have found beneficial effects on the defining symptoms of ADHD and associated aggressiveness as long as medication is taken.

Because stimulant medicines have a high potential for abuse, the U.S. Drug Enforcement Administration has placed stringent controls on their manufacture, distribution and prescription. These drugs are listed under CII, and DEA requires special licenses for these activities, and prescription refills are not allowed. One of the major controversies regarding ADHD concerns the use of psychostimulants to treat the condition. Because psychostimulants are more readily available and are being prescribed more frequently, concerns have intensified over their potential overdose and abuse. Ritalin has become a recreational drug. A recently identified drawback of Ritalin is its popularity as an illicit drug. The annual survey, ‘Monitoring of Future’ by the university of Michigan warns of a trend concerning Ritalin abuse. From 1993 to 1994 the number of high school seniors admitting to having abused Ritalin has doubled, representing about 350,000 students nation-wide. It is known as “Vitamin R”, “R-ball”, or “the smart drug”, and it is often used for long hours of studying.

When the drug is taken as prescribed by the specialist, Ritalin is a mild stimulant, but not without worrisome side effects. Effects associated with moderate doses may include decrease in appetite and insomnia. These effects may occur early in the treatment and may decrease with continued dosing. It is well known that psychostimulants have abuse potential. Very high doses of psychostimulants, particularly of amphetamines, may cause central nervous system damage, cardiovascular damage, and hypertension. In addition, high doses have been associated with compulsive behavior and, in certain vulnerable individuals, movement disorders.

CONCERTA
For several years the drug Ritalin has benefited children with attention deficit hyperactivity disorder. But the drug needs to be taken up to 3 times a day. The U.S. Food and Drug Administration on August 2000 approved a new formulation of methylphenidate, which only needs to be taken once a day. This new drug is called Concerta and is manufactured by ALZA Corporation. The drug is taken in the morning with or with out breakfast, freeing the child to go about his or her daily activities without the inconvenience or potential embarrassment of having to take another dose at school. Concerta is available in two tablet strengths. Each extended-release tablet for once-a-day oral administration contains 18 or 34mg of methylphenidate HCl,
and is designed to have a 12-hour duration of effect. The 54mg tablets are meanwhile being tested on.

**DESCRIPTION**

Concerta is a central nervous system stimulant. Chemically, methylphenidate HCl is d,l (racemic)methyl α-phenyl-2-piperidineacetate hydrochloride. Its empirical formula is C₁₄H₁₉NO₂ • HCl. Its Structural formula is:

![Structural formula of methylphenidate HCl]

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

Concerta also contains the following inner ingredients: butylated hydroxytoluene, carnauba wax, cellulose acetate, hydroxypropyl methylcellulose, lactose, phosphoric acid, poloxamer, polyethylene glycol, polyethylene oxides, povidone, propylene glycol, sodium chloride, stearic acid, succinic acid, synthetic iron oxides, titanium dioxide, and triacetin.

**SYSTEM COMPONENTS AND PERFORMANCE**

**OROS Osmotic Technology**

OROS technology improves oral drug dosing by providing rate-controlled delivery of medication thereby reducing the number of times per day the medication is taken. A single tablet using the OROS system can provide controlled rates of up to 600 mg of drug for up to 24 hours. Most recently, OROS technology has been incorporated into Concerta (methylphenidate HCl) Extended-Release Tablets (CII), the first once-daily methylphenidate treatment for ADHD.¹¹

**Benefits of OROS Technology**

OROS osmotic technology provides more controlled therapeutic drug levels in the blood throughout the dosing interval. This minimizes the peak and trough plasma concentrations associated with multiple immediate release medications, because the system regulates the release of drug. This can be a significant benefit for patients by providing controlled symptom relief and reducing the number of doses compared to many conventional therapies. OROS technology sustains rates of drug delivery independent of gastrointestinal acidity, alkalinity or food content, unlike many medications which can be influenced by variable conditions in the gastrointestinal tract.
How OROS Works
OROS technology uses osmotic pressure to deliver medication at a controlled rate. OROS technology features a semi-permeable rate-controlling membrane surrounding an osmotic core, which contains a push layer and a drug layer. Once in the body’s gastrointestinal tract, water enters the OROS system and dissolves or suspends the drug in the tablet’s core. The drug is then released through one or more laser-drilled holes in the membrane at a controlled rate. An advanced OROS system has been developed to overcome the challenges of medications that require a more patterned delivery profile throughout the day. The new generation OROS system features an immediate release outer drug layer, and a tri-layer core with two internal drug compartments and a push compartment. Illustration of the tri-layer is shown on figure 1.

![Diagram of OROS system](image)

Figure 1

CLINICAL PHARMACOLOGY
Pharmacodynamics
Methylphenidate HCl is a central nervous system (CNS) stimulant. The mode of therapeutic action in Attention Deficit Hyperactivity Disorder (ADHD) is not known. Methylphenidate is thought to block the reuptake of norepinephrine and dopamine into the presynaptic neuron and increase the release of these monoamines into the extraneuronal space. Methylphenidate is a racemic mixture comprised of the d- and l-isomers. The d-isomer is more pharmacologically active than the l-isomer. [12]

Pharmacokinetics
Absorption
Methylphenidate is readily absorbed. Following oral administration of Concerta to adults, plasma methylphenidate concentrations increase rapidly reaching an initial maximum at about 1 to 2 hours, then increase gradually over the next several hours. Peak plasma concentrations are achieved at about 6 to 8 hours after which a gradual decrease in plasma levels of methylphenidate begins. Concerta every day minimizes the fluctuations between peak and trough concentrations associated with immediate-release methylphenidate three times a day. The relative bioavailability of Concerta every day and methylphenidate three times a day in adults is comparable.
Mean methylphenidate plasma concentration in 36 adults
A single dose of Concerta 18 mg once daily
Vs.
Immediate release methylphenidate 5-mg three times daily (every 4 hours)

Metabolism and Excretion
[14C] ritalinic acid is the major metabolite of methylphenidate. In humans, methylphenidate is metabolized primarily by de-esterification to a-phenyl-piperidine acetic acid (PPA) which has little or no pharmacologic activity. In adults the metabolism of Concert once-daily as evaluated by metabolism to PPA is similar to that of methylphenidate three times daily. The metabolism of single and repeated once daily doses Concerta is similar. After oral dosing of radiolabeled methylphenidate in humans, about 90% of the radioactivity were recovered in urine. The main urinary metabolite was PPA, accounting for approximately 80% of the dose.

Food Effects
In patients, there were no differences in either the pharmacokinetics or the pharmacodynamic performance of Concerta when administered after a high fat breakfast. There is no evidence of dose dumping in the presence or absence of food.

SAMPLE POPULATION
Gender
In healthy adults, the mean dose-adjusted values for Concerta were 36.7 ng·h/ml in men and 37.1 ng·h/ml in women, with no differences noted between the two groups.

Race
In adults receiving Concerta, dose-adjusted was consistent across ethnic groups; however, the sample size may have been insufficient to detect ethnic variations in pharmacokinetics.

Age
The pharmacokinetics of Concerta has not been studied in children less than 6 years of age.
Renal Insufficiency
There is no experience with the use of Concerta in patients with renal insufficiency. After oral administration of radiolabeled methylphenidate in humans, methylphenidate was extensively metabolized and approximately 80% of the radioactivity were excreted in the urine in the form of PPA. Since renal clearance is not an important route of methylphenidate clearance, renal insufficiency is expected to have little effect on the pharmacokinetics of Concerta.

CLINICAL STUDIES
Concerta was demonstrated to be effective in the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in three double-blind, active- and placebo-controlled studies in 416 children 6 to 12 years old. The controlled studies compared Concerta given once daily (18, or 36 mg), methylphenidate given three times daily over 12 hours (15, 30, or 45 mg total daily dose), and placebo in two single-center, 3-week crossover studies (Studies 1 and 2) and in a multicenter, 4-week, parallel-group comparison (Study 3). The primary comparison of interest in all three trials was Concerta versus placebo. The Diagnostic and Statistical Manual, 4th edition, of the American Psychiatric Association (DSM-IV) provides criteria for three subtypes of ADHD.

(Combined Type, Predominantly Inattentive Type, or Predominantly Hyperactive-Impulsive Type). These criteria were used for diagnosis in all three studies. Community schoolteachers using the Inattention/Overactivity with Aggression (IOWA) Conners scale evaluated symptoms of ADHD. Statistically significant reduction in the Inattention/Overactivity subscale versus placebo was shown consistently across all three controlled studies for Concerta once daily. The scores for Concerta and placebo for the three studies are presented in Figure 2.
SIDE EFFECTS
Common side effects are headache, upper respiratory tract infection, stomachache, vomiting, and loss of appetite, sleeplessness, increased cough, sore throat, sinusitis, and dizziness. Patients who have significant anxiety, tension, agitation, glaucoma, tics, Tourette’s syndrome, or are taking prescription monoamine oxidase inhibitor should not take Concerta.

CONCLUSION
Attention deficit hyperactivity disorder or ADHD is a commonly diagnosed behavioral disorder of childhood. Despite progress in the assessment, diagnosis, and treatment of ADHD, this disorder and its treatment have remained controversial in many public and private sectors. The major controversy regarding ADHD continues to be the use of psychostimulants and the potential abuse. Although an independent diagnostic test for ADHD does not exist, evidence supporting the validity of the disorder can be found. Further research will need to be conducted with respect to the dimensional aspects of ADHD, as well as the coexisting conditions present in both childhood and adult ADHD. The impact of ADHD on individuals, families, schools, and society is profound and necessitates immediate attention. Lack of consistent improvement beyond the core symptoms leads to the need for treatment strategies that utilize combined approaches.

The risks of treatment, particularly the use of stimulant medication, are of considerable interest. Substantial evidence exists of wide variations in the use of psychostimulants across communities and physicians, suggesting no consensus among practitioners regarding which ADHD patients should be treated with psychostimulants. As measured by attention/activity indices, patients with varying levels and types of problems may benefit from stimulant therapy. However, there is no evidence regarding the appropriate ADHD diagnostic threshold above which the benefits of psychostimulant therapy outweigh the risks.

Despite the fact that the cause behind ADD is unknown, the demand for convenient medications are very high. Concerta, a new formulation of methylphenidate, is the first product to incorporate the new OROS tri-layer system. This system of using osmotic pressure, is designed to last 12 hours with just one dose and to sustain therapeutic effect throughout the school day, after school, and during homework. The tablet, developed in conjunction with leading ADHD experts, was designed based on the pharmacokinetic profile of methylphenidate given three times a day, without the fluctuations of medication in the bloodstream.

Finally, after years of clinical research and experience with ADHD, the knowledge about the cause or causes of ADHD remains speculative. Consequently, there are no strategies for the prevention of ADHD.
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THE FUTURE OF ANTIDEPRESSANTS:
Depression, Substance P, and MK-869
by
Jennifer R. Rowley
April 2001

Recent research involving the localization of substance P in the brain suggests that antagonists of this neurokinin (NK1) may be a new weapon against neurochemical disorders such as depression and anxiety. The phase I clinical trials of MK-869 has shown comparable antidepressive affects to modern antidepressant drugs, such as SSRIs, with fewer occurrence of adverse effects. This innovation, though still in clinical trials, is an important step forward in the treatment of psychobiological disease.

DEPRESSION

According to recent statistics, approximately 10 to 20% of the population is affected by the heterogeneous mood disorder known as depression. This figure is staggeringly large in comparison to any other disease in America. For example, the number one killer of women in America is heart disease. In 1997 one percent of the population was afflicted with fatal heart disease. Fifteen percent of all patients diagnosed with clinical depression succeed in their suicide attempts. The average age of diagnosis of clinical depression is the mid-twenties, and women are two times more likely than men to be diagnosed with clinical depression. The purpose of these cold facts and figures is not to alarm, but to illustrate the importance of psychopharmacological research. But is depression truly a physical disease and not mediated solely by depressing environmental factors?

Another important illustration strongly suggests that environmental factors are not the sole cause of depressive symptoms. This is an important realization due to the fact that if the causes of depression were largely or completely due to environmental factors then a chemical therapy would not be effective. The fact is that this affliction has been recognized and described for over 3000 years. Hippocrates described the symptoms of what modern people call depression, and named this disease melancholia. From this evidence it can be deduced that contemporary environments cannot be the sole influence of this disease. In other words, it is not the pollution of our cities, stress, or even modern technology that cause depression. It must, then, be something inside of the human body that is the source of the symptoms of depression. It is generally accepted that the causality of clinical depression is a biochemical dysfunction in the absence of ‘identifiably depressing external situations’ (Baby et al. 1999). When depression is caused by internal factors such as neurochemistry, it is termed clinical depression.

Modern treatments have reflected the theory of biochemical dysfunction since the 1950's when tricyclic antidepressant drugs were introduced as a chemical therapy. Today the most commonly dispensed antidepressant pharmacotherapies are the monoamine oxidase inhibitors (MAOIs), and the selective serotonin reuptake inhibitors (SSRIs). Unfortunately the amelioration that these and past therapies provide is achieved at the cost of enduring, for some, many side effects. These side effects cause many patients to reject these drugs as therapy and can lead to further illness, inability to cope, and even suicide. For this reason, new kinds of drug
therapies are needed. A hopeful prospect in solving this problem involves the neurokinin known as substance P.

SUBSTANCE P

Recent research involving the neurokinin known as substance P has lead to the discovery of a new theory of the mechanism of depression, and to a possible new treatment for depression, which may produce less adverse effects. Substance P was discovered in 1931 and was thought originally to be involved in the mechanism of physical pain. It was found that “substance P is released locally during inflammatory responses that are neurogenically mediated. Also, substance P is released in the spinal cord in pain pathways. However, antagonists of substance P do not appear to reduce neurogenic inflammation nor do they block pain in clinical trials (Stahl 1999).” A new body of research was spurred when unexpected findings of improved mood were observed in subjects who had received a substance P antagonist. Significant interest in substance P as related to psychological disorders has only been apparent since about 1981. The first significant findings were in rats and guinea pigs, where both species have similar NK1 receptor pharmacology to human beings. The findings of these studies have been significant steps in the pursuit of new antidepressant therapies.

Before describing the findings of these studies, it might help to explain what substance P is, the structure of substance P, and what is known about how it works. According to the most recent research substance P “is a member of the family of structurally related peptides named tachykinins.” Tachykinins, called neurokinsins in the human body, are active peptides which excite neurons, evoke behavioral responses, are potent vasodilators and secretagogues (substances stimulating secretion as by the stomach or pancreas), and contract many smooth muscles either directly or indirectly. “There are three tachykinin receptors that have been termed NK1, NK2, and NK3. Although substance P can activate all three tachykinin receptors, its potency is greatest at NK1 receptors.” The next description is the most information known about the mechanism of substance P in the human body. “Neurons in sympathetic ganglia are surrounded by a dense network of substance P-immunoreactive fibers. These fibers are peripherally directed branches of sensory nerves projecting from dorsal root ganglia. When substance P is applied to these neurons it causes a slow excitatory postsynaptic potential similar to that caused by stimulation of sensory [branches] to the ganglia. Both potentials are blocked by substance P (or NK1) antagonists.” Finally, the body of substance P is made up of amino acids. The order of the amino acids is: H-Arg-Pro-Lys-Pro-Gln-Gln-Phe-Gly-Leu-Met-NH2. The structure of substance P is shown in figure 1. Now that the definition, function, and structure of substance P have been discussed, it is now practical to move on the research involving this amazing neurokinin.

In a study, published in June of 2000, by Schoborg et al. it was found that “intravenous injection of substance P increases renal nerve firing and heart rate in spontaneously hypertensive rats and Wistar-Kyoto rats by stimulating sympathetic ganglia (Schoborg et al. 2000).” This study considers the role of neurokinin-1 (NK1) receptors in mediating interactions of substance P within nerve cells. After the rats were injected with substance P the NK1 receptor antagonist was injected. Three different antagonists were tested. The findings of this study suggest that the increasing blood pressure response to substance P is “mediated by ganglionic NK1 receptors and that NK1 receptors also have a prominent role in mediating the renal nerve and heart rate responses to” substance P (Schoborg et al. 2000). This means that substance P produces physical affects to which an NK1 receptor antagonist has the ability to prevent or reverse the affects of.
A study published in 1999 suggested the amygdala as the likely site at which the antidepressant and anxiolytic effects of substance P antagonists are seen (Smith et al. 1999). For this study the subjects were male Mongolian gerbils. The idea of the study was to examine the
“distribution of NK1 receptor immunoreactivity in amygdala subnuclei in normal animals. The gerbils were given an overdose of pentobarbitone prior to perfusion fixation. The gerbils were then placed in restraints for one hour. At this time the gerbils were terminally anaesthetized, their brains removed and processed. It was found through this process that “the anterior and amygdaloid-hippocampal area displayed the highest density of immunoreactivity, followed by the medial nucleus,” etc. The main finding of this study is that most of the stress induced NK1 receptor absorption, as well as the effects of the drug treatments of this condition were constrained to a specific site in the brain called the basolateral subnucleus.

Preclinical data that has lead to a specific promising NK1 antagonist have come from four study findings. The first was that after the substance GR73682 induced vocalizations in guinea pigs, the antidepressant drugs imipramine, fluoxetine, and the MK-869 analogue L-722,060 inhibited these vocalizations where the less active enantiomer of MK-869 L-733,061, and the anxiolytics diazepam and buspirone did not. A second study found that vocalizations produced by guinea-pig pups separated from their mothers and siblings were completely inhibited by “acute administration of antidepressant drugs and by MK-869, L-760,735 (and MK-869 analogue) and L-733,060. Two other studies were included in the preclinical trials that further strengthened the body of research, but are not necessary to mention for the purposes of this report. In the 1998 publication, Kramer et al. concluded that, “…selective pharmacological blockade of substance P receptors is capable of inhibiting behavioral responses to psychological stress in a manner resembling the effect of clinically used psychotherapeutic agents (Kramer et al. 1998).”

It is now understood that NK1 antagonists work, and as well as the possible site of action. The next step is to discuss how this information has affected the pharmacology of antidepressant drugs. The first successful attempt at building an NK1 antagonist was achieved by Merck. The first clinical trials of their drug, MK-869 showed very promising results.

MK-869 RESEARCH

“The first clinical trial of substance P (NK1) antagonist for treatment of clinical depression involved Merck compound MK-869, which is a synthetic bis(trifluormethyl) morpholine. MK-869 is an orally bioavailable and long-acting non-peptide substance P antagonist (Baby 1999).” Kramer et al. investigated the safety and efficacy of this drug for treating humans. They ran trials using MK-869 (300mg/dose), the antidepressant drug paroxetine (20mg/dose), and a placebo. It was hypothesized that MK-869 could block “more than 90% of central substance P receptors” at a 300mg dosage level. Two hundred and thirteen subjects were taken off all previous medication for a four-week “wash out” period prior to the trials. The subjects were then randomly assigned to one of the three groups, then received instructions and their medications. “Clinical efficacy was measured at the end of weeks 1, 2, 4, and 6 or upon termination using the 21-item Hamilton depression total score as the primary outcome measure and a variety of secondary measures.” The investigators reported that the primary outcome confirmed that MK-869 is a very effective antidepressant drug. The results of the study showed that 54% of the subjects who received MK-869 showed improvements of 50% from their baseline, in comparison to 46% for subjects who received paroxetine, and 25% for placebo. The findings in terms of safety can be seen side by side in Table 1. As you can see, MK-869 has less adverse effects in most categories than paroxetine. The most important finding is that subjects who were administered MK-869 reported the same amount of sexual dysfunction as the placebo group.
MK-869, and has begun Phase II trials on a more potent version. Thus, the future of NK1 antagonists is also unclear. It may be predicted, however, that this novel remedy of the psychological dysfunction known as depression is one that will prevail in further testing. In formulating this hypothesis many factors have been thought through.

One of the most interesting thoughts in regards to any psychopharmaceutical is the placebo effect. The placebo effect can be simply defined as a subject’s ability to be cured in response to administration of a sugar pill or injection through simply thinking that they might be taking the true drug being tested. Basically, people simply believe that they will be cured, and they are. This effect has two consequences for a drug being tested. The first one is known as a false positive. This is when a drug is approved, or believed to work, which is actually ineffective, but appears useful solely due to its placebo effect. The other consequence of the placebo effect is a false negative. This is when there is a failure to prove the effectiveness of a drug that is truly effective due to the fact that the efficacy of the drug in question cannot be differentiated from that of the placebo. The only way to reduce the effect of the placebo is by innovative experimental design. It is this researcher’s opinion that the result of the Phase II trials of MK-869 produced a false negative.

Another thought on this researcher’s mind is the number of subjects tested in the trials. In order to gain a realistic gauge of effectiveness a large sample of the population is necessary. If ten percent of the population is affected by depression, and there are 864 million people in America, the sample population should be more than two hundred and thirteen. This is not to mention that sometimes several trials of the same experiment are needed in order to test the virtuousness of the experimental design. In studies involving subjects with psychological dysfunction, one must expect around a 30% dropout rate. This means that by the end of the study only 150 or so subjects remained. This is an unsatisfactory measure of the population by this researcher’s standards.

In regards to side effects of such a drug, it is possible that new side effects could be uncovered at a later date. Since substance P is involved in the mechanism of neurotransmission and reception in many sites in the body, it is possible that some kind of neurological problem could arise. The full duties of substance P in the body are not known for sure. Thus, inhibiting the absorption of what could be a key player in emotional, neurological, and possibly some other kind of control could have long lasting effects. The good news is that current research shows that, in comparison to other psychopharmaceuticals, NK1 antagonists have many fewer occurrences of known side effects, especially sexual dysfunction. Sexual dysfunction is one of the main reasons why a patient will stop taking their, most times extremely necessary, medication. Thus, if a new drug, which produces less sexual dysfunction as a side effect, can be found then more people can be free of symptoms that inhibit their ability to live a normal lifestyle, which of course is the goal of all pharmaceutical advances.

In the case of MK-869, it is unclear whether its clinical inconclusiveness was due to experimental design, drug efficacy, or the mechanism of administration. If it is drug efficacy then the more potent version of MK-869 in Phase II trials at this time should triumph. If the experimental design is the problem then it may be a while before we see any of this breed of antidepressants because a good experimental design is not the easiest thing to come up with. Regardless, it is the belief of this researcher that the possibility of a substance P receptor antagonist functioning as an antidepressive agent is a definite. The research has been done, and the statistics analyzed and it is very conclusive that NK1 receptor antagonism is a possible route to further treating depression and possibly other psychological dysfunction.
TABLE 1  
(Adapted from Baby et al. 1999)

<table>
<thead>
<tr>
<th>Adverse Effects</th>
<th>MK-869</th>
<th>Paroxetine</th>
<th>Placebo</th>
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</thead>
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<tr>
<td>Headache</td>
<td>32</td>
<td>28</td>
<td>24</td>
</tr>
<tr>
<td>Somnolence</td>
<td>20</td>
<td>19</td>
<td>9</td>
</tr>
<tr>
<td>Nausea</td>
<td>18</td>
<td>29</td>
<td>10</td>
</tr>
<tr>
<td>Asthenia/Fatigue</td>
<td>14</td>
<td>19</td>
<td>4</td>
</tr>
<tr>
<td>Insomnia</td>
<td>11</td>
<td>14</td>
<td>9</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>11</td>
<td>15</td>
<td>9</td>
</tr>
<tr>
<td>Sexual Dysfunction</td>
<td>3</td>
<td>26</td>
<td>4</td>
</tr>
</tbody>
</table>

The results of the first clinical trials show that MK-869 is as effective, if not more effective at relieving symptoms of depression compared to current antidepressants, it is safe, and it generally produces less adverse effects than current antidepressants, and in some cases less than placebo. One drawback that was noted in another report was that the effect of MK-869 was not significant until the second or third week of trials. This means that a patient taking this medication would not feel relieved from depressive symptoms until the second or third week of drug therapy.

FIGURE 2

MK-869 (17 is the research compound used for the trials talked about in this article.)

14, R₁ = F, R₂ = CH₃, R₃ = H
15, R₁ = H, R₂ = CH₃, R₃ = H
16, R₁ = CF₃, R₂ = H, R₃ = F
17, R₁ = CF₃, R₂ = CH₃, R₃ = F

(Hale et al. 1998)

The results of the Phase II clinical trials of MK-869 are not as impressive as the prior studies. In this trial the MK-869 group did only slightly better than the placebo group. The other, currently used antidepressant posed against the placebo, also did not beat the placebo. Unfortunately, regardless, due to these results, Merck has pulled MK-869 from further testing. However, whether or not NK1 antagonists are useful as antidepressant substances is still under question. For this reason, Merck has sent another, more potent compound, similar to MK-869 into Phase II studies.

THE FUTURE

The future of any drug is not always what it seems. For MK-869 it is not clear as to what its fate may be. At this time we know that Merck has concluded its Phase II trials on the drug.
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Acquired Immune Deficiency Syndrome (AIDS)

By: Ramin Sadeghi
Class: Organic Chemistry 236
Instructor: Dr. Hank Mancini
04 / 20 / 2001
Abstract:

One can hardly appreciate the advances made in AIDS research without some knowledge of the complexities of the AIDS virus itself. Acquired Immune Deficiency Syndrome or, as it is commonly known, AIDS, is a fatal disease. It is caused by a virus called human immunodeficiency virus or HIV for short.

Virology plays a central role in the multidisciplinary nature of AIDS research. The design of specific therapies, for example, is based on details of the life cycle of the AIDS virus—how it infects cells, multiplies itself, and eventually kills cells. This project demonstrates the cunning of this wily foe, identifies the holes in our understanding of the virus, and previews the way in which science plans to outsmart this very smart and fatal virus.

History of AIDS: ¹,²

In 1981 unusual infections were identified in a small number of homosexual men in California and New York. The infections responded poorly to therapy and ended in the death of the patient. Physicians concluded that the patients had developed an illness never before described in the medical literature. The new condition was named the Acquired Immunodeficiency Syndrome, or AIDS.

The name AIDS acknowledged all of the fundamental characteristics of the illness, in particular the underlying impairment of the immune system and resulting inability to fight infections. The word acquired was chosen because the illness was not inherited or the result of other recognized conditions; the illness developed during a period of health with no identifiable explanation for the immunodeficiency. The word syndrome signified that the disease could present with many different clinical manifestations but that the affected patients ultimately had the same underlying illness.

Several years elapsed between the first reports of AIDS and the identification of the virus that caused it, the human immunodeficiency virus (HIV). The name acquired immunodeficiency syndrome was selected in 1981 to describe what scientists and the medical community knew about the illness at the time that it was named. The term AIDS is now a part of everyday speech.

Normal immunity: ³

Normal immunity is the ability of a healthy body to resist the development of disease. Any physical barrier that prevents the entry of a pathogen, a microbe, or substance that can cause disease, is in a very general way part of the immune system. Cough, intact skin, acid in the stomach, and digestive enzymes in tears are all barriers to the entry of potential pathogens.

While these physical barriers contribute to immunity, a more specific protection against pathogens occurs from a more basic defense. This defense has white blood cells as the principal component. Of the white blood cells, it is the subtype known as
Lymphocytes that are key to many forms of immunity and specifically those that are altered in AIDS. There are two principal defenses mounted by the lymphocytes: the cellular immune response and the humoral immune response.

T lymphocytes, a class of white of white blood cells, mediate the cellular immune response. In HIV infection, a subset of T lymphocytes called CD4 lymphocytes are infected and killed by the HIV. It is the loss of CD4 cells that produces the immune deficiency of AIDS. In addition to lymphocytes, there are other kinds of blood cells, including monocytes, macrophages, granulocytes, and natural killer cells, that play supporting roles in the cell-mediated immune response.

The humoral immune response relies on proteins produced by B-lymphocytes. B-lymphocytes circulate in body fluids and become activated when they contact a pathogen. These activated cells secrete antibodies - proteins that bind directly to pathogens and facilitate their elimination from the body.

*How does HIV decrease immunity?*

HIV preferentially infects two cell types. Both part of the immune system: CD4 lymphocytes (a subset of the T lymphocytes) and macrophages. The lymphocytes are a class of white blood cell of which there are two primary kinds: B-lymphocytes and T lymphocytes. B-lymphocytes secrete antibodies that are proteins directed against foreign substances including microorganisms and viruses. They are not directly infected by HIV. T lymphocytes have a wide range of functions important for activating, modulation. And effecting the immune response. The subset of T cells called the CD4 lymphocyte or T-helper cells are critically important for coordinating and carrying out much of the immune response to tumors, viruses, fungi, and other types of microorganisms. It is these types of lymphocytes that HIV selectively infects and destroys.

A second cell type infected by HIV is the macrophage. This cell participates in the immune response by interacting directly with CD4 lymphocytes. A highly daily production of individual HIV virions within the body is necessary for loss of CD4 cells. Scientists showed in numerous trials that administering drugs active against HIV retards and perhaps prevents the loss of CD4 cells in HIV-infected individuals. These observations indicate that the ongoing production of HIV leads to loss of CD4 lymphocytes.

*Type of Virus:*

HIV is a member of a group of viruses called retroviruses. As with all viruses, Retroviruses are simple microscopic organisms dependent on a host for reproduction. They lack an independent metabolism and cannot grow without energy and nutrients supplied by a host cell. During infection of a host cell, retroviruses use cellular proteins to generate new genetic material and all the components from which a new virus is constructed. Retroviruses differ from most other viruses by virtue of their reproductive strategy.
In contrast with human cells as well as many other viruses that carry genetic information in the form of DNA, retroviruses carry genetic information in the form of RNA, another nucleic acid. Retroviruses convert viral RNA to DNA once the virus has infected the host cell.

During infection of a host cell, retroviruses use cellular proteins to generate new genetic material and all of the components that together form the offspring virus that emerges from the infected cell. RNA is converted into DNA through a process called reverse transcription, which is the defining characteristic of all retroviruses.

**The HIV virus structure:**

Retroviruses are some of the simplest viruses that exist. Their genetic information is carried in a small number of genes, almost always ten or fewer. Genes are the individual units of nucleic acid that determine hereditary characteristics. Retroviruses are roughly spherical with the outermost surface covered by a membrane (see Figure 1-1).

![HIV structure diagram](image)

**Figure 1.1.**
HIV, the AIDS virus. A computer-generated schematic of HIV reveals that the genetic material of HIV (RNA) is protected by a protein coat, which is itself surrounded and protected by a membrane-like envelope.

Like all viruses, HIV is biologically simple. It consists of a few proteins encased with its genetic information in a protein core. Some viruses, including HIV, have an extra layer of protection: a membrane-like “envelope” surrounding the protein core. The envelope includes the viral proteins gp120 and gp41. Viruses are parasites and require a host cell in order to replicate themselves. Lacking any metabolic or biochemical components of their own, they pirate their host’s metabolic machinery for reproduction. A single virus particle (a virus free of a host cell) is called a virion. Figure 1.1 offers a schematic representation of the HIV virion.
RNA and DNA: HIV is classified as an RNA virus because its genetic information is encoded in ribonucleic acid (RNA) rather than deoxyribonucleic acid (DNA). The discovery of RNA viruses is relatively recent (1961). Prior to this, all viruses were presumed to be DNA viruses because it was believed that only DNA contained genetic information. Now nucleic acid research allows scientists to read and “map” genes contained in the RNA of HIV.

RNA viruses that convert their RNA to DNA once they enter a susceptible (host) cell are known as retroviruses. “Retro” refers to the one backward step in the viral life cycle in which the normal pattern of DNA conversion to RNA is reversed. (See figure 1.2 for a diagram of these processes.) In animal cells, for example, DNA is converted, or transcribed, into RNA as an intermediate step in protein synthesis. Retroviruses, however, must first convert their RNA to DNA to take full advantage of the cell’s biochemistry.

Once viral RNA undergoes “reverse transcription,” the newly synthesized viral DNA can be incorporated into the infected cell’s DNA. This integrated DNA is then converted into a specialized type of RNA known as messenger RNA (mRNA). The cell then generates proteins from this mRNA.

Normal cellular pattern

Retroviral pattern

\[\text{RNA} \rightarrow \text{DNA} \rightarrow \text{mRNA} \rightarrow \text{Proteins}\]

\[\text{DNA} \rightarrow \text{Reverse transcription} \rightarrow \text{INTEGRATION}\]

Figure 1.2. Protein Syntheses.

The HIV life cycle:

In the broadest sense, the HIV life cycle is a scenario of invasion, assembly line replication, and destruction of the host cell. Figure 1.3 illustrates this sequence, from host-cell invasion through the emergence of the new virus particles.
HIV ENTRY INTO CELLS:
HIV must enter a host cell in order to reproduce itself; therefore, much research has been devoted to determining the mechanisms of host-cell selection and invasion. Certain immune system cells—T4 helper/inducer cells and macrophages, for example—display a molecule on their surface known as the CD4 receptor. This receptor provides an entry route for HIV, allowing the glycoprotein knobs of the HIV envelope to “dock” to the cell surface.

Internalization of HIV:
After the virus is docked, the cell then internalizes HIV by one of two possible routes: endocytosis (the cell fully engulfs the virus) or fusion of the viral envelope and cell membrane. Once HIV is internalized, the cell absorbs the virus’s outer envelope and leaves viral RNA, enzymes, and the protein coat free within the cell’s interior. The virus sheds its protein coat, so that the RNA can be replicated (using cellular enzymes) and converted to viral DNA (using the virus’s own enzyme reverse transcriptase).

![Diagram of HIV life cycle](image)

Figure 1.3. The HIV life cycle. Free virus enters a susceptible cell by means of the CD4 receptor. Once internalized, the virus replicates viral RNA (for new virus particles) and also transcribes viral RNA into viral DNA (reverse transcription). Viral DNA then integrates into cellular DNA, which is ultimately translated into active proteins, both cellular proteins and viral proteins. New viral particles are assembled; these particles then “bud” from the cell, acquiring envelopes as they burs from the cell membrane.

**REVERSE TRANSCRIPTION:**

Synthesis of viral proteins begins with reverse transcription of viral RNA; viral RNA must be converted into viral DNA before begin “translated” into functional proteins.
Although it possesses its own enzymes for conversion (reverse transcription) and integration (endonuclease), the virus must depend on the cell’s biochemistry for all other phases of protein synthesis. Ultimately, newly replicated copies of viral RNA are assembled into the new protein coats produced via reverse transcription and cellular transcription of viral genes.

**ASSEMBLY AND BUDDING:**

Once viral DNA is integrated into cellular DNA, it is transcribed into messenger RNA (mRNA). The cell then uses this mRNA to translate nucleic acid sequences into amino acid sequences. The cell manufactures viral proteins as large precursor proteins, which are inactive unless cleaved by the viral protease enzyme. HIV protease cleaves the precursor proteins into active HIV proteins, which are assembled with newly replicated RNA into new viral particles. These viral particles “bud” from the cell, taking along cell membrane components for a new envelope.

**The incubation period for AIDS:**

The incubation period for AIDS is the time that elapses between HIV infection and the development of an AIDS-defining condition. The median time between infection with HIV and the development of an AIDS-defining condition is about ten years. A large study of homosexual men from San Francisco initially helped define the incubation period of patients infected with HIV. Of the 288 men in this study, 33% developed AIDS 4-5 years after infection. Mathematical modeling of this group predicted a median of 10 years for the development of AIDS.

**Symptoms of AIDS:**

It may take months or even years after infection for symptoms of AIDS to appear at all. Here are some early signs of trouble we need to watch for:

- Tiredness, a very low energy level, an inability to be as active as before, without any apparent reason, over a period of several months.
- Loss of weight, perhaps fifteen pounds or more, or 10 percent of body weight, over a three-month period, without any dieting or change of eating habits.
- Swollen lymph glands in the groin, the neck, underarms, that last for several months and gave no apparent cause.
- Fevers, persisting over several months, for which there is no apparent cause, sometimes these fevers “spike” or shoot up suddenly.
- Chronic diarrhea.
- Night sweats, waking up in the night with the bed soaked from sweat.
- Flu or coldlike symptoms that last for a month or more.
- Rashes and other strange skin irritations that appear over period of time and then may disappear of persist.
Further symptoms:
Other symptoms are more directly related to the opportunistic infections related to AIDS:
➢ A dry, persistent, heavy coughs those lasts for month or more.
➢ Shortness of breath
➢ Purple or reddish areas on the skin, or growths with a raised surface on the skin usually appearing on the arms or legs, but also occurring on the mucous membranes in the mouth, and nose.

Transmission of HIV:
HIV transmitted through three routes: Sexual exposure, Contact with blood contaminated with HIV, and transmission from a mother to a child through pregnancy and birth. The vast majority of people are infected through sexual contact of one from or another. Statistics reveal that over one-half of all cumulative AIDS cases in the United States in 1999 were in homosexual and bisexual men.
HIV is present in many body fluids:

<table>
<thead>
<tr>
<th>Body site</th>
<th>HIV present</th>
<th>Transmission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood</td>
<td>Yes</td>
<td>Sharing needles, contaminated blood transfusion, and blood product</td>
</tr>
<tr>
<td>Breast milk</td>
<td>Yes</td>
<td>Maternal-child transfer</td>
</tr>
<tr>
<td>Feces</td>
<td>Yes</td>
<td>Implicated in a case of exposure to bloody feces</td>
</tr>
<tr>
<td>Saliva</td>
<td>Yes</td>
<td>Suspected in a case of exposure to bloody saliva</td>
</tr>
<tr>
<td>Semen</td>
<td>Yes</td>
<td>Sexual intercourse, insemination</td>
</tr>
<tr>
<td>Skin</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Tears</td>
<td>Yes</td>
<td>Unproved as a route of transmission</td>
</tr>
<tr>
<td>Urine</td>
<td>Yes</td>
<td>Unproved as a route of transmission</td>
</tr>
<tr>
<td>Vaginal/cervical</td>
<td>Yes</td>
<td>Genital to oral contact and genital to genital contact</td>
</tr>
</tbody>
</table>

Treatment of HIV infection:
The battle against AIDS is being waged on many fronts. One of the most intriguing is the effort to design drugs to specifically combat the AIDS virus. The anti-HIV drug program is based on:
a) Stopping viral multiplication or otherwise interfering with viral function will be beneficial to the patient.
b) Elimination of HIV will prevent or cure AIDS.
c) Natural or synthetic immunomodulators (substances that bolster the immune system) may be necessary to combat the effects of HIV because the virus infects several essential immune system cells.
**Drug Design Considerations**

*Mechanism of Action:* A primary consideration in the testing of any drug is its mechanism of action, how a drug achieves its effects. To combat HIV, the most effective drug mechanism is likely to be the interruption of the viral life cycle. Thus, current efforts focus on designing drugs to attack HIV at vulnerable stages in its life cycle in order to disrupt viral growth.

A variety of different drugs active against HIV exist. Most of the agents with demonstrated clinical utility act directly on the virus. These drugs can be understood by grouping them with the different stages of the HIV life cycle that they attempt to inhibit. The first step in HIV reproduction is attachment of the virus to the host cell and entry of the virus into the cell (figure 1.4). Agents that interfere with the binding and entry of HIV to cells gave been identified but were ineffective in all studies. Early approaches used soluble CD4 molecules to mimic the natural receptor for HIV and bind HIV before it encountered cells susceptible to infection. Use of this agent failed to produce useful virologic activity in clinical trials. Other approaches that exploit a newly identified molecule on the surface of lymphocytes called fusin may yield new drugs, but no drugs that inhibit fusin exist at this time.

![Diagram of the HIV life cycle](image)

**Figure 1.4:** Antiviral agents may inhibit any of several steps in the HIV life cycle:
1) attachment to host cell membrane, 2) reverse transcription of viral RNA to DNA, 3) transcription of viral cDNA integrated into host cell DNA, or 4) translation and assembly of viral RNA and proteins.

The next useful drug target is reverse transcription. This step requires the enzyme reverse transcriptase, which is provided by HIV. Reverse transcriptase transcribes, or copies, viral RNA in to DNA that is then introduced into the DNA of the host cell.
Because this is essential to HIV reproduction, reverse transcription is a particularly attractive target for drugs. Agents that inhibit reverse transcriptase benefit infected humans. Zidovudine (ZDV or AZT), and lamivudine (3TC) are the most common reverse transcriptase inhibitors used to treat patients with HIV infection.

Zidovudine is a pyrimidine nucleoside analogue drug. The chemical name of Zidovukine is 3'-azido-3'-deoxythymidine and the molecular formula is C_{10}H_{13}N_{3}O_{4}. The structure formula of brand name Retrovir Zidovudine is shown. Zidovudine is a thymine analogue in which the 3'hydroxy (-OH) groups is replaced in a substitution reaction by an azido (-N_{3}) group.

Zidovudine, formerly called azidothymidine or AZT, was originally tested as an anticancer drug in the 1960s; because of its mechanism of action (described below), the drug was evaluated in 1985 for the treatment of AIDS. Zidovudine subsequently became the first AIDS drug approved by the Food and Drug Administration (FDA).

At the molecular level, the mechanism of action of zidovudine is treatment of growing polynucleotide chains that is, DNA. In the context of AIDS, Zidovudine exerts an antiviral effect on HIV-infected cells: it terminates the synthesis of viral DNA from the genetic material of the virus, RNA. (This phase in the viral life cycle is called reverse transcription). During reverse transcription, the catalyst for the conversion of RNA to viral DNA (known as reverse transcriptase) is more sensitive to Zidovudine than is the cell's comparable catalyst. Studies show that Zidovudine competes with the correct DNA precursor molecule, so that the drug does not inhibit reverse transcription 100% of the time. Furthermore, the virus is never eliminated from the cell because even a single copy of viral RNA represents a potentially infectious particle. Results from on-going clinical studies reported at the Conference show that Zidovudine continues to be tolerated by select AIDS/ARC patients in extended treatment trials.

The mortality rate of AIDS patients receiving Zidovudine is lower than that for untreated patients. This finding led the FDA in 1986 to offer Zidovudine to all AIDS patients receiving a placebo in the early Zidovudine clinical trials.

**Conclusion:**

I believe that combinations of anti-HIV drugs as the choice of treatment of AIDS for the future is better than using drugs separately. The advantages and biological basis of using combination therapy are significant:

- Drugs that target different steps in the viral life cycle and gave been proven not to act antagonistically in tissue culture-will gave a greater potential of inhibiting HIV growth.
- Using drugs in combination generally allows lower single doses of each drug to be used, thereby decreasing the chances of toxic side effects.
- Using more than one drug reduces the risk of specific drug-resistant strains of HIV.
- Combination treatment increases the chances of accessing HIV in different cell types.

Because the HIV virus can survive in the human body and in the blood, so I think if we transfer the same environment and conditions that is available outside of the cell to the inside of the cell, we will be able to kill the virus.

The other way that we can cure AIDS is to change the blood of a person with HIV infection, and replace it with healthy and safe blood. In this case, the HIV virus which can survive in the blood, will exit the body. I believe that although the drugs can control the progress of the virus, but also they have side effects. I think the cure of AIDS and any other disease is in the nature. Medicines that we derive from vegetables and fruits are healthier and do not have any side effects. Maybe one-day anti-virus of any virus can be find in that virus and the medicine use the virus against itself.
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Acetaminophen Toxicity in Dogs

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Chemistry 236
Dr. Mancini
April 27, 2001
Abstract

Acetaminophen, otherwise known as Tylenol or paracetamol, is extremely toxic to dogs when ingested. When a dog has ingested acetaminophen, it should be seen by a licensed veterinarian immediately. Treatment for this can range from very conservative efforts to very aggressive. In some cases, whether treated or not, death may result. Pet owners should never attempt to treat the symptoms of their dog without first contacting their veterinarian.

Acetaminophen can be easily obtained from a local drug store or pharmacy. Its purchase does not require a prescription. Tylenol, as it is commonly referred to, is an analgesic, not an anti-inflammatory. It is usually successful in relieving minor aches and pains in humans as well as reducing fever. This medication is a white crystalline powder and has a bitter taste. It dissolves in boiling water and in alcohol.\(^1\) The purpose of acetaminophen, when taken for pain by humans, is to act as an inhibitor of cyclooxygenase or otherwise known as prostaglandin H2 synthase. This enzyme catalyzes the early steps of the messaging system between the tissues to express pain.\(^2\) So in effect, acetaminophen works to increase the pain threshold by inhibiting cyclooxygenase. It may also inhibit chemical mediators that sensitize the pain receptors in addition to blocking prostaglandin synthesis.\(^3\) In most species, this chemical reaction is conjugated by sulfation or glucuronidation.\(^4\) Acetaminophen (\(4^{'-}\text{Hydroxyacetanilide\ N-acetyl-p-aminophenol\ N-}\ (4\text{-Hydroxyphenyl})\text{acetamide}\)) may be synthesized in three steps:

\[
\text{Synthesis of Acetaminophen}
\]

1. \(\text{NO}_2\)
   \(\text{OH}\)
   \(\text{OH}\)
   \(\text{20\% HNO}_3\)
   \(\text{25 C}\)
   \(\text{NO}_2\)
   \(\text{OH}\)
   \(\text{OH}\)
   \(\text{(30-40\%)}\)

2. \(\text{NO}_2\)
   \(\text{OH}\)
   \(\text{1) HCl}\)
   \(\text{2) OH}\)
   \(\text{NO}_2\)
   \(\text{OH}\)
   \(\text{OH}\)
   \(\text{NH}_2\)
   \(\text{OH}\)

3. \(\text{NO}_2\)
   \(\text{OH}\)
   \(\text{CH}_3\text{COOH}\)
   \(\text{(CH}_3\text{CO}_2\text{H)}\)
   \(\text{O}\)
   \(\text{(CH}_3\text{CO}_2\text{H)}\)
   \(\text{CH}_3\)
   \(\text{H}\)
   \(\text{N}\)
   \(\text{C}\)
   \(\text{O}\)
   \(\text{CH}_3\)
   \(\text{OH}\)
Upon ingestion of a non-toxic dose, usually a small amount of acetaminophen is oxidized to reactive metabolites. These highly reactive molecules are then scavenged by glutathione and excreted as mercapturic acid derivatives. These derivatives are biologically inactive and are not dangerous.\textsuperscript{5}

Acetaminophen is one type of nonsteroidal anti-inflammatory drug (NSAID). Because it can be so effective for pain relief in humans, some people give it to their dogs. In other cases, dogs may accidentally eat acetaminophen tablets if the drug is improperly stored. In any case, if too much acetaminophen becomes ingested it is toxic. Some veterinarians recommend a normal dose of acetaminophen within a range of 15 mg/kg; given by mouth every six hours.\textsuperscript{6} There are so many other pain relieving drugs on the market for dogs, however, that most veterinarians would not recommend giving any acetaminophen to dogs.

Acetaminophen is absorbed from the gastrointestinal tract very quickly and toxicity can occur in the dog if it ingests 100-150+ mg/kg of the non-steroidal drug. For instance, a ten-pound dog would be in danger if it consumed two regular strength Tylenol tablets or even one and a half extra strength Tylenol tablets. Let’s consider the amount of acetaminophen in over the counter examples. A bottle of Children’s Tylenol\textsuperscript{®} contains 80 mg of acetaminophen; Regular Strength Tylenol\textsuperscript{®} contains 325 mg of acetaminophen; Extra Strength Tylenol\textsuperscript{®} contains 500 mg of acetaminophen.\textsuperscript{7} So it can be very easy for the lay person to estimate a toxic dose incorrectly to a dog. Within a matter of a few hours (usually 1-4 hours of ingestion), a dog that has ingested a high level of acetaminophen will begin to feel discomfort and display signs of toxicity.\textsuperscript{8} Dogs with acetaminophen toxicity may become depressed, anorexic, vomit, and have abdominal pain. Dogs, which are moderately affected, may recover within 48-72 hours, however in severe cases, the dog may have extensive liver damage and/or die. Without treatment, liver damage generally occurs 12-15 hours after the ingestion of acetaminophen.\textsuperscript{9} A recent study was conducted where a group of veterinarians found that after obtaining liver tissues on deceased dogs, the hepatic lobules were severely necrotic with only a very thin layer of hepatocytes around the outer perimeter.\textsuperscript{10} This clearly illustrates severe liver damage with no chance of regeneration. In addition to this, many case studies show that the gastrointestinal tract suffers extensively from this non-steroidal anti-inflammatory drug. Experiencing abdominal pain, the dog may tense the abdomen and lay out stretched on the ground. It is important to be aware of any abnormal behavior one’s dog exhibits; not all dogs whine or cry out when in pain. Many dogs have a much higher pain tolerance than humans and may never vocalize.

When ingested, acetaminophen under goes many chemical reactions in the body. At some point in this chain reaction, acetaminophen is oxidized to an extremely reactive metabolite, N- acetyl-para-benzoquinoneimine (NAPQI). By way of a long and complicated process, NAPQI metabolite binds to liver cell membranes, causing damage to the lipid layer. This in turn causes hepatocyte damage and finally death. Further, NAPQI causes severe oxidative stress to red blood cells in effect damaging the heme ions. This damage results in methemoglobin. In this situation ferrous iron is oxidized to ferric iron converting hemoglobin to methemoglobin, which cannot carry oxygen. Methemoglobinemia causes the mucus membranes to appear brown in color and is usually accompanied with tachycardia, tachypnea, weakness, and lethargy. The oxidation of hemoglobin also causes Heinz body formation. Heinz bodies or eccentrocytes appear
on a blood smear as single, rounded protrusions of the red blood cell membrane. They have a pale ring of cytoplasm around the base of the projection. Acetaminophen also causes anemia, hemoglobinuria, icterus and elevated liver enzymes.

When a dog is presented to a veterinarian with acetaminophen toxicity, the doctor will place an IV catheter and begin fluids. Many times these patients are dehydrated and need fluid and electrolyte replacement therapy. A baseline blood panel will be performed, checking the liver, kidney, and pancreatic enzymes. A blood smear will also be examined under the microscope to check for such abnormalities as Heinz bodies. It may be recommended by the veterinarian that the patient be hospitalized for several days in a critical care environment with constant monitoring.

Treatment depends on the presentation of the patient and stabilizing him or her takes precedence. If a dog presents labored breathing for example, the first priority in treatment is oxygen therapy. Such secondary conditions may arise if the owner makes any delay in seeking medical attention. In addition, the veterinarian may find that a blood transfusion is in order if the red blood cells are too compromised to function effectively. The overall objective of treatment for acetaminophen toxicity in dogs is to replenish the glutathione, convert the methemoglobin back to hemoglobin, and to prevent or treat any liver/hepatic necrosis.

If the dog recently ingested acetaminophen (within 4 hours) the first order of business may be to induce vomiting. This is to be performed under the supervision of the veterinarian. While hydrogen peroxide (1-2 ml/kg) is a useful emetic, apomorphine is most commonly used to induce vomiting. This is generally a powder or small tablet (1.5-6 mg/kg), which is gently placed in the conjunctival sac where it dissolves. Some veterinarians find gastric lavage useful as well. In this situation, the dog is anesthetized and the veterinarian passes a long hose through the mouth to the stomach. Here, using warm tap water, the stomach is pumped. The goal in each of these procedures is to rid the stomach of the acetaminophen before it is completely absorbed by the gastrointestinal tract. Another means to stymie the absorption of acetaminophen is to feed the dog activated charcoal (1-3 g/kg). Activated charcoal adsorbs acetaminophen preventing it to cause serious problems biochemically as it travels down the gastrointestinal tract. The activated charcoal should be repeated every 3-4 hours because acetaminophen undergoes enterohepatic recirculation; meaning that it continues to filter and recirculate within the confines of the liver before it is completely metabolized. Activated charcoal, resembling an almond flavor, is quite tasty to some dogs and very foul to others. Activated charcoal may be mixed with food for willful ingestion by the patient or force-fed to the dog with a large syringe. In extreme cases, a tube may be passed down the esophagus of the dog and the activated charcoal passed down into the tube to the stomach. Lastly, if the dog does not have diarrhea or is not severely dehydrated, it is recommended to administer a medicine to the dog that will stimulate the evacuation of the bowels. This first step is basically a decontamination phase where the veterinarian attempts to “head off” and stop the acetaminophen toxicity forcing it to exit the body in a decontaminating form.

The next phase of treatment involves treating a toxic dog showing the clinical signs of toxicity where the ingestion time is longer than four hours. One preferred drug is N-acetylcysteine (Mucomyst). This may be administered either by mouth or IV. The oral route is preferred due to the absorption of the Mucomyst from the gastrointestinal tract into the circulation of the liver where it then increases in concentration so as to
detoxify the liver. One consideration however is that activated charcoal inactivates
Mucomyst if both are administered orally at close time intervals. There should be
approximately 30-60 minutes lapse between the activated charcoal administration and the
Mucomyst. Mucomyst directly binds to acetaminophen metabolites and inactivates them.
These inactivated metabolites then serve as a glutathione precursor for future necessary
chemical reactions. Hence, Mucomyst provides an alternate substrate for conjugation
with the reactive metabolites of acetaminophen so as to reduce the extent of liver injury
or methemoglobinemia.

Other types of therapy include the administration of Vitamin C (ascorbic acid).
This provides a reserve system for the reduction of methemoglobin back to hemoglobin.
Because the administration of Vitamin C can cause gastrointestinal upset, a
gastrointestinal protecting agent is recommended; for example, cimetidine (tagamet) or
pepcid (famotidine) is recommended. According to the Journal of Veterinary Emergency
and Critical Care, the use of Mucomyst, Vitamin C and cimetidine together has been
shown to be more effective than any of the three agents used alone. Supportive therapy
should extend so far as oxygen therapy in the event of labored breathing, intravenous
fluids to keep the patient well hydrated, red blood cell transfusion if the cells are too
damaged to efficiently carry oxygen, and sodium bicarbonate in the event that severe
acidosis results. Overall patient care may result in 72 hours of continuous
hospitalization. Below is a chart to outline the clinical signs and treatment for
acetaminophen toxicity in dogs discussed thus far.

<table>
<thead>
<tr>
<th>Size (mg/kg)</th>
<th>Clinical Signs</th>
<th>Specific Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 200</td>
<td>Anorexia, depression, vomiting, abdominal pain, icterus, methemoglobinemia, hemoglobinuria, weight loss</td>
<td>Mucomyst at 140 mg/kg</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 500</td>
<td>Profound depression, vomiting, severe methemoglobinemia, hemoglobinuria, and hematuria, edema of forelegs, paw and face, possible shock and death</td>
<td>Mucomyst at 280 mg/kg Vitamin C 20-30 mg/kg</td>
</tr>
</tbody>
</table>
Other supportive therapy includes continued blood count monitoring via CBC. A CBC is a blood differential analysis, which basically illustrates the condition of organs and enzymatic function. Below is an example of a CBC and its description of the differentials for a puppy under six months of age.

<table>
<thead>
<tr>
<th>Test</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALB</td>
<td>2.10-3.60g/dl</td>
</tr>
<tr>
<td>ALKP</td>
<td>46-337 U/L</td>
</tr>
<tr>
<td>ALT</td>
<td>8-75 U/L</td>
</tr>
<tr>
<td>AMYL</td>
<td>300-1300 U/L</td>
</tr>
<tr>
<td>BUN</td>
<td>7.0-29.0 mg/dl</td>
</tr>
<tr>
<td>Ca</td>
<td>7.80-12.60 mg/dl</td>
</tr>
<tr>
<td>CHOL</td>
<td>100.0-400.0 mg/dl</td>
</tr>
<tr>
<td>CREA</td>
<td>0.30-1.20 mg/dl</td>
</tr>
<tr>
<td>GLU</td>
<td>90.0-140.0 mg/dl</td>
</tr>
<tr>
<td>PHOS</td>
<td>5.10-10.40 mg/dl</td>
</tr>
<tr>
<td>TBIL</td>
<td>0.00-0.80 mg/dl</td>
</tr>
<tr>
<td>TP</td>
<td>4.80-7.20 g/dl</td>
</tr>
<tr>
<td>GLOB</td>
<td>2.30-3.80 g/dl</td>
</tr>
<tr>
<td>HCT</td>
<td>37.0-55.0%</td>
</tr>
<tr>
<td>HGB</td>
<td>12.0-18.0 g/dl</td>
</tr>
<tr>
<td>MCHC</td>
<td>30.0-36.9 g/dl</td>
</tr>
<tr>
<td>WBC</td>
<td>6.0-16.9 x10^9/L</td>
</tr>
<tr>
<td>GRANS</td>
<td>3.3-12.0 x10^9/L</td>
</tr>
<tr>
<td>L/M</td>
<td>1.1-6.3 x10^9/L</td>
</tr>
<tr>
<td>PLT</td>
<td>175-500 x10^9/L</td>
</tr>
</tbody>
</table>

Hence, for the duration of the patient’s stay, blood work, IV fluids and any other supportive care should be continued until no clinical signs remain and all test results are normal.

In sum, administering acetaminophen to dogs for pain or a fever is very toxic. The physical conditions that arise are progressive depression, vomiting, abdominal pain and dark colored urine and serum. These symptoms may all lead to chronic liver failure and depletion of red blood cells and eventually end in death. It is imperative to seek veterinary assistance immediately once acetaminophen ingestion has been determined. Aggressive treatment begins with the induction of vomiting, the administration of activated charcoal, the placement of a catheter to administer IV fluids followed by the
administration of Mucomyst. This may then be followed up with Vitamin C supplements and cimetidine. Owners should be prepared to leave the dog in the hospital for no less than 72 hours for critical care nursing including repeat blood work and other diagnostic tests that the veterinarian deems necessary. Unfortunately dogs that have accidentally ingested acetaminophen will do it again if the opportunity presents itself. Not all dogs, as with other animals, completely understand the severity of the situation nor do they learn and/or retain a memory of what owners might classify as “a lesson learned” from a dangerous situation.

What the future holds for this type of misuse of acetaminophen will take an extremely educated and conscious pet owner. There will always be those members of society who suffer financially no matter what the economy. Many people have pets that simply cannot afford them. In some cases, the owners are blessed with good healthy pets; but others are not so lucky. As long as there are those pet owners who cannot afford to take their dog to the veterinarian every time it has a fever or is in pain, society will continue to have dogs mistreated with non-steroidal anti-inflammatory drugs. As long as people cannot afford it, they will continue to medicate from home. Some pet owners have the idea that “if it works well for me and makes my headache go away then it will also help Fluffy.” Unfortunately some think that more is better and if one tablet is recommended by the manufacturer then two tablets will be even better! In addition, pets can be as mischievous as children. They get into things and open bottles of medication that some humans cannot open with ease. Accidents will always happen no matter how careful we try to be. The point is, as long as there exists dogs, drugs, and people, acetaminophen toxicity will continue. One purpose of this paper as well as other journals and articles is to raise the public awareness. Place any and all medication out of reach away from pets and children and never medicate your dog as you would yourself without first consulting your veterinarian.
Sources


MEPHYTON
(Phytonadione, Vitamin K₁)

Ryan Schonscheck
CHM 236

Dr. Mancini

April 27, 2001
Abstract

Vitamins are compounds that are necessary for growth and health. They are needed only in small amounts and usually are available in everyday diets. This paper will cover aspects involving Mephyton (Phytonadione) or Vitamin K₁. The paper will mainly focus on pharmacological aspects of this vitamin. It will also include a brief discussion on the clotting process.

Historical Background

Vitamin K was discovered as a result of a series of experiments carried out by Henrick Dam on the possible essentiality of cholesterol in the diet. He studied the distribution and lipid solubility of the active component in vegetable and animal sources and proposed that the antihemorrhage vitamin was a new fat-soluble vitamin. Vitamin K received its name in 1935 when it was termed the “Koagulation” vitamin.³ By 1939 vitamin K₁ had been extracted from alfalfa and identified as 2-methyl-3-phyltyl-1, 4-naphthoquinone. The FDA originally approved Vitamin K in 1940.

Mephyton (Vitamin K₁) is a vitamin that is clear, yellow, viscous, and nearly odorless liquid. It is fat-soluble, and soluble in chloroform, slightly soluble in ethanol, but insoluble in water.² The inactive ingredients include acacia, calcium phosphate, colloidal silicon dioxide, lactose, magnesium stearate, starch, and talc.

Mephyton (Phytonadione, Vitamin K₁)

Phytonadione is a 2-methyl-3-phyltyl-1, 4-naphthoquinone.
Empirical Formula: C₃₁H₴₆O₂

*The methyl group at the 2 position is essential for activity
1. The clotting process begins when the endothelium of a vessel is damaged and connective tissue in the vessel wall is exposed to blood. Platelets adhere to collagen fibers in the connective tissue and release a substance that makes nearby platelets sticky.

2. The platelets from a plug provide emergency protection against blood loss.

3. This seal is reinforced by a clot of fibrin when vessel damage is more severe. Fibrin is formed via a multi step process: Clotting factors released from the clumped platelets or damages cells mix with clotting factors (II, VII, IX, and X) in the plasma. This forms an activator that converts a plasma protein prothrombin to its active form, thrombin. Calcium and vitamin K are some of the essential plasma factors required for this step. Thrombin is the enzyme that catalyzes the final step of the clotting process. This step is the conversion of fibrinogen to fibrin. The threads of fibrin become interwoven into a patch. Illustration (b) demonstrates how the red blood cells are trapped in the clot of fibrin. (3)
Clinical Pharmacology

Mephyton is a synthetic compound that is chemically indistinguishable from naturally-occurring vitamin K by posing the same degree and type of activity necessary for the production via the liver of active prothrombin (Factor II), proconvertin (Factor VII), plasma thromboplastin component (Factor IX), and Stuart factor (Factor X). The major function of vitamin K is as an essential cofactor for microsomal enzyme that catalyzes the carboxylation of multiple peptide-carboxyglutamic acid residues in inactive hepatic precursors of factors II, VII, IX, and X. The result is gamma-carboxyglutamic acid residues that convert the precursors into active coagulation factors. The active coagulation factors are secreted by liver cells into the blood.\textsuperscript{(4,5)}

In this figure, the vitamin K-dependent proteins circulate as inactive forms until converted to their active forms which are indicated by a subscript "a". These conversions occur in stages where an active protease, a substrate, and a protein cofactor (indicated within a triangle) form a \( \text{Ca}^{2+} \) mediated association with a phospholipid surface. The protein cofactors V and VII are activated by thrombin (IIa) to achieve their full activity. The clotting system is divided into two pathways. The extrinsic pathway which involves a tissue factor in addition to
blood components. The second is the intrinsic pathway, which involves components present in the blood. Protein C functions as an inactivating component for the cofactor proteins, and shut down the overall reaction.

When taken orally, Mephyton is absorbed from by an energy-dependent process from the proximal portion of the small intestine into the lymphatic system. This process requires the presence of both bile salts and pancreatic juice. The lymphatic system has been demonstrated to be the major route of active transport of the absorbed vitamin K from the intestine. After absorption, vitamin K, is initially concentrated in the liver. The concentration declines rapidly, and very little vitamin K accumulates in tissues. Unfortunately, the metabolic fate of vitamin K is uncertain. Almost no free unmetabolized vitamin K is present in bile or urine. In normal humans and animals, vitamin K is virtually devoid of pharmacodynamic activity. In deficient vitamin K humans and animals, the pharmacological action is related to its normal physiological function. That physiological function is to promote the hepatic biosynthesis of vitamin K-dependent clotting factors. Vitamin K does not correct abnormal platelet function. It may have decreased effectiveness in humans and animals with hepatic impairment because as stated earlier, the liver is the site of blood clotting factor synthesis.

**Vitamin K Content and Requirements**

<table>
<thead>
<tr>
<th>Vitamin K Content of Various Common Foods</th>
<th>Vitamin K, g/100g</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 10</td>
<td>10-50</td>
</tr>
<tr>
<td>Fluid Milk</td>
<td>Cheese</td>
</tr>
<tr>
<td>Skeletal Meats</td>
<td>Butter</td>
</tr>
<tr>
<td>Whole Corn</td>
<td>Liver (most)</td>
</tr>
<tr>
<td>Whole Wheat</td>
<td>Eggs</td>
</tr>
<tr>
<td>Bread</td>
<td>Corn Oil</td>
</tr>
<tr>
<td>Potatoes</td>
<td>Sunflower Oil</td>
</tr>
<tr>
<td>Carrots</td>
<td>Oats</td>
</tr>
<tr>
<td>Tomatoes</td>
<td>Green Beans</td>
</tr>
<tr>
<td>Oranges</td>
<td>Peas</td>
</tr>
<tr>
<td>Peaches</td>
<td>Coffee (dry)</td>
</tr>
<tr>
<td>Apple Sauce</td>
<td></td>
</tr>
</tbody>
</table>

Vitamin K is found in both plant and animal sources. It is found in various foods including green leafy vegetables, meat, and dairy products. It can also be produced by intestinal bacteria. Mephyton is found in plants, and is the only natural vitamin K available for therapeutic use.
The vitamin K requirement is extremely low for an adult human. A studied was conducted on the vitamin K requirement of starved intravenously fed debilitated patients given antibiotics to decrease intestinal vitamin K synthesis from bacteria. The studied determined that doses of intravenous phytonadione (vitamin K₁) that measured \(1 \text{ g/kg/day} \) was sufficient to prevent any decrease in clotting factor synthesis. Vitamin K deficiency causes an increase in bleeding tendency demonstrated by ecchymoses, epistaxis, hematuria, GI bleeding, and postoperative and intracranial hemorrhage.

**Dosage and Administration**

The dose of vitamin K is different for different individuals. The following include the average doses of vitamin K. To correct excessively prolonged prothrombin times caused by oral anticoagulant therapy, 2.5mg to 10 mg, or up to 25 mg is administered orally. In rare instances 50 mg maybe required. If in 12 to 48 hours after oral administration, the prothrombin time has not been shortened, the dose should be repeated.

If hypoprothrombinemia due to conflicting with other medications occurs, if possible, discontinuation or reduction of the dosage of drugs interfering with coagulation mechanisms such as antibiotics is recommended. In this case, 2.5mg to 25 mg is recommended. The amount and route of administration may depend on the severity of the condition and response obtained. The oral route should be avoided when the clinical disorder would prevent proper absorption. Bile salts must be given with the tablets when the endogenous supply of bile to the gastrointestinal tract is deficient.

For problems with blood clotting or increased bleeding in adults, 2.5 mg to 25 mg is taken orally. A usual dosage of 2 mg to 25 mg is administered by injection into a muscle or under the skin. Whether administered orally or by injection, both maybe repeated if necessary. For children, the usual dosage is 2.5 mg to 10 mg injected into the muscle or under the skin. The dose maybe repeated after six to eight hours if necessary. Oral administration is not recommended. For infants, the usual dose is 1 mg to 2 mg injected into a muscle or under the skin. The dose maybe repeated after four to eight hours.

**Drug Interactions**

When taking vitamin K, it is especially important to determine if any other prescription medications or over the counter medications or vitamin supplements interact with the vitamin. The following is a list of prescription medications that may interact with vitamin K:

- Acetyldroxamic acid (Lithostat)
- Antidiabetics
- Furazolidone (Furoxone)
- Methyldopa (Aldomet)
Dapsone
Primaquine
Quinidine (Quinidex)
Sulfonamides (Sulfa Medicine)

Nitrofurantoin (Furadantin)
Procainamide (Pronestyl)
Quinine (Quinamm)
Sulfoxone (Diasone)

Patients taking anticoagulants (blood thinners) such as Warfarin should not take any supplement that contains vitamin K (unless it has been ordered by a doctor). Warfarin antagonizes the actions of vitamin K. Vitamin K antagonists inhibit the effect of vitamin K during the hepatic synthesis of factors II, VII, IX, and X. This results in the synthesis of biologically inactive but immunologically detectable forms of the proteins. The vitamin K antagonists have the potential to be thrombogenic by inhibiting the synthesis of functional protein C (which functions as a inactivating component for the cofactor proteins), as well as antithrombotic by inhibiting the synthesis of factors II, VII, IX, and X. Aspirin is also a concern due to its anticoagulant properties.

Side Effects

Along with the needed effects of vitamin K, some unwanted or side effects exist. These side effects are not common in individuals taking vitamin K. These side effects may occur when high doses of vitamin K3 is administered, or when taken with Menadiol: decrease in appetite, decreased movement or activity, difficulty breathing, enlarged liver, general body swelling, irritability, muscle stiffness, paleness, yellow eyes or skin. When the vitamin is injected, rare side effects exist. These side effects include: difficulty swallowing, fast or irregular heartbeat, lightheadedness, shortness of breath, and skin rash. When taken orally, flushing or redness of the skin, dizziness, fast and/or weak heartbeat, and increased sweating. All of these possible side effects occurred in people taking vitamin K, but they were all rare instances.

Conclusion

In conclusion, this paper has discussed the importance and effects vitamin K can have on the human body. This included blood clotting, which is important to understand because of the importance vitamin K has on this vital process. Clinical pharmacology of vitamin K detailed the process of how important active cofactors are, and how this amazing process takes place in the body. Fortunately the accessibility of vitamin K is common in many foods, and the average need of vitamin K is low in the human body. Vitamin K is just one of the many vitamins that is essential in the body to help maintain good health. In the future, research will unlock all the mysteries of this vitamin, and new medications as well as the individuals taking them, will only prosper.
References


Micromedex Inc. 2000
CLONIDINE

Jennifer Seward
Organic Chemistry 236
April 27, 2001
Abstract:
Clonidine is primarily used as an antihypertensive agent. This paper discusses the history of clonidine, its chemical structure and mentions two ways in which the product is synthesized. The paper further delves into the mechanics of clonidine and how it is believed to work in the human body in terms of site of action and metabolism. It also explores new areas that clonidine is being used in and discusses possible new arenas that clonidine could be utilized for in the future. It also looks at potential problems that could arise from the use of clonidine in children and the elderly.

Background:
Clonidine was originally formulated in 1962 by Stahle in Ingelheim, Germany. It was initially manufactured to be a nasal decongestant that would be administered via the nasal passages. The first clinical trials were performed on members of the staff at Stahle. During these trials, clonidine's true purpose was determined.

According to Bock, the drug was first given to a secretary at Stahle suffering from a cold. She was given an initial dose of 10-15 drops of a 0.3% clonidine solution (approximately 2 mg). After 10 or 15 minutes, she fell asleep in a chair and did not awaken until the next day at noon. After administration of the drug, her vital signs were monitored. It was noted that at one point her pulse rate dropped to a low of 48 beats/minute.

Another staff member performed a personal experiment on himself by taking 2 mg of clonidine orally after witnessing the effects the drug had on the secretary. During the trial, he noted his vital signs as well as any side effects that he was feeling from the drug. At one point, his pulse rate fell to a low of 24 beats/minute after which he slept for 19 hours. Upon waking, his pulse rate had only risen to 40-48 beats/minute and his blood pressure was only 90/60 mm Hg. He also reported feeling dryness of the mouth and difficulty in writing due to feeling so fatigued. It was not until 30 hours after ingestion and also after taking a medication to raise his blood pressure that his blood pressure returned to 125/75 mm Hg and his pulse rate to 72 beats/minute. These trials labeled the most important therapeutic actions and side effects of clonidine.

Clonidine was not released in the United States until 1974. This delay was mostly due in part to Boehringer Ingelheim not being represented in the American market.

Chemistry:
Clonidine is a white, crystalline solid that is soluble in water or alcohol. The molecular formula of clonidine is C_{10}H_{19}Cl\textsubscript{2}N\textsubscript{3}. It has a molecular weight of 230.096 g.\textsuperscript{2} The melting point range of clonidine is 136-138°C. The structure of clonidine is a benzene ring with chlorine attached at the two and six position and nitrogen attached at the one position. Attached to the nitrogen is a double bond connected to a five-membered ring. The ring does not have carbons present in the two or five position but instead has nitrogen with an attached hydrogen. The following picture in Figure 1 illustrates the structure of clonidine. There are no chiral carbons present in this molecule.
One derivative of clonidine is clonidine hydrochloride. It has a molecular weight of 266.56 g with a melting point range of 310-312°C. The only difference is the addition of HCl in the molecule. The structure of clonidine hydrochloride is illustrated in Figure 2 and how it looks in the body is illustrated by Figure 3.

Clonidine is sold as a tablet, an injectable, and also as a transdermal patch. The tablets are available in the following dosage strengths: 0.1 mg, 0.2 mg, and 0.3 mg. The patches are sold as 2.5 mg, 5 mg, and 7.5 mg (to deliver 0.1 mg, 0.2 mg, and 0.3 mg/day respectively for one week). The injectable form is packaged as a 10ml vial with a concentration of 100 mcg/ml and is only used for epidural administration. The tablet and injectable formulations are actually the clonidine derivative, clonidine hydrochloride. The patch is not the derivative. Other names that clonidine is sold under include Duraclon (injectable), Catapres (tablet) and Catapres-TTS (patch).

Preparation:
There are two different preparations that were found listed for the synthesis of clonidine. While they both start with 2,6-dichloroaniline, the process by which the remainder of the molecule is added is quite different.

The first preparation is described in Remington's. Remington's describes the preparation of clonidine in the following manner. \(^3\) Ammonium thiocyanate converts 2,6-dichloroaniline to the thiourea which is treated with methyl iodide to yield the S-methylthiuronium salt. The latter compound, with ethylene diamine, closes the imidazole ring to afford the product. The following in Figure 4 is a model of this synthesis.
According to U.S. Patent 3,988,345, the only problem with this synthesis is that it does not produce a high yield of product and gives off H₂S gas which has a foul smell. They suggest the following preparation in order to produce a 90.3% yield.
In this preparation illustrated by Figure 5, 8.1 g of 2,6-dichloroaniline and 10.45 g of 1-benzoyl-2-imidazolidin-2-one are stirred with 73 ml of POCl₃ for 70 hours at 50°C. The mixture is completely concentrated by evaporation in vacuo, the residue is dissolved in 200 ml of methanol and the solution is heated to the reflux temperature for 4 hours. It is then completely concentrated in vacuo, the residue is dissolved in 100 ml of warm ethanol, the solution is cooled to 0°C, and alcoholic hydrochloric acid and 200 ml of ether are added. After standing at 0°C, the mixture is filtered and the crystals are washed with alcohol ether and dried. This represents a 90.3% yield of theory relative to the 2,6-dichloroaniline. Figure 5 is a model of this synthesis.

Biological Reactions and Applications:
Clonidine is mainly used as an antihypertensive agent. It is usually used in combination with other antihypertensive medications. The normal adult dosage is between 0.2 mg/day up to 1.2 mg/day given in divided doses. The maximum daily dosage that can be given is 2.4 mg/day. Doses must be gradually increased or decreased 0.1 to 0.2 mg per day. Injectable clonidine, which is administered as an epidural, is usually given at 30 mcg/hr.

It is important when discontinuing the use of clonidine that it be done over the course of a week or more. Rebound hypertension is one of the most severe side effects of discontinuing clonidine therapy. Rebound hypertension is a rapid increase in blood pressure equal to or greater than before the drug was initially started. Other side effects of clonidine include sedation, hypotension, and short-term stimulation of growth hormones in both children and adults. The patches can cause rashes on the skin if the site of application is not varied.

Clonidine is metabolized mostly in the kidneys but is also metabolized in the liver. While data differs, somewhere between 38% to 65% is excreted by the kidneys into the urine unchanged. The half-life of clonidine is between 6 to 20 hours in patients with normal renal function and 18 to 41 hours in people with renal impairment. Clonidine should only be used in pregnant or lactating women if it is necessary.

Clonidine is classified as an alpha₂-adrenergic agonist. In the CNS, alpha -adrenoceptors are located in the brain stem, involving the nucleus tractus solitarii, the vasomotor center, and the nucleus of the vagal nerve. Alpha₂-adrenergic receptors, in specific, have been found to be widely distributed in the brain and spinal cord. A high density⁶ of alpha₂ receptors have been found in the nucleus tractus solitarius, an area involved in the control of blood pressure. High densities of receptors were found over the nuclei, while immediately adjacent areas had very low or negligible levels. Parts of the hypothalamus also had elevated levels of receptors.

There were also elevated densities of alpha₂ adrenergic receptors found in several areas previously shown to have elevated densities of opiate⁷ receptors. These areas include the substantiae gelatineae of the spinal cord and trigeminal nucleus, the locus coeruleus⁸ (a tiny blue streak on the dorsolateral tegmentum of the pons), and the dorsal medial thalamus.

It is unknown whether clonidine acts on the presynaptic or postsynaptic alpha₂-adrenoreceptors. Figure 6 displays the two possible ways that clonidine might interact with the alpha₂-adrenergic receptors. In either case, the inhibition of signals at either the presynaptic or postsynaptic alpha₂-
adrenergic receptors is the major reason for clonidine's hypotensive effect. By slowing down the impulses to areas of the brain in charge of the autonomic rhythms of the heart, clonidine is able to diminish blood pressure and heart rate.

Figure 6

Other Uses for Clonidine:
One additional use for clonidine, besides the treatment of hypertension, is pain management. The injectable version of clonidine is used for just this purpose as an epidural. It is believed that in this manner, clonidine prevents pain signals from being transmitted to the brain. It is normally used in conjunction with opiates, such as morphine, for the treatment of severe pain in cancer patients due to an increased tolerance to pain medication. In the study that was performed, clonidine/opiate therapy was initiated in cancer patients suffering from varying types of cancer. These types included: breast, colon, colorectal, melanoma, and lung to name a few.

The study determined an overall 45% success rate in those receiving combination therapy versus only a 21% success rate in the placebo group. While these numbers might not be very different overall, clonidine showed a much higher success rate for those suffering from neuropathic pain rather than those suffering from somatic/visceral pain. The study also pointed out that patients who fail to achieve pain relief with systemic opioids eventually fail epidural or intrathecal pain treatment as well. Blood pressure and pulse rate must be monitored while clonidine is being administered.

Clonidine is not indicated in patients with pheochromocytoma. However, it has been used to aid in the diagnosis of pheochromocytoma in hypertensive patients and those with borderline catecholamine values. Plasma norepinephrine concentrations are generally unchanged following a single dosage of clonidine.
Other unlabeled uses of clonidine include the treatment of Tourette's syndrome, alcohol withdrawal, methadone/opiate detoxification, menopausal flushing, mania, restless leg syndrome, smoking cessation, and Attention Deficit Hyperactivity Disorder (ADHD). Some children with ADHD are given clonidine to induce sedation so that they may sleep during the night. Clonidine is also used to assist in alcohol withdrawal, methadone/opiate detoxification and smoking cessation. It is unclear how clonidine aids in alcohol and smoking withdrawal.

Clonidine should be used with caution in people receiving calcium channel blockers, beta blockers or drug known to affect sinus node function or AV nodal conduction. This is due to the additive effects of the medications and could lead to possible hypotension. People taking tricyclic antidepressants should avoid clonidine use. Also those using prazosin or levodopa should be cautious of taking clonidine concurrently. Alcohol and other sedative drugs should also be avoided. It is important as with any other prescription drug that a patient receive periodic check-ups while using clonidine.

One problem with using clonidine therapy is that the person must understand that it is important to not miss a dose. Children must be assisted by their parents to ensure that the proper amount of drug is taken as needed. An overdose in an adult or especially a child requires medical attention to ensure the safety of the patient. When children are prescribed clonidine, they must understand that they are the only ones to receive the medication and not give any to friends. In the elderly, it is important that doses not be missed or doubled-up on due to the potential for rebound hypertension or hypotension respectively. Also, in those with renal impairment, the doses must be adjusted do to the extended half-life of the drug.

People should also use caution when operating heavy machinery while taking clonidine. This includes driving. Clonidine takes some initial adjustment to get use to. When clonidine therapy is first initiated, fatigue can be a major issue.

In the future, clonidine could also be used to help people with insomnia due to its sedative effect or possibly for those with twitches or tremors as demonstrated in its unlabeled use with Tourette's.

A controlled release tablet would also a possible product venture for clonidine. This would help to diminish the possibility of missed doses since the drug currently has to be taken twice or more a day in intervals. This would also help decrease the risk to the patient of rebound hypertension. This would have to be used strictly in those patients taking clonidine to manage chronic hypertension and who would be taking clonidine long-term.

Clonidine is a very powerful but useful drug. Even though it has been present in the United States for almost 30 years, there is an entirely new realm that clonidine could be used for in the future.
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A New Outlook In Treating Osteoarthritis: Glucosamine Sulfate Supplementation

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Abstract

Osteoarthritis is a highly prevalent disease afflicting over 21 million people. A relatively new nutritional supplement on the shelves now is glucosamine sulfate. This paper covers the historical background, synthesis/manufacturing process, mechanism of action, benefits, and adverse affects associated with glucosamine sulfate. Particular attention is focused on the comparison of glucosamine sulfate to the traditional treatment of analgesics and non-steroidal anti-inflammatory drugs (NSAIDs).

Introduction to Osteoarthritis

To understand the role that Glucosamine Sulfate plays, it is important to understand joint structure and disease. Osteoarthritis is a painful degenerative joint disease. It can affect any joint in the body. It is the most common form of arthritis and is the leading cause of physical disability, increased health care usage, and impaired quality of life [1]. An estimated 12% of the U.S. population aged 25 years and older have clinical signs and symptoms of osteoarthritis. Perhaps an even more awakening statistic is that in patients over 45 years of age, 90% will demonstrate some degree of radiographic features of osteoarthritis in those joints that bear weight [2]. The most common form of osteoarthritis is termed “primary” and is associated with an initial roughening and eventual wearing away of the articular cartilage. The picture below graphically shows this wearing away of cartilage.

New hope for stiff joints

New research suggests that the progression of osteoarthritis, a form of arthritis characterized by cartilage deterioration, can be slowed by taking the nutritional supplement glucosamine sulfate.

**Healthy Joint**
- Muscle
- Cartilage
- Tendon
- Bone
- Joint capsule

**Osteoarthritic Joint**
- Loose cartilage particles
- Bone spur
- Cartilage destruction

A simple naturally occurring molecule that plays a significant role in the structure of cartilage and other connective tissues, glucosamine may help damaged cartilage repair itself.

Source: [3].
Articular cartilage is made up of connective tissue that consists of collagen and proteoglycans. Collagen is a strong, fibrous insoluble protein. Proteoglycans are large, carbohydrate-rich protein chains made up of 95% polysaccharides, and 5% protein called glycosaminoglycans [4]. Glycosaminoglycans are composed of repeating two-sugar units that contain glucosamine sulfate and other amino sugars. The cartilage in osteoarthritis is damaged, undergoes a reduction in the amount of proteoglycans, and is unable to repair itself effectively. This results in a vicious cycle of further cartilage damage [5]. The proteoglycan that is depleted more than others is hyaluronic acid.

Traditionally, osteoarthritis treatment includes physical (i.e. physical therapy), pharmacological (i.e. Ibuprofen, Aspirin), and surgical interventions. Pharmacological treatments have been divided into three categories, 1) Analgesics and non-steroidal anti-inflammatory drugs (NSAIDs), 2) symptomatic slow-acting drugs for osteoarthritis, and 3) Chondroprotective or disease modifying drugs. The supplement Glucosamine Sulfate falls under the second category [6].

**Historical Background of Glucosamine Sulfate**

Glucosamine sulfate is a synthetic version of a bodily substance that helps to build cartilage. Glucosamine is a modified sugar produced from glucose where an amino group has replaced one of the hydroxyl groups on the ring. D-glucosamine sulfate is produced from glucosamine and N-Acetyl glucosamine in the body where the added sulfate group increases the attraction for water in these substances. Glucosamine is naturally present in the body and is found in most foods we eat.

While glucosamine has been used to treat osteoarthritis in Europe since the 1980's, its use in the United States has been confined mainly to arthritic animals. It was first marketed to treat horses. Glucosamine has been studied for years, and articles documenting its effectiveness go back to the 1970s. Most of the clinical studies involving glucosamine have utilized the sulfate salt, other forms available include the hydrochloride, N-acetyl, and chlorohydrate salts, in addition to glucosamine alone.

At first, many experts were skeptical about the benefits of glucosamine, but growing research is quickly changing some doctor’s minds. Glucosamine is now one of the highest selling supplements on the market. Americans bought $400 million worth of glucosamine last year.
Manufacturing/Synthesis

Glucosamine is normally synthesized by the addition of an amino group to glucose, followed by acetylation. The form of glucosamine sulfate available in capsule form is obtained from the chitin of crab shells. Hydrolysis takes place upon standing in concentrated acid with change in specific rotation, $[\alpha]^{20}_D -15^\circ \rightarrow +56^\circ$, and D-glucosamine can be isolated by cautious hydrolysis with acid or with chitinase, an enzyme preparation from snails [7].

Chitin Structure:

Source: [8].

A patent invented by Rovati Luigi reveals how glucosamine sulfate is manufactured/synthesized for commercial production [9].

A reaction vessel equipped with means for vigorous agitation and a cooling jacket or nest of tubes is charged with 35 liters of anhydrous methanol, to which is added, in small pieces, 700g of metallic sodium. To the sodium methanolate solution, at a temperature of about 30°C, 6 kg of glucosamine hydrochloride is added in a single batch with vigorous agitation for five minutes.

At the end of the five minutes, the resultant suspension is rapidly centrifuged to eliminate the sodium chloride. The solution of glucosamine base in methanol (the filtrate) is put into a reaction vessel, cooled to 0°C and slowly approximately one liter of fuming sulphuric acid.
containing 20% of sulphur trioxide. The additions of fuming sulphuric acid are stopped when it is found that the pH value no longer tends to rise again. A 20% concentration of sulphur trioxide has been found to be the best for the yield and quantity of the product.

The additions having ceased, the suspension obtained is agitated, still at 0°C, for about one hour, and then 50 liters of acetone is added. The material is then centrifuged again, and washed fully with acetone and then with ether. The product is placed, as finely divided as possible and in as thin a layer as possible, into an oven already heated to 50°C.

The dry product is at once ground, and then enclosed in small drums well insulated against moisture and protected with silica gel. It should also be noted that often even the bottles of glucosamine sulfate sold to the consumer at retail stores contain silica gel packets to further protect the product from moisture.

**Mechanism of Action**

The mechanism of action of glucosamine in the treatment of osteoarthritis is not well known. Experiments do suggest, however, that glucosamine may stimulate cartilage matrix formation, reduce enzymatic digestion of cartilage components, and provide anti-inflammatory effects. Several forms of glucosamine make up the following metabolic pathway in the body [10]:

\[
\text{D-Glucose} \rightarrow \text{D-Glucosamine} \rightarrow \text{N-Acetyl Glucosamine} \rightarrow \text{D-Glucosamine Sulfate}
\]

The rate of conversion of D-Glucose to D-Glucosamine tends to be the limiting step within the overall Glucosamine chain of conversion. Simply looking at the above metabolic pathway, it can be seen why directly supplementing Glucosamine Sulfate is advantageous. The entire metabolic pathway is virtually skipped over.

The only question would be then, would Glucosamine sulfate be absorbed in its direct form? The answer is a resounding yes. The use of the non-salt glucosamine fails to provide bioavailable glucosamine, because the compound in not well absorbed in the gastrointestinal tract, however the sulfate salt is readily absorbed.

At 37°C glucosamine has a pKₐ of 6.91. This means that at pH 7.4 (i.e. the blood), 25% of glucosamine is ionized, and 75% not ionized. At pH 6.8 (i.e. the small intestines), 46% is ionized and 54% is not ionized. At pH 1-3 (i.e. stomach), glucosamine is completely ionized. The pKₐ of glucosamine is therefore very favorable for an absorption from the small intestines and in general, for the crossing of biological barriers in the body [11].

The sulfate salt is readily absorbed from the small intestine since the majority is in the unionized form at the pH of this portion of the gastrointestinal tract. Over 90% of a typical oral dose will be absorbed, and only 10% appearing in the feces. Of the absorbed glucosamine, 25% will be excreted in the urine, 65% excreted as exhaled carbon dioxide, with the remaining 10% remaining in the tissues. Clinical studies involving laboratory animals have shown the appearance of radioactive-labeled glucosamine in cartilage in as little as four hours following oral administration.
Once the glucosamine is taken up into the chondrocytes of cartilage, it is incorporated into proteoglycans. Adequate availability of sulfate seems to be required for the synthesis of the glycosaminoglycans from these proteoglycans. The proteoglycans bind cations and water to form a viscous, elastic matrix that helps to lubricate the joint.

So as it can be seen that bypassing the rate limiting step of D-Glucose to D-Glucosamine, by supplementing glucosamine sulfate, the body has more available glucosamine to produce the necessary cartilage building blocks of proteoglycans and glycosaminoglycans.

An additional explanation for why glucosamine supplementation counteracts osteoarthritis is that glucosamine stimulates the production of hyaluronic acid in joint synovial fluid. Glucosamine is a starting block for the synthesis of hyaluronic acid. Glucosamine makes up over 50 percent of hyaluronic acid, the principal component of synovial fluid, which acts to increase the viscosity or fluid thickness within the joints.

If there is a lack of glucosamine in the body, then the synthesis of hyaluronic acid is also jeopardized, therefore providing a stepping stone toward increased wear and tear of the joint.

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Hyaluronic acid, is a linear polysaccharide composed of repeating disaccharide units of N-acetyl-glucosamine and D-glucuronic acid [12].

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**Benefits**

As it can be seen, the benefits of glucosamine sulfate supplementation can be quite helpful for those individuals suffering from arthritis, and perhaps even more beneficial for those who have not shown any arthritic defects.

Numerous double blind studies have shown that glucosamine sulfate produces much better results than NSAIDs in relieving pain and inflammation of osteoarthritis[13]. While NSAIDs offer purely symptomatic relief and may actually promote the disease process, glucosamine sulfate addresses the root of the problem. It has been known for years that prolonged continued use of NSAIDs can cause adverse side effects such as stomach and kidney problems.

After all, the goal for any ailment is to address the root of the problem, rather than mask it as NSAIDs do. A double blind, placebo-controlled, randomized trial showed that glucosamine significantly reduced progression of knee osteoarthritis over a three year period. Patient's treated
with placebo had an average joint space narrowing of approximately 0.1mm per year, whereas no joint space narrowing occurred in the glucosamine group.

In another double-blind clinical study of 178 osteoarthritis patients it was found that glucosamine supplementation generally showed a stronger effect and was better tolerated than ibuprofen.

These are just a couple of examples of clinical studies which show the positive effect of glucosamine supplementation. Glucosamine has been studied since the 1970's, and with 300 scientific investigations, and 20 blind studies, the results have been favorable. The only discrepancy seems to be how good glucosamine works. It is not disputed that glucosamine is better than a placebo, the current debate is the question of “How well does glucosamine work?”.

Certainly other factors play into how well glucosamine works. Factors such as age, genetics, and how developed the arthritis is; all contribute to how effective glucosamine supplementation can be. More accurate and reliable studies are in the works as to how well glucosamine works.

There are other possible uses of glucosamine as well. Glucosamine has also been suggested for the use in wound treatment, since hyaluronic acid aids in the migration and proliferation of cells required for the healing process to proceed. This use of glucosamine is a newly formulated idea, and to date, no clinical studies have been performed to address this issue. However, this issue certainly warrants further research.

**Adverse Affects**

Unlike the non steroidal anti-inflammatory drugs usually prescribed for arthritis, glucosamine does not produce serious side effects[14]. In some studies, patient’s have complained of mild symptoms such as heartburn, diarrhea, indigestion, and nausea. It should be noted however, that the incidence of these adverse effects were generally similar to those seen in placebo-treated subjects. There have been no reports of significant drug interactions with antibiotics or antidepressants. One study found that the most common adverse affects including heartburn and diarrhea were present in only 2-3% of subjects.

Recently, clinical studies have shown that there may be an adverse affect of glucosamine to glucose tolerance in diabetic rats. This could be of great concern to older, glucose intolerant individuals. Critics of these studies are quick to point out the that the route of administration of the glucosamine was intravenous and the doses utilized in the studies were large, and thus render the results not applicable to humans. After all, large doses of just about anything can be harmful to the body. Studies in humans have failed to demonstrate a significant effect on blood glucose. Further research into this area is certainly warranted, but initial findings seems to show no serious long term side effects of glucosamine sulfate.
Conclusion

The costs of osteoarthritis alone warrant further research into the supplementation of glucosamine sulfate. It is important to note that not only does osteoarthritis have direct costs to the American healthcare system, but also indirect costs such as lost time from work.

Glucosamine sulfate is certainly not a cure all for osteoarthritis. Things such as diet and exercise are also very viable treatment approaches for osteoarthritis. However, it may be time to replace the traditional NSAIDs and their known adverse side effects with a natural remedy such as glucosamine sulfate. It appears that the adverse affects associated with glucosamine are less severe than the traditional NSAIDs.

One of the daunting problems associated with glucosamine supplementation, or any natural over-the-counter supplement for that matter, is the purity and controls over manufacturing of the supplement. Although there are government agencies (FDA) that attempt to control and monitor the manufacture's label claim concerning the purity of the substance, concern is still voiced over stricter control. Perhaps an answer to this concern is to make glucosamine sulfate a prescription drug, where the control on manufacture and purity is much more strict. After all, glucosamine sulfate is a prescription drug in Europe, and these stricter controls are implemented.

On the horizon is one of the largest studies on glucosamine. The National Center for Complimentary and Alternative Medicine recently announced its sponsorship of the first U.S. multicenter clinical trial. The trial is to involve 1,124 patients in nine centers and will examine the efficacy of glucosamine sulfate given over 16 weeks. If the results are positive, as has been shown by the over 300 other smaller studies, then glucosamine sulfate may become part of mainstream American medicine as it has been in Europe for the last two decades.
Bibliography


ACCUTANE
MINA YOUSSEF
4-27-01
Isotretinoin is the generic name for the acne medicine, accutane. Acne or acne vulgaris as it is said in medical terms, is currently one of the highest percentages in the clinics that affect about 80% to 90% of young adults that may persist indefinitely. Because of the severity of acne vulgaris the physical and psychological impact and understanding of the pathophysiology clinical manifestations and the treatment modality of acne vulgaris that is very essential. 1

The chemistry of isotretinoin is a synthetic retinoid. The drug is the 13-cis isomer of the naturally occurring all trans-retinoic or said to be tretinoin. Modification of the terminal carboxy group of retinoic acid to the cis configuration is associated with fewer adverse effects and enhanced biologic activity compared to the all-trans configuration. 2 Isotretinoin which is a crystalline powder occurs as a yellow-orange to orange. The drug is sparingly soluble in alcohol and insoluble in water. Isotretinoin is available commercially as a soft gelatine capsule containing a suspension of the drug in soy bean oil. For preservation, the capsule contains parabens.

![Chemical Structure of Isotretinoin](attachment:chemical_structure.png)

Stability of isotretinoin is photosensitive and will degrade when it is exposed to light. Commercially available isotretinoin liquid filled capsules should be stored at tight, light resistant container at about 15-30 degrees centigrade. The capsules are also stable for two years after the date of the manufacturer. 2

The principal pharmacologic effect of isotretinoin appears to be the regulation of the cell as well as it's proliferation and differentiation. The drug also affects the function of the monocytes and lymphocytes, resulting in modulation of cellular immune responses in mesenchymal tissue. The drug isotretinoin exhibits some anti-inflammatory and antineoplastic activity. The exact mechanism of how the drug works is not fully known, but data from invitro study indicates that retinoin increase cellular mitotic activity, DNA and RNA synthesis, protein synthesis, are post-translational glycosylation of protein. The effects of the drug itself may result from the complexity of the mechanism of action, individual or disease-specific differences in response to the drug itself, or the difference in cytosol-binding protein in various tissues all around the body. The isotretinoin, the intracellular cytosol binding protein have been identified. The receptor proteins are very similar in the molecular weight and composition but possess distinctly different binding specificity. The role of cytose-binding protein is to mediate the action of retinoin, but how this is done has not been fully understood. The amount of information that is known and explained is that the retinoin-binding protein complex distributes into the cell nucleus where it affects the DNA, RNA, glycoprotein synthesis and its protein. At high concentrations, retinoin exert a detergent-like effect on cell membranes that result in
decreased membrane stability. When the drug is in vitro it disrupts the lysosomal membrane of the cell, resulting it to release its lysosomal enzymes. Although the actual effects of retinoin of lysosomal membranes in vivo remain to be clearly determined, it has been suggested that some adverse effects of retinoin may result from the detergent-like activity. The binding of isotretinoin to its specific cytosole-binding protein may prevent this detergent-like effect, and at lower concentrations, the drug may actually stabilize cell membranes.

A common inflammatory pilosebaceous disease characterized by comedones, papules, pustules, inflamed nodules superficial pus-filled cysts, in extreme cases canalizing and deep, inflamed, sometimes purulent sacs would be the best definition of acne vulgaris. Although acne vulgaris is traditionally associated with adolescence, it can occur in the neonatal period and into the fourth decade of life. During the first week of life a newborn baby, the prevalence of acne form lesions may account. The cause of this is the baby being under the influence of maternal and androgens, so that neonates sebaceous glands are stimulated. Sebaceous gland become quiescent again until puberty, and the peak incidence of acne is in the mid to late teens. It is known to be more slightly common in males than in females and the severe forms of acne are much more common in male patient. Another factor responsible for acne is post adolescent women then men is the hormonal factor. Racial differences that has been reported include a higher prevalence in white American versus Japanese men, and a higher incidence of nodulocystic acne vulgaris in white versus black males.

The lesions of acne are divided into two types, the noninflammatory types and the inflammatory types. The distribution of acne is characteristically known to be on the oily skin of the face, back, chest, and shoulder, are all examples of the inflammatory types.

"Noninflamatory lesions include open and closed comedones which are blackheads and whiteheads. An open comedones consists of a small flat or raised area with a central pore filled with impacted keratin and lipid. The comedo is actually a pilosebaceous follicle filled with a keratin plug. The tip of the plug is dark owing to oxidation and melanin pigment deposition into the plug (not dirt)." A closed comedo pore would be largely covered by epithelium. Inflammatory lesions all tend to show marked lymphocytic infiltration in and about follicles in the dermis.

Acute and chronic inflammation are accompanied by the rupture of the follicular structure and abscesses form on the skin. Scarring then follows the marked inflammation usually associated with cysts.
are again a wide range of lesion that are seen including some large pustules, and scarring is occurring upon healing.

A close-up view of acne scars is on this patient the scars are depressed, but hypertrophic scars may also occur. 4

The inflamed lesions of acne involve stagnation of sebum and comedo formation in the pilosebaceous follicle, with bacterial invasion in this adolescent. Acne is seen here in a young teenager, through it may continue or occur initially into the adult years. 5

Treatment of acne vulgaris always depends on the severity of the disease on each individual differently. Some treatments include topical salicylic acid and topical tretinoin. The sebaceous gland function can always be alerted through the use of isotretinoin. When given for estrogen therapy, it is only given to patients with the evidence of ovarian androgen excess. Estrogen are normally prescribed in the form of oral contraceptives.

Although it was thought that at least 50 microgram of estrogen per day is needed for a full therapeutic response, it has now been said, thanks to recent evidence that only as little as 35 microgram of estrogen is suggested in the newer triphasic contraceptives, maybe fully sufficient to treat acne. The most effective method of sebum suppression is through isotretinoin therapy. This is administered with vitamin A derivatives and it is reserved for severe cases of cystic acne. Isotretinoin acts by markedly suppressing sebaceous gland function and abnormal keratinization and directly by decreasing bacterial growth. Systemic antibiotics used in acne includes a few prescription drugs which include erythromycin. Erythromycin (1g/day) when given is a cost-effective form of acne therapy, but develops resistance more quickly than tetracyclines. Long-term antibiotic therapy can lead to secondary gram negative that may require therapy with antibiotics such as isotretinoin.

In summary a rational first approach to treating acne vulgaris includes comedolytic therapy with tretinoin. A response requires a few months of therapy and if necessary antibiotics are given. Isotretinoin should be reserved for specific situations. 1
About Accutane

Definition:

Isotretinoin is a powerful drug used in the treatment of acne. Four to five months of isotretinoin treatment usually leads to clearing of acne for one year or more after the medicine is stopped. Most other acne-controlling medicines are antibacterial agents, which are effective only if the medicine is used daily.

Side Effect Summary:

Chapped lips 90%

Dry skin and itching 80% - the use of daily alpha hydroxacids will help prevent this side effect.

Dryness of nose, mild nosebleed 80%

Irritation of the eyelids and eyes 40% - Vitamin E 400 IU each day may lessen this side effect.

Joint and muscle pains 15%

Temporary hair thinning 10%

Rash 7%
The side effects of the drug are numerous but a few are given in specificity that are needed to be organized and put in consideration of patients who take isotretinoin as their drug. One of the most common side effect with prolonged antibiotic use is candidal vaginitis, especially when the patient is pregnant. Other side effects are also caused by oral isotretinoin. The drug is dispensed with warnings against pregnancy. Because severe fetal abnormalities are likely if pregnancy occurs while the woman is taking the drug. The most common side effects, seen in about 90% of patients, are dryness of conjunctivae and mucosae of the genitalia and chapped lips. Musculoskeletal symptoms, pain or stiffness of large joints of the lower back, may also occur in about 15% of patients. Triglyceride levels may increase to a level at which the drug should be discontinued. Liver function is only occasionally affected. 6 The impressive clinical performance of isotretinoin is tempered by the multitude of side effects, which range from drying of the mucous membrane to hyperglyceridemia. Extreme caution should be used when prescribing isotretinoin to a woman of child bearing age. 1

Some more side effects of drug, includes mucocutaneous effect. The most frequent adverse effect of isotretinoin is the inflammation of the lips which occurs in more than 90% of patients receiving the drug of acne.

Conjunctivitis and irritation of the eyes occur in about 40% of patients receiving isotretinoin for acne. Another factor is thinning of the hair, infection of the skin, and photosensitivity may occur about 5-10% of patient receiving the drug. Other effect of isotretinoin are metabolic effects. It causes decreases in serum in high density lipoprotein (HDL) concentration have occurred in about 50% of patients, and increases in serum cholesterol concentration have occurred in about 7% of patients that were receiving the drug.

Adverse in musculoskeletal effects include bone or joint pain generalized muscle ache, arthralgia occur in about 16% of patients receiving the drug.

Hematologic effect of the drug include 10-20% of patients receiving the drug and include decreased hemoglobin concentration and hematocrit, decreased erythrocyte and leukocyte counts, and increase platelets counts. Increase or decrease reticulocyte counts, anemia and thrombocytopenia also have been reported.
The Nervous System effects also have an adverse on isotretinoin that includes lethargy, fatigue and headache. Mental depression has also been in some patients receiving isotretinoin as well as retinal hemorrhages. Adverse of GI effects of the drug include anorexia, nausea and vomiting, increased appetite, and thirst. The drug has also been temporally associated with inflammatory bowel syndrome in patients without a history of intentional disorders. Weight loss and mild GI bleeding have also been reported rarely in patients receiving isotretinoin. Hepatic effects are abnormalities in liver function, test results are occasionally resolved despite continued therapy or following doses reduction. Ocular effects are conjunctivitis and irritation of the eyes, isotretinoin therapy has been associated with development of corneal opacities in patient with cystic acne and more frequently in patient with disorders of keratinization when higher doses of the drug were used. Cataract have also been reported in patients receiving the drug. Visual disturbances have also been reported in patients receiving isotretinoin.

Visual disturbances have been manifested principally as decreased visual acuity or blurred vision, but tunnel vision, temporary loss of vision, double vision, photophobia and difficulty in seeing have also occurred.

Precautions and Contradictions of isotretinoin should be prescribed by clinicians with special competence in the diagnosis and treatment of severe recalcitrant acne, and who are experienced in the use of systemic retinoid and fully understand the teratogenic risks of the drug. Because of the risk of adverse effects, which may be severe, isotretinoin therapy should be reserved for patients with severe cystic acne who are unresponsive to conventional acne therapies, including oral and/or topical anti-infectives. 2

My future prediction about accutane and what it will do to its future patients is promising. According to my research and all that I have read about in different books, and articles, I found out the side effects of isotretinoin are absolutely amazing in numerous amounts that affect every single part of the body, whether internally or externally which ranges from deep to superficial according to the severity of the acne on the patient and how long the patient was on accutane, taking medication once or twice daily and also in how small or large the dose was. My prediction about this drug is that I think that isotretinoin will continue to serve its patients in the right way and now since there are a lot of doctors who are aware of all the complications and side effects, I highly think that all the physicians will lean towards using ointments and minimize the use of tablets. Therefore, that will decrease the side effects that occur from the tablets and hopefully lessen them by the use of ointments on the external part of the skin. In regards to the sensitivity of the sun on the skin, I think that the ointments will be made especially to be for sensitive skin, and so when the patient is exposed to sun light they will not be affected by the ultra violet rays of the sun. I also think that the ointment will go one step further and instead of just being used for treatment of acne it will also be used for the prevention of acne. Scientists will also be able to predict if certain individuals will get acne by doing hereditary analysis and be able to identify patients with high risk of getting acne. Hereditary predictions will look towards finding a gene that causes the effect of acne in the body, and then be able to stop it by applying the ointment on the skin before it even starts to break out. In an overall conclusion I see accutane going towards a positive direction.
Bibliography


