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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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,

lactation, or desire to become pregnant; current or recent energy restricted diet; or administration during the previous three months of any drug which might interfere with cimetidine or disturb the metabolism. The study group comprised 51 women and nine men from the outpatient clinic (table I), who gave informed consent for a 16 week study of weight loss.

TABLE I—*Data on patients before entering the trial by study group. Values are mean (SD) unless stated otherwise*

	Cimetidine (n=30)	Placebo (n=30)
Sex (F/M)	26/4	25/5
Age (years)	37 (11)	37 (11)
Body weight (kg)	95·5 (17·8)	95·9 (12·8)
Height (m)	1·69 (0·09)	1·68 (0·09)
Body mass index (kg/m^2)	33·4 (3·8)	34·1 (4·1)
Waist (cm)	104·3 (12·7)	104·0 (11·7)
Hip (cm)	116·3 (9·2)	118·4 (9·8)
Waist:hip ratio	0·90 (0·09)	0·88 (0·07)
Systolic blood pressure (mm Hg)	127 (22)	123 (16)
Diastolic blood pressure (mm Hg)	81 (12)	79 (11)

The study consisted of two consecutive eight week periods. After stratification according to whether or not the patients' body mass index exceeded 33·9 kg/m^2 the patients were randomised in blocks of six to receive either cimetidine or placebo during the first period with a computer generated random code. Patients were allocated to the coded treatment as they entered the study. Patients who received placebo during the first period received cimetidine during the second. Patients who received cimetidine during the first period, however, were assigned to get either cimetidine or placebo during the second period by predetermined randomisation (fig 1). This design was chosen to allow an evaluation of cimetidine over a longer period of treatment.

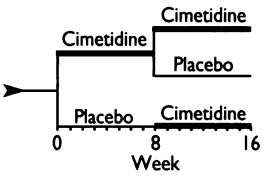

FIG 1—*Flow diagram showing design of study*

Cimetidine suspension (Tagamet) 200 mg/10 ml and placebo suspension were supplied in identically appearing sachets by SmithKline Beecham, United States. Peppermint flavour was added to both suspensions to cover the taste and smell of cimetidine. Patients took 200 mg of cimetidine suspension or an identical placebo suspension three times daily 30 minutes before breakfast, lunch, and dinner.

The patients were instructed to follow a 5 MJ diet and to supplement this diet with 9 g per day of testa *Triticum tricum* fibre (Tricum/Cyanamid, Sweden). To help patients keep account of their energy intake, we used an educational system of isoenergetic and freely exchangeable units illustrated on counters.[2]

ASSESSMENT OF PATIENTS

Patients were seen at the same time of day, twice before randomisation and weekly thereafter. Every week the patients were asked to report any side effects according to a checklist consisting of nine items plus an open ended question.

Patients were given a written and oral education programme.[2,3] All unused drugs were collected, recorded, and checked for compliance every week. Patients returning more than 20% of the prescribed medication during either study period, and patients who did not attend the clinic at least every second week, were considered non-compliant and ineligible for inclusion in the analyses.

At the end of each treatment period (week 7 and week 15) the patients were asked whether they believed they had received cimetidine or placebo or were unable to guess. They were also asked to indicate one or more reasons for their guess. The following options were available: the suspension was efficient, inefficient, tasted like medicine, did not taste like medicine, caused side effects, did not cause side effects, or other.

Weight was measured to the nearest 0·1 kg with electronic scales (Seca 707, Seca, Copenhagen). Perception of hunger was measured weekly on a visual analogue scale.

The waist and hip circumferences were measured with a flexible tape, maintaining close skin contact without compressing underlying tissues. The waist was defined as the circumference located midway between the lower rib margin and the iliac crests. The hip was defined as the widest circumference over the great trochanters.[4] Circumferences were obtained with the subjects standing.

Blood pressure was measured in the sitting position after at least 10 minutes' rest. A large cuff (15×43 cm bladder) was used when the overarm circumference exceeded 35 cm; otherwise a normal cuff (12×35 cm bladder) was used.

Blood haemoglobin, serum sodium, potassium, creatinine, alkaline phosphatases, aspartate aminotransferase, blood glucose, and thyroid hormone concentrations were measured before the trial and at weeks 8 and 16. All measurements were made in the hospital's central laboratory by routine methods. The revised Helsinki declaration was observed, and the study was approved by the Copenhagen municipal ethics committee.

STATISTICS

On the basis of a previous study we assumed that diet alone would give a mean loss over eight weeks of 6 (SD 2) kg. To detect an extra loss of 2 kg or more with cimetidine (which we took as being a clinically relevant weight reducing effect) with an α risk of 0·05 (two sided) and a power of 0·90 required 60 patients, allowing for a 30% withdrawal rate.

Student's t test was used to compare mean weight losses, and 95% confidence intervals are given. Non-parametric analyses gave similar results. Statistical significance was taken as $p < 0·05$.

Multivariate analyses with linear models were used to relate weight loss to drug, trial period, age, sex, and social class. The weight loss was also related to the patients' guesses about treatment, their correctness, and their reasons. The normal approximation to the binomial distribution was used to judge the correctness of the guesses in the two trial periods.[5] Paired proportions were compared by the sign test.

Results

The two treatment groups were comparable at baseline (table I). Fifty five of 60 patients (92%) completed the first period and 50 patients (83%) completed both periods. One patient was withdrawn

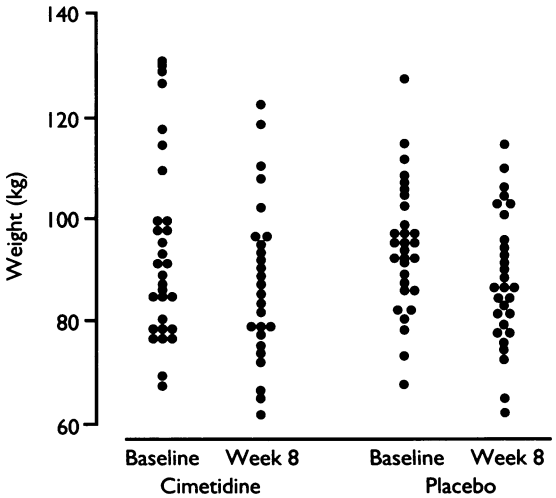

FIG 2—*Body weight at baseline and at eight weeks in cimetidine and placebo groups*

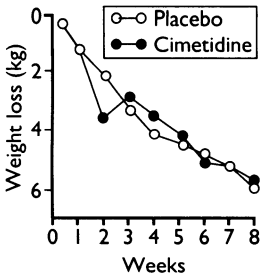

FIG 3—*Absolute weight loss during first period in the cimetidine group and in the placebo group. Weight loss was identical in the two groups during the first week*

because she became pregnant; the remaining patients were withdrawn because of failure to attend or lack of motivation for continuation of the study. All patients complied with the prescribed medication during both periods.

During the first period the mean loss was 5·7 (SD 3·9) kg in the cimetidine group (n=26) and 5·9 (2·5) kg in the placebo group (n=29) (fig 2). The difference in mean weight loss was insignificant (p= 0·78, 95% confidence interval −2·0 to 1·5 kg) (fig 3). Mean weight loss in the second period was significantly less than in the first period in all groups (2·1 (−1·2 to 2·9) kg, $p<0·0001$). No carry over effect was noted (fig 4). The weight loss during both periods was significantly less in women (7·3 kg) than in men (12·4 kg) ($p<0·002$), but no differences were found with age or social class. No effect of cimetidine on perception of hunger was seen (data not shown). The patients' body mass index, waist and hip measurements, waist-hip ratio, and systolic and diastolic blood pressures decreased similarly in the cimetidine group and the placebo group during the first period (table II). Biochemical tests showed no adverse effects from the treatments.

EFFECTIVENESS OF BLINDING

Only four patients had received cimetidine before the trial, and none of them guessed the drug correctly. Correct guesses of the treatment were significantly more prevalent than expected (table III). There was a non-significant tendency towards more correct guesses during the second period. Of 15 patients who guessed correctly during the first period, only one guessed wrongly in the second, whereas of seven patients who guessed wrongly in the first period, five gave correct guesses in the second (p=0·22 for comparison of the two periods). Improvement in the guesses was not confined to patients whose treatment had changed from the first period. Seven of eight patients who received cimetidine during both trial periods guessed the drug correctly after the second period.

Because of the sex difference in weight loss, only women were included in the multivariate analyses. Guesses were not related to weight loss when all guesses were considered or when only correct guesses were included. However, weight losses tended to be high for patients who guessed cimetidine wrongly and low for those who wrongly guessed placebo (table IV). After the first period, 11 patients indicated that their suspension tasted like medicine or had side effects. Seven of these patients put forward a guess of their current medication; six guessed cimetidine and one guessed placebo because of lack of effect. All seven guesses were correct (p=0·02). Table V lists the number of patients reporting side effects.

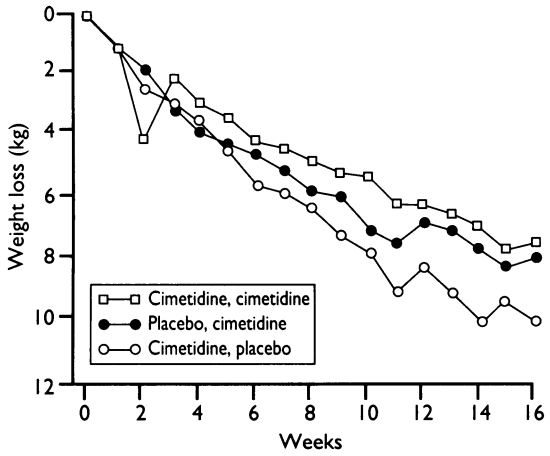

FIG 4—*Absolute weight loss during first and second periods. Weight loss was identical for all groups during the first week*

TABLE II—*Mean (SD) clinical characteristics for cimetidine and placebo group at week 0 and week 8*

	Cimetidine		Placebo		
	Week 0 (n=30)	Week 8 (n=26)	Week 0 (n=30)	Week 8 (n=29)	p Value
Body mass index (kg/m^2)	33·4 (3·8)	31·2 (3·7)	34·1 (4·1)	31·1 (5·0)	0·78
Waist (cm)	104·3 (12·7)	98·3 (10·1)	104·0 (11·7)	100·1 (10·6)	0·20
Hip (cm)	116·3 (9·2)	112·9 (8·9)	118·4 (9·8)	115·5 (9·9)	0·18
Waist:hip ratio	0·90 (0·09)	0·87 (0·07)	0·88 (0·07)	0·87 (0·08)	0·51
Systolic blood pressure (mm Hg)	127 (22)	120 (18)	123 (16)	120 (15)	0·56
Diastolic blood pressure (mm Hg)	81 (12)	74 (12)	79 (11)	73 (10)	0·94

TABLE III—*Patients' guesses about treatment related to actual treatment after seven weeks of the first and second periods of treatment*

	Guess			
	Cimetidine group	Placebo group	Could not guess	p Value
Drug in first period:				
Cimetidine	8	9	9	
Placebo	3	17	9	0·05
Drug in second period:				
Cimetidine	19	4	14	
Placebo	0	7	6	0·0001

Five patients had dropped out at the end of the first period and 10 at the end of the second period.

TABLE IV—*Relation between guess about current treatment (cimetidine or placebo) and weight loss during the first eight week period of treatment (women only)*

	Mean (SD) weight loss	No of patients
All guesses:		
Cimetidine	6·2 (3·1)	9
Placebo	5·0 (2·3)	22
Unable to guess	5·2 (2·4)	16
Correct guesses:		
Cimetidine	6·0 (3·2)	7
Placebo	5·8 (2·0)	14
Wrong guesses:		
Cimetidine	7·0 (3·5)	2
Placebo	3·6 (2·4)	8

TABLE V—*Number of patients reporting side effects*

	Cimetidine		Placebo	
Side effect	First period (n=30)	Second period (n=42)	First period (n=30)	Second period (n=13)
Dizziness	0	1	0	0
Anxiety	0	1	0	0
Depression	0	1	0	0
Headache	4	6	7	2
Constipation	6	5	4	3
Nausea	4	3	2	0
Vomiting	0	2	0	0
Abdominal pains	3	5	1	0
Rhinitis	0	1	0	0
Pharyngitis	0	1	0	0
Tonsillitis	1	0	2	0
Sinusitis	1	0	0	0
Influenza	1	0	0	1
Psoriasis	0	1	0	0
Anaemia	0	1	0	0

Only side effects reported by one or more patients in the cimetidine group have been included (all 60 patients reported at least one side effect).

Discussion

In contrast to a recent Norwegian study,[1] we found no effect of cimetidine on either weight loss or perception of hunger in obese patients. The second phase of the trial, with crossover or continuation of drug treatment, seemed to confirm the inefficiency of cimetidine as adjuvant to a diet in treating obesity (fig 3).

The Norwegian study included 60 overweight subjects and was a double blind, randomised, placebo controlled trial,[1] designed like the first period of our study. The cimetidine and placebo suspensions were also identical to those used in our study. However, the

mean weight loss in the Norwegian study was significantly higher in the cimetidine group than in the placebo group (difference=7·3 kg, $p<0·001$, 95% confidence interval 6·4 to 8·2). A weight reducing effect of 7·3 kg over eight weeks is much greater than that achieved with any other previously tested anti-obesity drug.

The second aim of our study was to evaluate the success of the blinding and its relation to weight loss. The double blind, randomised trial is considered the gold standard for therapeutic research.[6-8] In contrast to recommendations,[9,10] however, the effectiveness of the blinding has only rarely been tested and related to outcome. In a placebo controlled study of the effect of vitamin C on the common cold, an apparent dose related effect on the duration of symptoms was noted, but the effect disappeared when subjects identifying the vitamin by its special taste were excluded.[11] Our results indicate that unblinding may be particularly likely to invalidate studies with a crossover design. Unfortunately, crossover studies are often insufficiently analysed.[12,13] Since data from the two periods are often pooled, unrecognised bias caused by unblinding during the second period can make the whole study unreliable.

In a study of fenfluramine and placebo in obesity 71% of the patients correctly identified their treatment, most because of side effects of the active drug.[14] Fenfluramine was effective, and there was a tendency towards a greater weight loss in patients taking fenfluramine who gave correct guesses. However, this tendency was also noted for patients receiving placebo. Unfortunately, the number of patients was too small to allow a meaningful comparison of fenfluramine and placebo in this respect, since only three patients taking the drug and three taking placebo guessed wrongly.

We found cimetidine to be inefficient as a treatment for obesity. Despite the fact that the drug had only few side effects, our patients guessed their therapy (cimetidine or placebo) correctly more often than expected by chance, especially during the second period of treatment. Our patients were seen in groups and were able to exchange experiences and suggestions. Therefore, patients obtaining a better than average weight loss would be expected to believe they were being given cimetidine. However, this was not so. The "placebo effect," calculated as the difference in mean weight loss between those who believed they were receiving active treatment and those who believed they were receiving placebo, was insignificant, being only 1·2 kg (−0·8 kg to 3·2 kg). In accordance with international manuscript guidelines[10] we suggest that the success of the blinding be routinely included as an important variable in controlled clinical trials.

We thank the clinical dietitians Grete Hansen and Anne W Rasmussen for their skilled help.

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Modified paediatric resuscitation chart

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Abstract

***Objectives*—To determine whether a modified paediatric resuscitation reference chart improves the speed and accuracy of calculation of doses of drugs in simulated paediatric cardiopulmonary arrests when compared with the chart devised by Oakley.**

***Design*—A prospective study in which a series of randomly assigned questions was used to compare the performance of doctors using the two charts.**

***Setting*—Accident and emergency departments in two hospitals.**

***Subjects*—31 senior house officers.**

***Main outcome measures*—The speed and accuracy of calculation of volumes of drugs to be administered.**

***Results*—The modified chart significantly increased the accuracy of the calculations (62/62 *v* 43/62, $p<0·05$), the speed of correct calculations (6·8 s *v* 36·0 s, $p<0·0001$), and the number of calculations that were completed (62/62 *v* 50/62, $p<0·001$).**

***Conclusions*—The modified paediatric resuscitation chart should supersede the existing chart.**

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Introduction

Paediatric cardiopulmonary arrest is an uncommon occurrence which any doctor may be called on to manage. Oakley reported problems in treating this condition and identified two main factors contributing to delays in making decisions.[1] The first is the wide variation in the weights of children of different ages, making selection of the correct dose of drug difficult when a child's weight or age is unknown. The second is the infrequency of cardiopulmonary arrest in children, resulting in a tendency for doctors to forget recommended doses. Oakley asked 34 junior doctors of various grades and specialties about their knowledge of doses of drugs, sizes of endotracheal tubes, and defibrillation energy for children of various ages and weights. The results of his study led him to devise a reference chart, which was produced by the *BMJ* (figure). Although this chart is widely used, no studies evaluating its use have been published.

We have observed the use of the chart in several accident and emergency departments and found the following problems: some of the doses of drugs on the