

Effect of a Ma Huang and Guarana Herbal Supplement on Energy Expenditure

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A. Study Purpose and Rationale

Herbal supplements containing ephedra sinica (ma-huang) and caffeine are widely sold on the internet, via radio and in health food stores as weight loss agents. Currently, these substances are not FDA regulated. Advertisements for these herbal drugs claim weight loss occurs by increasing the body's metabolism. The purpose of this study is to determine if an herbal dietary supplement containing Ma Huang (ephedrine alkaloids) and Guarana (caffeine) alters energy expenditure.

Given the obesity epidemic, the use of over the counter dietary aids is likely to increase. In a survey of greater than fourteen thousand adults, 1 % reported ephedra product use. More than 28% of young obese women and about 8% of normal weight women reported use of nonprescription weight loss products. The highest use of ephedra products occurred in women age 18-34 with a body mass index greater than 25.¹

Ephedrine acts as a sympathomimetic agent both by directly stimulating beta receptors and by causing release of norepinephrine from sympathetic nerves. Caffeine acts as an adenosine antagonist and may potentiate the effects of ephedrine by blocking the negative feedback of adenosine on release of norepinephrine.²⁻⁴ Ephedrine alone has been shown to induce thermogenesis and lead to weight loss in genetically obese rodents however controlled trials in humans did not show sustained weight loss.² Methylxanthines such as caffeine or theophylline alone have not been shown to effectively affect energy expenditure or weight.⁵ However, 20 mg of Ephedrine plus 200 mg of caffeine has been shown to have synergistic effects in increasing energy expenditure after a one time administration.² In mice, chronic treatment with ephedrine plus caffeine has been shown to reverse obesity caused by chemical lesions in the hypothalamus⁵ but not to change the weight of lean mice.³ In rhesus monkeys, ephedrine plus caffeine increased resting energy expenditure (REE) by 21% in obese monkeys and 24% in lean monkeys. The treatment led to weight loss primarily through a reduction in body fat. This combination also had an anorexic effect in the obese group.⁶ It should be noted that both mice and rhesus monkeys have functional brown adipose tissue which when recruited can raise metabolic rate; therefore, these results may not apply to humans who have less brown adipose tissue. In a non-blinded study with humans, a ephedrine/methylxanthine mixture was shown to normalize the lower postprandial thermogenic response seen in a weight matched group that had previously been obese compared to a never-obese group.³ Overall the combination showed a mild increase in 24 hour energy expenditure in the post-obese group but not in the never obese group.³ In a randomized double blind controlled trial conducted over 6 months, a combination of 60 mg ephedrine and 600 mg caffeine in association with a reduced calorie diet resulted in a 3.4 kg greater weight loss than placebo or either drug alone.⁷ This study was continued as an open label trial with ephedrine plus caffeine for a further 6 months which resulted in a further weight loss of 1.1 kg for those who completed the study.⁸ The weight loss effects of ephedrine plus caffeine plateaued after 20 weeks; in addition, chronic treatment was required to maintain weight loss.^{4,8}

The aforementioned studies were all conducted with manufactured drugs. Ephedra capsules have been shown to have similar pharmacokinetics to ephedrine.⁹⁻¹⁰ One study directly addressed the efficacy of the herbal counterpart. Boozer et al. showed that over 8 weeks, obese subjects treated with an equivalent of 72 mg ephedrine/day and 2,40 mg caffeine/day lost 2.7 kg compared to placebo.⁴ In this study, subjects were not energy restricted but were counseled on diet and exercise.

The studies evaluating thermogenesis of caffeine and ephedrine in humans only measured energy expenditure following daily doses of the drugs. To our knowledge, no study has evaluated the long term effects of caffeine/ephedrine or guarana/ephedra combinations on REE in humans. The goal of this study

would be to address the claim made in the advertisements for these herbal products that basal metabolic rate is increased. This study would contribute to the understanding of obesity by determining if the initial thermogenic effect of these drugs are longstanding or if the human body acclimates to the effect. The results of this study would help clinicians to educate and counsel patients who wish to use these products. In addition, further information about the safety of these drugs may be elicited.

The hypothesis of this study is that 48 mg of ephedrine alkaloids and 200 mg of caffeine a day will increase resting metabolic rate after eight weeks of use.

B. Study Design and Statistical Analysis

Subjects who meet criteria will be randomly assigned by block randomization to either the drug or the placebo arm. Subjects will be blinded to which arm they are assigned.

Prior to beginning ingestion of any drug, a baseline evaluation will be done by a medical doctor. Subjects will undergo an initial nutritional counseling session to inform them of current recommended guidelines for a healthy diet. Subjects will be asked to keep a food journal for two weeks prior to taking any drug to evaluate average daily caloric intake. In addition they will be asked to answer the Arizona Activity Frequency Questionnaire (AAFQ) which is a validated questionnaire for the estimation of physical activity energy expenditure." Subjects will be weighed at the start and end of this 2 week time period to assess for weight stability. Following this 2 week start up period, subjects' REE will be measured by indirect calorimetry on 3 mornings and averaged to assess baseline REE.

Subjects who are randomized to receive the study drug will receive 48 mg of ephedrine alkaloids a day and 200 mg of caffeine divided into twice a day dosing. Each caplet will contain about 12 mg ephedrine alkaloids and 50 mg caffeine. The first dose will be 2 capsules to be taken between 6 and 9 am 30 minutes before a meal and the second dose will be 2 capsules to be taken between 3 and 6 pm 30 minutes before a meal. Subjects in the placebo arm will take similar appearing capsules of equal weight containing alfalfa. The dosing schedule will be the same.

The first dose of the study drug (24 mg ephedrine alkaloids/ 100 mg caffeine) or placebo will be administered in a supervised setting and energy expenditure will be measured by an investigator blinded to the subject's study arm for the five hours following ingestion to evaluate the initial thermogenic effects of the study drug. This time period was chosen because ephedra has a peak effect at 3 hours when taken on an empty stomach and an elimination half life of 5 hours.⁹

Participants will be asked to take the study drug or placebo for eight weeks. Pills will be distributed to subjects in premeasured pill boxes on a weekly basis. Subjects will be asked to return pill boxes and unused pills will be counted to assess compliance. During this time period subjects will be asked to not ingest additional caffeine, ephedra or pseudoephedrine products. They will also be asked not to change their regular exercise routine. The AAFQ will be re-administered at 4 weeks and upon completion of the study. They will also be asked to keep a daily food journal during the study time period so that daily caloric intake can be assessed.

Biweekly visits will be required to measure blood pressure, heart rate and to assess for possible side effects. Side effect profile will also be assessed at the final evaluation.

After eight weeks of use of the drug or placebo, REE will again be measured on 3 mornings and averaged. Energy expenditure measurement post ingestion of the drug or placebo will also be repeated.

Studies have shown a mean resting metabolic rate of 1550 kcal/24 hrs with a standard deviation of 131 in obese women and a mean resting metabolic rate of 1421 with a standard deviation of 189 in normal weight women.¹² Using these numbers 35 subjects are needed to achieve a power of eighty percent. However, other studies using both herbal and manufactured combinations of ephedrine and caffeine have had a 25% drop out rate.^{4,7} Therefore, 44 subjects will be chosen for each study arm.

A ten percent change in REE which would yield an average increase of 140-150 kcal/day would be considered significant as this value would lead to a - pound weight loss per week. Both differences in REE and differences in thermogenic response to the capsule between the placebo and study drug arms will be analyzed using a student's paired t-test and analysis of variance to evaluate if differences occur by

chance. Covariants in the analysis of variance will include percent body fat, weight, exercise and caloric intake. All data will be analyzed using intention to treat to reduce bias due to drop outs.

C. Study Procedure

The likely duration of the entire study is about 11 weeks. All procedures are done for the sole purpose of research. The initial evaluation will include medical history, physical exam, EKG, pregnancy test, blood serum measurement of liver function tests, thyroid function tests, lipid panel, fasting glucose, baseline electrolyte analysis and blood count, urinalysis, height, weight, and percent body fat.

Indirect calorimetry will be performed at the initiation and the completion stages of ingestion of placebo or drug. This procedure requires the participant to arrive fasting in the am and to lie in an air tight canopy. The end expiratory volume as well as oxygen and carbon dioxide concentration is then measured after a 30 minute acclimation period at 5 minute intervals. The subject is to remain tranquil with little outside stimulation. The subject is unlikely to experience any discomfort.¹³

In order to determine safety of the regimen, biweekly visits will be required to measure blood pressure, heart rate and weight. In addition fasting blood glucose will be measured using a peripheral finger stick as these drugs have been shown to increase glucose levels.

D. Study Drugs

The product to be used is Metabolife 356® which is not FDA approved but which is available to the public as a nonregulated herbal supplement. This preparation was chosen because it is a commercial herbal mixture containing Ma Huang and Guarana. The company claims that this product is "regularly tested to confirm the active ingredients are present as indicated on the product label". In addition, in a recent study high pressure liquid chromatography analysis revealed these capsules contained an average of 50 mg caffeine and 12.9 mg total ephedrine alkaloids with a range of 47-55 mg caffeine and 12.2-13.4 mg total ephedrine alkaloids.⁴ Although this range variation is about 10%, analysis of 20 herbal supplements containing ephedra demonstrated lot to lot variation of greater than 20% in more than half the supplements and as high as 180% in two of the supplements. In this study the mean measured total alkaloid content of a Metabolife 356® caplet was 11.9 mg with a 10% variation.¹⁴

Samples of both placebo and drug capsules will be analyzed by an independent laboratory for ephedrine, total ephedrine alkaloid and caffeine content using high pressure liquid chromatography.

This drug is administered orally in caplet form which is the standard method. Total daily dose will be 48 mg ephedrine alkaloids in the form of ephedra and 200 , mg caffeine in the form of guarana. The dose recommended on the Metabolife 356® bottle is 2 capsules taken 2 or 3 times a day at least four hours apart. The twice a day dosing was chosen instead of thrice a day to reduce possible side effects such as insomnia irritability palpitations and elevated blood pressure.

The long term studies using manufactured caffeine and ephedrine comb not show serious side effects in 180 patients without other diseases^{7,8} nor did the study of 67 subjects with the herbal drug Metabolife 356®.⁴ It has been suggested that tachyphylaxis limits the minor side-effects.⁴ A review of serious events due to ephedra found 43 definitely or probably related adverse events in 2 years leading to 3 deaths. Adverse effects included hypertension, palpitations, arrhythmia, myocardial infarction, stroke and seizure. Not all of the adverse effects occurred in people with known cardiovascular risk factors.¹⁵ The incidence of adverse effects could not be determined but were felt to be uncommon.

It is possible that untoward effects of herbal ephedra and guarana are underreported because these substances are not regulated.

E. Medical Device

N/A

F. Study Questionnaires

Subjects will be asked to answer the Arizona Activity Frequency Questionnaire (AAFQ) three separate times during the study period: upon initial evaluation, at the half point and upon completion of the study. The AAFQ is a validated questionnaire for the estimation of physical activity energy expenditure.¹¹ This questionnaire has been validated in women using doubly label water.¹¹

G. Study Subjects

Inclusion criteria will be women between the ages of 20 and 45 with a body mass index (BAU) of greater than 24 but less than 35 who report having a stable Weight and size for the past six months. Although eventually the effects of herbal ephedra and guarana will need to be studied in both men and women, studies have shown that women are more likely to use these medications;¹ therefore, the investigators will focus their initial efforts on women. The upper age limit of 45 is to prevent any confounding effects of menopause on change in REE. This study is limited to subjects who are Overweight or moderately obese as in general patients with severe obesity are more likely to be at risk for cardiovascular event. People of normal or lower than average weight will be excluded as practically they are less likely to use the drug¹, in studies lean subjects were less likely to demonstrate effects of caffeine/ephedrine medications³ and if they do lose weight they may suffer harm from becoming underweight.

Exclusion criteria will include pregnancy; a history of stroke or myocardial infarction; hypertension; diabetes; current tobacco usage; asthma; liver disease; cardiac disease including moderate valvular disease; thyroid disease; renal disease; use of medications other than birth control pills and including pseudoephedrine; menopause; use of ephedra products within the past six months; and scheduled surgery during the study period.

Participants will be removed from the study if they have three-blood pressure measurements of greater than 135/85 or one systolic blood pressure measurement of greater than 180 or diastolic blood pressure of greater than 110. Subjects will also be removed for development of any arrhythmia other than sinus tachycardia or for a heart rate greater than 85% of the predicted maximum based on age (220-age) on more than one occasion. Two fasting glucose measurements of greater than 126 or one!! greater than 200 will also result in the removal of the subject from the study.

H. Recruitment of Subjects

Subjects will be recruited from the medical and graduate school of Columbia Presbyterian Medical Center using flyers. In addition, letters will be sent to appropriate candidates from the database of medical students willing to participate in medical research. The primary physician will be contacted to determine the patient's suitability.

I. Confidentiality of Study Data

All subjects will be issued a unique code number without any personal identifiers. All tubes and charts will be labeled only with the unique code. The subjects' codes will only be known to the investigators and all data will be kept in a locked storage cabinet.

J. Potential Conflict of Interest

None of the investigators have a conflict of interest.

K. Location of the Study

Columbia University College of Physicians and Surgeons

An independent laboratory (San Rafael Chemical Services, Salt Lake City, UT) will analyze the capsules. Otherwise, all portions of the study will be conducted, at CPMC.

L. Potential Risks

As the incidence of side effects is unknown, actual risk is unknown. However, these substances have been associated with seizures, hypertension, hemorrhagic stroke, arrhythmias, myocardial infarction and unstable angina." In most cases adverse events occurred in the setting of use of additional stimulants or extreme exercise. An attempt to minimize risks will be made by close monitoring of the subjects during the study period.

M. Potential Benefits

Potential benefits to the patient include possible weight loss with reduction in the cardiovascular and musculoskeletal problems associated with excess weight!,

N. Alternative Therapies

The alternative would be to not participate in the study and to not be exposed to these substances.

O. Compensation to Subjects

In order to increase compliance with the daily food journals, subjects will be asked to submit their food journals each week. With each submission of their weekly food journal, they will earn \$20 for possible total earnings of \$200.

P. Costs to Subjects

There will be no costs to the participants. All travel expenses will be reimbursed. In addition the investigators will cover any medical expenses incurred from participation in this study not covered by the subject's medical insurance.

Q. Minors as Research Subjects or Use of Radiation or Radioactive Substances

N/A

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