PHARMACODYNAMICS AND
DRUG ACTION

Short-term metabolic and hemodynamic effects of ephedra and guarana combinations

Objective: Serious adverse health events have been reported with the use of dietary supplements containing ephedra and guarana. We sought to determine whether repeated dosing and multi-ingredient formulations contribute to the adverse effects of these supplements.

Methods: In this study, 16 healthy adults (8 women) took 2 doses each of ephedra-guarana alone, Xenadrine RFA, a multicomponent dietary supplement containing 25 mg ephedra alkaloids and 200 mg caffeine, or placebo 5 hours apart in a randomized, double-blind, 3-arm crossover study.

Results: Peak plasma ephedrine levels averaged 130 to 140 ng/mL. Compared with placebo, Xenadrine and ephedra-guarana significantly increased heart rate (maximum increase, 9.4 ± 8.6 beats/min; \( P = .002 \)), blood pressure (maximum increase in systolic and diastolic pressure, 11.5 ± 10.7 mm Hg and 7.3 ± 7.4 mm Hg, respectively; \( P = .015 \)), postprandial glucose concentration (maximum change, 41.0 ± 18.8 mg/dL; \( P < .0001 \)), and insulin concentration (maximum change, 41.2 ± 47.8 \( \mu \)IU/mL; \( P = .005 \)). Serum potassium concentrations were significantly decreased by both treatments. Hemodynamic and metabolic changes were observed after both the first and second doses. However, plasma free fatty acid concentrations increased after the first dose only. Xenadrine RFA produced higher increases in glucose concentration than ephedra-guarana, but no other pharmacodynamic differences between the treatments were found.

Conclusions: Consumption of 2 doses of ephedra and guarana supplements, per supplement label recommendations, results in persistent increases in heart rate and blood pressure and unfavorable actions on glucose and potassium homeostasis. Such effects could be detrimental in persons with hypertension, atherosclerosis, or glucose intolerance, conditions that are strongly associated with obesity. (Clin Pharmacol Ther 2005;77:560-71.)

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Dietary supplements that contain ephedra alkaloids were marketed and widely used in the United States for weight loss and energy enhancement until the Food and Drug Administration (FDA) banned ephedra as a dietary supplement ingredient in April 2004. The FDA’s action was based on a risk/benefit analysis that included a consensus evidence-based report showing only modest, short-term weight loss benefits of ephedra, countered by a large number of reported cases of ephedra-related toxicity, including strokes, cardiac arrhythmias, seizures, and sudden death. Several published studies have demonstrated that ephedra-containing dietary supplements can increase systolic blood pressure (SBP) and heart rate and produce cardiac rhythm disturbances in healthy individuals.

Label directions for weight loss dietary supplements recommended 2 to 3 servings per day, taken approximately 1 hour before meals, not to exceed a total

560
ephedra alkaloid intake of 100 mg daily. These recommendations appear to be based on dosing regimens for pharmaceutical ephedrine taken orally for asthma. Peak ephedrine plasma levels of approximately 75 ng/mL are reached 2 to 3 hours after oral administration.\textsuperscript{\textdegree}Caffeine is metabolized extensively by hepatic cytochrome P450 enzymes, including oral contraceptives, alcohol, smoking, and pregnancy.\textsuperscript{18}

We recently compared the effects of pharmaceutical ephedrine and caffeine taken alone and together and found that the individual pharmacologic effects of ephedrine and caffeine were small but the drugs in combination produced significant increases in SBP and heart rate.\textsuperscript{19} Ephedrine and caffeine exhibited different effects on metabolic parameters involved in glucose homeostasis. Ephedrine increased fasting glucose and insulin concentrations on a short-term basis and had an additive effect with caffeine in raising plasma free fatty acid (FFA) concentrations. Caffeine alone did not significantly increase fasting glucose or insulin concentrations.

In an earlier study in which a single dose of a dietary supplement containing ephedra and guarana was administered to healthy adults, we found that apparent tolerance developed to the vasopressor actions but not to the chronotropic effects of the herbal stimulants.\textsuperscript{8} Depletion of stored norepinephrine has been proposed as a mechanism for immediate tolerance.\textsuperscript{20} It is not known whether repeated ingestion of ephedra and guarana within a recommended dosing interval will produce greater or lesser cardiovascular responses.

The objectives of this study were 2-fold, as follows: (1) to determine whether repeated dosing of ephedra and guarana combinations, as directed on product labels, intensifies cardiovascular and metabolic effects or whether short-term tolerance to these stimulant actions develops and (2) to compare the pharmacologic characteristics of a multicomponent ephedra dietary supplement with a simple combination of ephedra and guarana.

**METHODS**

**Subjects**

Sixteen healthy adults (8 women) aged 18 to 45 years were recruited for this study. All volunteers gave written informed consent before study participation. The Committee on Human Research at the University of California, San Francisco, approved the study protocol and the subject consent form. Eligibility for subject enrollment was determined by medical history, physical examination, and screening laboratory tests that included complete blood cell count; serum chemistry tests to assess liver, renal, and thyroid function; urine toxicology testing for illicit drug use; and urine pregnancy testing for women. Any person with a history of cardiac, thyroid, liver, or renal disease; hypertension; diabetes; psychiatric or seizure disorder; prostatic hypertrophy; narrow-angle glaucoma; pregnancy; or lactation was excluded. Tobacco and marijuana smokers and heavy users of caffeine (>3 cups of coffee or equivalent per day), as well as persons taking prescription medications including oral contraceptives, were excluded. Subjects taking herbal products or over-the-counter drugs that contain ephedrine and related alkaloids were asked to stop taking them for at least 24 hours before study participation.
Study design

This study was a randomized, double-blind, 3-arm crossover study involving administration of 2 oral doses of (1) placebo, (2) Xenadrine RFA (Cytodyne Technologies, Lakewood, NJ), and (3) ephedra plus guarana. The 2 active treatments contained nearly equal doses of ephedra alkaloids and caffeine, as shown in Table I. Doses were packaged in identical gelatin capsules and administered at 9 AM and 2 PM on each study day, consistent with dosing recommendations for Xenadrine RFA. The treatment order was determined by use of an online randomization program. A 1-week washout period occurred between study days.

Subjects were asked to abstain from caffeine intake for 24 hours and fast for 8 hours before the study. They were admitted to the San Francisco General Hospital General Clinical Research Center at 7 AM on each study day and given a standard light breakfast. Baseline electrocardiogram and vital signs were recorded, predose blood samples were collected, and a urine sample was analyzed for drugs of abuse. At 9 AM, subjects received the first study drug dose and then were asked to rest quietly throughout the day. Exercise was not permitted. Subjects were given caffeine-free meals at 3 and 8 hours after dosing, and identical breakfast and lunch foods and beverages were ingested during each study visit.

Venous blood samples were collected from an indwelling catheter at baseline; at 30, 60, 90, 120, 180, and 300 minutes after each dose; and at 8, 12, 18, and 24 hours after the second dose. Heart rate and blood pressure were measured before each blood draw by a Critikon Dinamap automated sphygmomanometer (GE Medical Systems Information Technologies, Waukesha, Wis). Urine was collected over the entire 29-hour study period and kept refrigerated. The pH and volume of each void were recorded.

Plasma and urine sample analysis

Blood was centrifuged, and the separated plasma was stored at −20°C for subsequent analysis of potassium, glucose, insulin, lactate, and FFA concentrations, as well as ephedrine alkaloid and caffeine levels. Aliquots of the total volume of urine collected over a 29-hour period were frozen and later analyzed for electrolytes and ephedra alkaloid and caffeine concentrations. Plasma and urine samples were stored at −20°C for up to 18 months before analysis. No significant changes in ephedra alkaloid or caffeine concentrations were ob-

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Multicomponent dietary supplement*</th>
<th>Ephedra plus guarana†</th>
</tr>
</thead>
<tbody>
<tr>
<td>List per dose</td>
<td>Pantothenic acid (40 mg), bitter orange (5 mg synephrine), ma huang (20 mg ephedrine), guarana extract (200 mg caffeine), and ThermoSynergist Blend (white willow bark [15 mg salicin], ginger root, l-tyrosine, acetyl-l-carnitine, 3,3′,4,7-tetrahydroxyflavone, magnesium phosphate, and dimethylaminethanol)</td>
<td>Ephedra extract (325 mg)</td>
</tr>
<tr>
<td>Average measured quantities of ephedra alkaloids and caffeine per capsule/tablet</td>
<td>10.1 mg EPH</td>
<td>20.0 mg EPH</td>
</tr>
<tr>
<td></td>
<td>1.8 mg PSE</td>
<td>1.9 mg PSE</td>
</tr>
<tr>
<td></td>
<td>0.2 mg NEPH</td>
<td>0.3 mg NPH</td>
</tr>
<tr>
<td></td>
<td>0.2 mg NPSE</td>
<td>0.2 mg NPSE</td>
</tr>
<tr>
<td></td>
<td>0.4 mg MEPH</td>
<td>0.8 mg MEPH</td>
</tr>
<tr>
<td></td>
<td>0.03 mg MPSE</td>
<td>0.04 mg MPSE</td>
</tr>
<tr>
<td></td>
<td>12.7 mg total alkaloids</td>
<td>23.2 mg total</td>
</tr>
<tr>
<td></td>
<td>92.6 mg caffeine</td>
<td>alkaloids</td>
</tr>
</tbody>
</table>

EPH, Ephedrine; PSE, pseudoephedrine; NEPH, norephedrine; NPSE, norpseudoephedrine; MEPH, methyllephedrine; MPSE, methylpseudoephedrine.

*Two capsules of Xenadrine RFA constitute 1 dose.
†One tablet of Pure Ephedrine and 2 capsules of GNC Herbal Plus Guarana constitute 1 dose.
served for standards and quality control specimens that had been stored at −20°C for up to 18 months.

Plasma ephedra alkaloid and caffeine concentrations were quantified by a liquid chromatography–tandem mass spectrometry (LC-MS/MS) method that has been previously described. The limits of quantitation of this method are 1 ng/mL for ephedra alkaloids and 10 ng/mL for caffeine. Intraday precision (percent coefficient of variation) and accuracy (percent of expected value) ranged from 0.2% to 3.2% and 97.0% to 103%, respectively, for the ephedra alkaloids over the concentration ranges of 1 to 700 ng/mL and 0.3% to 2.4% and 99.5% to 110%, respectively, for caffeine over the concentration ranges of 10 to 3500 ng/mL in spiked plasma quality control specimens. Interday precision and accuracy were 0.9% to 4.0% and 97.7% to 102%, respectively, for the ephedra alkaloids over the concentration ranges of 10 to 700 ng/mL and 1.8% and 103% to 108%, respectively, for caffeine at concentrations of 500 and 3500 ng/mL in spiked plasma quality control specimens.

The plasma insulin levels were determined by radioimmunoassay (Linco Research, St Charles, Mo), and FFA concentrations were measured by an enzymatic colorimetric assay (Wako Chemicals, Richmond, Va).

**Pharmacokinetic analysis**

Ephedrine, pseudoephedrine, and caffeine pharmacokinetic parameters were estimated by noncompartmental methods by use of WinNonlin (version 3.1; Pharsight, Mountain View, Calif). The area under the plasma concentration–time curve (AUC) was calculated by use of the log-linear trapezoidal rule for the total period and extrapolated to infinity [AUC(0–∞)]. The apparent volume of distribution (V/F) was based on the t1/2 and AUC(0–∞). Total drug clearance was calculated as the total dose divided by the AUC(0–∞), and renal clearance was calculated as the amount of drug excreted in the urine divided by the total AUC. The maximum plasma concentration (Cmax) and time to Cmax (tmax) were estimated directly from the plasma concentration–time data.

**Pharmacodynamic analysis**

Differences from baseline between treatment and placebo values were compared for SBP, diastolic blood pressure (DBP), heart rate, and metabolic parameters. To evaluate differences in cardiovascular responses after each dose, estimates of AUC for changes over time were compared for the postdose periods of 0 to 5 hours and 5 to 17 hours at which time SBP, DBP, and heart rate returned to baseline. For metabolic parameters, AUCs were estimated for 2 postdose periods of 0 to 5 hours and 5 to 10 hours, until the time of the last blood collection. Treatment-related cardiovascular and metabolic changes were also analyzed for gender differences in response.

**Statistical analysis**

Results are expressed as mean ± SD or median ± 95% confidence interval in the text and tables and, for clarity, as mean ± SEM in the figures. Pairwise comparisons of changes from baseline were made between treatments at all times after dosing with paired t tests or with Wilcoxon signed ranks tests for nonparametric data. The Mann-Whitney test was used to test for gender differences. All data were analyzed by use of SAS (version 8.2; SAS Institute, Cary, NC). Differences at P < .05 were considered statistically significant.

**RESULTS**

**Subjects**

The study was completed by 8 men and 8 women. The ethnic/racial makeup included 7 white subjects, 4 Hispanic subjects, 2 Asian subjects, 2 black subjects, and 1 Native American subject. Subjects ranged in age from 26 to 40 years (mean, 31.4 years) and in weight from 53.2 to 92.1 kg (mean, 73.2 kg). There were no study-related adverse events that required intervention, and no protocol deviations occurred. One subject’s screening urine toxicology test result was positive for amphetamines during a study visit; however, he denied any illicit substance use and his previous test results were negative, so this was, therefore, presumed to be a false-positive result.

**Product analysis**

Capsules of Xenadrine RFA, Pure Ephedrene (NVE Pharmaceuticals, Andover, NJ), and GNC Herbal Plus Guarana (General Nutrition Corp, Pittsburgh, Pa) were analyzed in duplicate for concentrations of ephedra alkaloids and caffeine by use of an LC-MS/MS method that was developed and validated in our laboratory, and the labeled and measured concentrations are shown in Table I. The mean doses were 25.4 mg total ephedrine alkaloids and 185 mg caffeine for the Xenadrine RFA treatment and 23.2 mg total ephedrine alkaloids and 167 mg caffeine for the ephedra-guarana treatment.

**Pharmacokinetics**

The maximum plasma concentrations for both ephedrine and caffeine occurred at 8 hours, which
was 3 hours after ingestion of the second dose (Fig 1). Peak ephedrine levels ranged from 91.5 to 200.3 ng/mL, with a mean maximum concentration of 130.8 ng/mL for Xenadrine RFA and 140.1 ng/mL for ephedra/guarana (Table II). Renal clearance of ephedrine was significantly lower with Xenadrine RFA than with ephedra-guarana (13.4 L/h versus 17.3 L/h, \( P = .04 \)). No other significant differences in ephedrine pharmacokinetics were observed between the 2 treatments. Differences in caffeine \( C_{\text{max}} \) and total AUC between the 2 treatments reflect the slightly different caffeine doses in the 2 formulations; however non–dose-related pharmacokinetic differences were also observed. Although elimination half-lives were similar for the 2 treatments, caffeine CL/F (clearance divided by bioavailability), renal clearance, and V/F were significantly lower with Xenadrine RFA than with ephedra-guarana. There were no significant gender differences in ephedrine or caffeine pharmacokinetics.

Table II. Pharmacokinetics of ephedrine and caffeine after Xenadrine RFA and ephedra-guarana were orally administered at 0 and 5 hours

<table>
<thead>
<tr>
<th></th>
<th>Ephedrine</th>
<th>Caffeine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Xenadrine RFA*</td>
<td>Ephedra-guarana†</td>
</tr>
<tr>
<td>( C_{\text{max}} ) (µg/mL)</td>
<td>0.13 ± 0.03</td>
<td>0.14 ± 0.03</td>
</tr>
<tr>
<td>( t_{\text{max}} ) (h)</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>( t_{1/2} ) (h)</td>
<td>5.85 ± 0.88</td>
<td>6.29 ± 1.27</td>
</tr>
<tr>
<td>AUC(0–∞) (h · µg/L)</td>
<td>1795 ± 503</td>
<td>1922 ± 636</td>
</tr>
<tr>
<td>V/F (L)</td>
<td>202.5 ± 56.5</td>
<td>200.7 ± 49.5</td>
</tr>
<tr>
<td>CL/F (L/h)</td>
<td>24.3 ± 6.7</td>
<td>23.0 ± 7.2</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± SD, except \( t_{\text{max}} \), for which median values are shown.

\( C_{\text{max}} \), Maximum plasma concentration; \( t_{\text{max}} \), time to maximum plasma concentration; \( t_{1/2} \), elimination half-life; AUC(0–∞), area under plasma concentration versus time curve extrapolated to infinity; V/F, apparent volume of distribution divided by bioavailability; CL/F, clearance divided by bioavailability.

*One dose of Xenadrine RFA consists of 25.4 mg total ephedra alkaloids and 185 mg caffeine.
†One dose of ephedra-guarana consists of 23.2 mg total ephedra alkaloids and 167 mg caffeine.

Fig 1. Plasma concentrations (Conc) of ephedrine after dosing at time 0 and 5 hours with Xenadrine RFA (circles) and ephedra-guarana (squares). Data are given as mean ± SEM (N = 16).
Pharmacodynamics

Cardiovascular effects. Both treatments significantly increased SBP and DBP over baseline measurements, with peak changes observed 2 to 3 hours after each dose (Fig 2). The maximum increase in SBP was 11.5 ± 10.7 mm Hg, which occurred 8 hours after dosing with ephedra-guarana \((P = .015, \text{ versus placebo})\). Peak changes in DBP occurred 90 minutes after ephedra-guarana \((7.3 \pm 7.4 \text{ mm Hg}, P = .015)\) and 8 hours after Xenadrine \((7.1 \pm 6.6 \text{ mm Hg}, P = .031)\). Compared with Xenadrine, ephedra-guarana produced significantly greater changes in SBP at 2 hours \((P = .040)\) and DBP at 5.5 hours \((P = .029)\) after dosing.

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**Fig 2.** Changes in systolic blood pressure (SBP) (A) and diastolic blood pressure (DBP) (B) after oral dosing at time 0 and 5 hours with Xenadrine RFA (circles), ephedra-guarana (squares), and placebo (triangles). Data are given as mean ± SEM (N = 16).
Heart rate was significantly increased over baseline measurements by both Xenadrine and ephedra-guarana relative to placebo (Fig 3). The maximum heart rate changes occurring at 5 hours were 8.9 \pm 6.5 beats/min with Xenadrine and 9.4 \pm 8.6 beats/min with ephedra-guarana (\(P = .002\) for both versus placebo). There were no significant differences in heart rate effects between Xenadrine and ephedra-guarana. No changes were observed in the electrocardiogram performed 2 hours after dosing.

The calculated change in AUC (\(\Delta AUC\)) for SBP, DBP, and heart rate over time after each dose, from 0 to 5 hours and 5 to 17 hours, is shown in Table III. Both Xenadrine and ephedra-guarana produced significantly higher \(\Delta AUCs\) for SBP and DBP from 0 to 5 hours than placebo. From 5 to 17 hours, Xenadrine significantly increased the \(\Delta AUC\) for SBP but not DBP. Ephedra-guarana resulted in a higher \(\Delta AUC\) for both SBP and DBP relative to placebo. Heart rate \(\Delta AUC\) was significantly increased during both time intervals for Xenadrine and ephedra-guarana compared with placebo. There were no significant differences in \(\Delta AUC\) between Xenadrine and ephedra-guarana.

**Table III.** Pharmacodynamic responses after 2 oral doses of Xenadrine RFA and ephedra-guarana were administered at 0 and 5 hours

<table>
<thead>
<tr>
<th></th>
<th>(\Delta AUC ) from 0 to 5 h</th>
<th>(\Delta AUC ) from 5 h to end*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Xenadrine RFA</td>
<td>Ephedra-guarana</td>
</tr>
<tr>
<td>SBP (mm Hg · h)</td>
<td>16.7 ± 32.2†</td>
<td>34.4 ± 28.4‡</td>
</tr>
<tr>
<td>DBP (mm Hg · h)</td>
<td>10.9 ± 21.7†</td>
<td>19.9 ± 22.4†</td>
</tr>
<tr>
<td>Heart rate</td>
<td>5.46 ± 19.8†</td>
<td>1.97 ± 24.9†</td>
</tr>
<tr>
<td>(beats/min · h)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose (mg/dL · h)</td>
<td>81.4 ± 46.3‡</td>
<td>55.4 ± 68.3†</td>
</tr>
<tr>
<td>Insulin (mIU/mL · h)</td>
<td>−19.8 ± 76.1†</td>
<td>−58.8 ± 116.9</td>
</tr>
<tr>
<td>FFAs (mEq/L)</td>
<td>0.87 ± 0.70‡</td>
<td>0.91 ± 0.71†</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± SD. All comparisons of Xenadrine RFA to ephedra-guarana were nonsignificant.

\(\Delta AUC\): Change in area under curve; SBP, systolic blood pressure; DBP, diastolic blood pressure; FFAs, free fatty acids.

*For SBP, DBP, and heart rate, the time period ranges from 5 to 17 hours; for glucose, insulin, and FFAs, it ranges from 5 to 10 hours.

†\(P < .05\), compared with placebo.

‡\(P < .005\), compared with placebo.

Heart rate was significantly increased over baseline measurements by both Xenadrine and ephedra-guarana relative to placebo (Fig 3). The maximum heart rate changes occurring at 5 hours were 8.9 ± 6.5 beats/min with Xenadrine and 9.4 ± 8.6 beats/min with ephedra-guarana (\(P = .002\) for both versus placebo). There were no significant differences in heart rate effects between Xenadrine and ephedra-guarana. No changes were observed in the electrocardiogram performed 2 hours after dosing.

The calculated change in AUC (\(\Delta AUC\)) for SBP, DBP, and heart rate over time after each dose, from 0 to 5 hours and 5 to 17 hours, is shown in Table III. Both Xenadrine and ephedra-guarana produced significantly higher \(\Delta AUCs\) for SBP and DBP from 0 to 5 hours than placebo. From 5 to 17 hours, Xenadrine significantly increased the \(\Delta AUC\) for SBP but not DBP. Ephedra-guarana resulted in a higher \(\Delta AUC\) for both SBP and DBP relative to placebo. Heart rate \(\Delta AUC\) was significantly increased during both time intervals for Xenadrine and ephedra-guarana compared with placebo. There were no significant differences in \(\Delta AUC\) between Xenadrine and ephedra-guarana.

**Metabolic effects.** Postprandial blood glucose levels were significantly increased by Xenadrine and ephedra-
guarana compared with placebo (Fig 4, A). The peak rise in glucose level of 41.0 ± 18.8 mg/dL occurred 5 hours after dosing with Xenadrine, which corresponded to 2 hours after subjects ate lunch. This peak glucose increase was significantly higher than seen with ephedra-guarana (27.4 ± 26.0 mg/dL, \( P = .03 \)) or placebo (6.8 ± 19.9 mg/dL, \( P < .0001 \)). The effect of Xenadrine on glucose concentration was prolonged, with differences from placebo achieving statistical significance from 90 minutes to 7 hours. Glucose concentrations again increased significantly with both Xenadrine and ephedra-guarana 2 hours after the evening meal, which was 10 hours after the first dose and 5 hours after the second dose.

Plasma insulin concentrations were also higher in the Xenadrine and ephedra-guarana conditions after lunch but not after dinner (Fig 4, B). The peak insulin rise was 41.2 ± 47.8 \( \mu \)IU/mL at 5.5 hours after ephedra-guarana dosing, which was nearly 10-fold higher than the postprandial insulin change seen with placebo (4.5 ± 25.7 \( \mu \)IU/mL) (\( P = .005 \)). Comparison of \( \Delta AUC \) values in Table III shows that Xenadrine had a greater effect than ephedra-guarana on glucose and insulin concentrations and that Xenadrine’s effect on glucose and insulin
concentrations was significantly greater than that of placebo during both time periods.

Plasma FFA concentrations were increased by Xenadrine RFA (circles), ephedra-guarana (squares), and placebo (triangles) from 90 minutes to 3 hours (Fig 5), with a maximal median change in FFA concentrations of 0.406 mEq/L with ephedra-guarana ($P < .005$, versus placebo). FFA levels rapidly returned to baseline levels after the lunch meal, and no subsequent rise in FFA concentrations was observed after the second dose. There was no difference in effect on FFA concentrations between Xenadrine and ephedra-guarana. The $\Delta$AUCs for FFA concentrations were increased for both Xenadrine and ephedra-guarana relative to placebo during the 0- to 5-hour period but not during the 5- to 10-hour period.

As seen in Fig 6, serum potassium concentrations were significantly decreased by Xenadrine and ephedra-guarana from 2 to 5 hours after dosing and by Xenadrine at 8 hours relative to placebo. The maximal decrease in potassium concentration, which occurred at 3 hours, was $0.28 \pm 0.23$ mmol/L with Xenadrine versus $0.006 \pm 0.32$ mmol/L with placebo ($P = .001$). Of 16 subjects, 15 had at least 1 potassium measurement that was below the reference
range of 3.5 mmol/L after receiving Xenadrine or ephedra-guarana.

**Gender differences**

The hyperglycemic effect of Xenadrine was more pronounced in men than in women, with a maximal glucose change from baseline versus placebo of 26.5 ± 17.6 mg/dL in men compared with 3.7 ± 16.1 mg/dL in women (P = .018) at 6 hours. No gender differences in insulin effects were seen. The AUC from 0 to 5 hours for FFA concentrations was greater in women (0.79 ± 0.71 mEq/L · h) than in men (0.23 ± 0.21 mEq/L · h) for Xenadrine versus placebo (P = .014). No significant gender differences were observed in cardiovascular responses to the treatments.

**DISCUSSION**

This study shows for the first time that combinations of herbal caffeine and ephedra alkaloids taken in recommended amounts result in plasma ephedrine levels that slightly exceed usual therapeutic ranges and produce significant cardiovascular and metabolic changes. These results provide further evidence that this combination could have potentially deleterious effects when used for weight loss, particularly in individuals with underlying hypertension, glucose intolerance, or coronary artery disease, conditions frequently associated with obesity.

Peak ephedrine plasma concentrations averaged 130.8 ng/mL and 140.1 ng/mL after 2 doses of Xenadrine and ephedra-guarana, respectively, which are nearly 2-fold higher than the reported maximum concentrations of 75 to 80 ng/mL (range, 45-139 ng/mL) for ephedrine taken as a bronchodilator. In contrast to short-term therapeutic use for acute asthma, prolonged ephedrine use taken 2 to 3 times per day for the purpose of weight loss would be expected to produce high steady-state concentrations of ephedrine. Xenadrine was associated with slower renal clearance of ephedrine and caffeine and lower V/F and total clearance of caffeine than ephedra-guarana. There were no treatment-related changes in mean urine pH that would affect renal excretion of ephedrine. These pharmacokinetic differences between treatments may be a result of decreased bioavailability or interference with renal elimination by the other constituents in the multicomponent formulation. However, the overall effect on ephedrine and caffeine absorption and elimination appears to be small.

We previously found that combinations of ephedrine and caffeine raise fasting levels of glucose and insulin. In this study Xenadrine and ephedra-guarana significantly increased postprandial glucose and insulin concentrations. Compared with ephedra-guarana, Xenadrine had a greater effect in raising glucose levels, suggesting an additive hyperglycemic action of 1 or more of the other constituents in the dietary supplement. The mechanism whereby ephedrine and caffeine increase blood glucose concentration is believed to be catecholamine-induced inhibition of glucose uptake by adipose and skeletal muscle cells and promotion of endogenous glucose production. Increased fatty acid mobilization probably contributed to the increase in glucose and insulin concentrations but appeared to be a significant factor only after the first dose (Fig 5). FFA levels declined after lunch, presumably related to decreased lipolysis resulting from the insulin surge associated with the meal plus ephedrine-caffeine–induced hyperglycemia. The lack of an increase in fatty acid levels after the second dose suggests that repeat dosing of ephedra and guarana does not produce more lipolysis than a single dose.

Men exhibited a greater postprandial hyperglycemic response to Xenadrine than women, but there was no gender difference in insulin response. Women, on the other hand, had a greater increase in FFA concentrations after the first dose of Xenadrine. This observation may be a result of differences in body composition between men and women, with women having more adipose tissue and men having greater skeletal muscle mass. It may be that the sympathomimetic effects of ephedra and caffeine result in greater skeletal muscle–induced glucose intolerance in men but promote greater fatty acid release from adipose tissue in women. Additional studies that include body composition analysis by dual-energy x-ray absorptiometry (DEXA) are underway to explore gender differences in metabolic responses to sympathomimetic herbal combinations.

The actions of ephedra and guarana in raising blood glucose and insulin levels could be detrimental if recurrent or prolonged. Chronic hyperglycemia is deleterious to pancreatic islet cell function and may lead to progressive β-cell failure. In addition, cycling of FFAs (ie, adipose tissue release with subsequent reesterification and reuptake) leads to overproduction of very-low-density-lipoprotein and hepatic steatosis. These effects could exacerbate obesity-related conditions such as insulin resistance and metabolic syndrome.

Resting energy expenditure and energy substrate metabolism were not evaluated in this study; however, other investigators have reported that combinations of ephedrine and caffeine increase oxygen consumption and raise basal metabolic rate. Astrup proposed...
that the thermogenic response induced by ephedrine is a result of increased energy expenditure in resting skeletal muscle. It is conceivable that exercise would lessen the unfavorable metabolic effects of ephedra and guarana by enhancing skeletal muscle glucose utilization and increasing fatty acid oxidation. Future studies are needed to examine the effects of exercise on the metabolic effects of stimulant-containing dietary supplements.

Both Xenadrine and ephedra-guarana significantly increased SBP, DBP, and heart rate after both doses. Blood pressure changes were maximal in the 2- to 3-hour period after each dose, with peak values occurring at 8 hours, which corresponded to maximum plasma concentrations of ephedrine and caffeine. Heart rate was maximally increased at 5 hours after the first dose. As shown in Table III, ΔAUCs for heart rate and blood pressure were significantly increased for both postdosing periods, indicating that short-term tolerance to the vasopressive and chronotropic effects of ephedrine and guarana does not develop. This study involved administration of just 2 doses of ephedra and guarana, and it is possible that tolerance to the cardiovascular effects may develop with longer use. However, in a study involving dogs, only minimal diminution of the pressor response was observed after 10 repeated doses of ephedrine. In addition, in a previous human study of pseudoephedrine, tachyphylaxis to the pressor effect was observed, but heart rate remained significantly elevated after 14 days of treatment.

Although ephedra-guarana produced slightly higher peak changes in SBP and DBP, particularly after the first dose, there were no statistically significant differences in ΔAUCs between Xenadrine and ephedra-guarana for SBP, DBP, or heart rate. Therefore it appears that ephedra and guarana are the predominant cardiovascular stimulant ingredients in Xenadrine RFA and that contributions from the other supplement constituents are not significant.

The effect of Xenadrine and ephedra-guarana in decreasing serum potassium concentrations is presumably a result of catecholamine-induced intracellular shift of potassium. Supplement-induced hypokalemia could be worsened in the context of inadequate potassium repletion as a result of fasting or dieting. Significant hypokalemia increases the potential for development of lethal cardiac dysrhythmias, particularly in the setting of sympathomimetic drug-induced cardiac stimulation.

In summary, we found that repeated dosing of ephedra and guarana produced elevated ephedrine blood concentrations, increased heart rate and blood pressure, and had unfavorable effects on glucose and potassium homeostasis. These findings provide further evidence that dietary supplements containing combinations of sympathomimetcs could potentially have unfavorable cardiovascular effects, particularly in individuals with underlying hypertension, glucose intolerance, or atherosclerosis. Under the nonfasting conditions of this study, FFA concentrations increased only after the first dose of ephedra and guarana, suggesting that repeated daily dosing of these products will not result in more lipolysis than a single dose. Increased glucose elevation was the only substantial difference between the pharmacodynamic effects of the multicomponent dietary supplement (Xenadrine RFA) and ephedra-guarana administered alone. The other herbal constituents of the dietary supplement do not appear to significantly affect the cardiovascular effects of the primary herbal stimulants ephedra and guarana.

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Drs Haller and Benowitz have served as expert witnesses in litigation involving manufacturers of dietary supplements that contain ephedra. Dr Jacob has no conflict of interest to disclose.

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