Electrocardiographic and Hemodynamic Effects of a Multicomponent Dietary Supplement Containing Ephedra and Caffeine
A Randomized Controlled Trial

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Dietary weight-loss supplements often combine ephedra and caffeine with various other natural ingredients. In the United States, more than 3 billion doses of these herbal preparations are sold annually, resulting in $7 billion in sales. Ephedra is a sympathomimetic amine structurally related to amphetamines, while caffeine is a methylxanthine-derived phosphodiesterase inhibitor. The doses of the other natural ingredients are not always disclosed, their pharmacology and pharmacokinetics are generally not well characterized, and drug interaction data between ingredients are lacking. Nevertheless, consumers are drawn to herbal preparations because of their nonprescription status, direct-to-consumer advertising, and the perception that natural products are innately safe. Unfortunately, the perception of safety may be the result of a lack of data. Questions regarding safety have been raised by anecdotal cases of sudden cardiac death and cerebrovascular accidents. Therefore, further study of these preparations is warranted.

Metabolife 356, a multicomponent dietary supplement containing ephedra and caffeine (DSEC) in addition to several other components, is the top-selling dietary weight loss supplement. Given its common use, anecdotal reports of cardiovascular and cerebrovascular adverse events, and paucity of safety data, further research with this DSEC was warranted.

Objective To determine the impact of the DSEC on corrected QT (QTc) interval duration and systolic blood pressure (SBP).

Design Randomized, double-blind, placebo-controlled, crossover study conducted from January to May 2003.

Setting and Participants Fifteen healthy volunteers (mean [SD] age, 26.7 [2.52] years; weight, 72.7 [14.93] kg), 6 (40%) of whom were women, recruited from the University of Connecticut, Storrs campus.

Intervention A single dose of the DSEC (containing 19 ingredients including ephedra [12 mg] and caffeine [40 mg]) or matching placebo were administered in a crossover fashion with a 7-day washout period between treatments.

Main Outcome Measures Maximal QTc interval and SBP assessed at 1, 3, and 5 hours after dosing for the DSEC relative to placebo.

Results Individuals receiving the DSEC had a longer maximal QTc interval (mean [SD], 419.4 [11.8] vs 396.1 [15.7] milliseconds; \(P<.001\)) and higher SBP (mean [SD], 123.5 [10.98] vs 118.93 [9.62] mm Hg; \(P=.009\)) compared with placebo. Participants who received the DSEC were more likely to experience a QTc interval increase of at least 30 milliseconds vs placebo (8 individuals [53.3%] vs 1 individual [6.7%]; relative risk, 2.67 [95% confidence interval, 1.40-5.10]). There were no significant sex-related differences.

Conclusions The ephedra- and caffeine-containing dietary supplement Metabolife 356 increased the mean maximal QTc interval and SBP. Since the actual ingredient or ingredients in Metabolife 356 responsible for these findings are not known, patients should be instructed to avoid this and similar dietary supplements until more information is known about their safety.

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Development Inc, Toronto, Ontario), and Xenedrine (Cytodyne Technologies, Hicksville, NY) contain 30, 12, and 12 labeled ingredients with 8, 4, and 4 similarly labeled ingredients overlapping with Metabolife 356, respectively, including ephedra and caffeine. This pharmacodynamic study evaluated the effect of the DSEC on the corrected QT (QTc) interval and systolic blood pressure (SBP).8-11

METHODS

Design

This was a randomized, double-blind, placebo-controlled, crossover study conducted from January to May 2003. The study was approved by the institutional review board at the University of Connecticut and all patients provided written informed consent.

Individuals at least 18 years of age and in general good health expressing interest in participating in the study were evaluated for exclusion criteria. Individuals were excluded if they had a cardiac rhythm other than normal sinus, history of atrial or ventricular arrhythmia, family history of premature sudden cardiac death, left ventricular hypertrophy, atherosclerosis, hypertension, palpitations, T-wave abnormalities, QTc interval greater than 440 milliseconds, thyroid disease, type 1 or 2 diabetes mellitus, recurrent headaches, depression, any psychiatric condition or neurological disorder, history of alcohol or drug abuse, renal or hepatic dysfunction, concurrent use of potentially interacting drugs (anticoagulants, monoamine oxidase inhibitors, over-the-counter medications containing pseudoephedrine, or any dietary supplements), or were unwilling to sign informed consent. Pregnant or lactating women were also excluded from participation, and urine dipstick tests were used to confirm lack of pregnancy.

Individuals included in the study were randomized to receive DSEC or placebo as their first treatment using a random permuted block method with a block size of 4 patients per group. During the first phase of the study, participants received 1 capsule of either DSEC or matching placebo. Each opaque DSEC capsule had the contents of 1 Metabolife 356 tablet (Table 1), representing the smallest standard single dose of Metabolife 356.6-7 Following a 7-day washout period, participants returned for the second phase of the trial and received the other treatment (FIGURE). During each phase, pharmacodynamic and electrocardiographic variables were evaluated immediately before the ingestion of the capsule (pre-ingestion) and 1, 3, and 5 hours postdosing. This interval was chosen based on the half-lives of ephedra (3-6 hours) and caffeine (3 hours) and because the product labeling indicates that Metabolife 356 can be taken as frequently as 3 to 4 times a day during waking hours.7

Electrocardiographic Measurement

The primary electrocardiogram (ECG) end point was the maximum postdosing QTc interval attained over 5 hours in DSEC vs placebo groups. Maximum postdosing QTc was determined by averaging the QTc intervals from all evaluable leads in each of the 3 postdosing ECGs and selecting the ECG with the greatest average QTc interval in both groups. Maximum postdosing QTc was assessed because the time to maximal absorption of the various ingredients in DSEC is not established. The maximum P-wave, PR, QRS, QT, and RR intervals were similarly measured. The QTc interval was calculated using Bazett’s formula [QTc = QT/(RR)1/2] for the primary analysis since it is the most commonly used clinically, but the Framingham Linear Correction formula was also used [QTc = QT + 1.54 (1 − RR)] since Bazett’s formula may overcorrect at heart rates (HRs) above 60/min.12,13 P-wave and QTc interval dispersion (measures of the degree of heterogeneity in conduction throughout atrial and ventricular tissue, respectively) were measured by subtracting the longest and shortest P-wave or QTc intervals on the selected 12-lead ECG, respectively. The HR was calculated based on the average RR interval using the formula: (60/[RR interval/1000]).

Twelve-lead ECG readings (Welch-Allyn, Skaneateles Falls, NY) were obtained while participants were in the recumbent position and breathing freely and were recorded with 1 mV/cm standardization and paper speed of 25 mm/s. Electrocardiographic variables were manually derived by a single blinded study investigator using a precision ruler of 0.5-mm scale (Schadler-Quinzel, Parsippany, NJ).12

Hemodynamic Measurements

The primary hemodynamic end point was the maximum SBP attained over the 3-hour study for Metabolife 356 vs placebo groups. Secondary selected he-

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modynamic end points included the maximum attained values for the following: diastolic BP, cardiac index (CI), thoracic fluid content (TFC), systemic vascular resistance index (SVRI), stroke volume index (SI), left cardiac work index (LCWI), systolic time ratio (STR), pre-ejection period (PEP), acceleration index (ACI), and velocity index (VI) over 5 hours. The CI, SI, LCWI, STR, PEP, ACI, and VI are indexes of myocardial inotropy. The TFC and SVRI are measures of preload and afterload, respectively.

Hemodynamic parameters were obtained through the use of bioelectrical impedance cardiography (ICG) (Bio-Z, Cardiodynamics International Corp, San Diego, Calif). To measure and calculate hemodynamics, ICG sensors were placed bilaterally on the root of the neck and on the thorax at the level of the xiphoid process while an oscillometric cuff placed over the brachial artery. To minimize circadian variations in BP, participants completed both phases of the study at the same time of day.

**Adverse Effects**

Adverse effects were identified by asking at each postdosing ECG/hemodynamic time point, “Have you experienced any potential adverse effects since the last time period?” If a potential adverse effect at a previous time point was identified, the individual was asked, “Do you still have the adverse effect you reported previously?” and “Is it worse than last time or better than last time?” Answers were recorded and any individual reporting an adverse effect reported at the 5-hour postdosing time point was followed up for an additional hour.

### Statistical Analysis

Continuous data are presented as mean (SD) with dichotomous variables expressed as percentages. Intragroup and intergroup comparisons of continuous data were performed using a paired *t* test. When data were analyzed using the nonparametric Wilcoxon signed rank test, results did not differ; the parametric analyses are presented. *χ²* Analysis of categorical data was also performed. A *P* value ≤.05 was considered statistically significant. Since baseline data did not differ significantly other than for SBP, maximum postdose values were compared directly. The baseline SBP among patients receiving placebo as their second treatment were higher than those receiving DSEC, but by 1 hour these patients had SBPs not different from those of DSEC at baseline. Therefore, maximum SBP values were also compared directly.

A prespecified power analysis was conducted under the assumption that an intergroup difference in either SBP by 4 (4) mm Hg or in the QTc interval by 6 (3) mm Hg would be significant. We selected a QTc interval difference between groups of 6 milliseconds because that was the maximum normal variability based on Molnar et al; the SBP difference of 4 mm Hg between groups was based on Corea et al. The SDs for the ECG and SBP used in our power calculations were derived from our previous evaluations of the ECG and BP effects of herbal products in young healthy volunteers. Using an *α* of .05 and a power of 80%, the necessary sample sizes were 10 and 4 patients, respectively.

### RESULTS

Fifteen participants (mean [SD] age, 26.7 [2.52] years; weight, 72.7 [14.93] kg; 6 women; 11 white, 3 black, 1 Asian; with mean [SD] body mass index of 24.1 [3.89]) were randomized and completed the study protocol (Figure). None had comorbid conditions or were taking medications other than oral contraceptives. Pretreatment values for DSEC and placebo were similar except for SBP (114.3 [9.8] vs 119.9 [10.7] mm Hg; *P* = .003). This resulted from differences in SBP for patients taking placebo as a second treatment vs those receiving placebo first (124.9 [12.6] vs 114.3 [3.3] mm Hg; *P* = .049).

### Electrocardiographic Effects

After dosing, the maximum QTc interval (Bazett) was 5.9% higher with DSEC than placebo (*P* < .001) (Table 2). After receiving DSEC, participants were more likely to have a QTc interval increase of at least 30 milliseconds compared with placebo (8 individuals [53.3%] vs 1 individual [6.7%]; relative risk, 2.67 [95% confidence interval, 1.40-5.10]). No participant in either group had a QTc interval increase of 60 milliseconds or higher or a QTc value greater than 500 milliseconds. Average QTc interval (Bazett) increases from baseline were 27.20 (12.67) milliseconds for DSEC and 2.63 (24.81) milliseconds for placebo (*P* = .03 and *P* = .69). The QTc interval (Bazett) was greater in the DSEC group than the placebo group at every postingestion time point (Table 2). When the Framingham Linear Correction was used, the difference in the postdosing QTc values between the DSEC and placebo groups was of the same magnitude and direction (ie, 23.7-millisecond in-

### Table 2. Evaluation of Baseline and Postdosing Maximal QTc Intervals and QTc Intervals Over Time*

<table>
<thead>
<tr>
<th>Time, milliseconds</th>
<th>Placebo Group</th>
<th>DSEC Group</th>
<th><em>P</em> Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>393.5 (20.4)</td>
<td>392.2 (24.0)</td>
<td>.88</td>
</tr>
<tr>
<td>Postdosing maximum</td>
<td>396.1 (15.8)</td>
<td>419.4 (11.8)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>1-Hour postdosing</td>
<td>388.6 (18.3)</td>
<td>407.5 (14.6)</td>
<td>.002</td>
</tr>
<tr>
<td>3-Hour postdosing</td>
<td>385.4 (12.7)</td>
<td>410.6 (19.6)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>5-Hour postdosing</td>
<td>380.6 (12.8)</td>
<td>415.5 (11.2)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Abbreviation: DSEC indicates Metabolife 356, a multicomponent dietary supplement containing ephedra and caffeine.

*Data are presented as mean (SD)
crease with DSEC; \( P = .005 \). Women had a nonsignificantly higher baseline QTc interval (Bazett) than men (395.8 [29.6] vs 382.2 [13.9] milliseconds; \( P = .25 \)), but the QTc interval change from baseline after DSEC ingestion was similar in both groups (women, 28.1 [25.3] vs men, 26.6 [18.4] milliseconds; \( P = .90 \)). P-wave duration was 17% higher with DSEC than placebo (\( P = .02 \); Table 3). QTc interval dispersion was 50% greater and P-wave dispersion was 40.4% greater with DSEC than placebo (\( P = .01 \) for both).

Hemodynamic Effects
The maximum SBP 5 hours postdosing was 4.8% greater (\( P = .009 \)) and the maximum SI was 7.9% greater (\( P = .003 \)) in the DSEC group than the placebo group. The baseline SBPs were nonsignificantly lower among women than men (114.5 [6.4] vs 119.1 [7.3] mm Hg; \( P = .23 \)), and SBP after DSEC ingestion increased less in women (women, 6.0 [1.9] vs men, 11.3 [10.7] mm Hg; \( P = .24 \)). The STR was 4.8% lower with DSEC than placebo (\( P = .04 \)). No other significant hemodynamic differences occurred between groups (Table 3).

Table 3. Maximum Postdosing Electrocardiographic and Hemodynamic Values

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Electrocardiographic</th>
<th>Hemodynamic</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Placebo Group</td>
</tr>
<tr>
<td>P-wave measurement, ms</td>
<td>93.2 (7.5)</td>
<td>94.0 (6.0)</td>
</tr>
<tr>
<td>Average</td>
<td>117.3 (16.2)</td>
<td>117.0 (12.2)</td>
</tr>
<tr>
<td>Dispersion</td>
<td>55.3 (19.9)</td>
<td>61.3 (9.15)</td>
</tr>
<tr>
<td>Average interval measurement, ms</td>
<td>177.2 (26.1)</td>
<td>182.3 (28.5)</td>
</tr>
<tr>
<td>PR</td>
<td>94.5 (28.4)</td>
<td>90.5 (9.7)</td>
</tr>
<tr>
<td>QT</td>
<td>342.6 (20.9)</td>
<td>348.9 (30.9)</td>
</tr>
<tr>
<td>RR</td>
<td>785.7 (102.6)</td>
<td>834.2 (134.4)</td>
</tr>
<tr>
<td>QT dispersion, ms</td>
<td>39.3 (17.9)</td>
<td>48.0 (12.7)</td>
</tr>
<tr>
<td>QTc dispersion, ms</td>
<td>55.3 (17.6)</td>
<td>63.8 (10.3)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Heart rate, beats/min</th>
<th>Systolic blood pressure, mm Hg</th>
<th>Diastolic blood pressure, mm Hg</th>
<th>Cardiac index, L/min/m²</th>
<th>Stroke index, mL/m²</th>
<th>Systemic vascular resistance index, dynes/cm²/s/m²</th>
<th>Acceleration index, 100⁻¹×s⁻²</th>
<th>Velocity index, 1000⁻¹×s⁻¹</th>
<th>Thoracic fluid content, kOhm⁻¹</th>
<th>Left cardiac work index, kg m⁻²</th>
<th>Systolic time ratio</th>
<th>Prejection period, ms</th>
<th>Left ventricular ejection time, ms</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>79.2 (9.1)</td>
<td>117.3 (7.3)</td>
<td>73.9 (8.3)</td>
<td>3.1 (0.4)</td>
<td>38.7 (4.3)</td>
<td>2221 (315.1)</td>
<td>112.5 (33.5)</td>
<td>54.7 (12.9)</td>
<td>31.0 (6.0)</td>
<td>3.5 (0.7)</td>
<td>0.5 (0.1)</td>
<td>124.7 (15.8)</td>
<td>260.4 (19.7)</td>
</tr>
</tbody>
</table>

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Table 3. Maximum Postdosing Electrocardiographic and Hemodynamic Values

*Table 3. Maximum Electrocardiographic and Hemodynamic Values

EFFECTS OF A DIETARY SUPPLEMENT CONTAINING EPHEDRA AND CAFFEINE

**Hemodynamic Effects**

The maximum SBP 5 hours postdosing was 4.8% greater (\( P = .009 \)) and the maximum SI was 7.9% greater (\( P = .003 \)) in the DSEC group than the placebo group. The baseline SBPs were nonsignificantly lower among women than men (114.5 [6.4] vs 119.1 [7.3] mm Hg; \( P = .23 \)), and SBP after DSEC ingestion increased less in women (women, 6.0 [1.9] vs men, 11.3 [10.7] mm Hg; \( P = .24 \)). The STR was 4.8% lower with DSEC than placebo (\( P = .04 \)). No other significant hemodynamic differences occurred between groups (Table 3).

**Adverse Events**

All patients receiving DSEC reported nonspecific symptoms (jitteriness, quiescence, or “not feeling quite right”). No adverse effects were reported while patients were receiving placebo (\( P < .001 \)). One woman developed sinus tachycardia at a rate of 120/min with palpitations 1 hour after taking DSEC, which persisted through the 5-hour time point but subsided 1 hour after the study was completed. Two premature ventricular complexes developed in 1 patient 5 hours after taking DSEC and subsided 1 hour later. A hand tremor developed in 1 patient after taking DSEC that subsided 5 hours postdosing.

**COMMENT**

The DSEC prolonged the QTc interval by an average of 27 milliseconds vs baseline, and postdosing levels were 23 milliseconds higher than placebo. Overall, 53% of participants had QTc interval increases of at least 30 seconds while taking the DSEC. The European Center for Proprietary Medicinal Products recognizes a drug-induced increase in the QTc interval of at least 30 milliseconds as a potential cause of concern germane to the development of torsade de pointes with increases of at least 60 milliseconds or any postdosing value at least 500 milliseconds a definite cause for concern.

Although there are no official Food and Drug Administration standards on QTc interval prolongation, in a preliminary concept article, the following signals for increased risk of proarrhythmia were identified: an increase of at least 30 or 60 milliseconds from baseline or postdosing values of at least 450, 480, or 500 milliseconds. In actual practice, the Food and Drug Administration has been even more stringent. Cisapride and terfenadine were removed from the US market due to cases of reported proarrhythmia and prolonged QTc intervals in the range of 13 to 17 milliseconds without concurrent drug interactions and 23 to 74 milliseconds with such interactions. The antipsychotic ziprasidone has a bolded warning included in the package insert because of 20-22 cases of reported proarrhythmia and QTc interval prolongation, in a preliminary concept article, the following signals for increased risk of proarrhythmia were identified: an increase of at least 30 or 60 milliseconds from baseline or postdosing values of at least 450, 480, or 500 milliseconds. In clinical trials with sotalol, the risk of torsade de pointes was related to the dose and QTc interval. At a 160-mg dose, the average QTc interval was 467 milliseconds and the incidence of torsade de pointes was 0.5%. When the dose was increased to 640 mg, the average QTc was 490 milliseconds and the incidence of torsade de pointes was 3.7%.

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The DSEC increased the maximum P-wave duration and P-wave dispersion. Patients with paroxysmal atrial fibrillation are more likely to have increases in these variables. Gardner et al26 studied 10 patients taking Metabolife 356 (2 tablets 3 times daily for 14 days) with continuous Holter monitor and periodic BP monitoring and found that the number of atrial premature complexes on days 3 and 14 were increased by 402% and 285%. This was caused by dramatic increases within 2 participants and no appreciable changes in the other 8 participants in that study. The small numbers and high SDs precluded a significant result. These investigators did not evaluate QTc interval effects. Although the risk of atrial arrhythmias may be increased, the degree of risk with Metabolife 356 cannot be determined at this time.

In a meta-analysis of ephedra and ephedrine products vs control, the odds ratio of heart palpitations was 2.29 (95% confidence interval, 1.27-4.32). Whether these patients were experiencing palpitations of atrial or ventricular origin is unknown, but our data and those from Gardner et al suggest that palpitations may have been from either source.

Through bioelectrical ICG, we were able to determine which of the constituent hemodynamic effects contributed to the increases in SBP given the equation [BP = CI × SVRI where CI=HR × SI]. There was a qualitative increase in CI caused by a significant increase in SI, which is the amount of blood that the heart ejects into the arterial circulation per beat (standardized to body surface area) and is a preload-dependent measure of myocardial inotropy. Since DSEC did not alter TFC or SVRI, measures of preload and afterload, respectively, the increase in myocardial inotropy is likely related to a direct effect and not caused by a fluid shift into the central circulation.

There are several study limitations precipitated primarily by safety concerns. First, we studied young healthy volunteers without comorbid conditions and normal baseline QTc intervals rather than obese participants or those looking to enhance athletic performance. In a previous study of patients without concurrent drugs or comorbid diseases, the QTc interval was larger with increasing age, and therefore the younger population we studied reduces the likelihood that QTc would exceed 500 milliseconds. Comorbid conditions excluded in our study were found to increase the risk of proarrhythmia with other agents prolonging the QTc interval. We evaluated the lowest dose of Metabolife 356 and did not assess a dose-response relationship. Ziprasidone and antiarrhythmic drugs have clear dose-dependent increases in the QTc interval. Given the multi-ingredient nature of Metabolife 356 and other top-selling products, we cannot determine which ingredient or combination of ingredients causes the effects seen. However, in a previous similar study of caffeine alone, caffeine did not alter the PR, QRS, QT, or QTc intervals, and SBP was increased only among caffeine-naive individuals at 3 hours. Therefore, the effects seen are likely not due to caffeine. Whether dietary supplements with similar ingredients would have similar effects is not known. Future studies are needed not only to determine which ingredients in Metabolife 356 can cause electrocardiographic and hemodynamic alterations, but also to determine whether pharmacokinetic or pharmacodynamic interactions between components or concurrent renal or hepatic disease attenuate or intensify the effect. Finally, this study was too small to evaluate the actual occurrence of ventricular arrhythmias.

CONCLUSION
This study demonstrated that a single dose of a dietary supplement containing ephedra and caffeine significantly prolongs the QTc interval and P-wave duration, risk factors for the development of ventricular and atrial arrhythmias, respectively. Systolic blood pressure is also increased. Metabolife 356 and products sharing similar ingredients should be avoided until more information is known.

REFERENCES


The great men of culture are those who have had a passion for diffusing, for making prevail, for carrying from one end of society to the other, the best knowledge, the best ideas of their time; who have labored to divest knowledge of all that was harsh, uncouth, difficult, abstract, professional, exclusive; to humanize it, to make it efficient outside the clique of the cultivated and learned, yet still remain the best knowledge and thought of the time, and a true source, therefore, of sweetness and light.

—Matthew Arnold (1822-1888)