

Ischemic Stroke Associated With Use of an Ephedra-Free Dietary Supplement Containing Synephrine

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In response to concerns regarding the safety of ephedra-containing dietary supplements, manufacturers have marketed “ephedra-free” products. Many of these contain synephrine, a sympathomimetic amine from the plant *Citrus aurantium*. Synephrine is structurally similar to ephedrine and has vasoconstrictor properties. We describe a 38-year-old patient with ischemic stroke associated with an ephedra-free dietary supplement containing synephrine and caffeine. The patient presented with memory loss and unsteady gait after taking 1 or 2 capsules per day of a dietary supplement (Stacker 2 Ephedra-Free) for 1 week. He had no notable medical history or major atherosclerotic risk factors and took no other medications. Physical examination showed a mildly ataxic gait and substantial impairment of both concentration and memory. Computed tomography and magnetic resonance imaging of the brain showed subacute infarctions in the left thalamus and left cerebellum in the distribution of the vertebrobasilar circulation. Other causes of ischemic stroke were evaluated, and findings were unremarkable; a vasospastic origin was considered most likely. The patient was discharged with nearly complete resolution of symptoms. Synephrine, a sympathomimetic amine related to ephedrine, may be associated with ischemic stroke. Consumers and clinicians need to be informed about the potential risks of ephedra-free products.

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CNS = central nervous system; ED = emergency department; FDA = Food and Drug Administration

Of the \$37.1 billion spent by Americans for weight loss products and services in 2001, \$17.7 billion was spent for dietary supplements. Spending for weight loss is estimated to increase at an annual rate of 6% to 7%.¹ During the past decade, there have been hundreds of reports of severe neurologic and cardiovascular complications associated with use of ephedra alkaloid-containing supplements. Nearly 1000 suspected cases of ephedrine toxicity from ma huang (*Ephedra sinica*), reported to the

US Food and Drug Administration (FDA) between 1995 and 1997, were reviewed extensively.² In 2000, Haller and Benowitz³ published a similar review of 140 ephedra-associated adverse events that were reported to the FDA. Both reviews identified serious neurologic and cardiovascular sequelae associated with ephedra use, including stroke, myocardial infarction, seizure, and sudden death.^{2,3}

In December 2003, the FDA announced that ephedra-containing products were considered too unsafe for unregulated sale.⁴ A ban on their sale was announced in February 2004 and was enacted on April 12, 2004.⁵ It is likely that a combination of the FDA ban on ephedra-containing products in the United States and the “bad press” regarding safety concerns about ephedra led manufacturers worldwide to develop “ephedra-free” products as alternatives.⁶ The ephedra ban does not preclude the use of other structurally related sympathomimetic amines in products for weight loss and energy enhancement. Despite little supporting evidence, ephedra-free products are portrayed almost uniformly as a safer alternative to ephedra. Synephrine (also referred to as *p*-synephrine and oxedrine),⁷ is a sympathomimetic amine derived from the plant *Citrus aurantium*.^{8,9} *C. aurantium* (previously called *Fructus aurantii*) is known commonly as bitter orange, Seville orange, green orange, sour orange, or zhi shi. In traditional Chinese medicine, synephrine is used frequently to stimulate overall gastrointestinal function and as a general tonic. Synephrine has become the most frequently used ephedra replacement in dietary supplements and is listed often as “extract of *C. aurantium*” or “extract of bitter orange.”

As an indirect-acting sympathomimetic amine, synephrine has structural and pharmacological similarity to ephedrine and phenylpropanolamine, both of which have been banned from sale in the United States because of their association with adverse cardiovascular events (Figure 1). A recent case report described an association between acute myocardial infarction and consumption of a synephrine-containing supplement.¹⁰ Another recent case report described exercise-induced syncope associated with QT prolongation in a young, otherwise healthy woman who was taking a synephrine-containing product (Xenadrine EFX).¹¹ We describe a patient with ischemic stroke associated with short-term daily use of an ephedra-free product

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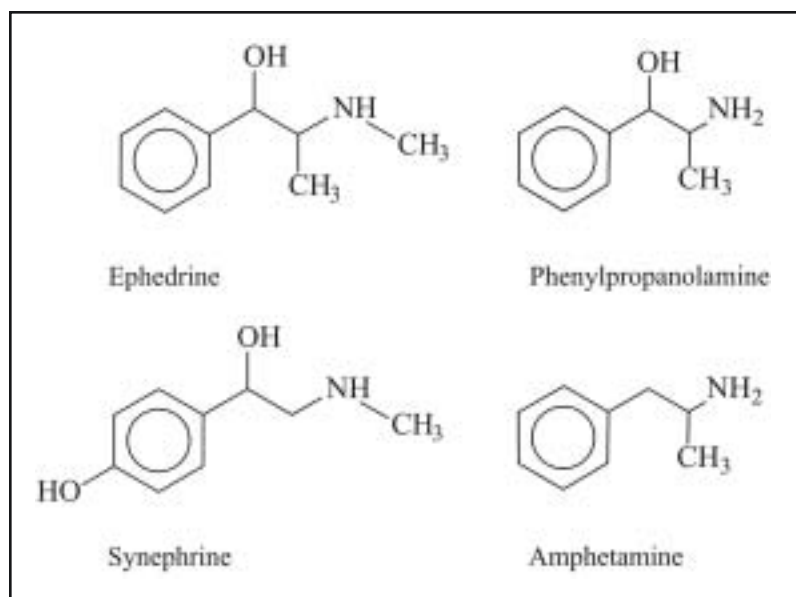


FIGURE 1. Chemical structures of synephrine, phenylpropanolamine, amphetamine, and ephedrine.

that contained synephrine, which, to our knowledge, is the first reported occurrence.

REPORT OF A CASE

A 38-year-old man presented to the emergency department (ED) with recent onset of dizziness, difficulty in concentrating, memory loss, and unsteady gait. He had no notable medical history, no major risk factors for atherosclerotic disease, and no family history of atherosclerotic disease; he had been taking no long-term medications. The patient had a remote history of light cigarette smoking (approximately 5 cigarettes per day) and used no alcohol or illicit drugs.

For 1 week before presentation, the patient took 1 or 2 capsules per day of the weight loss dietary supplement Stacker 2 Ephedra Free for mild obesity (he was 5-7 kg overweight). This dosage was less than the 3 capsules daily suggested by the manufacturer. According to the container label, each capsule contained 6 mg of synephrine and 200 mg of caffeine alkaloids (kola nut extract). The patient denied taking other medications or herbal preparations that week or in the recent past. During the 4 days before presentation, he experienced several episodes of "dizziness" and had trouble "thinking." Three days before presentation (a Friday), he increased his dosage from 1 to 2 capsules daily. Later that day, the patient experienced a severe "dizzy" episode associated with brief loss of consciousness. This event was not associated with postural change, diaphoresis, chest pain, or palpitations. On Monday morning, the patient noted a transient episode of diplopia, which resolved after 30

minutes. He described "not feeling right" that morning and had difficulty ambulating and locating his keys. While at work as a city bus driver, the patient was unable to recall the details of the bus route that he drove daily. He came to the ED directly from work. He continued to take 2 capsules per day of the dietary supplement until presentation to the ED.

The patient's initial vital signs were as follows: blood pressure, 120/72 mm Hg; heart rate, 56 beats/min; respiratory rate, 16/min; and temperature, 36.0 C. His blood glucose level at triage was 95 mg/dL, and electrocardiography showed a normal sinus rhythm at 50 beats/min with a corrected QT interval of 430 ms. On physical examination, the patient appeared alert and was grossly oriented to person and place. He showed mild ataxia with a slightly wide-based gait and had difficulty performing tandem gait. He was right-hand dominant.

Although joint position sense and temperature sensation were intact, the patient experienced postural instability when standing with outstretched arms. Fine finger motion exercises were better on the right hand than the left, and results of rapid-alternating-motion and finger-to-nose exercises were normal. There was no dysfunction in the territory of the cranial nerves, and strength and reflexes, including Babinski sign, were normal and symmetrical throughout. The patient could not recall his own or his wife's birthday, the current year, or the names of famous public figures. He also described difficulty concentrating and was unable to perform the serial 7s test. He was able to read and comprehend. Computed tomography of the brain performed within 1 hour of presentation showed acute to subacute

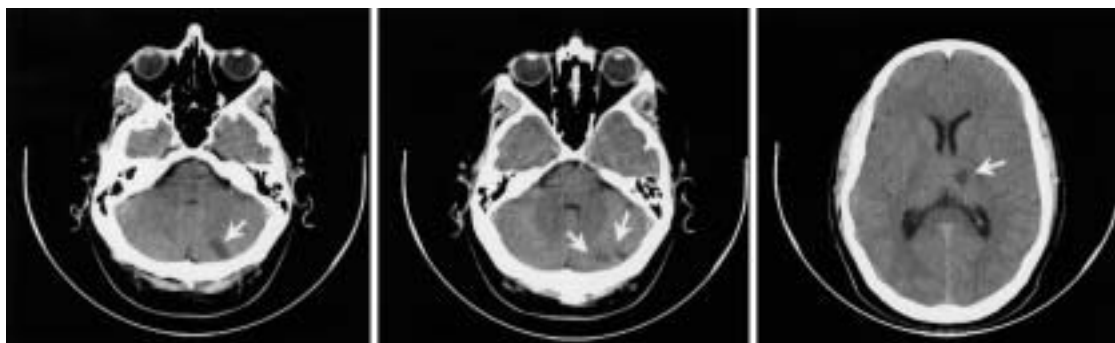


FIGURE 2. Non-contrast-enhanced computed tomograms of the head show multiple subacute infarctions (white arrows) in the left cerebellum (left, middle) and left thalamus (right).

infarctions in the left thalamus and multiple infarctions in the left cerebellum (Figure 2). These infarctions were in the distribution of the vertebrobasilar circulation. Magnetic resonance imaging performed shortly afterward confirmed findings of recent thalamic and cerebellar infarctions (on diffusion-weighted images) and showed an additional infarction of indeterminate age in the temporal lobe (Figure 3).

Findings from routine admission laboratory analyses, including a urine toxicology screen for commonly abused drugs, were unremarkable. The erythrocyte sedimentation rate, hemoglobin A_{1c} level, serum lipid profile, serum homocysteine level, coagulation studies (including thrombin time and fibrinogen), and thrombophilia panel (including antithrombin, protein C and protein S, factor II and factor VIII, factor V Leiden/activated protein C resistance lupus anticoagulant/Dilute Russell Viper Venom Time) were all normal. Results from an extensive evaluation for ischemic stroke, which included transthoracic and transesophageal echocardiography and carotid artery Doppler ultrasonography showed no abnormalities. Furthermore, magnetic resonance angiography of the intracranial and extracranial cervical (neck) arteries showed both normal course and

caliber of all vessels, including vertebral, basilar, and posterior cerebral arteries.

The patient made a nearly complete clinical recovery with only residual, mild, subjective impairment of concentration and was discharged after approximately 1 week with aspirin and immediate-release dipyridamole. His discharge diagnosis was ischemic stroke, presumably of vasospastic origin, probably secondary to synephrine. The patient was advised to discontinue use of that supplement and to avoid other dietary supplements for weight loss or energy enhancement. Although a follow-up appointment was arranged, the patient did not return and could not be reached after hospital discharge. This case was reported to the FDA MedWatch program.¹² The case also was reported to the manufacturer, who indicated that no similar adverse effects had been submitted to them regarding synephrine-containing products (D. Caldwell, oral communication, January 2005).

DISCUSSION

The multivessel distribution, stuttering clinical course, and normal magnetic resonance angiography in our patient

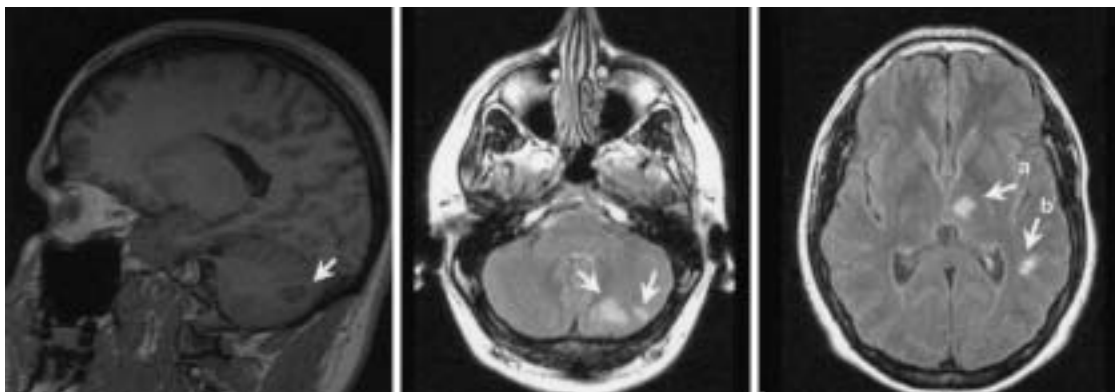


FIGURE 3. Magnetic resonance images of the brain show multiple subacute infarctions (white arrows) in the left cerebellum (left, middle), left thalamus (right, a), and left temporal lobe (right, b).

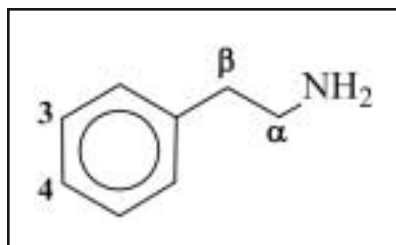


FIGURE 4. Generic sympathomimetic phenylethylamine structure with activity alteration. See Table 1 for details.

could be consistent with a diagnosis of stroke of vasospastic origin. Onset of the patient's symptoms of dizziness, gait instability, memory loss, and cerebral infarctions coincided temporally with his ingestion of a synephrine and caffeine-containing weight-loss supplement. On presentation, electrocardiography showed no notable QT prolongation, but a dysrhythmic event leading to hypotension, dizziness, and syncope could not be excluded. However, it is highly doubtful that such an event could produce the pattern of infarction seen in this patient. No other etiology for his stroke was identified despite a comprehensive evaluation; moreover, the dietary supplement was the only vasoactive medication in the patient's recent medical history.

Dietary supplement manufacturers suggest that synephrine has fewer undesirable central nervous system (CNS) effects (eg, less nervousness, jitteriness, anxiety, tremor, and insomnia) than ephedra. Internet resources for the general public describe *C aurantium* as an herbal supplement that directly stimulates fat metabolism, suppresses appetite, and increases metabolic rate and caloric expenditure without negative cardiovascular adverse effects.¹³⁻¹⁶

Other direct-acting and indirect-acting sympathomimetic phenylethylamines are well known to cause periph-

eral, coronary, and cerebral ischemia from vasospasm. In the largest review of ma huang (ephedrine)-associated adverse cardiovascular effects, 16 strokes were identified, of which 75% were ischemic and 25% were hemorrhagic.² Vasospasm can occur in large cranial arteries or in small arteries in the microvasculature and can be evenly and/or unevenly distributed. The deleterious effects of vasospasm can be exacerbated further by sympathomimetic-induced platelet aggregation.

Synephrine shares structural similarity with other sympathomimetic phenylethylamine drugs such as ephedrine, amphetamine, and phenylpropanolamine (Figure 1). All phenylethylamine compounds comprise an aromatic ring with a substituted ethylamine side chain (Figure 4). Substitutions on the aromatic ring and at the β or α carbons or the amine positions of the side chain determine pharmacological activity (Table 1).

In synephrine, substitutions at position 4 of the aromatic ring, the β carbon, and the amine group of the carbon side chain suggest that synephrine may be a potent α - and β -adrenergic agonist. Moreover, substitution of a hydroxyl group both at the β carbon and at position 4 of the aromatic ring likely reduces the ability of the drugs to penetrate the CNS; hence, the drug should have fewer CNS adverse effects. Furthermore, single (rather than double as in catecholamines) hydroxylation of the benzene ring suggests that synephrine is not degraded by catechol-*O*-methyltransferase, thereby enhancing oral efficacy and prolonging its duration of action. Although synephrine may stimulate lipolysis by binding at β_3 -adrenergic receptors in adipose tissue, its clinical effect on weight loss is uncertain.

At least 2 animal studies suggest that synephrine is a vasoconstrictor with dose-dependent effects on arterial blood pressure.^{17,18} Interestingly, *C aurantium* extract was

TABLE 1. Summary of α and β Carbon, Amine and Aromatic Ring Substitutions in Sympathomimetic Phenylethylamines, and Their Associated Pharmacological and Clinical Effects*

Substitution	Pharmacological effect	Clinical effect
α carbon	Resists oxidation by monoamine oxidase Indirect acting	Increased duration of action for noncatecholamines
β carbon	Decreases CNS penetration Hydroxyl (-OH): mandatory for adrenergic activity	Fewer CNS symptoms Increased HR and BP
Amino group	No substitution: $\alpha > \beta$ effects Methyl (-CH ₃) group: maximum α and β effects Larger group: $\beta > \alpha$ effects t-butyl group: β_2 selective	Increased BP Increased HR and BP Increased HR, inotropy, and bronchodilation Bronchodilation
3-,4- of aromatic ring	Hydroxylation at 3- and 4- (yield catechol nucleus): increased α and β effects Absence of hydroxylation (at one or both positions) prevents degradation by catechol- <i>O</i> -methyltransferase	Increased HR and BP; no CNS effects Increased oral bioavailability and prolonged duration of effect

*BP = blood pressure; CNS = central nervous system; HR = heart rate.

found to induce L-type calcium channel opening in guinea pig ventricular myocytes.¹⁹ The L-type calcium channel is the target of calcium channel antagonists, which are used commonly to treat hypertension and tachycardia. A review of several poorly controlled human studies showed a trend toward increased blood pressure after both treatment with parenteral synephrine and ingestion of synephrine from natural products.²⁰ Another recent review failed to show a weight loss benefit.²¹ Of note, synephrine (oxedrine), sold as Sympatol, Ocuton, Sympathomim, Sympalept, and Fraxipos, has been used clinically as a nasal and ocular decongestant as well as an agent for treating hypotensive states; most of these drugs are no longer commercially available.^{7,22}

In many ephedra-free, *C aurantium*-derived products, *p*-synephrine is the main active ingredient; other active components include hesperidine, *N*-methyltyramine, hordenine, octopamine, and tyramine.^{8,9} Octopamine, sometimes listed in supplement ingredients, is structurally similar to tyramine and appears to stimulate primarily the β_3 -adrenergic receptor.²⁰ It is possible that these amines, in combination, have synergistic cardiovascular effects. The product in our case, as with many other similar products, also contained a high dose of caffeine. Caffeine is believed to potentiate the cardiovascular effects of other sympathomimetic agents.²³⁻²⁵

Two established clinical tools were used to assess the probability that an adverse drug reaction occurred in our patient.^{26,27} If our patient's adverse event of cerebral ischemia is considered the first reported with use of synephrine, this adverse event was *possibly* associated with use of Stacker 2 Ephedra Free. If our patient's adverse event is considered a sympathomimetic class effect, the infarctions were *probably* associated with exposure to this drug. For obvious reasons, the patient was not rechallenged.

CONCLUSION

In an otherwise healthy young man with no defined risk factors, an ischemic stroke was associated with recent use of Stacker 2 Ephedra Free, a supplement that contains the vasoactive sympathomimetic amine synephrine and caffeine. Two similar agents, ephedra (ephedrine) and phenylpropanolamine, have been banned by the FDA secondary to serious neurologic and cardiovascular adverse effects. The medical community needs to be aware of the potential risks of ephedra-free products, to continue to report adverse events to the FDA MedWatch program (1-800-FDA-1088 or online at www.fda.gov/medwatch), and to continue to advocate for better regulation of dietary supplements.¹²

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