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EPHEDRINE: AN HERBAL TOXICOLOGICAL HAZARD

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ABSTRACT

Many individuals are currently using herbal products that are toxicologically unsafe due to inaccurate dosages and/or addition of harmful substances of which the consumer is unaware. This is primarily because the health supplement industry has failed to supply adequate research and regulation on its products. This paper makes a brief review of the general field of toxicology, but ultimately narrows its scope to an in-depth consideration of ephedrine, an ancient Chinese medicinal herb capable of concerted stimulation of the sympathetic nervous system. Ephedrine use has resulted in negative reactions in a number of cases.

INTRODUCTION

Increasing numbers of Americans are using herbs and over-the-counter (OTC) products for self-medication (Sandberg & Krema 1986). According to Dr. Varro Tyler, Purdue University (1993), interest in herbal medicine, which originated during the last decade, will continue through the 1990s and into the 21st century. This movement had its origin in many people's disillusionment with modern medicine, particularly its high cost and inability to cure everything. This, along with the widespread belief that plant remedies are naturally superior to man-made drugs, has produced a wave of enthusiasm and promotion on the part of the public that can only be described as an "herbal renaissance"(Tyler 1993).

It is this renaissance that is alarming medical doctors, not because patients are using alternative forms of health care, but because the doctors are witnessing adverse effects in their patients due to improper use of herbs and a lack of research and regulation on the part of the supplement industry. An increasing number of doctors such as Kerry Friesen M.D., Internal Medicine, of Chattanooga Primary Care, are becoming aware of this problem and are doing their own research and investigations to promote public awareness and safer use of herbal products.

In addition, a new branch in the field of toxicology, herbal toxicology, is evolving to investigate medicinal herbs for adverse side effects just as other branches of toxicology research the synthetic drugs of the pharmaceutical industry. In this paper a brief introduction to the field of toxicology will be made, but ultimately an analysis of ephedrine, an example of a potentially toxic herb, will be conducted.

MODERN TOXICOLOGY

Toxicology is the study of the adverse effect of chemicals on living organisms. The toxicologist is trained to examine the nature of these adverse effects and to assess the probability of their occurrence. Simple definitions are not adequate to explain an entire field because toxicology has evolved as a multidisciplinary field of study based on the work of pharmacologists, chemists, and specialists in the study of living organisms. Therefore, one must understand that toxicology is still developing and expanding, and its definition will continue to encompass new branches of investigation (Doull et al. 1980).

Toxicology, in a variety of specialized and primitive forms, has been a relevant part of the history of man. Ancient records such as the Ebers papyrus (circa 1500 B.C.) demonstrate that early man was well aware of the toxic effects of animal venoms and poisonous plants. One finds mention of hemlock, which later became the state poison of the Greeks; aconite, an arrow poison of the ancient Chinese; opium, used as both poison and antidote; and heavy metals like lead, copper, and antimony (Ottoboni 1991).

One of the most prominent figures in the history of toxicology is Philippus Paracelsus (1493-1541) who was responsible for making the most significant biomedical changes since the time of Aristotle. His views continue to remain an integral part of the present structure of modern toxicology. He promoted a focus on the "toxicon," the toxic agent, as a chemical entity and made four statements which continue to hold true today. In addition, he published a book, *Bergsucht*, which was the first treatise in the medical literature to provide a comprehensive description of the occupational diseases of miners due to chronic arsenic and mercury poisoning. Today, Paracelsus is remembered primarily for his insightful question

and answer: "What is it that is not poison? All things are poison and nothing is without poison. It is the dose only that makes a thing not a poison"(Doull et al. 1980).

Mattieu Orfila (1787-1853), a Spanish physician in the court of Louis XVIII, is said to have ushered in the era of modern toxicology. Orfila attempted to create a systematic correlation between the chemical and biologic information of the then-known poisons. He also singled out toxicology as a discipline distinct from others and defined toxicology as the study of poisons (Timbrell 1982).

Since the time of Paracelsus and Orfila toxicology has become a broad, recognized science. Many health improvements have been made because of the work of toxicologists. For example, one of the most widely publicized epidemiological and toxicological issues of the last several decades has been the connection between smoking and lung cancer (Stout 1996). Of course, most individuals living in the twentieth century are familiar with the dangers of poisoning by cadmium, lead, mercury, copper, zinc, silver and other metals (Lewis 1995). And only one year ago Janette Raloff stated that toxicologists have discovered that almost all U.S. drinking water contains toxic contaminants (1996).

In addition, toxicologists are responsible for discovering antibiotic resistance genes which have been incorporated into food products (Choo 1994). They have also found that cocaine use increases myocardial ischemias (Hollander 1996). And most citizens of industrialized countries are aware of the potential toxicological effects that pesticides and other agricultural products have on humans (Temple 1996). It is also safe to assume that most members of such countries have at least heard about the toxicological effects of excessive alcohol consumption.

It is evident that toxicology is a well established and significant contributor to public health, but the use of OTC drugs and herbal remedies is stimulating the development of a new branch of study. This branch is necessary due to the public's increasing acceptance of and participation in self medication.

HERBAL TOXICITY

A new, relatively unrecognized branch in the field of toxicology deals with herbal toxicity. In 1994 \$813.8 million of the health food stores' \$4.815 billion in sales was from herbal remedies, and in 1995 the OTC herbal remedies business reported over \$1.5 billion in sales (Evers 1995). The danger of herbal medicine exists because of society's romanticized view that equates "natural" with "safe." Unfortunately, the assumption that natural products are safe is false (Evers 1995).

By law drug labels must provide essential information, but herbal remedies are marketed as "dietary supplements" with little of the type of information needed to enable people to use these remedies properly (Kupec 1995). The 1994 Health Education Act is responsible for creating this broad new category, separate from food or drugs, that is practically free from FDA regulation. It includes vitamins, minerals, herbs, and amino acids (Jones 1996).

Because there are no quality-control regulations, the manufacturers of herbal medicines do not have to prove that their products are safe or effective, and they are able to make claims without scientific data supporting them (Treasure 1996). Unlike drug

manufacturers, food supplement manufacturers are not required to track, investigate, or report to anyone adverse reactions to their products (Kupec 1995).

It does not take long to realize that the consumer is the loser. Individuals are taking products that are inadequately labeled and may contain other ingredients. In the worst case people are acquiring toxic levels of certain herbal alkaloids leading to serious side effects and possibly death. Ephedrine is the perfect example of an herb that is capable of such results.

EPHEDRINE

For many centuries, as early as 2800 B.C., alkaloids of Ma Huang, the original name for ephedrine, were extracted from *Ephedra sinensis* and *E. vulgaris*, members of the Ephedraceae family, to be used as a respiratory medicine and stimulant in Chinese medicine (Latimer 1996). It was from the crude extract of *Ephedra vulgaris* that the active principle was extracted in 1885 and named ephedrine by Nagai. In 1920 Spath and Gohring were able to synthetically synthesize ephedrine via organic methods (Korolkovas1988) (Appendix A). Since that time ephedrine herbal and synthetic alkaloids have been used clinically as well as homeopathically.

To appreciate the effect of ephedrine on the human body one must first understand a little about the autonomic nervous system which is affected by it. Ephedrine belongs to a class of molecules called adrenergic agents, also known as adrenomimetics or adrenergic stimulants, which mimic adrenaline-like substances that normally stimulate the adrenergic nerves of the sympathetic nervous system. The two primary types of adrenergic receptors,

alpha and beta, are further divided into α_1 , α_2 , β_1 , and β_2 depending on their function (Korolkovas 1988).

α_1 -adrenoceptors are present at postsynaptic sites of neurons and occur at vascular and other smooth muscles, myocardium, hepatocytes, and adipocytes. α_2 -adrenoceptors are present at both pre- and postsynaptic sites. Presynaptic α_2 -adrenoceptors occur in all organs subject to neuronal control by the sympathetic nervous system. Postsynaptic α_2 -adrenoreceptors occur in vascular smooth muscle, pancreatic islets, platelets, adipocytes, as well as in the central nervous system in the kidney and eye. β_1 -adrenoceptors occur in heart, coronary arteries, intestinal muscle, and adipocytes; they are associated with cardiac stimulation and lipolysis. β_2 -Adrenoceptors are located in most arteries, lung, and uterine muscle; their stimulation causes bronchodilation and vasodilation (Lees 1981)(Appendix B).

Adrenomimetics are capable of binding to adrenoceptors because of their close structural similarities to adrenaline (Appendix C). Ephedrine lacks the phenolic hydroxyl groups that adrenaline contains, but does not lack the ability to mimic adrenaline. Its aromatic ring allows it to attach to receptors via van der Waals forces and charge transfer. In addition, its alcoholic hydroxyl group allows hydrogen bonding and electrostatic bonding with the receptor. Finally, ephedrine's amino group in cationic form can interact with the receptor's anionic phosphate group (Korolkovas 1988).

Adrenomimetics are capable of three classifications of actions upon the nervous system: direct, indirect, and mixed. Direct acting adrenomimetics directly stimulate one or more receptors. Indirectly acting adrenomimetics act by either releasing catecholamines like

epinephrine from storage granules or through inhibition of norepinephrine uptake at the neuronal membrane. Ephedrine, an adrenomimetic of mixed action, is capable of both of the above modes of action and is one of the few molecules that fits into this category (Korolkovas 1988).

Ephedrine is a very unique molecule capable of numerous modes of action that could prove beneficial to humans, yet it could also serve rather detrimental purposes if used with improper care. For medical purposes ephedrine is used as a nasal decongestant (Efedron, Novafed, and Sudafed), a vasoconstrictor in anorectal preparations, an adjunct in local anesthesia, a treatment for allergic conjunctivitis, a bronchodilator, and an ocular decongestant (Korolkovas 1988). Herbalists, dieters, and weight lifters currently use herbal ephedrine as a stimulant, weight-loss enhancer, and bronchodilator (Lewis 1977). Herbal use presents major toxicological problems due to the fact that ephedrine is a molecule of mixed action, allowing it to affect many different adrenoreceptors at one time.

At the April 12, 1996, meeting of the American Academy of Neurology, Dr. Gary Franklin announced that Chinese herbs containing the food/energy supplement ephedrine can cause serious neurologic side effects (Anonymous₁ 1996). Other researchers have found that ephedrine is responsible for producing cerebral hemorrhage and cardiac arrhythmias which can result in cardiac arrest and death (Anonymous₂ 1996). It is also known to cause less severe side effects such as nervousness, headache, insomnia, and dizziness (Tyler 1993).

The Texas Department of Health (TDH) has been a leader in tracking toxicological problems related to ephedrine use. Since 1993 the TDH has identified more than 900 cases of adverse reactions to ephedrine, including reports of eight deaths that are most likely

related to its use. In the August 16, 1996, issue of *Morbidity Mortality Weekly Report*, Dr. D. M. Perrotta presented three cases identified by the TDH as being related to ephedrine use.

Patient 1. In December 1993, a 44-year-old man died from acute coronary artery thrombosis approximately three weeks after beginning daily use of a dietary supplement containing ephedrine. He was an active swimmer and tennis player with no known cardiovascular risk factors. He received the dietary supplement from his family physician during a routine physical examination when he requested a substitute for his daily coffee and cocoa. He used the product as directed and eliminated his coffee and cocoa use. On December 19, 1993, after playing tennis and returning home, he sustained a cardiorespiratory arrest. An autopsy revealed an acute thrombus in the left anterior descending coronary artery. All other coronary lumina were nonoccluded, although calcified with focal narrowing to approximately fifty percent.

Patient 2. In May 1995, a 35-year-old woman who was taking no other prescription or over-the-counter (OTC) medications began use of a dietary supplement containing ephedrine for weight loss. She used the supplement within the dosage recommended on the label for approximately 30 days, discontinued use of the supplement while on a one week vacation, and then resumed the usual dosage when she returned on June 24, 1995. On June 25, while sleeping, she had acute onset of symptoms including anterior chest pain that radiated to her left shoulder and arm, numbness of the left arm and hand, diaphoresis, and shortness of breath. She was taken to the hospital, and her pain remitted after she was treated with nitroglycerin and morphine. Although an electrocardiogram and cardiac

enzymes indicated an acute myocardial infarct, cardiac catheterization indicated normal cardiac function and normal coronary arteries. She had no history of cardiovascular risk factors. She was discharged with a diagnosis of acute myocardial infarction secondary to cardiac spasm and was advised to discontinue use of the dietary supplement that contained ephedrine. Since discontinuing use of the product, she has had no additional cardiac-related symptoms.

Patient 3. On August 17, 1995, a 38-year-old woman with no history of seizures experienced two petit mal seizures beginning at 11 p.m. She experienced two additional petit mal seizures the following morning, and that afternoon had onset of a generalized tonic-clonic seizure lasting approximately two minutes, during which she required respiratory assistance. On August 17, she had taken two tablets of an ephedrine-containing dietary supplement at 10 a.m. and two more 5 hours later as directed on the product label. She denied use of other drugs except oral contraceptives. From August 19 to August 22, she experienced five additional episodes of unresponsiveness while sitting or standing; while waiting in the office of a neurologist, she sustained an additional generalized seizure witnessed by the neurologist and staff, and was hospitalized for monitoring, treated with antiseizure medication, and diagnosed with new onset of tonic-clonic seizures with complex partial seizures. Other possible causes of seizures were excluded. She was discharged and was advised to avoid any medications or products that contained ephedrine, pseudoephedrine, or related drugs. Since discontinuing use of the product, she has had no additional seizures.

In addition to tracking cases related to ephedrine use the TDH is actively conducting herbal toxicological studies. Recently, TDH investigators purchased an herb-based product labeled “no side effects” that also listed wild Chinese ginseng as the only ingredient. Laboratory analysis indicated that a single tablet contained 45 mg of ephedrine and 20 mg of caffeine. Users were instructed to take five tablets per use, representing a total dose of 225 mg of ephedrine (Jones 1996). The normal dosage for OTC bronchodilator products is 12.5 to 25.0 mg of ephedrine (Korolkovas 1988).

The majority of ephedrine users do not know the potential of the drug they are using, but a growing number of people are knowingly using ephedrine as a stimulant. Weight lifters use products such as Mini-Thins, Heads Up, Max Alert, GoPower, Turbo-tabs, and 357 Magnum to enhance energy levels while they work out (Perrotta 1996). Others are using ephedrine to mimic illicit drugs such as 3,4-methylenedioxy-methamphetamine, “ecstasy” (Kupec 1995). It is possible to purchase products such as Herbal Ecstasy and Cloud 9 through the Internet and in health stores. The makers of these products claim that the purchaser will experience “euphoric stimulation, highly increased energy levels, tingly skin sensations, enhanced sensory processing, increased sexual sensations, and mood elevations” (Perrotta 1996). In addition, the U.S. Drug Enforcement Administration has discovered that a number of people are chemically synthesizing ephedrine into methamphetamine due to close structural similarities (Kupec 1995)(Appendix C). This has prompted the FDA to consider taking ephedrine off the OTC listing, but would not affect the sale of herbal ephedrine.

CONCLUSION

Natural remedies have been used for centuries as is evident from ancient records. However, the potential toxicities that result from herbal medication have just recently been formally investigated. Data on herbal dosages are still lacking, and as Paracelsus said, the dose makes the poison. This principle is no more evident than in the use of ephedrine.

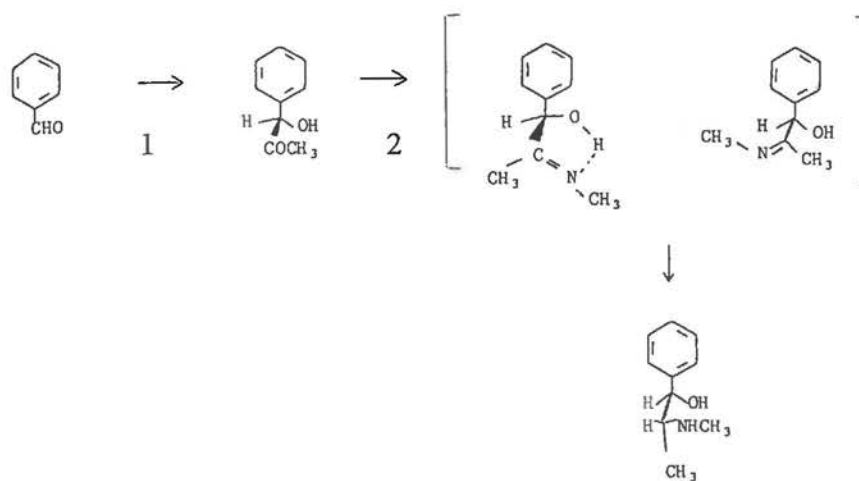
Ephedrine is a strong sympathetic nervous system stimulant capable of remarkable healing, but is also capable of producing death in certain cases. Toxicologists and physicians must continue to study ephedrine and other dangerous herbal products, but patients and consumers must also take part. It is the duty of the consumer to cautiously use herbal products and to fully understand the potential effects of the product they are using. If an herb such as ephedrine is going to be used in place of a drug, it must be treated as a drug.

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Synthetic Synthesis of Ephedrine



1. Benzaldehyde is fermented with glucose and yeast.
2. Reductive amination is employed to introduce the nitrogen atom (Lednicer 1977).

Responses Mediated by Adrenoceptors

Cell, Organ, or System Affected	Adrenoceptor Type	Response
Heart	$\beta_1 > \beta_2$ β_1 β_1 β_1 (?also α)	Increased automaticity
		Increased conduction velocity
		Increased excitability
		Increased force of contraction
Blood vessels	α β_1 β_2	Constriction of arteries and veins
		Dilatation of coronary arteries
		Dilatation of most arteries
Lung	α $\beta_2 > \beta_1$	Bronchoconstriction Bronchodilatation
Skeletal muscle	β_2	Increased force and duration of contraction of fast contracting muscle; decreased force and duration of contraction of slow-contracting muscle (hence tremor)
Smooth muscles		
Uterine muscle	β_2	Relaxation
Eye	α	Mydriasis
Intestinal muscle	β_1	Relaxation
Mast cells	α β	Augmentation of release of mediators of anaphylaxis
		Inhibition of release of mediators of anaphylaxis
Platelets	α_2, β	Aggregation promoted
Metabolism		
Gluconeogenesis	α	Promoted
Glycogenolysis	α (liver) β_1 (heart) β_2 (skeletal muscle)	Promoted
		Promoted
		Promoted
Lipolysis (white adipocytes)	β_1	Promoted
Calorigenesis (brown adipocytes)	β_1	Promoted
Hormone secretion		
Glucagon	β_2	Promoted
Insulin	α β_2	Inhibited
		Promoted
Parathyroid hormone	β	Promoted
Renin	β_1	Promoted
Neurotransmitter release		
Acetylcholine	α	Facilitated (skeletal neuromuscular junction); inhibited (sympathetic ganglia and intestine-leading to inhibition/relaxation)
Noradrenaline	α_2 β (? β_2)	Inhibited Facilitated

(Lees 1981).

