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Safety and efficacy of long-term treatment with ephedrine, caffeine and an ephedrine/caffeine mixture

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Summary

In a randomized, placebo-controlled, double blind study, 180 obese patients were treated by diet (4.2 MJ/day) and either an ephedrine/caffeine combination (20mg/200mg), ephedrine (20mg), caffeine (200mg) or placebo 3 times a day for 24 weeks. 141 patients completed this part of the study.
All medication was stopped between week 24 - 26 in order to catch any withdrawal symptoms.
From week 26 to 50, 99 patients completed treatment with the ephedrine/caffeine compound in an open trial design, resulting in a statistically significant (p=0.02) weight loss of 1.1kg.
In another randomized, double-blind, placebo-controlled 8 week study on obese subjects we found the mentioned compound showed lean body mass conserving properties.
We conclude that the ephedrine/caffeine combination is effective in improving and maintaining weight loss, further it has lean body mass saving properties. The side effects are minor and transient and no withdrawal symptoms have been found.

Introduction

Obesity, like many other diseases of the affluent society, is often developed without subjective symptoms for the patient, but after one, two or maybe three decades the accompanying complications such as type 2 diabetes, hypertension, hyperlipidemia and arteriosclerosis are likely to develop and to reduce the expected lifespan. Until lately researchers in the pharmacological field limited themselves to a 2 branched model, as anti-obesity agents should be either thermogenic, anorectic or a combination of the two. Many naturally occurring substances, like growth hormone, insulin, thyroid hormones, androgens, serotonin and catecholamines, were tested for their properties, most of them with disappointing results due to either lack of effect or severe side effects.
From the veterinary laboratories we learned that β_2 agonists were found to increase lean body mass in animals.
We have, as have others[4], earlier tested the acute response of the sympathomimetic compound ephedrine in different doses[1] and in different combinations with the methylxanthine derivative caffeine[2] in healthy volunteers. As others[3] we found an acute stimulation of the energy expenditure.
The following study was therefore to test the weight reducing effect on obese subjects of the only ephedrine/-caffeine compound which exerted a supra-additive acute thermogenic response [2].

Methods and Patients

Study design
A double blind randomized parallel study with four treatment groups in a 2 x 2 factorial design. All patients were treated with the trial medication and prescribed a 4.2 MJ/day diet for 24 weeks. The patients completing the 24 weeks of treatment were examined for abstinence symptoms two weeks after discontinuation of treatment. Subsequently, all remaining patients were offered a further 24 weeks of treatment with the most active compound in an open label design.
The study was carried out according to the principles of the declaration of

Table 1 Patient characteristics

	E+C	Ephedrine	Caffeine	Placebo
Number	45	45	45	45
Sex (♀/♂)	39/6	40/5	42/3	34/11
Age (years)	33±11	36±12	37±11	36±12
Height (cm)	169±7	167±7	167±7	168±9
Body weight (kg)	94,6±14	93,7±13	94,0±10	96,9±16
Overweight (%)	49±17	50±18	52±13	52±16

Means ± s.d. are presented. None of the differences between the groups were statistically significant. Overweight (%) calculated from ideal body weight given by Metropolitan Life Insurance Company for medium frame (1983).

Helsinki II and was approved by the local ethical committee.

Patients

One hundred and eighty patients were recruited from a waiting list.

Inclusion criteria :
1) age between 20-65 years
2) 120-180% of ideal body weight (Metropolitan Life Insurance Company medium frame 1983)
3) informed consent

Exclusion criteria :
1) diastolic blood pressure above 110 mmHg or in antihypertensive treatment other than diuretics.
2) actual or desired pregnancy
3) lactating
4) severe psychiatric or somatic disease
5) Any possible contraindication to trial medication
6) evidence of alcohol or drug abuse
7) treatment with drugs known to promote obesity.
8) change of oral contraceptives 3 months before start of trial
9) treatment with methylxanthines 1 month prior to start
10) weight loss of more than 8 kg 2 month prior to start

Treatment

The patients were assigned to groups receiving either E + C (ephedrine 20mg +caffeine 200mg), E (ephedrine 20mg), C (caffeine 200 mg) or placebo, three times a day one hour before meals. The tablets were indistinguishable in weight, appearance and taste. Prior to the study the bioavailability and absorption of ephedrine and caffeine were found to be identical whether given separately or in combination. The subjects were given careful instructions about a diet consisting of a nutrition powder (NUPO®) delivered free of charge and providing 1,6 MJ/day, supplemented with a free choice of natural foods to a maximum energy intake of 4,2 MJ/day. Patients were seen and weighed every two weeks. In groups of 14-18 they were given dietetic instructions, nutritional education and behaviour therapy lasting 1-2 hours. The following variables were recorded before the study and at 12, 24 and 50 week: a 9-lead ECG, fasting blood glucose, total cholesterol, triglyceride, full blood count, biochemical screening, analysis of urine, and caffeine consumption during the previous week.

Statistics

Demographic data for each particular visit of the four treatment groups were compared by two-way ANOVA.

Results

At entry the four groups of obese patients were similar in age, body weight and degree of overweight (table 1). Although the placebo group had a higher ratio of men, the distribution between the groups was not significant. Gender was included as a factor in the analysis (ANOVA) of weight loss.

Withdrawals

Two patients were excluded after they had entered the trial, because they showed symptoms consistent with some of the exclusion criteria.

141 of the 180 patients completed the first 24 weeks of treatment. The withdrawals were equally distributed between the four groups. Six patients withdrew due to adverse reactions, three of these received E+C. Their symptoms were 1) vertigo, tachycardia

Table 2 Completers week 0 - 50

	E+C	Ephedrine	Caffeine	Placebo
Number	24	24	26	25
Sex (♀/♂)	21/3	22/2	25/1	16/9
Age (years)	34	37	36	40
Height (cm)	169	167	165	168
weight week 0	96,1	97,5	94,4	101,1
weight week24 (kg)	80,2	81,7	82,2	87,4
% weight loss	16,2	16,1	13,0	13,4
weight week50 (kg)	80,0	81,8	79,7[1]	85,7
% weight loss	16,6	15,9	15,6	15,0

% weight loss is the percentual weight lost from week 0.
Mean weight loss for all 99 patients between week 24 and 50 (treatment E+C) was 1.1 kg (p=0.02).
1) Only the weight loss (2.4 kg) in the caffeine group from week 24 to 50 was significant p=0.01.

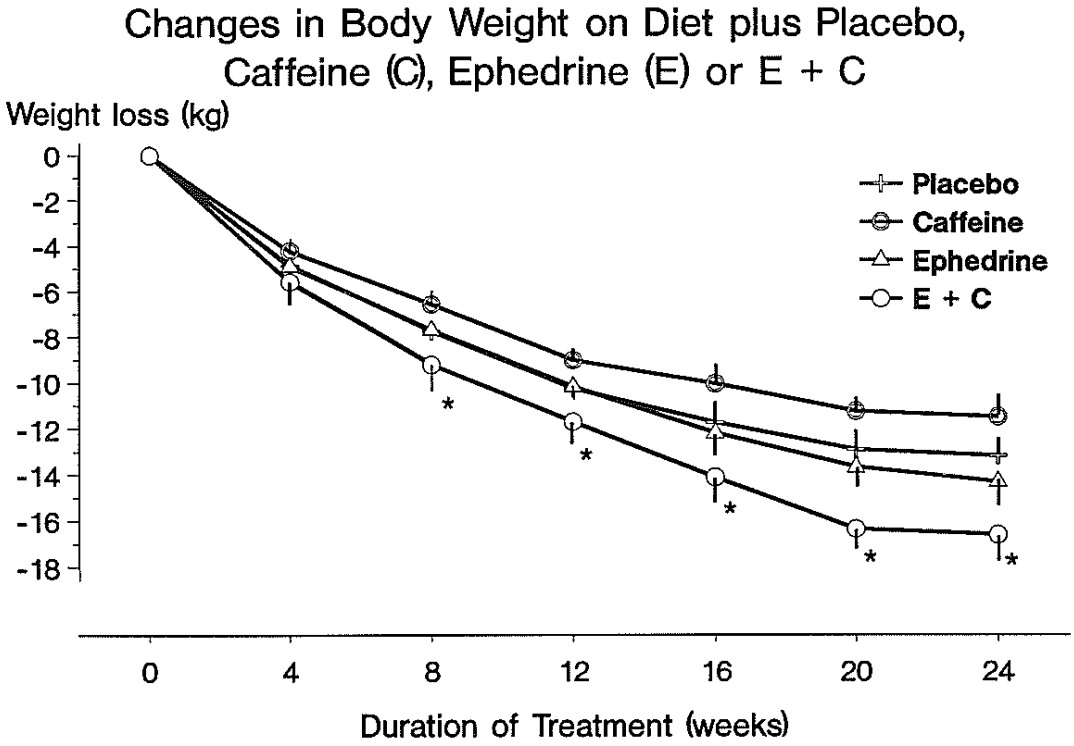

Figure 1

and syncope 2) hypertension (185/125mmHg) 3) euphoria and increased sweating. One in the ephedrine group had depressed mood, insomnia, tremor and tachycardia. In the caffeine group one patient had neurotic symptoms and another had brachycardia, tiredness and dizziness. After discontinuation of treatment all six patients recovered.

Weight loss week 0-24

There was a pronounced weight loss in all groups significant at each time point from week 4 to week 20, whereas body weight was almost stable from week 20 to 24 (Figure 1). After 24 weeks the total mean weight losses were E+C: 16.6±6.8kg; E: 14.3±5.9 kg; C: 11,5±6.0 kg; placebo 13.2±6.6. The initial mean body weight of the placebo group was 2-3 kg greater than the three other groups and as heavier patients tend to loose more weight than less obese patients when challenged with the same energy intake, we found it more correct to express the mean weight loss as a percentage of the initial body weight E+C 17.5%, E 15.3%, C 13.1%, placebo 13.5%. The weight loss percent in both the E+C and the E group was significantly greater than in the placebo group from week 8 to week 24. At no time was there a significant difference between percentual weight losses in the E+C and the E group. When the weight losses were adjusted for differences in initial body weight the E+C group lost 3,8 kg more than the placebo group. Ephedrine without caffeine slightly (1.7kg) improved the weight loss achieved by the very effective diet (placebo=13.0 kg). At any time there was a supra-additive effect of the E+C compound compared with the sum of weight losses of E and C assessed separately.

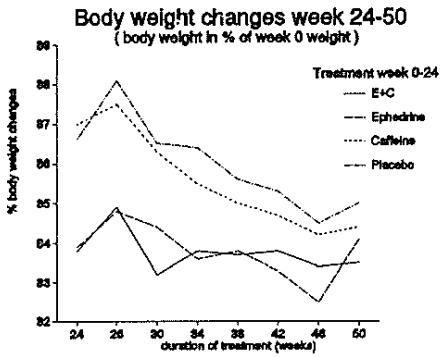

Figure 2

Weight loss week 24-50

This analysis deals only with the 99 patients completing week 50 (table 2). Note that the medical treatment was ceased between week 24 and 26 subsequently all patients received the E+C compound. Many of the 42 drop-outs between week 26 and week 50 were patients who had reached their ideal weight or

were satisfied with the weight loss they had obtained. The weight losses for all 99 patients were minor (1.1 kg) but statistically significant (p=0.02), only the caffeine group had a weight loss (2.5kg) to reached statistically significance (p=0.01) within the group. Body weight changes week 24 to 50 for each group (Figure 2), illustrates that the difference between the groups found at week 24 was smaller at week 50. This is due to better weight losses in the C and placebo group while the E+C and E group mostly maintained the achieved weight loss.

Side effects
The majority of patients reporting side effects were affected only in the first four weeks, in which 27 symptoms were reported by 21 patients receiving E+C, 25 symptoms by 12 patients in the E group and 22 symptoms by 11 patients receiving C, and 5 symptoms by 3 patients in the placebo group.
Two weeks after cessation of treatment (week 26) headache and tiredness were more frequently reported from the E+C group, whereas complaints of hunger were more frequent in the E group. In the C group only headache was reported more frequently than in the placebo group.

Other variables
Systolic and diastolic blood pressure decreased significantly in all treatment groups, with out any significant differences between the four groups.
Mean heart rate decreased 4-6 beats/min only in the C and placebo group.
At week 24 significant decreases in blood glucose, triglyceride and total cholesterol were found in all groups without group differences. The decreases were maintained in all groups at week 50. All other measured variables, such as full blood count, sodium, potassium, bilirubin, liver enzymes, creatinine, uric acid and urine analyses were without any significant group differences.

Discussion

The major finding of this drug study indicates that a combination of ephedrine(20mg)+caffeine(200mg) taken orally 3 times a day as an adjuvant to a low calorie diet improves weight loss. Furthermore, this combination can improve weight loss after a major dietary weight loss was achieved over 24 weeks. In other long term drug trails[5] it has failed to maintain a weight loss after 6-12 months of treatment. The differences between the weight losses of the four treatment groups has been reduced at week 50, however the C and placebo group did not catch up with the E+C and E groups, which could implicate that the time of introduction plays a role[6]. The preferred obesity treatment is a reduction of fat mass saving lean body mass, but unfortunately we did not measure body composition in the above study. A subsequent double-blind placebo controlled trial on obese females of only 8 weeks[7] was too short a period to show any differences in weight loss, but long enough to demonstrate a pronounced difference in the fat mass lost (Figure 3) measured by electrical bioimpedance. In the same study 24 hour energy expenditure was measured in our respiratory chambers at day 0,1 and 56 and it turned out that E+C reduced the fall in energy expenditure normally following a diet, and the higher energy expenditure in the E+C group was covered solely by fat oxidation.

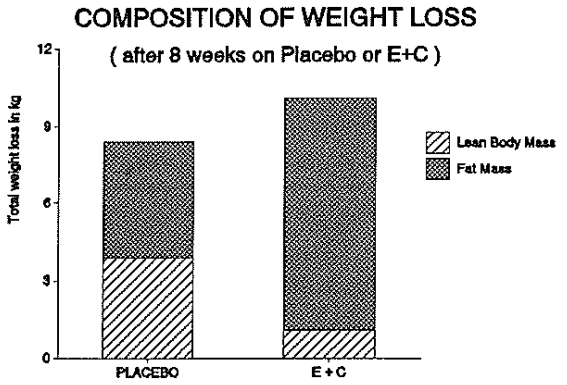

Figure 3

In conclusion, the E+C compound improves and maintains the total weight loss during 50 weeks, altering the composition of the weight loss by saving lean body mass and increase the fat loss. The side effects such as tremor, tachycardia and insomnia are temporary. We found no serious withdrawal symptoms.

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