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FILE: ▪Ephedra (*Ephedra sinica*)
▪Cardiovascular Adverse Events

HC 090255-300

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RE: A Case Report of an Adverse Outcome Associated with Ephedra Use

Chen-Scarabelli C, Hughes S, Landon G, et al. A case of fatal ephedra intake associated with lipofuscin accumulation, caspase activation and cleavage of myofibrillary proteins. *Eur J Heart Fail.* 2005;7:927–930.

Case reports of adverse events (AEs) are important sources of information. They can alert clinicians and policy makers to previously unrecognized problems with prescription or over the counter (OTC) drugs and supplements. While the strength of case reports can be limited by confounding factors, such as the use of multiple drugs and supplements by patients, and the algorithm used to determine associations between a drug and AE, all AEs must be evaluated carefully so that potential dangers can be identified and appropriate action taken.

This article discusses the death of a 45-year old woman secondary to cardiovascular collapse. The authors conclude that the woman died "while taking ephedra," and patients should be warned "about the risk of serious adverse effects, which may follow ephedra intake." A closer look at the case, however, reveals greater ambiguity than the headline and conclusion would lead the casual reader to believe.

The patient was admitted to the hospital (location unspecified) suffering from cardiovascular collapse after taking aspirin, "while using Xenadrin diet supplements. Two capsules of Xenadrin RFA-1 (Cytodyne Technologies, Lakewood, NJ) contain 125 mg bitter orange (*Citrus* x *aurantium*; 4% synephrine), 335 mg ephedra (*Ephedra sinica*; a.k.a. ma huang; 6% ephedrine), 910 mg guarana (*Paullinia cupana*) extract (22% caffeine), 105 mg white willow (*Salix alba*) bark (15% salicin), 100 mg acetyl L-carnitine, 80 mg L-tyrosine, 50 mg ginger (*Zingiber officinale*) root, and 40 mg vitamin B5. Her medication list also included Prozac® (fluoxetine) and Nicotrol inhaler (nicotine inhalation system used to help people quit smoking). No dosages for any medications or other supplements were reported. Additionally, she had a 25 pack-year history of smoking, which she had quit eight months before this event.

Although the ephedra-containing supplement was on her medication list, no data were presented proving the woman had actually taken this supplement recently. No toxicology tests for ephedra alkaloids, such as ephedrine, were reported. Ephedrine is believed to be the major central nervous system (CNS) activating constituent of ephedra. Peak ephedrine absorption occurs approximately

two to four hours after consumption, and the mean half-life (time it takes for half of a given constituent to be metabolized or excreted) is six hours.[1]

Tests conducted revealed cannabinoids (from marijuana, *Cannabis sativa*) and elevated cardiac markers CK-MB and troponin I (indicators of heart tissue damage during a heart attack). An electrocardiogram (ECG) was abnormal and showed sinus tachycardia (elevated heart rate) and ischemic damage (low oxygen). A repeat ECG four days later showed that a myocardial infarction (heart attack) had occurred. Computer tomography (CT) brain scan showed cerebral edema (fluid in her brain), but no intracranial bleeding or masses. Ejection fraction (amount of blood expelled from the heart with each beat) was 25% (normal is > 55%). She died after six days on life support.

The patient suffered serious cardiac pathology; however, the authors noted that microscopic evaluation of the heart muscle did not show tissue derangement consistent with, "pathological features previously described in patients who experienced sudden death associated with ephedra intake." In addition, although these features mentioned by the authors of this report had been associated with cardiac damage by ephedra in a previously case series,[2] six of the seven cases of sudden cardiac death attributed to ephedra in this earlier study were refuted by Grover Hutchins,[3] an anatomic pathologist, whose findings were included in a presentation by the Expert Panel of the Ephedra Education Council to the Department of Health and Human Services' Public Meeting on the Safety of Dietary Supplements Containing Ephedrine Alkaloids on August 8 and 9, 2000.[4] In his analysis, Dr. Hutchins concluded, "there are significant relevant omissions in the description of fatal cases. These omissions seriously weaken the strength of any attribution of the sudden deaths to ephedra alkaloids".[3]

Similarly, the present case study also suffers from omissions that weaken the strength of association between the tragic death of this patient and ephedra. As previously noted, no toxicology data were reported demonstrating that the patient actually contained ephedrine alkaloids in her blood. This information would have supported the hypothesis that the patient actually ingested the dietary supplement. Additionally, microscopic examination of her cardiac tissue did not demonstrate anatomic derangements consistent with those ascribed to ephedra. Furthermore, although the specific product reported was identified, analysis of the dietary supplement for contaminants of any nature which could have caused the pathology reported was not conducted. In view of these omissions, it seems plausible that one can not sufficiently prove in this case report that ephedra caused this AE.

—John Neustadt, ND

References

[1]Safety assessment and determination of a tolerable upper limit for ephedra. *Cantox Health Sciences International*. Available at: http://www.crnusa.org/cantoxreportindex.html. Accessed August 30, 2005.
[2]Samenuk D, Link MS, Homoud MK, et al. Adverse cardiovascular events temporally associated with ma huang, an herbal source of ephedrine. *Mayo Clin Proc.* Jan 2002;77(1):12-16.
[3]Hutchins GM. Ma huang toxicity. *Mayo Clin Proc.* Jul 2002;77(7):733.
[4]Public meeting on the safety of dietary supplements containing ephedrine alkaloids, August 8-9, 2000. *Department of Health and Human Services, United States Public Health Service, Office on Women's Health.* Available at: http://www.4woman.gov/owh/public/. Accessed August 29, 2005.

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