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The Dietary Supplement Ephedrine - Should It Be Banned?

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Introduction

Ephedra has been used over 4000 years in China as an extract from Tsaopen-Ma Huang for cough and bronchitis. Ephedra today is found in over 200 dietary supplements because of its known effective ability to promote weight and body fat reduction. (2) Ephedrine is believed to increase catecholamine levels at synaptic areas in the brain and in the heart, which have a direct stimulatory effect on alpha and beta-adrenergic receptors. Ephedrine will therefore increase heart rate, cardiac output and peripheral resistance and as a result increase blood pressure. (4)

However, it has been linked with dizziness, tremors, headaches, irregular heart rates and seizures to myocardial infarctions and strokes. Further, sleeplessness, restlessness, irritability, headache, vomiting, urinary disorders and rapid heartbeat have also been linked with ephedrine use. (4) Doses over 100mg per day are thought to be life threatening because it can trigger a sharp rise in blood pressure and the rhythm of the heart. (1)

Combinations with other stimulant such as caffeine have also connected ephedrine to cardiac arrhythmia and ventricular tachycardia. Ephedrine has been linked to ischemic and hemorrhagic stroke and intravenous administration of ephedrine has been linked to acute myocardial infarction. (2) As a result, the NFL, as well as the International Olympic Committee has banned the use of ephedrine in its athletes. In light of the recent Steve Bechler heat stroke tragedy, Major League Baseball is currently trying to decide whether or not to follow in the tracks of the NFL and IOC. The FDA is also increasing its investigative efforts in response to the public's requests to ban ephedrine.

The pathophysiology for complications of the heart is thought to result from intense vasoconstriction in cerebral and coronary arteries, whose effects may be exacerbated by increased myocardial oxygen needs. Chronic use of the sympathomimetic leads to frequent and prolonged state of ischemia causing fibrosis of the tissue and even death.

Some Cardiovascular Effects of Ephedrine

In 1998, a Clinical Physiology study found that ephedra (50 mg/day) when taken with caffeine causes an increased ejection fraction and cardiac load during exercise after 10 days of treatment with a low calorie diet. When compared to a placebo group, the placebo group had similar weight loss but decreased ejection fraction and decreased cardiac load. Further, the study found that the hemodynamic parameters of ejection fraction and cardiac load didn't change with administration of ephedrine and caffeine at rest and during handgrip exercise. (5)

A study conducted in 2002 by the Miami Research Associates and funded by Xenadrine™ manufacturer Cytodyne Technologies (a member of the EEC or the Ephedra Education Council) where a total of 30 healthy overweight/obese volunteers underwent a randomized double-blind, placebo-controlled clinical trial found that 40 mg of ephedra in conjunction with 200 mg of caffeine taken for 14 days showed that the herbal ephedrine and caffeine product, "appeared to be as safe as the placebo in terms of its cardiovascular effects." It also stated that the herbal ephedrine and caffeine containing product "had no effect over 14 days on heart rate, systolic and diastolic blood pressure, serial EKG's or Doppler echocardiograms." The study also stated that coronary vasospasms were not found in the treated patients and also made a differentiation

between herbally derived ephedra and the possible real culprit to adverse side effects linked with ephedrine: synthetically produced ephedrine. (6)

Following the Cytodine study, Christine Haller of UCSF conducted a study of the pharmacology of ephedra alkaloids and caffeine after single-dose dietary supplement. The study followed the effects of a thermogenic dietary supplement labeled to contain 20 mg of ephedrine alkaloids and 200 mg of caffeine after an overnight fast in 8 healthy adults. The study found that the botanical stimulants like those used in the Cytodine study "have disposition characteristics similar to their pharmaceutical counterparts and that they can produce significant cardiovascular responses after a single dose." (7) This study was simple, yet effective in showing that despite the dietary supplement manufacturers' desire to show that ephedrine doesn't really affect the heart, it in fact does have significant cardiovascular effects.

What has the FDA Done?

The FDA in 2000 reviewed 140 reports of adverse events related to the use of dietary supplements containing ephedra that were submitted to the FDA between June of 1997 through March of 1999. Reviewing AERs (Adverse Event Reports) in a retrospective study, Haller reviewed the 140 reports to determine the likelihood that ephedra alkaloids were indeed the causes of adverse symptoms. In the study, 47% of the symptoms were adverse events that were "definitely, probably, or possibly related to the use of supplements containing ephedra alkaloids." Hypertension was the most frequent adverse effect, followed by palpitations and increased heart rate. Haller reported that there were 10 deaths and 13 cases of permanent impairment that were at least temporally linked to ephedrine administration. Compelling was that of the 23 sudden catastrophic cerebrovascular and cardiovascular events, 11 occurred in "healthy persons". The study ceded that experimental studies show that ephedrine only affects the heart rate and blood pressure moderately, but the adverse events from ephedrine use may be due to individual susceptibility, the additive effect of caffeine, variability in the content of the active chemicals and other preexisting medical conditions. The study concluded that, "dietary supplements that contain ephedra alkaloids pose a serious health risk to some users," and that the "findings indicated the need for a better understanding of the determinants of individual susceptibility to the serious adverse effects of dietary supplements containing ephedra alkaloids so that appropriate dosage guidelines and warnings can be devised." (8)

The Industry's Response

In response to this study, the Ephedra Education Council (EEC), which comprises its funding and membership from manufacturers of the dietary supplements, posted a few rebuttals to the FDA sponsored study. Some of what the EEC found faulty of the FDA findings were that: (a) The AERs are not an adequate database from which to conduct a scientific or medical analysis of the safety of these products, (b) in several AERS where the product is identified, information regarding its constituents is missing, (c) many have no dosage information, (d) and there are no medical records for the AERs. What the EEC insisted was that there is no association between ephedra when appropriately consumed and serious adverse events. (9)

The EEC also posted a study conducted by Kimmel (10) who takes 36-pages to conclude that there is no statistical difference in the incidence of stroke, myocardial infarction and seizure in patients who use ephedrine and don't use ephedrine. Interestingly, the study used AER's as a

primary source of information. Further, instead of specific numbers of cases, the study reported incidence per 100,000. The study also didn't produce information regarding the constituents and doses of the active chemicals of the supplements. The study didn't include medical records or product information. The conclusions were based on calculations of numbers and data that are impossible to be reproduced by anyone other than Kimmel. A PubMed search with the exact title didn't bring any results and it can be assumed that the study was never published by any widely accepted scientific journal.

Up until the present time, the FDA studies (such as the NEJM study by Haller) which have been the more compelling evidence opposing the safety of ephedrine, have come forth as a product of AER review in retrospective studies. In 2002, the Mayo Clinic Proceedings published another of these retrospective studies conducted by David Samenuk. (4) His objective was to analyze 37 cases where ma huang (herbal source of ephedrine) use was temporally related to stroke, myocardial infarction or sudden death. The study concluded that cardiac or vascular disease is not a prerequisite for ma huang related adverse events and that the adverse cardiovascular toxic effects of ma huang were not limited to massive doses. Therefore ephedrine may be associated with serious medical complications. This study also ceded that the report had the, "limitation of being an observational study and as such does not definitively establish the relationship between ma huang use and the risk of adverse cardiovascular events. However, like the cases of fenfluramine-phentermin, our observations raise important public health issues that warrant further research." (4)

Where Do We Go From Here?

Thus far, it has been very difficult to prove that ephedrine is linked beyond a reasonable doubt to various deleterious cardiovascular effects. It is assumed that progressive studies are difficult to do because of the ethical dilemma of administering very high doses of ephedra. Such studies may be unethical especially because previous studies based on AERs say that there is little or no health benefit from the supplements and the associate risks can be very deadly. (8)

However the next logical step seems to be to have the FDA develop safe dosing recommendations and demand proper labeling. (11) Gerley's study of the content versus label claims in ephedra-containing dietary supplements points out that assay of 20 ephedra-containing dietary supplements showed that the actual active chemical composition of the dietary supplements, "differed markedly from label claims and was inconsistent between two lots of some products." (12) The reason for such inconsistencies have been due to the fact that there are no Good Manufacturing Practices (GMP) regulations specifically designed for dietary supplements. A proposal for such has been submitted.

One of the main reasons for the weaknesses of the AER based studies are in that the exact dosages of ephedra are nearly impossible to determine because of the laxity and the lack of regulation of universal standards and recommended dosages as well as inaccuracies that are bound to have occurred in the reporting of the actual dosages.

A clear understanding of the deleterious effects of ephedrine seems to be elusive and the FDA has not conducted very convincing clinical studies of the harmful effects of ephedrine. The EEC claims that under the DSHEA, congress gave the Food and Drug administration the power to make sure that dietary supplements including Ephedra are safe and are accurately and truthfully

labeled. (13) Herbal supplements are officially classified as a food and not a drug. (14) The DSHEA passed by congress and signed into law in 1994, states that the FDA can ban a supplement if significant or unreasonable risk is established with use the dietary supplement, as well as if the supplement may render injury under the recommended or suggested conditions indicated on a product's label. Thus the burden of proof lies with the governmental agencies. To exonerate itself, the FDA points to the manufacturers and cites lack of funds to do necessary and proper investigation of the supplements. (14)

Eventually, a universal standard of proper dosage and proper labeling must be enforced. Once that standard is put into place, there can be a more substantial base of evidence to determine the safety of ephedrine. The standard will also create a basis from which prosecution and litigation of the companies can occur. Until then, the dietary supplement industry seems to have free reign and no real pressure to recall ephedrine-containing products because of the lack of clear scientific evidence. The industry with its incredible success and a very vast collection of resources and political sway may prolong the relatively unchecked availability of the supplement. At the very least, more convincing studies of the deleterious effects of ephedrine need to be conducted.

A question that lingers is why the industry is not voluntarily recalling its products at the first hint of litigation. Recent Fen-Phen settlements are in the billions of dollars. Can the industry swallow such settlements in the light of its incredible success? How many more high-profile deaths like Corey Stringer and Steve Bechler must take place before the manufacturers stop putting the supplements on the shelves? It seems that the manufacturers are taking advantage of a toothless or napping FDA as well as the lack of overwhelming and lucid evidence. Reform is a long-term hope, but a universal standard needs to be created soon.

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