

Absence of QTc-Interval–Prolonging or Hemodynamic Effects of a Single Dose of Bitter-Orange Extract in Healthy Subjects

Bokyung Min, Pharm.D., Deborah Cios, Jeffrey Kluger, M.D., FACC,
and C. Michael White, Pharm.D.

Study Objective. To evaluate the hemodynamic and electrocardiographic effects of a single dose of commercially available bitter-orange dried-fruit extract, which is increasingly being used in dietary supplements.

Design. Randomized, double-blind, placebo-controlled, crossover study.

Setting. University of Connecticut, Storrs Campus.

Subjects. Eighteen healthy volunteers aged 18 years or older.

Intervention. Subjects were given either placebo or bitter-orange dried-fruit extract (450 mg standardized to 27 mg of m- or p-synephrine) in phase 1. The opposite treatment was given during phase 2 after a washout period of at least 7 days.

Measurements and Main Results. The rate-corrected QT (QTc) interval and blood pressure were measured before dosing and at 1, 3, 5, and 8 hours after dosing. Mean \pm SD values of the maximum postdose values were compared between groups. Subjects receiving bitter-orange extract versus those receiving placebo had similar postdose QTc intervals (402 ± 29 vs 403 ± 24 msec, $p=0.653$), systolic blood pressure (114 ± 10 vs 115 ± 8 mm Hg, $p=0.686$) and diastolic blood pressure (68 ± 9 vs 68 ± 8 , $p=0.879$).

Conclusion. Bitter-orange dried-fruit extract standardized to m- or p-synephrine 27 mg did not significantly alter the QTc interval or blood pressure after a single dose was administered. Future studies are necessary to ensure the safety of this herbal product with multiple doses.

Key Words: QTc interval, bitter-orange dried-fruit extract, m-synephrine, p-synephrine, hemodynamic effects, electrocardiographic effects.

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In the United States, over 3 billion doses of natural weight-loss supplements are sold

From the School of Pharmacy, University of Connecticut, Storrs, Connecticut (Drs. Min and White, and Ms. Cios); and the Divisions of Cardiology (Drs. Kluger and White) and Drug Information (Drs. Min and White), Hartford Hospital, Hartford, Connecticut.

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Address reprint requests to C. Michael White, Pharm.D., Drug Information Center, Hartford Hospital, 80 Seymour Street, Hartford, CT 06102-5037; e-mail: cmwhite@harthosp.org.

annually, resulting in \$7 billion in sales.¹⁻² From 1995–1997, 926 cases of possible ephedra toxicity, including 16 strokes, 10 myocardial infarctions, and 11 sudden deaths, were reported to the U.S. Food and Drug Administration (FDA).³ Ephedra-containing products were banned in 2004, but a federal judge recently ruled that the FDA overstepped its authority and the ban was lifted.⁴ Ephedra contains both direct and indirect sympathomimetic compounds—including ephedrine, pseudoephedrine, and norpseudoephedrine—that stimulate β_1 -, β_2 -, and α_1 -adrenergic receptors.

All FDA-approved drugs are required to

undergo initial safety evaluation of the effects of the drug on blood pressure and the QT interval. However, dietary, nutritional, and herbal supplements do not have to undergo a safety evaluation before marketing. In a previous study, Metabolife 356 (Metabolife International Inc., San Diego, CA), an ephedra-containing product, elevated the rate-corrected QT (QTc) interval by 23 msec and systolic blood pressure by 5 mm Hg compared with placebo.⁵ Unfortunately, this simple safety evaluation was not conducted before numerous adverse events were reported.

Bitter orange is a natural product used extensively in the ephedra-free weight-loss supplement market. However, the electrocardio-graphic and hemodynamic effects of bitter orange have not been rigorously studied. The active component in bitter orange is m-synephrine (natural phenylephrine). However, bitter orange may also contain p-synephrine (oxedrine), octapamine, and N-methyltyramine, which act as direct or indirect sympathomimetics and can stimulate β_1 -, β_2 -, and α_1 -adrenergic receptors.⁶

The main constituent of bitter orange is thought to be m-synephrine, which is an α_1 -selective adrenergic receptor agonist. Bitter orange is listed by the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure as a cause of resistant hypertension,⁷ but this has not been adequately studied. In one study, bitter orange juice (~13–14 mg as m- or p-synephrine) was given to healthy, normotensive volunteers.⁸ Systolic blood pressure in these subjects increased by 4 mm Hg above baseline compared with 2 mm Hg in the placebo group after 5 hours, but the increase was not significant.

One case report described a 20-year-old woman with no significant medical history who developed intractable ventricular fibrillation after overdosing on weight-loss pills containing synephrine.⁹ Another case report described a 55-year-old smoker, also a woman with no significant medical history, who was diagnosed with acute lateral-wall myocardial infarction.¹⁰ A review of her drug therapy revealed that she had taken a multicomponent dietary supplement containing bitter orange 300 mg for the past year (direct or indirect sympathomimetic content was unknown).

Case reports are important for their description of potential associations between product use and patient harm. However, they cannot prove that a drug was related to an adverse effect or determine the potential mechanism of harm. A

preliminary cardiovascular safety probe to assess blood pressure and the QTc interval can help investigators determine whether there is a signal for cardiovascular risk with use of bitter orange.

The objective of our study was to evaluate the impact of bitter-orange dried-fruit extract on hemodynamic and electrocardiographic variables in healthy volunteers.

Methods

Study Design and Subjects

This randomized, double-blind, placebo-controlled, crossover study was approved by the University of Connecticut's institutional review board. Study enrollment was from October 2004–February 2005. All participants signed informed consent.

Study subjects were healthy volunteers aged 18 years or older. Subjects were excluded if they had abnormal sinus rhythm, history of atrial or ventricular arrhythmia, left ventricular hypertrophy, coronary or cerebrovascular disease, hypertension, palpitations, T-wave abnormalities, baseline linear QTc interval greater than 440 msec, thyroid disease, type 1 or 2 diabetes mellitus, recurrent headaches, depression, any psychiatric or neurologic disorder, history of alcohol or drug abuse, renal or hepatic dysfunction, or family history of premature sudden cardiac death. Subjects also were excluded if they took anticoagulants, monoamine oxidase inhibitors, drugs metabolized by cytochrome P450 (inducers, inhibitors, or substrates), dietary or nutritional supplements other than a multivitamin, or stimulants, including systemic and/or topical over-the-counter decongestants, within 6 months from the day of screening. Women who were pregnant or lactating were also excluded; urine dipstick tests were used to confirm lack of pregnancy.

Subjects were randomly assigned to receive one dose of bitter-orange dried-fruit extract or placebo at the start of phase 1. After a washout period of at least 7 days, subjects entered phase 2 and received the opposite therapy. At least 12 hours before and during each phase of the study, subjects abstained from caffeine (in diet, drug therapy, or other source), herbal products (e.g., bitter-orange extract, ma-huang), or stimulants (e.g., systemic or topical decongestants, ephedrine).

One of the investigators reformulated each bitter-orange dried-fruit tablet (Nature's Way; Springville, UT) as an opaque capsule (Capsugel, Pfizer Inc., Morris Plains, NJ) using lactose

Table 1. Comparison of Hemodynamic Variables Between Study Groups

Variable	Placebo Group (n=18)	Bitter-Orange Extract Group (n=18)	p Value
Baseline			
Systolic blood pressure (mm Hg)	111 ± 14	110 ± 12	0.762
Diastolic blood pressure (mm Hg)	65 ± 11	63 ± 10	0.419
Cardiac index (L/min/m ²)	3.0 ± 0.4	2.9 ± 0.3	0.426
Systemic vascular resistance index (dyn•sec•cm ⁻⁵ •m ²)	2039 ± 378	2059 ± 416	0.811
Thoracic fluid content (ml)	33 ± 7	35 ± 7	0.122
Maximum postingestion			
Systolic blood pressure (mm Hg)	115 ± 8	114 ± 10	0.686
Diastolic blood pressure (mm Hg)	68 ± 8	68 ± 9	0.879
Cardiac index (L/min/m ²)	3.1 ± 0.5	3.1 ± 0.4	0.625
Systemic vascular resistance index (dyn•sec•cm ⁻⁵ •m ²)	2158 ± 425	2214 ± 349	0.362
Thoracic fluid content (ml)	34 ± 7	35 ± 7	0.483

Data are mean ± SD.

monohydrate powder (Humco Corp., Texarkana, TX) as filler. Each tablet contained bitter-orange extract 450 mg standardized to m- or p-synephrine 27 mg (i.e., 6%) from *Citrus aurantium*. Matching placebo capsules contained only lactose.

During both study phases, hemodynamic and electrocardiographic variables were measured immediately before ingestion of the study drug (baseline) and at 1, 3, 5, and 8 hours after ingestion. The duration of observation was based on the product label of the bitter-orange extract (twice/day with meals) and the time frame of qualitative systolic blood pressure elevation used in another study.⁸ To minimize circadian variation in blood pressure and electrocardiographic parameters, measurements in phase 2 were begun within 1 hour of those in phase 1 for each subject.

Hemodynamic Monitoring

Blood pressure was measured with subjects at rest using a Bio-Z (Cardiodynamics International Corp., San Diego, CA) cuff measurement. This FDA-approved, noninvasive machine uses blood pressure and thoracic electrical bioimpedance to calculate and measure cardiac index, systemic vascular resistance index, and thoracic fluid content.¹¹ Mean ± SD baseline and maximum postingestion blood pressure and hemodynamic parameters were selected for statistical comparison between groups.

Electrocardiographic Monitoring

Standard 12-lead electrocardiograms (ECGs)

were performed at rest using the MAC 5000 machine (GE Healthcare Technologies, Waukesha, WI), which uses 1-mV/cm standardization at 25 mm/second. The ECGs were printed out for interval measurement. A blinded investigator read P-wave and PR, QRS, QT, and RR intervals from lead II under magnification using a precision ruler with a scale of 0.5 mm (Schadler-Quinzel, Parsippany, NJ). The QT interval was determined by extrapolating the T-wave downslope to the isoelectrical line. The QTc interval was corrected using Bazett's formula ($QTc = QT/[RR]^{1/2}$) and the Framingham linear method ($QTc = QT + 0.154[1 - RR]$). The mean ± SD values of each interval (P wave, and PR, QRS, QT, RR, or QTc interval) at baseline and the maximum postingestion values were selected for statistical comparison between groups.

Adverse Event Monitoring

Adverse events were evaluated during the postingestion period at 1, 3, 5, and 8 hours by asking subjects, "Have you experienced any unpleasant feelings or symptoms since you took the experiment medication?" When subjects reported any symptom, they were followed for progress of the symptom (same, worse, or improved) or a new onset of adverse events until the end of the study. We allowed only administration of acetaminophen for possible intolerable headaches during the study.

Statistical Analysis

All data are mean ± SD. A paired *t* test was used for between-group comparisons at baseline

Table 2. Comparison of Electrocardiographic Variables Between Study Groups

Interval	Placebo Group (n=18)	Bitter-Orange Extract Group (n=18)	p Value
Baseline (msec)			
P wave	84 ± 12	83 ± 12	0.914
PR	142 ± 22	141 ± 20	0.822
QRS	78 ± 20	77 ± 16	0.672
QT	355 ± 19	360 ± 20	0.334
RR	819 ± 72	819 ± 85	0.987
Framingham QTc	383 ± 21	387 ± 21	0.109
Bazett's QTc	393 ± 25	399 ± 25	0.095
Maximum postingestion (msec)			
P wave	90 ± 14	90 ± 13	0.997
PR	151 ± 23	151 ± 22	0.711
QRS	84 ± 20	82 ± 18	0.398
QT	377 ± 25	378 ± 23	0.776
RR	970 ± 107	993 ± 106	0.398
Framingham QTc	394 ± 20	391 ± 24	0.442
Bazett's QTc	403 ± 24	402 ± 29	0.653

Data are mean ± SD.

QTc = rate-corrected QT interval.

and for the maximum postingestion values. A p value less than 0.05 was considered to indicate a statistically significant difference.

Our primary end points were the effects of bitter-orange extract on systolic blood pressure and QTc interval. To calculate the sample with an α value of 0.05, the power of 80%, QTc-interval intergroup difference of 6 ± 3 msec, and systolic blood pressure intergroup difference of 4

± 4 mm Hg, 10–12 subjects were required. These differences were adapted from previous studies.^{12–14}

Results

Of the 20 subjects screened, one was taking over-the-counter cimetidine and was excluded from participating. Of the 19 enrolled subjects, one could not return for phase 2 due to a

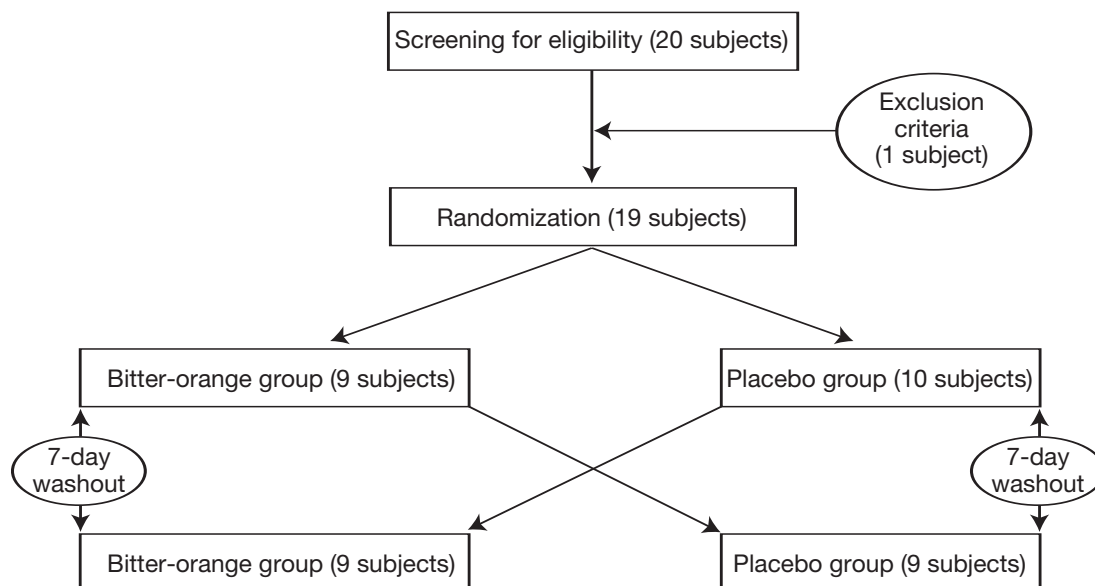


Figure 1. Study design and randomization of the subjects.

personal reason, had no study-related complaint, and received placebo in phase 1. As such, 18 subjects completed both phases of the study (Figure 1); nine were men, mean age was 24.9 ± 4.4 years, and mean weight 150 ± 28 lb. No significant differences in baseline or maximum postingestion hemodynamic or electrocardiographic parameters were noted between groups (Tables 1 and 2).

All subjects completed the study with no major adverse events. The most common complaint (six subjects) was headache. Five headaches were reported with bitter-orange extract and four with placebo; two subjects required acetaminophen for treatment. One subject had a heart flutter with placebo, and another felt tired in both study phases.

Discussion

A single dose of bitter-orange dried-fruit extract did not affect electrocardiographic parameters in the 18 healthy study subjects. Since m-syneprine is the main constituent in this bitter-orange product and stimulates only the α_1 -adrenergic receptor, this is not surprising. Phenylephrine $1.4 \mu\text{g}/\text{kg}/\text{minute}$ (mean dose) was previously shown not to affect the QTc interval.¹⁵ The literature suggests that it is β -adrenergic receptor stimulation (particularly β_2 stimulation) that causes prolonged ventricular repolarization.¹⁶ This is evidenced by the ability of isoproterenol (a β_1 - and β_2 -receptor agonist) to block ventricular cell delayed rectifier potassium channel current *in vitro*.

This pharmacologic relationship is further supported by a study in which epinephrine (an α_1 -, β_1 -, and β_2 -receptor agonist) elevated the QTc interval by 55 msec in patients with congenital long-QT syndrome, but concurrent propranolol (a nonselective β -antagonist) attenuated the effect.¹⁷ We cannot be sure that this lack of QTc-interval effect would be consistent with all bitter-orange products, since other direct or indirect sympathomimetics can be found in some bitter-orange preparations and may cause greater β -adrenergic receptor stimulation.

In one case report, a single dose of multi-component product containing bitter orange (standardized for m- and p-syneprine, N-methyltyramine, hordenine, octopamine, and tyramine) with caffeine was associated with a QTc interval of 516 msec.¹⁸ The patient, a 22-year-old woman, experienced syncope while

jogging, probably secondary to development of torsade de pointes. The amounts of the components of bitter orange in this weight-loss supplement is not disclosed by the manufacturer.

We did not observe any significant changes in blood pressure, cardiac index, or systemic vascular resistance index associated with bitter-orange dried-fruit extract. Since m-syneprine can stimulate α_1 -adrenergic receptors, an increase in systemic vascular resistance index would have been anticipated, but only a small, nonsignificant effect was noted. However, most healthy individuals have baroreceptor buffering capacity that limits the extent of blood pressure alterations secondary to sympathomimetics. This is accompanied by enhanced parasympathetic tone and reduced endogenous catecholamine secretion.¹⁹ People with muted buffering ability (e.g., elderly persons, patients with hypertension, and patients with cardiac disease) have markedly greater blood pressure increases than healthy individuals in response to sympathomimetics.

In a study of young (aged 25 yrs) versus old (aged 65 yrs), healthy, normotensive subjects, systolic blood pressure response to phenylephrine was compared.²⁰ After administration of intravenous phenylephrine, blood pressure increased by 2 and 5 mm Hg, respectively, in the young and old subjects. Baroreceptor buffering and cardiovagal baroreflex sensitivity, respectively, were 115% and 55% lower in older men.

In another study, a control group of healthy subjects was compared with a group of patients with essential hypertension.¹⁹ Intravenous phenylephrine $25 \mu\text{g}$ increased systolic blood pressure by 6 mm Hg in controls, but by 18 mm Hg in the patients with essential hypertension. As such, we cannot be sure whether the nonsignificant blood pressure changes in our study represent a lack of effect or a buffered response. Our data should not be extrapolated to subjects without adequate baroreceptor buffering ability; these patients should be studied separately.

Caffeine, a methylxanthine that enhances the pharmacologic effects of sympathomimetics, increased blood pressure synergistically with phenylpropanolamine in two studies.^{21, 22} Some manufacturers of herbal products have intentionally compounded their products with caffeine to allow for this synergistic effect. Even casual self-administration (of coffee, soda, or tea) can enhance the blood pressure effects of some sympathomimetics.²³ Caffeine synergizes sympathomimetics by reducing baroreflex sensitivity.²⁴ We intentionally prohibited caffeine

consumption in our study, so our data should not be extrapolated to subjects consuming caffeine and bitter orange concomitantly. Further study with this combination is necessary. Our subjects' abstention from caffeine may have resulted in the headaches reported by subjects.

In a study described earlier, in which fresh, bitter orange juice was administered and qualitative systolic blood pressure changes were seen, the subjects did not abstain from caffeine consumption.⁸ However, they were monitored for consistency of caffeine intake in the study's two crossover phases (bitter orange juice and water). Although the bitter orange juice contained only 13–14 mg of synephrine, caffeine consumption may have accentuated the blood pressure effect.

Ingesting markedly greater amounts of bitter-orange dried fruit or synephrine may not have the same benign hemodynamic and electrocardiographic result as noted in our study, even in young, healthy subjects. Ours was a single-dose study, and we cannot be sure that accumulation of synephrine or another compound would not have occurred with subsequent doses. Additional studies are needed to answer these questions. However, without an initial safety probe such as this to establish basal safety, a dose-response or long-term study could not be ethically conducted. We did not assay the concentrations of m- or p-synephrine and cannot independently validate the amount contained in the product we used.

Conclusion

Bitter-orange dried-fruit extract equivalent to synephrine 27 mg did not significantly alter blood pressure or electrocardiographic parameters in healthy, young subjects after administration of a single dose. Future studies are necessary to ensure the safety of this herbal product with multiple doses.

References

1. Agency for Healthcare Research and Quality. Ephedra and ephedrine for weight loss and athletic performance enhancement: clinical efficacy and side effects. Washington, DC: U.S. Department of Health and Human Services, 2001.
2. Cleland RL, Gross WC, Koss LD, Daynard M, Muoio KM. Weight loss advertising: an analysis of current trends. Washington, DC: Federal Trade Commission, 2002.
3. Samenuk D, Link M, Homoud MK, et al. Adverse cardiovascular events temporally associated with ma huang, an herbal source of ephedrine. *Mayo Clin Proc* 2002;77:12–16.
4. WebMD. Judge strikes down ephedra ban. Available from www.foxnews.com/story/0,2933,153502,00.html. Accessed April 14, 2005.
5. McBride BF, Karapanos AK, Krudys A, Kluger J, Coleman CI, White CM. Electrocardiographic and hemodynamic effects of a multicomponent dietary supplement containing ephedra and caffeine: a randomized controlled trial. *JAMA* 2004;291:216–21.
6. Fugh-Berman A, Myers A. *Citrus aurantium*, an ingredient of dietary supplements marketed for weight loss: current status of clinical and basic research. *Exp Biol Med* 2004;229:698–704.
7. Chobanian AV, Bakris GL, Black HR, et al. Seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure. *Hypertension* 2003;42:1206–52.
8. Penzak SR, Jann MW, Cold JA, Hon YY, Desai HD, Gurley BJ. Seville (sour) orange juice: synephrine content and cardiovascular effects in normotensive adults. *J Clin Pharmacol* 2001;41:1059–63.
9. Srivatsa UN, Ebrahimi R, El-Bialy A, Wachsner RY. Electrical storm: case series and review of management. *J Cardiovasc Pharmacol Ther* 2003;8(3):237–46.
10. Nykamp DL, Fackli MN, Compton AL. Possible association of acute lateral-wall myocardial infarction and bitter orange supplement. *Ann Pharmacother* 2004;38:812–16.
11. Cardiodynamics International Corporation. Bio-Z [impedance cardiography presentation slides]. Available from <http://www.cardiodynamics.com/PDF/ICG%20-%20Hospital%20Presentati on%20-%2012-08-04.pdf>. Accessed February 10, 2005.
12. Molnar J, Zhang F, Weiss J, Ehler FA, Rosenthal JE. Diurnal pattern of QT interval: how long is prolonged? *J Am Coll Cardiol* 1996;27:76–83.
13. Corea L, Cardoni O, Fogari R, et al. Valsartan, a new angiotensin II antagonist for the treatment of essential hypertension: a comparative study of the efficacy and safety against amlodipine. *Clin Pharmacol Ther* 1996;60:341–6.
14. Caron MF, Hotsko AL, Robertson S, Mandybur L, Kluger J, White CM. Electrocardiographic and hemodynamic effects of Panax ginseng. *Ann Pharmacother* 2002;36:758–63.
15. Sun ZH, Swan H, Viitasalo M, Toivonen L. Effects of epinephrine and phenylephrine on QT interval dispersion in congenital long QT syndrome. *J Am Coll Cardiol* 1998;31:1400–5.
16. Peralta EG. Dual modulation of a potassium channel by the m1 muscarinic and β -2 adrenergic receptors. *Life Sci* 1995;56:957–64.
17. Darbar D, Smith M, Morike K, Roden DM. Epinephrine-induced changes in serum potassium and cardiac repolarization and effects of pretreatment with propranolol and diltiazem. *Am J Cardiol* 1996;77:1351–5.
18. Nasir JM, Durning SJ, Ferguson M, Barold E, Haigney MC. Exercise-induced syncope associated with QT prolongation and ephedra-free Xenadrine. *Mayo Clin Proc* 2004;79:1059–62.
19. Jordan J, Tank J, Shannon JR, et al. Baroreflex buffering and susceptibility to vasoactive drugs. *Circulation* 2002;105:1459–64.
20. Jones PP, Christou DD, Jordan J, Seals DR. Baroreflex buffering is reduced with age in healthy men. *Circulation* 2003;107:1770–4.
21. Lake CR, Rosenberg DB, Gallant S, Zaloga G, Chernow B. Phenylpropranolamine increases plasma caffeine levels. *Clin Pharmacol Ther* 1990;47:675–85.
22. Brown NJ, Ryder D, Branch RA. A pharmacodynamic interaction between caffeine and phenylpropranolamine. *Clin Pharmacol Ther* 1991;50:363–71.
23. Schlemmer RF. Caffeine potentiates phenylpropranolamine lethality but not motor behavior [abstr]. *Fed Proc* 1984;43:572.
24. Mosqueda-Garcia R, Tseng CJ, Biaggioni I, Robertson RM, Robertson D. Effects of caffeine on baroreflex activity in humans. *Clin Pharmacol Ther* 1990;48:568–74.