Case Reports

Acute Myocardial Infarction Associated with Dietary Supplements

Containing 1,3-Dimethylamylamine and *Citrus aurantium*

Triston B. Smith, MD
Brian A. Staub, MD
Gayathri M. Natarajan, MD
David M. Lasorda, DO
Indu G. Poornima, MBBS

We describe the case of a previously healthy 22-year-old man who presented with anginal chest pain and was diagnosed with a non-ST-elevation myocardial infarction. For 3 weeks, he had been ingesting the dietary supplements Jack3d® (principal ingredient, 1,3-dimethylamylamine) and Phenorex™ (principal ingredient, Citrus aurantium*) daily, before undertaking physical activity. Coronary angiograms revealed a proximal left anterior descending coronary artery thrombus with distal embolization. A combined medical regimen led to resolution of the thrombus. Three months later, the patient was asymptomatic with no evidence of ischemia.*

The primary ingredients in the sympathomimetic supplements taken by our patient are controversial in the medical community and have been individually associated with adverse cardiac events. There are no safety data on their simultaneous use. We discuss other reports of adverse effects associated with these supplements and recommend that the relevant safety guidelines be revised. ***(Tex Heart Inst J 2014;41(1):70-2)***

Key words: *Citrus/adverse effects; coronary thrombosis/chemically induced; dietary supplements/adverse effects/standards; myocardial infarction/chemically induced/therapy; substance-related disorders/complications/diagnosis/therapy; synephrine/toxicity; treatment outcome*

From: *Divisions of Cardiology (Drs. Lasorda, Poornima, Smith, and Staub) and Internal Medicine (Dr. Natarajan), Allegheny General Hospital, Pittsburgh, Pennsylvania 15212*

Address for reprints: *Triston Smith, MD, Division of Cardiology, Allegheny General Hospital, 320 E. North Ave., Pittsburgh, PA 15212*

E-mail: *smith_triston@yahoo.com*

We present the case of a 22-year-old man, previously healthy and without cardiovascular risk factors, who presented with an acute anterior-wall myocardial infarction. For 3 weeks, before undertaking daily physical exercise, he had been ingesting dietary supplements containing 1,3-dimethylamylamine (DMAA) and *Citrus aurantium*. We outline our therapeutic approach, briefly review the literature relevant to the chief ingredients in the dietary supplements, and comment on safety guidelines.

Case Report

In September 2012, a 22-year-old white man with no relevant personal or family medical history was transferred to our hospital. He had typical anginal chest pain (Universal Pain Assessment Tool score, 8/10), which had started while he coached basketball one day before admission. He did not use tobacco, alcohol, or illicit drugs. However, 3 weeks before presentation, he had begun taking daily oral doses of the dietary supplements Jack3d® (USPlabs, LLC; Dallas) and Phenorex™ (Gaspari Nutrition; Lakewood, NJ) before undertaking physical activity.

The muscular patient had clear lung fields and no jugular venous distention. His heart sounds were normal without murmurs, rubs, or gallops. His abdomen was benign with normal bowel sounds. His peripheral pulses were palpable and equal bilaterally, and there was no lower-extremity edema. He was awake, alert, and oriented, and his vital signs were all normal.

An electrocardiogram showed sinus arrhythmia and anterior J-point elevation without findings of ischemia. A transthoracic echocardiogram revealed a normal left ventricular ejection fraction and no wall-motion abnormalities. A contrast computed tomogram of the chest showed no pulmonary embolus. Serologic markers of myocardial injury were elevated as follows: cardiac troponin T, 1.36 ng/mL; creatine kinase, 518 U/L; and creatine kinase-MB fraction, 25.1 ng/mL. The diagnosis was a non-ST-elevation acute myocardial infarction.

The patient reported no further chest pain. We gave him aspirin (325 mg) and atorvastatin (80 mg) orally and unfractionated heparin via continuous intravenous infusion. Two hours after the patient was admitted to the coronary care unit, several runs

of nonsustained ventricular tachycardia were detected, so he was taken to the cardiac catheterization laboratory. Coronary angiograms showed a filling defect consistent with thrombus in the proximal left anterior descending coronary artery, and distal tapering of that artery with Thrombolysis in Myocardial Infarction grade 2 flow due to distal thrombus embolization.

We took a cautious, noninvasive approach to management, giving the patient a 60-mg loading dose of prasugrel and an intravenous infusion of eptifibatide. After 48 hours, the thrombus had almost completely resolved. The patient's total cholesterol level was 106 mg/dL; low-density-lipoprotein cholesterol, 52 mg/dL, high-density-lipoprotein cholesterol, 42 mg/dL, and lipoprotein(a), 6 mg/dL. Investigation yielded no hypercoagulability. The patient was discharged from the hospital after 6 days and stopped taking the dietary supplements. Three months later, an exercise stress test revealed excellent functional capacity without symptoms and with no electrocardiographic evidence of ischemia. As of December 2013, he remained asymptomatic.

Discussion

In the absence of traditional atherosclerotic risk factors in our patient, we think that the acute coronary syndrome was caused by the sympathomimetic supplements that he was ingesting before exercise. The pre-exercise supplements Jack3d and Phenorex contain multiple ingredients, including caffeine, DMAA, and *C. aurantium*. Although the individual constituents of these 2 products have been reported to be "safe," little is known about pharmacologic actions or physiologic effects when they are combined or are taken along with other formulations. In accordance with the Dietary Supplement Health and Education Act of 1994, manufacturers in the United States are responsible for ensuring product safety before marketing a dietary supplement.[1] No structured post-marketing monitoring of the adverse effects of dietary supplements is in place.

1,3-Dimethylamylamine

1,3-Dimethylamylamine is a simple aliphatic amine with sympathomimetic properties. We have identified 30 names by which this substance is known: the most common are methylhexaneamine, 2-amino-4-methylhexane, 1,3-dimethylpentylamine, and 4-methyl-2-hexylamine. It is also known as Geranamine™ (Proviant Technologies, Inc.; Champaign, Ill).[2]

The exact source of DMAA is controversial. Although this substance, an extract of the *Pelargonium graveolens* plant,[4] is now marketed as a nutritional supplement, it was first patented by Eli Lilly in the 1940s as Forthane, an inhaled local vasoconstrictor agent used to treat nasal congestion.[3]

Case reports linking dietary supplements with acute myocardial infarction have emerged in the last few years.[4] In 2011, 2 United States soldiers (ages, 22 and 32 yr) died after sustaining heart attacks during fitness exercises. 1,3-Dimethylamylamine (present in Jack3d) was found during postmortem toxicologic screening. In February 2012, the U.S. Department of Defense removed Jack3d and all products containing DMAA from stores on military bases.[5] At least one case of cerebral hemorrhage linked to the recreational use of DMAA has been reported.[3] In March 2012, the New Zealand Health Ministry imposed a complete ban on DMAA.[6] In February 2012, The Medicines and Healthcare Products Regulatory Agency of the United Kingdom warned several companies to stop selling products that contained DMAA.[7]

In reaction to the increasing scrutiny of DMAA, USPlabs, a major producer of DMAA-containing products, sponsored several short clinical trials to prove its efficacy and safety. Bloomer and colleagues[2,8,9] conducted 7 clinical studies to evaluate DMAA's safety after single- and repeated-dose administration and a follow-up period of up to 10 weeks. The investigators found that DMAA can produce a mild and transient increase in systolic blood pressure; however, they reported no other hemodynamic changes and no severe adverse events. Of note, no long-term studies appear to have been conducted.

Citrus aurantium

Citrus aurantium, a principal ingredient of the pre-exercise supplement Phenorex, is also controversial in the medical community. Extracts of *C. aurantium* have attained substantial popularity in the treatment of obesity. The substance is marketed as an alternative to ephedrine alkaloids, which have been banned from dietary supplements by the U.S. Food and Drug Administration (FDA) since April 2004 because of an association with severe adverse health effects.[10]

Citrus aurantium contains synephrine alkaloids, which are structurally similar to ephedrine, amphetamines, phenylpropanolamine, adrenaline, and noradrenaline.[11] The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure lists *C. aurantium* as a cause of resistant hypertension.[12] The structural similarity suggests that *C. aurantium* would have pharmacologic actions similar to those of ephedrine and would evoke comparable physiologic responses.[13] Synephrine can exist in 3 positional isomeric forms—*ortho* (o-), *meta* (m-), and *para* (p-)—and each positional isomer can also be found in 2 enantiomeric forms.[14] P-synephrine (oxedrine) is an α-adrenergic agonist that also displays some β-adrenergic properties.[15] It is thought to be the primary ingredient in *C. aurantium* that contributes to weight loss. However, neither this theory nor the con-

tention that *C. aurantium* actually induces weight loss in human beings has been firmly established.[14]

The Canadian government has enacted restrictions on p-synephrine dosage and on the legality of combining p-synephrine with other ingredients; however, the U.S. government has not.[16] From April 2004 through October 2009, the FDA received 22 adverse-event reports, and 10 clinical case reports were published in regard to adverse events associated with *C. aurantium*-containing products.[17] Some authors have postulated that because these formulations were polyherbal and polyalkaloidal, *C. aurantium* might have been unjustly imputed in the association with adverse events.[17] Others have cited the traditional use of *C. aurantium* in Chinese medicine as justification of its safety in weight-loss products.[14,17-19] We think that both of these assumptions should serve as poignant reminders of the ephedra debacle, because these same rationales were the chief arguments to validate ephedra's use.[20]

Summary

Our patient was ingesting 2 dietary supplements with sympathomimetic properties that could lead to vasoconstriction or plaque rupture followed by thrombosis. On the basis of this case and previous reports, we propose that the safety guidelines for these supplements be revised. No safety data exist on the simultaneous use of these products. The manufacturing practice of producing polyherbal and polyalkaloidal products makes it difficult to prove the causality of any particular ingredient when adverse events occur. Regardless, the medical community, supplement users, and manufacturers should remain informed and report all suspected adverse events until unbiased and incontrovertible proof supports the safety of the supplements. In addition, post-marketing monitoring should be advocated if we are to understand the long-term effects of these agents.

References

1. U.S. Food and Drug Administration. Dietary supplements [Internet]. Available from: http://www.fda.gov/Food/DietarySupplements/default.htm [updated 2013 Aug 28].
2. Whitehead PN, Schilling BK, Farney TM, Bloomer RJ. Impact of a dietary supplement containing 1,3-dimethylamylamine on blood pressure and bloodborne markers of health: a 10-week intervention study. Nutr Metab Insights 2012;5:33-9.
3. Gee P, Jackson S, Easton J. Another bitter pill: a case of toxicity from DMAA party pills. N Z Med J 2010;123(1327):124-7.
4. Thomas JE, Munir JA, McIntyre PZ, Ferguson MA. STEMI in a 24-year-old man after use of a synephrine-containing dietary supplement: a case report and review of the literature. Tex Heart Inst J 2009;36(6):586-90.
5. Lattman P, Singer N. Army studies workout supplements after deaths [news article on the Internet]. Available from: http://www.nytimes.com/2012/02/03/business/army-studies-workout-supplements-after-2-deaths.html [2012 Feb 2; cited 2013 Dec 23].
6. DMAA latest party pill substance to get ban [news article on the Internet]. Available from: http://www.3news.co.nz/DMAA-latest-party-pill-substance-to-get-ban/tabid/423/articleID/245691/Default.aspx [2012 Mar 8; cited 2013 Dec 23].
7. Starling S. UK begins DMAA crackdown [news article on the Internet]. Available from: http://www.nutraingredients.com/Regulation/UK-begins-DMAA-crackdown?utm_source=copyright&utm_medium=OnSite&utm_campaign=copyright [2012 Feb 24; cited 2013 Dec 23].
8. McCarthy CG, Canale RE, Alleman RJ Jr, Reed JP, Bloomer RJ. Biochemical and anthropometric effects of a weight loss dietary supplement in healthy men and women. Nutr Metab Insights 2011;5:13-22.
9. Farney TM, McCarthy CG, Canale RE, Allman RJ Jr, Bloomer RJ. Hemodynamic and hematologic profile of healthy adults ingesting dietary supplements containing 1,3-dimethylamylamine and caffeine. Nutr Metab Insights 2011;5:1-12.
10. Fugh-Berman A, Myers A. Citrus aurantium, an ingredient of dietary supplements marketed for weight loss: current status of clinical and basic research. Exp Biol Med (Maywood) 2004;229(8):698-704.
11. Rossato LG, Costa VM, de Pinho PG, Carvalho F, de Lourdes Bastos M, Remiao F. Structural isomerization of synephrine influences its uptake and ensuing glutathione depletion in rat-isolated cardiomyocytes. Arch Toxicol 2011;85(8):929-39.
12. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, et al. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension 2003;42(6):1206-52.
13. Bent S, Padula A, Neuhaus J. Safety and efficacy of citrus aurantium for weight loss. Am J Cardiol 2004;94(10):1359-61.
14. Haaz S, Fontaine KR, Cutter G, Limdi N, Perumean-Chaney S, Allison DB. Citrus aurantium and synephrine alkaloids in the treatment of overweight and obesity: an update. Obes Rev 2006;7(1):79-88.
15. Santana J, Sharpless KE, Nelson BC. Determination of para-synephrine and meta-synephrine positional isomers in bitter orange-containing dietary supplements by LC/UV and LC/MS/MS. Food Chem 2008;109(3):675-82.
16. Health Canada relaxes P synephrine rules [news article on the Internet]. Available from: http://www.naturalproductsinsider.com/news/2011/10/health-canada-relaxes-rules-on-p-synephrine.aspx [2011 Oct 31; cited 2013 Dec 23].
17. Stohs SJ. Assessment of the adverse event reports associated with Citrus aurantium (bitter orange) from April 2004 to October 2009. J Funct Foods 2010;2(4):235-8.
18. Arbo MD, Schmitt GC, Limberger MF, Charao MF, Moro AM, Ribeiro GL, et al. Subchronic toxicity of Citrus aurantium L. (Rutaceae) extract and p-synephrine in mice. Regul Toxicol Pharmacol 2009;54(2):114-7.
19. Stohs SJ, Preuss HG, Shara M. A review of the receptor-binding properties of p-synephrine as related to its pharmacological effects. Oxid Med Cell Longev 2011;2011:482973.
20. Soni MG, Carabin IG, Griffiths JC, Burdock GA. Safety of ephedra: lessons learned. Toxicol Lett 2004;150(1):97-110.