ADVERSE CARDIOVASCULAR AND CENTRAL NERVOUS SYSTEM EVENTS ASSOCIATED WITH DIETARY SUPPLEMENTS CONTAINING EPHEDRA ALKALOIDS

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ABSTRACT

Background Dietary supplements that contain ephedra alkaloids (sometimes called ma huang) are widely promoted and used in the United States as a means of losing weight and increasing energy. In the light of recently reported adverse events related to use of these products, the Food and Drug Administration (FDA) has proposed limits on the dose and duration of use of such supplements. The FDA requested an independent review of reports of adverse events related to the use of supplements that contained ephedra alkaloids to assess causation and to estimate the level of risk the use of these supplements poses to consumers.

Methods We reviewed 140 reports of adverse events related to the use of dietary supplements containing ephedra alkaloids that were submitted to the FDA between June 1, 1997, and March 31, 1999. A standardized rating system for assessing causation was applied to each adverse event.

Results Thirty-one percent of cases were considered to be definitely or probably related to the use of supplements containing ephedra alkaloids, and 31 percent were deemed to be possibly related. Among the adverse events that were deemed definitely, probably, or possibly related to the use of supplements containing ephedra alkaloids, 47 percent involved cardiovascular symptoms and 18 percent involved the central nervous system. Hypertension was the single most frequent adverse effect (17 reports), followed by palpitations, tachycardia, or both (13); stroke (10); and seizures (7). Ten events resulted in death, and 13 events produced permanent disability, representing 26 percent of the definite, probable, and possible cases.

Conclusions The use of dietary supplements that contain ephedra alkaloids may pose a health risk to some persons. These findings indicate the need for a better understanding of individual susceptibility to the adverse effects of such dietary supplements. (N Engl J Med 2000;343:1833-8.)

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DIETARY supplements that contain ephedra alkaloids (also known as ma huang) and guarana-derived caffeine are widely consumed in the United States for purposes of weight reduction and energy enhancement. A number of reports of adverse reactions to dietary supplements that contain ephedra alkaloids, some of which resulted in permanent injury or death, have appeared in the medical literature.[1-6] In response to growing concern about the safety of ephedra alkaloids in dietary supplements, the Food and Drug Administration (FDA) requested an independent review of reports of adverse events related to the use of ephedra alkaloids to assess causation and determine the level of risk these products pose to consumers.

We conducted an in-depth review of 140 reports of adverse events involving dietary supplements containing ephedra alkaloids that were submitted to the FDA between June 1, 1997, and March 31, 1999, and applied a standardized rating system for assessing causation. We also evaluated factors that might increase the risk to consumers and the adequacy of warnings about potential risks included on product labels. The full report of our review of adverse events is available elsewhere.[7] Here, we summarize our findings.

METHODS

The objective of the review was to determine the likelihood that ephedra alkaloids (which were usually combined with caffeine) caused the reported adverse events on the basis of the information provided in the FDA MedWatch report, along with supplemental medical records. We independently reviewed each of the 140 cases. Causation was assessed according to the criteria described by Blanc et al.[8] and included an evaluation of the timing of the event in relation to the dose and duration of use of a product; an assessment of the pattern of response to determine whether it constituted a recognized reaction to the substance on the basis of previous reports of ephedrine or similar stimulants in the medical literature; and a determination of the contribution of any underlying diseases or medical conditions.

In general, we defined an adverse event as definitely related to the use of supplements containing ephedra alkaloids only if the symptoms recurred with the reintroduction of ephedra alkaloids or when the onset of symptoms coincided with the expected peak plasma concentration of the drug and resolved within an interval that was consistent with the expected duration of the effect of ephedrine. An adverse event was defined as probably related to the use of supplements containing ephedra alkaloids when the majority of the evidence supported the existence of a causal link but one or more aspects of the case, such as time since the last dose, were unknown or there was a minor inconsistency in the supporting evidence, such as a low reported dose. An adverse event was designated as possibly related to the use of supplements containing ephedra alkaloids when it was equally likely that the adverse event was not related to the use of ephedra alkaloids; for example, in the case of effects that have not been reported in the literature in association with ephedra alkaloids but that are pharmacologically plausible. Reports of ad-

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verse events that included scant medical history and incomplete information about the product involved were usually considered to have insufficient information to be assessed. This category was reserved for events in which the evidence was not substantial enough to consider them as possibly related to the use of supplements containing ephedra alkaloids. Adverse events were defined as probably unrelated to the use of supplements containing ephedra alkaloids if the evidence that ephedra alkaloids were the cause was weak or if the likelihood was strong that there was some other cause, either medical or toxicologic. When the scientific evidence or course of events was highly inconsistent with the known effects of ephedra alkaloids, the event was considered definitely unrelated; for example, in the case of symptoms that persisted long after the use of ephedra alkaloids had been discontinued or in the case of symptoms that had no association with the known pharmacodynamic effects of ephedra alkaloids. However, the event was considered related if the patient had a preexisting condition such as hypertension that could have been aggravated by the use of ephedra alkaloids and if the pattern of use met the criteria for causation.

In determining the likelihood of a causal link, we evaluated aspects of the medical history, dietary patterns, and social habits as possible contributing or causative factors. For example, we noted when events occurred while patients were fasting or in conjunction with high intakes of caffeine. We recognized that in the case of adverse events that were most likely not related to the use of supplements containing ephedra alkaloids one or more of the other ingredients in the supplement may have been causally related to the event.

Table 1. Age and Sex of Users of Supplements Containing Ephedra Alkaloids and Reasons for Use, According to Adverse-Event Reports.

Variable	No. of Users (%)
Age	
<18 yr	10 (7)
18–29 yr	34 (24)
30–45 yr	45 (32)
>45 yr	32 (23)
Unknown	19 (14)
Sex	
Male	56 (40)
Female	84 (60)
Reason for use	
Weight loss	83 (59)
To increase athletic performance	23 (16)
To increase energy	9 (6)
Unknown	24 (17)
Intentional misuse	1 (1)

RESULTS

Features of the Cases

The age and sex of the users of products containing ephedra aklaloids and the reported reasons for use are shown in Table 1. Although the labels of most such products state that they are not intended for use by persons less than 18 years of age, adverse events were recorded in at least 10 persons under this age. The youngest was 15 years old. Overall, 43 cases (31 percent) were considered to be definitely or probably related to the use of supplements containing ephedra alkaloids, 24 cases (17 percent) were considered to be unrelated to the use of such supplements, 44 cases (31 percent) were deemed possibly related to the use of such supplements, and in 29 cases (21 percent) the information provided was insufficient to assess causation. The types of adverse events that were definitely or probably related to the use of supplements containing ephedra alkaloids and those that were possibly related are summarized in Table 2.

Cardiovascular symptoms made up 47 percent of the adverse events that were definitely, probably, or possibly related to the use of supplements containing ephedra alkaloids. Hypertension was the single most frequent adverse effect, followed by palpitations, tachycardia, or both. Eighteen percent of related and possibly related adverse events involved the central nervous system. Strokes (n=10) and seizures (n=7) were the most frequent type of central nervous system event reported. The clinical outcomes of the definite, probable, and possible cases are listed in Table 3.

Ten events resulted in death (including 1 neonatal death and 1 fetal death), and 13 events resulted in permanent impairment, which represented 26 percent of the definite, probable, and possible cases. Nine serious adverse events occurred in persons who were taking relatively low doses of ephedra alkaloids (range, 12 to 36 mg per day) and who had no important medical risk factors. Features of the definite or probable and possible cases that resulted in death or permanent impairment or that necessitated substantial medical intervention are given in Tables 4 and 5, respectively.

Of the sudden catastrophic cerebrovascular and cardiovascular events, 11 occurred in previously healthy persons. Some of these cases, which were definitely or probably related to the use of supplements containing ephedra alkaloids, are described in detail in the following sections.

Examples of Severe Cerebrovascular Adverse Events

Patient 1

Patient 1 was a healthy 35-year-old woman who had taken aerobic-exercise classes for several years without incident (Table 4). In July 1997, she began taking one capsule of Shape-Fast Plus (according to the label, each capsule contained 15 mg of ephedra alkaloids and 40 mg of caffeine) three times a day before meals for weight loss; she was taking no other medications. She had been taking the product for one week when she collapsed during an aerobics class. Bystanders observed that her arms and legs were flexing and tensing. In the emergency department, her blood pressure was 110/38 mm Hg and the heart rate was 104 beats per minute. A computed tomographic scan of the head showed a subarachnoid hemorrhage. Cerebral angiography showed no evidence of a vascular aneurysm. A urine toxicology screen was positive for amphetamine, a result presumed to reflect a cross-reaction with the ephedrine and therefore to be false positive.

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TABLE 2. TYPES OF ADVERSE EVENTS THAT WERE DEFINITELY, PROBABLY, OR POSSIBLY RELATED TO THE USE OF SUPPLEMENTS CONTAINING EPHEDRA ALKALOIDS.

ADVERSE EVENT	DEFINITELY OR PROBABLY RELATED (N=43)	POSSIBLY RELATED (N=44)	TOTAL (N=87)
	no. of events (%)		
Cardiovascular			
Hypertension	10 (21)	7 (14)	17 (17)
Palpitations, tachycardia, or both	8 (17)	5 (10)	13 (13)
Arrhythmia	3 (6)	3 (6)	6 (6)
Myocardial infarction	2 (4)	0	2 (2)
Cardiac arrest or sudden death	5 (10)	3 (6)	8 (8)
Central nervous system			
Stroke	4 (8)	6 (12)	10 (10)
Transient ischemic attack	1 (2)	0	1 (1)
Seizure	1 (2)	6 (12)	7 (7)
Other	14 (29)	20 (40)	34 (35)
Total no. of events*	48	50	98

*The total number of events exceeds the total number of cases, since some cases involved more than one adverse event.

TABLE 3. CLINICAL OUTCOMES OF ADVERSE EVENTS THAT WERE DEFINITELY, PROBABLY, OR POSSIBLY RELATED TO THE USE OF SUPPLEMENTS CONTAINING EPHEDRA ALKALOIDS.

OUTCOME	DEFINITELY OR PROBABLY RELATED (N=43)	POSSIBLY RELATED (N=44)	TOTAL (N=87)
	no. of events (%)		
Death	3 (7)	7 (16)	10 (11)
Permanent impairment	7 (16)	6 (14)	13 (15)
Ongoing medical treatment	4 (9)	4 (9)	8 (9)
Full recovery	29 (67)	13 (30)	42 (48)
Unknown	0	14 (32)	14 (16)

Neurogenic pulmonary edema rapidly developed, necessitating endotracheal intubation and mechanical ventilation. Electrocardiographic findings and cardiac-enzyme levels were consistent with the occurrence of a small myocardial infarction. The treating cardiologist and neurologist thought that ephedrine induced the subarachnoid hemorrhage. The finding of amphetamine on the urine toxicology test supports the presence of ephedrine at the time of the event. Laboratory analysis of the supplement determined that the ephedrine content was 12.0 mg per capsule. At that time, the FDA's recommendation was a maximal dose of 8 mg per serving.[7]

Patient 10

Patient 10 was an apparently healthy 39-year-old man who experienced numbness of the right arm and leg on March 17, 1998, 90 minutes after drinking Ultimate Orange, which according to the label contained 415 mg of ma huang (ephedra alkaloids) per serving as well as guarana (a source of caffeine), and 5 minutes after running 3 miles (4.8 km) (Table 4). He also regularly took multivitamins and amino acid supplements, but no other medications. On presentation at a nearby hospital, his blood pressure was 140/78 mm Hg and his pulse was 60 beats per minute. A computed tomographic scan of the head revealed a left-sided intrathalamic hemorrhage. Cerebral angiography showed no evidence of vascular anomalies. The patient had gradual clinical improvement, and his symptoms resolved except for persistent sensory loss on the right side of his face. Chemical analysis of the Ultimate Orange product confirmed the presence of ephedrine, as well as of pseudoephedrine, norephedrine, and norpseudoephedrine.

Examples of Severe Cardiovascular Adverse Events

Patient 2

Patient 2 was a 22-year-old man with a history of asthma who collapsed while lifting weights at a gym on March 31, 1998 (Table 4). His medications included theophylline (Theo-Dur; 300 mg twice daily), albuterol (Ventolin; administered as necessary through a metered-dose inhaler), and a combination of chlorpheniramine maleate, phenylephrine hydrochloride, and phenylpropanolamine hydrochloride (Atrohist Plus SR). According to friends, he had consumed one 18-oz bottle of Ripped Force (which is listed as containing 20 mg of ephedrine alkaloids, 100 mg of caffeine, 250 mg of L-carnitine, and 240 μg of chromium) before working out and was regularly drinking three bottles of Ripped Force per day. He also took creatine and protein supplements. Witnesses reported that he had a seizure. Paramedics initially found him apneic and in ventricular fibrillation. He was successfully resuscitated. Computed tomography of the head showed cerebral edema but no hemorrhage or masses. An initial electrocardiogram showed atrial flutter, which subsequently converted to sinus rhythm. An echocardiogram revealed mild left ventricular hypertrophy. The plasma theophylline level was 11 μg per milliliter (therapeutic range, 10 to 20), and urinalysis revealed 12 μg of ephedrine per milliliter, 0.38 μg of pseudoephedrine per milliliter, and 0.41 μg of phenylpropanolamine per milliliter. The treating cardiologist thought that the combination of ephedra alkaloids and caffeine in Ripped Force and the theophylline and albuterol medications caused a ventric-

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TABLE 4. OUTCOME IN 11 PATIENTS WITH ADVERSE EVENTS THAT WERE DEFINITELY OR PROBABLY RELATED TO THE USE OF SUPPLEMENTS CONTAINING EPHEDRA ALKALOIDS.

PATIENT NO.	AGE (YR)/ SEX	NAME OF SUPPLEMENT	ESTIMATED DAILY DOSE OF EPHEDRA ALKALOIDS	DURATION OF USE	ADVERSE EVENT	OUTCOME	PREEXISTING CONDITIONS OR CONCURRENT RISKS
			mg				
1	35/F	Shape-Fast Plus	45	1 wk	Subarachnoid hemorrhage	Permanent disability	None
2	22/M	Ripped Force	20–60	Unknown	Arrhythmia, cardiac arrest	Permanent disability	Asthma
3	28/F	Herbalife's Thermo-jetics	21	1 day	Cardiac arrest	Permanent disability	None
4	43/M	Ripped Fuel	60	7 mo	Cardiac arrest	Death	Family history of coronary artery disease
5	37/F	Metabolife 356	36	1 wk	Severe hypertension, cardiac arrest, hypokalemia	Death	None
6	59/F	OmniTrim Extra Vitamin-Fortified tea	36	3 wk	Acute myocardial infarction	Coronary bypass surgery	Hypertension
7	38/M	Ripped Fuel	20	1 yr	Arrhythmia, cardiac arrest	Death	None
8	47/F	Total Control	44–66	9 mo	Hypertension, bilateral lacunar infarctions	Permanent disability	Concomitant ingestion of caffeine and ethanol
9	29/M	Ultimate Orange	30	2 wk	Stroke	Permanent disability	Concomitant use of dehydroepiandrosterone and androstenedione
10	39/M	Ultimate Orange	Unknown	Unknown	Hemorrhagic stroke	Permanent disability	None
11	47/M	Purple Blast	Unknown	3 wk	Hemorrhagic stroke	Permanent disability	Possible hypertension

ular arrhythmia that resulted in cardiac arrest. The patient suffered anoxic encephalopathy and remained in a vegetative state for several weeks. After one month in an acute care facility and six weeks at a rehabilitation facility, he was discharged with substantial residual neurologic impairment.

Patient 7

Patient 7 was an apparently healthy 38-year-old man who had been taking two capsules of Ripped Fuel (according to the label each capsule contains 10 mg of ephedrine and 100 mg of caffeine) each morning for one year as directed on the product label (Table 4). On June 6, 1996, he took his usual dose along with a cup of coffee and went jogging for 20 minutes. After returning home, he was talking with his family when he suddenly collapsed and appeared to have a tonic–clonic seizure. He had not reported any symptoms before collapsing. He was in full cardiac arrest when paramedics arrived and could not be resuscitated. Autopsy showed mild cardiomegaly with four-chamber dilatation and coronary artery disease, with narrowing of 50 to 75 percent in four vessels. The cause of death was acute arrhythmia resulting from atherosclerotic cardiovascular disease. Subsequent toxicology testing showed blood levels of 110 ng of ephedrine per milliliter (the therapeutic range used for bronchodilation is 20 to 80).[9] An addendum to the autopsy report included the comment, "ephedrine is a stimulant medication, and as such may have contributed to a fatal arrhythmia in the decedent."

DISCUSSION

Ephedrine and related alkaloids have been associated with adverse cardiovascular events, including acute myocardial infarction, severe hypertension, myocarditis, and lethal cardiac arrhythmias.[10,11] Constriction of coronary arteries and, in some cases, vasospasm are believed to be the mechanisms of myocarditis and myocardial infarction. The adrenergic effects of ephedrine shorten cardiac refractory periods, permitting the development of reentrant cardiac arrhythmias. Ephedrine can predispose patients to both hemorrhagic and ischemic stroke.[12] Subarachnoid hemorrhage is thought to be a result of the hypertensive action of ephedrine, which can be short lived, or of cerebral vasculitis, which has been described in association with a variety of sympathomimetic drugs.[13,14] Thrombotic stroke is presumably related to vasoconstriction of large cerebral arteries, which leads to local thrombosis as a result of stasis and sympathomimetic-induced platelet activation.

Caffeine is present in many products that contain ephedra alkaloids, and those who take these products might also be consuming considerable quantities of caffeine in coffee, tea, and soft drinks. Caffeine is like-

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TABLE 5. OUTCOME IN 15 PATIENTS WITH ADVERSE EVENTS THAT WERE POSSIBLY RELATED TO THE USE OF SUPPLEMENTS CONTAINING EPHEDRA ALKALOIDS.

PATIENT NO.	AGE (YR)/ SEX	NAME OF SUPPLEMENT	ESTIMATED DAILY DOSE OF EPHEDRA ALKALOIDS	DURATION OF USE	ADVERSE EVENT	OUTCOME	PREEXISTING CONDITIONS OR CONCURRENT RISKS
			mg				
1	46/M	Diet Fuel	Unknown	5–6 mo	Stroke	Death	None
2	22/M	Ripped Fuel	Unknown	Unknown	Hyperthermia, abnormal electrolyte levels, cardiac arrest	Death	None
3	64/F	Fit America Natural Weight Control Aid	Unknown	2 mo	Atrial fibrillation, stroke	Permanent disability	Hypertension, transient ischemic attack
4	47/F	Per-Form Dieter's Natural Tea	Unknown	6 mo	Rhabdomyolysis, hydronephrosis, hypokalemia	Prolonged hospital care	None
5	64/F	Shape-Fast	20	Unknown	Hemorrhagic stroke	Permanent disability	None
6	34/M	Herbalife's Thermojetics	Unknown	>3 wk	Atrial flutter, renal failure, hypokalemia, rhabdomyolysis	Death	None
7	32/F	Ripped Fuel	20	4 yr	Premature delivery (34 wk of gestation)	Death of neonate	Smoking
8	29/M	Ultimate Nutrition Product Ma Huang	Unknown	6–7 mo	Stroke	Permanent disability	None
9	15/F	Ripped Fuel	Unknown	2–3 wk	Arrhythmia, cardiac arrest	Death	None
10	41/F	Diet-Phen	12	1 mo	Hypertension, multiple brainstem infarcts	Permanent disability	Possible hypertension
11	22/F	Magic Herb	72	3 mo	Spontaneous abortion at 9 wk	Death of fetus	None
12	43/F	Metabolife 356	12	6 mo	Severe hypertension, hemorrhagic stroke	Permanent disability	None
13	18/M	Ultimate Orange	Unknown	Unknown	Seizure, hemorrhagic stroke	Death	None
14	61/F	Metabolife 356	24; increased to 60	1 mo	Hypertension, unstable angina	Coronary bypass surgery	Asthma
15	26/M	Ripped Fuel	20–60	3 yr	Status epilepticus, hypokalemia	Permanent disability	None

ly to enhance the cardiovascular and central nervous system effects of ephedrine. Caffeine acts by competitively antagonizing the receptors for adenosine, a hormone released by endothelial cells that dilates blood vessels.[15] By inhibiting adenosine-mediated dilatation of blood vessels, caffeine constricts blood vessels and may increase blood pressure in persons prone to hypertension. Caffeine also augments the release of catecholamines, an effect that, when combined with that of ephedrine, could lead to increased stimulation of the central nervous system and cardiovascular system.[16]

Phenylpropanolamine, another ephedrine alkaloid, was marketed with caffeine in various weight-reducing aids until 1983, when the combination was banned by the FDA after numerous reports of adverse effects. Several studies have shown that caffeine and phenylpropanolamine have an additive effect on blood pressure.[17] These interactions between phenylpropanolamine and caffeine support the idea that the combination of ephedrine and caffeine in a dietary supplement could increase the risk of adverse effects.

The quantity of ephedrine in dietary supplements, as reported on package labels, is typically about 20 mg per serving, and the usual dose frequency is two to three times per day. These products may contain larger or smaller amounts of ephedra alkaloids than are listed on the product label. For example, 11 of 20 supplements tested by Gurley et al.[18] either failed to list the alkaloid content on the label or had more than a 20 percent difference between the amount listed on the label and the actual amount.

Often, the dose of ephedrine that was associated with an adverse event was less than a typical dose of ephedrine used for bronchodilation (25 to 50 mg). Experimental studies show that ephedrine has only moderate effects on heart rate and blood pressure at these doses.[19,20] The discrepancy between such data and our findings of serious adverse events reported with the use of dietary supplements containing ephedra alkaloids may be due to individual susceptibility, the additive stimulant effects of caffeine, the variability in the contents of pharmacologically active chemicals in the products, or preexisting medical conditions.

Many of the cases we reviewed involved side effects

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such as anxiety, tremulousness, insomnia, palpitations, and personality changes that are well known to occur with the use of stimulant drugs. When ephedrine is used for medical purposes, these types of reactions are considered side effects and must be included in the assessment of risks and benefits. In fact, ephedrine is rarely prescribed today for medical purposes, because newer drugs have more specific actions and fewer side effects. The risks of taking ephedra alkaloids as a dietary supplement, however, are difficult to justify because the alkaloids have no demonstrated benefit. Unlike vitamins and minerals, ephedra alkaloid supplements are not essential for proper nutrition. People who take these products to increase their exercise capacity or to lose weight place themselves at risk without a substantial likelihood of benefit.

A limitation to the use of reports of adverse events as an indicator of a product's safety is that the number of people at risk for the event is unknown. Manufacturers of dietary supplements that contain ephedra alkaloids reported that 3 billion servings were sold in 1999.[21] The number of servings that were actually consumed is difficult to determine. Assuming that the products were consumed as directed — three doses per day for 12 weeks — then approximately 12 million people used these supplements in 1999.

Another limitation is that adverse events are known to be underreported. Several studies have shown that spontaneous reporting of adverse events to MedWatch is not routine, and the rate of reporting may be less than 15 percent.[22,23] The frequency of reports of adverse reactions to herbal products is thought to be even lower.[7,24] Therefore, the frequency of serious adverse events associated with the use of supplements containing ephedra alkaloids cannot be precisely determined with the use of current reporting mechanisms.

Because of the severity of the adverse events that we reviewed and, in particular, the occurrence of events that caused permanent disability and death, we conclude that dietary supplements that contain ephedra alkaloids pose a serious health risk to some users. Although the incidence of serious adverse effects cannot be determined from our analysis, our findings arouse concern about the risks of these products, given that they have no scientifically established benefits. Our findings indicate 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 dosing guidelines and warnings can be devised.

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