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Effects of a Weight-Loss Aid in Healthy Overweight Adults: Double-Blind, Placebo-Controlled Clinical Trial

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ABSTRACT

Objective: This study was undertaken to determine the effects of an ephedrine- and synephrine-based compound on body mass, body composition, metabolic variables, and mood states in healthy overweight adults.

Methods: Thirty subjects with a body mass index $>27 \text{ kg/m}^2$ were assigned randomly to the experimental group or the placebo group. The experimental group received a capsule containing ephedrine alkaloids 20 mg, synephrine 5 mg, caffeine 200 mg, and salicin 15 mg twice daily for 8 weeks, whereas the other group received a matching placebo. A registered dietitian instructed all patients about a 22-kcal/kg National Cholesterol Education Program Step One diet. In addition, all patients performed a cross-training exercise program 3 days per week under the guidance of an exercise physiologist. During the exercise sessions, patients achieved $\sim 70\%$ of age-predicted maximum heart rate.

Results: The experimental group had a significantly greater weight loss compared with the placebo group (3.14 kg vs 2.05 kg, respectively; $P < 0.05$). The experimental group experienced a 16% decrease in body fat compared with a 1% increase for the placebo group. The between-group difference was significant ($P = 0.005$). Both groups achieved a significant reduction in fat-free mass; however, the reduction in the placebo group was greater than that of the experimental group. This suggests a muscle-sparing effect in the experimental group. No significant changes in blood pressure, serial electrocardiograms, pulse rate, serum chemistry, or caloric intake were noted.

Conclusions: These findings indicate the apparent safety and efficacy of the ephedrine- and synephrine-based compound within the confines of this study.

Key words: ephedrine, exercise, fat loss, synephrine, weight reduction. (*Curr Ther Res Clin Exp.* 2000;61:199-205)

INTRODUCTION

Factors that are thought to contribute to obesity include genetics, lack of physical activity, overeating, and physiologic conditions.¹⁻³ Obesity is now

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reaching epidemic proportions in the United States. The prevalence of obesity has increased to an estimated 33% of the population.⁴ The health risks associated with obesity include type 2 diabetes mellitus; hypertension; coronary artery disease; hyperlipidemia; stroke; endometrial, postmenopausal breast, and colon cancers; sleep apnea; gallbladder disease; gastroesophageal reflux disease; fatty liver; osteoarthritis; gout; infertility; and thromboembolism.⁴ Prevention of obesity and treatment of overweight and obese patients include medical assessment, behavior modification, diet, exercise, and long-term follow-up.

In an effort to lose weight, people often restrict their total caloric intake. It has been demonstrated that caloric restriction results in an adaptive decrease in energy expenditure.⁵ This decrease in energy expenditure is directly correlated with a reduction in the functional capacity of the sympathetic nervous system (SNS).⁶ In addition, the SNS itself may be predisposed to defects, resulting in increased body weight in some individuals. Reduced SNS functioning physiologically translates into reduced adrenaline-induced (norepinephrine and epinephrine) thermogenesis.⁷ Norepinephrine and epinephrine affect the metabolism of carbohydrates, proteins, and lipids.

Genetically obese rats exhibit low sympathetic outflow or responsiveness in various tissues.⁸ The beta-adrenergic receptors are intrinsically involved in the pathways of glycogenolysis, lipolysis, and thermogenesis. Both lipolysis and thermogenesis are mediated via the beta-3 receptor.^{9,10} Indirect-acting sympathomimetic agents potentiate the release of epinephrine and norepinephrine at presynaptic sites in the SNS. Studies with indirect sympathomimetic agents such as ephedrine and synephrine (individually) in humans have shown these drugs to be effective weight-reduction agents. Often these compounds are combined with a methylxanthine (eg, caffeine or theophylline) to potentiate thermogenesis.¹¹⁻¹³ Despite their actions in facilitating weight loss, stimulatory agents have fallen out of favor with primary care physicians; they may cause palpitations, tremor, insomnia, nervousness, tachycardia, hypertension, dry mouth, addiction, and mood-altering effects.^{6,11}

These stimulatory agents are reportedly metabolized in the following manner: ephedrine or synephrine, when mixed with a methylxanthine, enhances the release of norepinephrine from the sympathetic nerve terminal. As the level of released norepinephrine increases, adenosine and prostaglandins are synthesized by the stimulated tissue and act as pre-junctional inhibitors. The thermogenic response may be limited by activation of cyclic adenosine monophosphate (cAMP) or by inhibition of intracellular feedback by phosphodiesterase. Octopamine, an alkaloid found with *Citrus aurantium* (the source for synephrine), acts as a coupling agent with alpha-2A adrenoreceptors in a dose-dependent manner, yielding a decrease in cAMP production.¹⁴ Thus methylxanthines, by antagonizing

adenosine and phosphodiesterases, reduce or remove these prejunctional and intracellular inhibitors, thereby increasing and sustaining activation of the effector cell by norepinephrine.⁶ The pharmacokinetics of ephedrine and synephrine differ. Data indicate that synephrine is less lipophilic than ephedrine; consequently, synephrine does not readily cross the blood-brain barrier.¹⁵

The primary objective of the present study was to assess the safety and efficacy of a product containing ephedrine, synephrine, caffeine, and salicin that has not previously been tested. Our second objective was to test the effect of the product plus a hypocaloric diet with exercise for weight and fat loss in healthy overweight adults.

PATIENTS AND METHODS

Using a double-blind, randomized, placebo-controlled protocol, 30 patients were assigned to either the experimental group or the placebo group. Healthy, physically active adults with a body mass index (BMI) >27 kg/m² were eligible to participate.

Exclusion criteria included a history of heart disease, hypertension, type 1 or 2 diabetes mellitus, or psychiatric disorders; use of monoamine oxidase inhibitor medication; pregnancy or lactation; thyroid disease; prostatic hypertrophy; caffeine sensitivity; allergy to any of the ingredients used in the test product; and current or recent use of an anorectic medication or a reduced-calorie diet. Patients who had no history of exercise or physical activity were also excluded because exercise naive individuals may have an alteration in body composition and weight from neuromuscular adaptations caused by the stimulus of exercise that does not occur in trained individuals.

The institutional review board approved all procedures. All patients gave written informed consent in a manner consistent with the Helsinki Declaration.

Patients in the experimental group received a capsule containing ephedrine alkaloids 20 mg, synephrine 5 mg, caffeine 200 mg, and salicin 15 mg twice daily for 8 weeks,* whereas patients in the placebo group received a maltodextrin placebo. All capsules were identical in weight, color, size, and shape. To best ensure compliance, any unused capsules were returned at the scheduled laboratory visit.

Each patient was assessed at baseline, week 4, and week 8. All appointments were with the same technician at approximately the same time of day and under the same conditions. Total body weight was measured using a balanced medical scale (Detecto Scale, Webb City, Missouri). Pa-

* Trademark Xenadrine™ (Cytodyne Technologies, Lakewood, New Jersey).

tients were weighed while wearing only essential clothing after they had fasted for 4 hours and urinated. Body composition was determined by skinfold caliper (Lange Caliper, Cambridge Scientific Industries, Inc., Cambridge, Maryland) at the chest, midaxilla, subscapular, suprailiac, triceps, abdomen, and thigh. Percentage body fat was calculated using the Jackson-Pollack equation (7-site) for body density and the Siri equation for determining body fat.^{16,17} In addition, all patients had blood drawn from their antecubital vein for serum multiple-assay chemical analysis (Health Profile, Quest Diagnostics, Wallingford, Connecticut). Each patient also underwent multiple serial electrocardiography (Burdick Eclipse 800, Deerfield, Wisconsin), blood pressure testing, pulse monitoring, and Profile of Mood State testing (Educational and Industrial Testing Service, San Diego, California) at baseline, week 4, and week 8.

Statistical Analysis

Baseline analyses were carried out using the Wilcoxon test; mean changes from baseline were tested within each group by the signed-rank test. Mean changes from baseline across study groups were examined using the Wilcoxon test. $P < 0.05$ was considered statistically significant.

RESULTS

Thirty patients entered the study and 25 (12 in the experimental group and 13 in the placebo group) completed the 8-week study. Five patients dropped out for reasons unrelated to the study (relocation, family illness, car accident, or child's illness). At baseline, the groups were similar in age, sex, systolic and diastolic blood pressures, Profile of Mood States results,

Table I. Baseline (mean \pm SD) physical characteristics, by group.*

	Group	
	Experimental	Placebo
Age (y)	43.06 \pm 9.87	42.07 \pm 10.46
Sex, no. (%)	12 (75)	11 (79)
Male	4 (25)	3 (21)
Female	28.66 \pm 2.49	27.33 \pm 2.43
Body mass index (kg/m ²)	0.81 \pm 0.09	0.82 \pm 0.09
Waist-to-hip ratio	82.07 \pm 14.4	78.13 \pm 13.1
Body weight (kg)	24.39 \pm 4.66	22.36 \pm 4.64
Body fat (%)	61.87 \pm 11.0	62.45 \pm 13.5
Fat-free mass (kg)		

* No significant differences between groups at baseline.

BMI, body weight, percentage body fat, fat-free mass, caloric intake, waist-to-hip ratio, blood glucose, and serum total cholesterol and triglycerides (Table I). Although the study included more males than females in each group (-3:1 ratio), none of the between-group differences at baseline were significant for any of the variables examined, indicating that there would be no effect on weight loss or body composition because of sex.

During the 8-week period, patients in the experimental group lost a significant amount of total weight (3.14 kg; $P < 0.05$) compared with those in the placebo group (2.05 kg). The experimental group also achieved a

Table II. Physical and physiologic findings (mean \pm SD) at baseline and week 8, by group.

	Experimental Group (n = 12)			Placebo Group (n = 13)		
	Baseline	Week 8	% Change	Baseline	Week 8	% Change
Waist-to-hip ratio	0.81 (0.09)	0.81 (0.09)	0	0.82 (0.09)	0.79 (0.07)	-4
Systolic blood pressure	123.8 (13.30)	120.5 (12.40)	-2.7	114.9 (16.20)	111.5 (8.62)	-3
Diastolic blood pressure	77.63 (11.00)	78.50 (9.20)	+1.0	74.43 (8.10)	73.83 (5.62)	1.0
Body weight (kg)	82.07 (14.40)	74.74 (14.90)	-9*	76.13 (13.10)	75.21 (13.70)	-3.8
Body fat (%)	24.39 (4.66)	20.53 (3.11)	-16†	22.36 (4.64)	22.58 (4.60)	+1
Fat-free mass (kg)	61.87 (11.00)	53.60 (12.40)	-3.7	62.45 (13.60)	58.38 (10.60)	-6.5

* $P < 0.05$, between groups.

† $P = 0.005$, between groups.

significant reduction in body fat (from 24.39% at baseline to 20.53% after 8 weeks; $P = 0.005$) compared with the placebo group. The mean change in body fat in the experimental group was 2.83 kg and in the placebo group 0.24 kg. Finally, in the experimental group fat-free mass decreased by 0.92 kg during the 8 weeks, whereas in the placebo group the decrease was 3.47 kg. This change in fat-free mass did not differ significantly between the 2 groups (Table II).

Results of liver function tests (alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transpeptidase) and renal function (blood urea nitrogen, serum creatinine) did not change significantly. All laboratory values (including serum glucose) remained within normal limits. Serial electrocardiograms and vital signs (pulse rate, systolic and diastolic blood pressures) did not change significantly during the study in either group.

Neither group experienced a significant change in hydration status. Similarly, no significant change was noted in mood state for fatigue or vigor levels.

DISCUSSION

In an attempt to lose weight, obese individuals often restrict their caloric intake. One of the results of a hypocaloric diet is a resetting of basal metabolism.⁵ The basal metabolic rate decreases in response to lower caloric intake, thus inhibiting further weight loss. A reduced metabolic rate will be accompanied by a loss of lean tissue. Reduced functionality of the SNS is apparent with caloric restriction and may be a cause of decreased energy expenditure. We postulated that although each patient in this study ate 22 kcal/kg (-1800 kcal/d), a decrease in metabolic rate was countered by stimulation of lipolysis. Patients in the experimental group achieved a significant reduction in body fat with thermogenic stimulants, which is consistent with previous research.¹⁸

Sympathomimetic agents such as ephedrine and synephrine used separately have been shown to facilitate weight loss.^{6,7,13} In the current study, patients in the experimental group lost significantly more weight than patients in the placebo group. The level of weight loss observed in the experimental group is consistent with previous research.

CONCLUSIONS

No significant changes in vital signs and other indicators of physiologic safety were noted, suggesting the safety of this ephedrine- and synephrine-based product within the confines of this study. The experimental group also exhibited a significant reduction in both body weight and body fat.

Acknowledgment

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