Effect of cimetidine suspension on appetite and weight in overweight subjects

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Abstract

***Objective*—To investigate the weight reducing effect of cimetidine, comparing it with placebo.**

***Design*—Block randomised parallel group double blind study using suspensions with identical appearance and taste.**

***Setting*—Primary care practice.**

***Subjects*—55 women and 5 men aged 18-59, body mass index 25-37 kg/m², completed the study according to the protocol.**

***Interventions*—Cimetidine suspension 200 mg or placebo 30 minutes was given before the three main meals for eight weeks. Subjects followed a diet restricted to 5 MJ/day supplemented with 9 g fibre per day.**

***Main outcome measures*—Weight reduction; abdominal and hip circumferences and systolic and diastolic blood pressures were also recorded.**

***Results*—Subjects given cimetidine lost a mean of 7·3 (95% confidence interval 6·5 to 8·3) kg more than subjects given placebo ($p < 0·001$); body mass index decreased 3·33 (SD 0·76) and 0·77 (0·43), respectively ($p < 0·001$). Abdominal and hip circumference was decreased more in the cimetidine group (8·6 (3·9) cm and 7·8 (3·1) cm) than in the placebo group (2·2 (1·5) cm and 2·1 (1·5) cm). Mean reductions in systolic and diastolic blood pressure were greater in the cimetidine group than the placebo group (mean 5·8 *v* 0·4 and 6·5 *v* 0·4, $p < 0·001$).**

***Conclusion*—Intake of cimetidine suspension 30 minutes before meals in overweight subjects may lead to reduced hunger, less food intake, and subsequent weight loss. This effect may be due to the suppression of gastric acid secretion. Cimetidine suspension may be a valuable adjunct in treating obesity.**

Introduction

Obesity is considered a major nutritional disorder in affluent nations, affecting from 10% to 50% of the adult population. According to the national health and nutrition examination survey, approximately 33 million adults in the United States are overweight, of whom more than a third are considered obese.[1] As obesity is associated with an increased risk of diabetes mellitus and hypertension[2] it is an important health problem. Moreover, according to the Framingham heart study,[3] small increases in weight above 110% of the metropolitan relative weight are associated with an increased risk of cardiovascular disease. This increased risk of heart disease was correlated with the severity of overweight in a prospective study of 115 000 women.[4]

Treatment of obesity by an energy restricted diet alone is often unsuccessful as many subjects simply cannot control their craving for food. They often complain of ulcer-like epigastralgia and heartburn that are relieved by food, thereby jeopardising their attempt to remain on their diet.

The present study explores the hypothesis that treatment with the H_2 receptor antagonist cimetidine may reduce the hunger sensation, possibly by reducing gastric acid secretion. This would help subjects to be more compliant with an energy restricted diet and achieve the desired weight loss. Cimetidine suspension was selected instead of tablets as it was thought that a 10 ml viscous suspension with a specific taste would further contribute to reducing the craving for food.

Materials and methods

The study population consisted of 60 patients (5 men) aged 18 to 59 years with body mass indexes (kg/m²) ranging from 25 to 37 coming to the medical centre for consultation about their weight problems. Subjects already on a restricted calorie diet, pregnant women, and insulin dependent diabetics had been excluded from participation, as were subjects taking diuretics, antibiotics, or corticosteroids or chronically using laxatives.

Eligible subjects were randomly allocated to receive either cimetidine suspension (Tagagel) 200 mg/10 ml or placebo suspension with an identical appearance and taste 30 minutes before breakfast, lunch, and dinner. The suspension was supplied in individual dose packets. Additionally, subjects were instructed to follow a 5 MJ (1200 kcal) daily diet based on sample menus distributed in the clinic. These sample menus were divided into breakfast, lunch, dinner, and an evening snack. Fibre supplements (Fiberform 3 g) were dissolved in a glass of water and taken immediately before the three main meals. Compliance with the diet was checked at each visit. No alcoholic beverages were allowed during the trial but patients who smoked were permitted to continue.

The study was conducted according to the declarations of Helsinki and Venice and with the approval of the local ethical committee. At baseline the physical examination included sitting blood pressure (mean of

Characteristics of study groups at baseline. Values are means (SD) unless otherwise stated

	Group given cimetidine suspension	Group given placebo
Sex (women/men)	28/2	27/3
Age (years)	39 (12)	40 (12)
Duration of obesity (years)	9·2 (10.0)	9·9 (13·1)
No of slimming attempts	6 (18)	14 (27)
Weight (kg)	78·9 (11·0)	77·7 (14·4)
Height (cm)	169 (6)	168 (10)
Abdominal circumference (cm)	88 (11)	87 (10)
Hip circumference (cm)	104 (8)	109 (10)
Body mass index (kg/m²)	27·72 (3·27)	27·62 (4·03)
Systolic blood pressure (mm Hg)	142 (20)	137 (17)
Diastolic blood pressure (mm Hg)	86 (10)	84 (9)
Pulse rate	69 (7)	69 (8)
Alcohol consumption (yes/no)	6/24	10/20
Smoking (yes/no)	8/22	11/19
Regular exercise (yes/no)	10/20	11/19

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both arms). Height, weight, abdominal circumference (umbilical level), and hip circumference (tuberculum majus) were recorded. The body mass index was calculated as kg/m² (body weight in kilograms divided by the square of the height in metres).

The study continued for eight weeks, with visits to the clinic scheduled at the same time each week. Subjects were weighed weekly and their records of the average degree of hunger felt before breakfast, lunch, dinner, and evening snack during the previous week were recorded on a 10 cm visual analogue scale. Compliance with drug treatment was checked by returned dose packets; 80% compliance was considered acceptable.

Two sample *t* tests were used to compare means of the two groups with respect to weight loss, percentage of baseline weight, body mass index, abdominal and hip circumference, degree of hunger sensation, and blood pressure.

Results

Sixty patients were randomised to receive either the active agent (n=30) or placebo (n=30). The two groups were well matched with regard to demographic data and pre-trial characteristics (table). The placebo group had a somewhat higher number of previous slimming attempts (p=0·26). Figure 1 shows weight

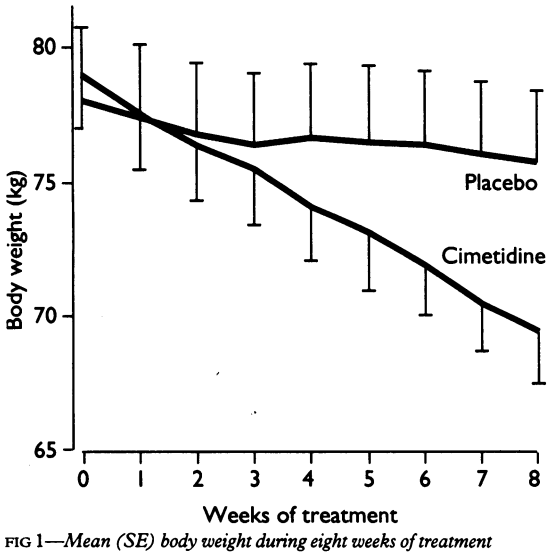

FIG 1—*Mean (SE) body weight during eight weeks of treatment*

during the eight week study period. The mean (SD) weight reduction in the placebo group was 2·2 (1·3) kg; in the cimetidine group it was 9·5 (2·1) kg. Throughout the study period the weight reduction observed in the group given active treatment was almost linear. The difference in the mean weight loss between the two groups was 7·3 (95% confidence interval 6·5 to 8·3) kg (p<0·001). Body mass index decreased 3·33 (0·76) and 0·77 (0·43) in the cimetidine and placebo groups respectively (p<0·001).

Figure 2 shows the mean decrease in abdominal and hip circumference. In subjects treated with placebo the mean (SD) decrease was 2·2 (1·5) cm and 2·1 (1·5) cm, respectively; for subjects treated with cimetidine suspension the corresponding figures were 8·6 (3·9) cm and 7·8 (3·1) cm. The mean degree of hunger sensation was consistently lower in the cimetidine suspension group than in the placebo group (fig 3) (p<0·001).

Also, the reduction of mean diastolic blood pressure was significantly greater in subjects treated with cimetidine than in those treated with placebo (mean 5·8 (range 0-10) mm Hg *v* (−5 to 20) mm Hg; p<0·001). Similarly, the reduction of mean systolic

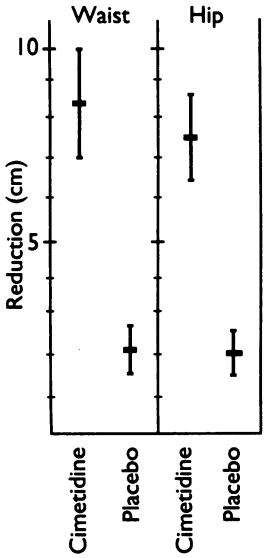

FIG 2—*Mean reduction of abdominal and hip circumference in the cimetidine and placebo group. Bars indicate 95% confidence intervals*

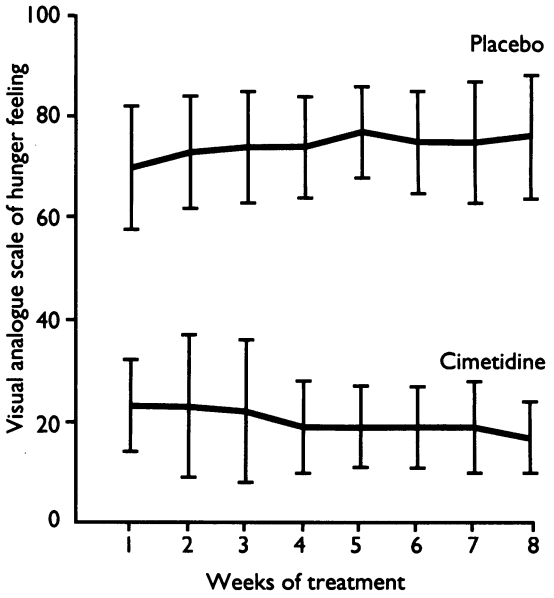

FIG 3—*Patients' recording of hunger sensation at end of week as measured on visual analogue scale (VAS). Mean (SD) consists of total of all meals and snacks*

blood pressure was greater in subjects receiving cimetidine suspension than in those receiving placebo (mean 6·5 (range 0-20) mm Hg *v* 0·4 (range −5 to 5) mm Hg; p<0·001).

Two patients receiving placebo discontinued treatment owing to rashes; otherwise, side effects in both groups were mild and transient. Headache was more common in subjects treated with cimetidine suspension, whereas constipation and other abdominal complaints were reported more by the placebo group.

Discussion

All patients lost weight during the eight week study period. The number of kilograms lost was significantly greater in the group treated with cimetidine suspension, which fared better than the 4-5 kg usually lost within eight weeks by motivated obese dieters (unpublished data). In this trial, to minimise confounding factors, no psychological or motivational support was given to either group, which may explain why the placebo group lost only 2·2 kg. Meta-analysis of 3864 patients showed that after 10-12 weeks of dietary or behavioral treatment, subjects lost 8-9% of their baseline weight,[5] which is less than the 12% lost by the subjects receiving active treatment in the present eight week study.

After the first week of treatment less hunger was perceived by subjects receiving active treatment than by those receiving placebo; this remained consistent throughout the trial. Suppression of hunger seems to have improved adherence to the low calorie diet, thus enhancing the weight loss noted by subjects receiving cimetidine suspension. The reason for this suppression of hunger, however, is unclear. Acid secretion may be involved in the physiological regulation of appetite. Inhibition of H_2 receptors, by reducing gastric acidity, may diminish the sensation of hunger. Normal appetite would not necessarily be influenced: a recent study found no change in body weight after three years of maintenance treatment with cimetidine for duodenal ulcer.[6] Cimetidine might suppress the hunger sensations induced by a low intake of food, leading to better compliance with the prescribed diet.

Some of the peptide hormones in the gastrointestinal tract have been implicated in the regulation of food intake. Cholecystokinin is a polypeptide hormone that has been shown to induce inhibition of food intake in both obese and non-obese subjects.[7,8] However, cimetidine given before pancreatic secretion was

monitored after endogenous stimulation did not affect the release of cholecystokinin.[9,10] Similarly, bombesin[11] and glucagon[12-14] have been shown to decrease food intake, but no information is available on the effect of cimetidine or acid reduction on the release of these peptides.

Results of the current trial raise several questions that need to be clarified in future investigations. The mechanism of action should be elucidated with regard to the possible involvement of gastrointestinal hormones that might serve as afferent signals to the hypothalamus. Whether other means of reducing gastric acid secretion have the same effect should be tested. Until this is known cimetidine suspension may serve as a valuable adjunct to diet in treating obesity, though additional research both on the long term effect of cimetidine suspension and on its mechanism of action in overweight subjects is necessary before general recommendations can be given.

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1 Simopoulos AP. Characteristics of obesity: an overview in human obesity. *Ann NY Acad Sci* 1987;**499**:4-13.
2 Simopoulos AP, Van Itallie TB. Body weight, health and longevity. *Ann Intern Med* 1984;**100**:285-95.
3 Hubert HB, Feinleib M, McNamara PM, Castelli WP. Obesity as an independent risk factor for cardiovascular disease: a 26-year follow-up of participants in the Framingham heart study. *Circulation* 1983;**67**:968-77.
4 Manson JE, Colditz GA, Stampfer MJ, Willett WC, Rosner B, Monson RR, *et al.* A prospective study of obesity and the risk of coronary heart disease in women. *N Engl J Med* 1990;**322**:882-9.
5 Wing RR, Jeffery RW. Outpatient treatments of obesity: a comparison of methodology and clinical results. *Int J Obesity* 1979;**3**:261-79.
6 Walan A, Strøm M. Metabolic consequences of reduced gastric acidity. *Scand J Gastroent* 1985;**20**(supp 111):24-9.
7 Pi-Sunyer X, Kissileff HR, Thornton J, Smith GP. C-terminal octapeptide of cholecystokinin decreases food intake in obese men. *Physiol Behav* 1982;**29**: 627-30.
8 Stacher G, Steinringer H, Schmierer G, Schneider C, Winklehner S. Cholecystokinin octopeptide decreases intake of solid food in man. *Peptides* 1982;**3**:133-6.
9 Anagnostides A, Chadwick VS, Selden AC, Maton PN. Sham feeding and pancreatic secretion. *Gastroenterology* 1984;**87**:109-14.
10 Bozhurt T, Adler G, Leferink S, Arnold R. Volume and enzyme kinetics of human pancreatic secretion after endogenous stimulation with the Lundh test meal. *Int J Pancrat* 1990;**6**:281-93.
11 Muurahainen NE, Kissileff HR, Thornton J, Pi-Sunyer FX. Bombesin: another peptide that inhibits feeding in man [abstract]. *Soc Neurosci* 1983;**9**:183.
12 Penick SB, Hinkle Jr LE. Depression of food intake in healthy subjects by glucagon. *N Engl J Med* 1961;**264**:893-7.
13 Penick SB, Hinkle Jr LE. The effect of glucagon, phenmetrazine and epinephrine on hunger, food intake and plasma nonesterified fatty acids. *Am J Clin Nutr* 1963;**13**:110-4.
14 Schulman JL, Carleton JL, Whitney G, Whitehorn JC. Effect of glucagon on food intake and body weight in man. *J Appl Physiol* 1957;**11**:419-21.

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Cimetidine suspension as adjuvant to energy restricted diet in treating obesity

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Abstract

***Objective*—To study the effect of cimetidine suspension compared with placebo suspension on weight loss in moderately obese patients taking a 5 MJ/day diet supplemented with dietary fibre. To determine the relation between the effectiveness of the blinding and weight loss.**

***Design*—Randomised double blind study with an eight week parallel group phase and a subsequent eight week crossover or continuation phase.**

***Setting*—Outpatient clinic.**

***Subjects*—60 patients (51 women) aged 18-60.**

***Main outcome measure*—Weight loss.**

***Results*—After eight weeks of treatment the mean weight loss in the cimetidine group (5·7 kg) was similar to that of the placebo group (5·9 kg; p=0·78, 95% confidence interval −2·0 to 1·5 kg). Body mass index, waist and hip measurements, waist-hip ratio, and systolic and diastolic blood pressures decreased similarly in the two groups. No association was found between weight loss and the patients' ability to guess if they were being given drug or placebo. Correct guesses of current drug were more prevalent than expected by chance (25/37 correct, p=0·05 for the parallel group phase; 26/30, p=0·0001 for the crossover phase).**

***Conclusions*—Cimetidine had no effect on weight loss in moderately obese patients. The study underlines the potential problem that blinding of patients to treatment can be compromised.**

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Introduction

In a recent eight week double blind Norwegian trial 60 overweight patients were given 200 mg of cimetidine suspension or placebo 30 minutes before breakfast, lunch, and dinner as adjuvant to a 5 MJ/day (1200 kcal/day) diet supplemented with 9 g of dietary fibre.[1] The mean weight loss during cimetidine treatment was 7·4 kg greater during treatment with cimetidine than during placebo ($p<0·001$) and the perception of hunger, measured on a visual analogue scale, was significantly less at all three meals in the cimetidine group. Furthermore, the reductions of abdominal and hip circumferences, as well as the fall in systolic and diastolic blood pressure, were significantly greater in the patients treated with cimetidine.

The suggested mechanisms of action were a suppression of gastric acid or suppression of hunger by blocking histamine H_2 receptors. The impact on appetite might help patients to a better and more prolonged compliance with a restricted diet, leading to greater weight loss.

The double blind principle is of great importance in most therapeutic research, especially when the outcome is subjective or may be influenced by subjective beliefs. However, the effectiveness of the blinding in double blind studies can often be questioned. We therefore did a confirmatory eight week double blind parallel group study with cimetidine. To this first phase we added an eight week crossover or continuation phase to expand on the findings of the previous trial.[1] Furthermore, we examined the success of the blinding and its relation to weight loss.

Patients and methods

Criteria for entry were age between 18 and 60 years, body mass index between 27 and 39 kg/m^2, and cooperation and motivation for participation. Criteria for exclusion were obesity due to any endocrinological disorder; history of treatment for depression; evidence of severe somatic or psychiatric disease or alcohol misuse; suspicion of active peptic ulcer; pregnancy,