9 Myers J, Segal RJ. Weight of the spleen. *Arch Pathol* 1974;**98**:33-5.
10 DeLand FH. Normal spleen size. *Radiology* 1970;**97**:589-92.
11 Rollo FD, DeLand FH. The determination of spleen mass from radionuclide images. *Radiology* 1970;**97**:583-7.
12 Larsen SM, Tuell SH, Moores KD, Nelpp WB. Dimensions of the normal adult spleen scan and prediction of spleen weight. *J Nucl Med* 1971;**12**:123-6.
13 Stewart JH. Haemolytic anaemia in acute and chronic renal failure. *Q J Med* 1967;**36**:85-105.
14 Loge JP, Lange RD, Moore CV. Characterization of the anemia associated with chronic renal insufficiency. *Am J Med* 1958;**24**:4-18.
15 Barber ND, Nakamoto S, McCormack LJ, Kolff WJ. Pathologic anatomy of 13 patients after prolonged periodic hemodialysis. *Journal of American Society of Artificial Internal Organs* 1963;**9**:21-7.
16 Neiman RS, Bischel MD, Lukes RJ. Hypersplenism in the uremic hemodialysed patient; pathology and proposed pathophysiologic mechanisms. *Am J Pathol* 1977;**60**:502-11.
17 Bommer J, Ritz E, Waldherr R. Silicone-induced splenomegaly: treatment of pancytopenia by splenectomy in patients on hemodialysis. *N Engl J Med* 1981;**305**:1077-9.
18 Murray JA, Slater DN, Parsons MA, Fox M, Smith S, Platts MM. Splenic siderosis and parenteral iron dextran in maintenance haemodialysis patients. *J Clin Pathol* 1984;**37**:59-64.
19 Nicholls AJ, Platts MM. Anaphylactoid reactions due to haemodialysis, haemofiltration, or membrane plasma separation. *Br Med J* 1982;**285**:1607-8.

*(Accepted 29 August 1984)*

# Comparison of cimetidine 800 mg once daily and 400 mg twice daily in acute duodenal ulceration

LUCIO CAPURSO, PIER ROBERTO DAL MONTE, FRANCESCO MAZZEO, GIORGIO MENARDO, ANTONIO MORETTINI, ALFREDO SAGGIORO, GIOVANNI TAFNER

## Abstract

**A double blind trial was conducted in seven centres to evaluate the safety and efficacy of cimetidine 800 mg given at night compared with 400 mg given at breakfast and at bedtime. Altogether 197 patients with active duodenal ulcer confirmed by endoscopy entered the study, of whom 187 were eligible for analysis. After four weeks' treatment the ulcer was healed in 76 of 91 patients (84%) receiving the once daily regimen and in 65 of the 96 patients (68%) receiving the twice daily regimen ($p < 0.05$). Both dosage regimens were equally effective in reducing ulcer pain and consumption of antacids. Pain relief was considerable within the first two weeks, and most of the patients were free of symptoms by the end of treatment. No patients were withdrawn because of adverse events as these were few and mild, consistent with the proved safety profile of cimetidine.**

**Cimetidine 800 mg given at night is as effective as 400 mg twice daily; the single dose regimen may improve patient compliance, thus facilitating treatment.**

**Department of Gastroenterology, Ospedale S Filippo Neri, Rome**
LUCIO CAPURSO, MD, head

**Gastroenterology Unit, Ospedale Bellaria, Bologna**
PIER ROBERTO DAL MONTE, MD, head

**Unit of Gastroenterology and Digestive Endoscopy, Ospedale Borgonovo Valtidone, Piacenza**
FRANCESCO MAZZEO, MD, head

**Division of Medicine, Department of Gastroenterology, Ospedale Pietra Ligure, Savona**
GIORGIO MENARDO, MD, head

**Department of Gastroenterology, Ospedale Ponte Novo, Careggi, Florence**
ANTONIO MORETTINI, MD, head

**Gastroenterology Unit, Ospedale Generale Provinciale, Mestre, Venice**
ALFREDO SAGGIORO, MD, head

**Gastroenterology Unit, Ospedale S Chiara, Trento**
GIOVANNI TAFNER, MD, head

Correspondence to: L Capurso, Ospedale S Filippo Neri, Via Martinotti, 20 Rome, Italy.

## Introduction

Evidence is growing that nocturnal hypersecretion of acid is an important factor in the pathogenesis of duodenal ulcer, as originally proposed by Dragstedt and Owens.[1] Pharmacological studies performed by Gledhill *et al* comparing a single 800 mg dose of cimetidine given at night with 400 mg given twice daily showed that both dosage regimens were equally effective in reducing mean 24 hour intragastric acidity and that nocturnal secretion of acid was significantly better controlled with cimetidine 800 mg at night than with the twice daily regimen.[2] On the basis of these findings they suggested that a single night time dose should be evaluated in a clinical trial. Results of an open randomised clinical trial of cimetidine 800 mg were recently published and showed that healing rates and duration of treatment were not different when cimetidine was given as 800 mg once daily or as 400 mg twice daily.[3]

The purpose of our multicentre study was to investigate in a double blind fashion the safety and efficacy of cimetidine 800 mg once daily compared with 400 mg twice daily in patients with duodenal ulceration.

## Patients and methods

Seven centres participated in this study. Patients with duodenal ulcer confirmed endoscopically within the previous four days were randomly allocated by a double dummy technique to receive cimetidine twice daily (one 400 mg tablet at breakfast and one 400 mg tablet at bedtime) or once daily (two 400 mg tablets at bedtime). Treatment was continued for four weeks, at the end of which patients were re-examined endoscopically. During the treatment period all other drugs for peptic ulceration were stopped except for a specific antacid to be taken solely for relief of pain not controlled by cimetidine. After two and four weeks the patients were examined clinically and interviewed about the occurrence of adverse reactions; details were obtained on ulcer pain and consumption of antacids, which they had previously recorded on diary cards.

## Results

At a previously determined date 197 patients were eligible for entry into the study; of these, 187 were eligible for analysis after

four weeks. Ninety one received the once daily dosage and 96 the twice daily dosage. Table I gives demographic data on the patients. The two groups were comparable for sex, age, duration of disease, smoking habit, and alcohol consumption, as calculated by appropriate statistical methods ($\chi^2$ test, Student's $t$ test, Mann-Whitney U test). Ten patients did not complete the study: four defaulted (that is, did not return), although one of these was included in the assessment of symptoms at week 2; one was withdrawn because of patient refusal; and five were withdrawn because of violation of the protocol (two took other drugs concomitantly, one showed non-compliance, one had an oesophageal ulcer at entry to the trial, and one did not adhere to the schedule of visits).

TABLE I—*Demographic data*

| | Cimetidine 800 mg once daily | Cimetidine 400 mg twice daily |
|---|---|---|
| Total No of patients | 91 | 96 |
| Men:women | 62:28 | 68:28 |
| Mean age (years) | 44·55 | 42·28 |
| Median (range) duration of disease (months) | 60 (1-420) | 60 (1-480) |
| Smoking habit: | | |
| Smokers | 49 | 56 |
| Non-smokers | 40 | 40 |
| Unknown | 2 | |
| Alcohol consumption: | | |
| Yes | 47 | 45 |
| No | 43 | 51 |
| Unknown | 1 | |

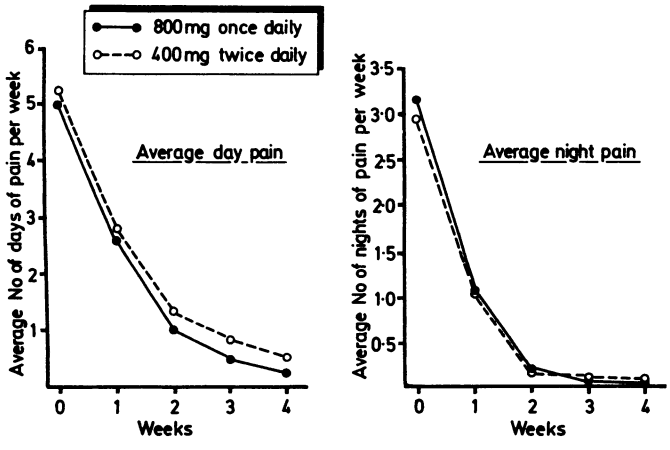
*Healing*—After four weeks' treatment the ulcer had healed in 76 of 91 patients (84%) receiving the once daily regimen compared with 65 of the 96 patients (68%) receiving the twice daily regimen. This difference of 16% was significant ($p<0·05$). There was a 95% certainty that the difference in healing at four weeks between the once daily and twice daily regimens lay between 2·9 and 29·1%, indicating the direction of the difference in favour of the once daily regimen.

*Assessment of symptoms*—Table II shows the proportions of patients who experienced pain during the day and the night throughout the four weeks of treatment. No significant difference in the overall proportions of patients with pain was observed between the two regimens either before or during treatment. The figure shows the decrease in the mean number of days or nights with pain during the four weeks of the study. Both dosage regimens were equally effective in reducing the incidence of pain.

*Consumption of antacids* did not differ significantly between the two treatment groups (table III) but was lower in the group receiving the once daily regimen.

TABLE II—*Numbers (%) of patients with pain*

| Cimetidine regimen | Week 0 | 1 | 2 | 3 | 4 |
|---|---|---|---|---|---|
| | *Night pain* | | | | |
| 800 mg once daily (n = 91) | 69 (76) | 47 (52) | 22 (24) | 5 (6) | 5 (6) |
| 400 mg twice daily (n = 96) | 66 (69) | 36 (38) | 15 (16) | 7 (7) | 7 (7) |
| | *Day pain* | | | | |
| 800 mg once daily (n = 91) | 86 (95) | 72 (79) | 44 (48) | 19 (21) | 11 (12) |
| 400 mg twice daily (n = 96) | 90 (94) | 79 (82) | 46 (48) | 30 (31) | 20 (21) |




Average numbers of days of pain during four weeks of treatment.

TABLE III—*Numbers (%) of patients taking antacids*

| | Week 1 | 2 | 3 | 4 |
|---|---|---|---|---|
| 800 mg once daily (n = 91) | 17 (19) | 11 (12) | 7 (8) | 6 (7) |
| 400 mg twice daily (n = 96) | 26 (27) | 22 (23) | 11 (12) | 7 (7) |

TABLE IV—*Adverse events*

| Adverse event | Cimetidine 800 mg once daily | Cimetidine 400 mg twice daily |
|---|---|---|
| | *Gastrointestinal* | |
| Constipation | | 3 |
| Diarrhoea | 1 | 1 |
| | *Central nervous system* | |
| Vertigo | | 3 |
| Insomnia | | 2 |
| Somnolence | 1 | 1 |
| Irritability | | 2 |
| Headache | | 2 |
| | *Skin* | |
| Dermatitis | | 1 |
| | *Liver* | |
| Increased serum transaminase activity | 2 | |
| Total No of reactions | 4 | 15 |
| Total No of patients | 4 | 11 |

*Adverse events*—Nineteen adverse events were reported by 15 patients (8%) during treatment (table IV), the proportion of patients with adverse events being higher in the group receiving the twice daily regimen (11% *v* 4%). None of these adverse events necessitated withdrawal from treatment, which is consistent with the proved safety profile of cimetidine. Two of the patients receiving the once daily regimen had a threefold to fivefold increase in transaminase activities after four weeks, which returned to normal two weeks after the drug was stopped.

## Discussion

Cimetidine 400 mg twice daily has been shown to be effective in promoting the healing of duodenal ulceration.[4-6] In this study a once daily regimen (800 mg at night) was compared with a twice daily regimen (400 mg at breakfast and at bedtime) for four weeks; a significant difference in favour of the once daily regimen ($p<0·05$) was found with regard to ulcer healing. Furthermore, a lower proportion of the patients given the drug once daily took antacids and suffered adverse reactions. In patients with duodenal ulcer secretion of acid at night is one of the most important pathogenetic factors, particularly as then there is no food to buffer the acid. Use of a larger dose of cimetidine at night can effectively control secretion of gastric acid at night, thereby establishing proper pH conditions for ulcer healing. The lower incidence of adverse reactions observed in the group given cimetidine once daily shows that a large nocturnal dose does not increase the risk of adverse events.

Our findings indicate that in a large proportion of patients with duodenal ulcer a single dose of 800 mg cimetidine at night is at least as effective and as safe as 400 mg twice daily in promoting the healing and alleviating the symptoms of duodenal ulcer. This more convenient single dose regimen may improve patient compliance and thereby facilitate the short term treatment of duodenal ulceration.

We acknowledge the valuable support rendered by the Smith, Kline and French medical department.

## References

1 Dragsted LR, Owens FM Jr. Supradiaphragmatic secretion of vagus nerves in treatment of duodenal ulcer. *Proc Soc Exp Biol Med* 1943;**53**:152-4.
2 Gledhill T, Howard DM, Buck M, Hunt RH. Single nocturnal dose of an $H_2$ receptor antagonist for the treatment of duodenal ulcer. *Gut* 1983;**24**:904-8.
3 Lacerte M, Rousseau B, Parent JP, Parè P, Levesque D, Falutz S. Single daily dose of cimetidine for the treatment of symptomatic duodenal ulcer: results of a comparative two centre clinical trial. *Curr Ther Res* 1984;**35**:777-82.
4 Delattre M, Prinzie A, Underwood D. The treatment of duodenal ulceration. A comparative trial of cimetidine (Tagamet) at daily dosages of 800 mg (400 mg b.i.d.) and 1000 mg. *Clinical Trials Journal* 1982;**19**:94-105.
5 Kerr GD. Cimetidine: twice daily administration in duodenal ulcer—results of a UK and Ireland multicentre study. In: Baron H, ed. *Cimetidine in the 80s*. Edinburgh: Churchill Livingstone, 1981:9-13.
6 Eckart V. Cimetidine: twice daily administration in duodenal ulcer—results of a European multicentre study. In: Baron H, ed. *Cimetidine in the 80s*. Edinburgh: Churchill Livingstone, 1981:14-20.

(*Accepted 7 September 1984*)

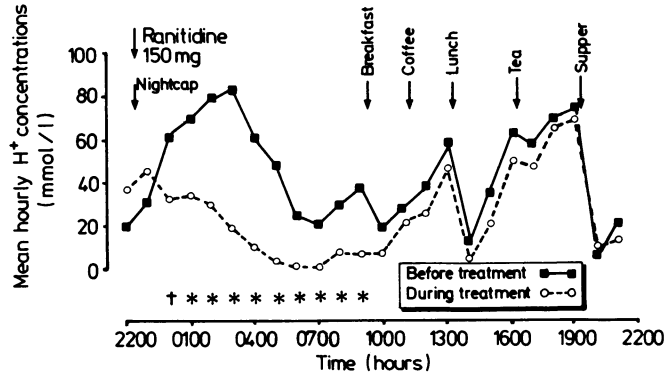
# SHORT REPORTS

## 24 Hour intragastric acidity during maintenance treatment with ranitidine

The recommended dose of ranitidine for the maintenance treatment of duodenal ulceration is 150 mg at bedtime.[1] Ranitidine is assumed to protect the patient from relapse of ulceration by decreasing nocturnal intragastric acidity, but the effect of this dose over 24 hours is not known.

### Patients, methods, and results

We studied eight men with a history of endoscopically proved duodenal ulceration on two occasions when they were in symptomatic remission—before and on the seventh day of treatment with ranitidine 150 mg at night. Their mean age was 46·5 (range 30-64) years and mean weight 75·1 (range 63-91) kg. Six were smokers and each consumed an average of 17 cigarettes during each 24 hour study period. No patient received any antisecretory drug within 14 days of the start of the study, which was approved by the hospital ethical committee.




Mean hourly intragastric $H^+$ concentrations in eight patients with duodenal ulcer before and during treatment with ranitidine 150 mg at night. (*= $p<0·001$, †= $p<0·01$; Wilcoxon's rank sum test.)

Our established technique for measuring intragastric acidity[2 3] was modified to take account of the single evening maintenance dose of ranitidine: the patients were admitted to the ward at 1900, a 10 FG nasogastric tube was passed at 1915, and a standard dinner was eaten at 1930. The 24 hour study period was from 2200 until 2100 the next day. Samples of gastric juice were aspirated every hour on the hour and their acidity measured using a combined glass electrode repeatedly calibrated with standard buffers of pH 7·00, 4·01, and 1·09 (Radiometer, Copenhagen). After the first study period each patient took ranitidine 150 mg at night by mouth for seven days, the last tablet being taken at 2215 during the second study period.

Mean 24 hour intragastric acidity decreased by 42% from 42·9 mmol/l to 24·8 mmol/l ($p<0·001$, two way analysis of variance). This change was due to a significant decrease in hourly intragastric acidity from 2400 to 0900 (figure). From 1000 to 2300 there was no significant change in mean hourly acidity. Median intragastric pH over 24 hours increased from pH 1·4 to pH 1·8 during maintenance treatment with ranitidine. No adverse drug effects were reported by any patient during the study.

### Comment

Ranitidine 150 mg twice a day decreases both daytime and nocturnal intragastric acidity, with median 24 hour intragastric pH rising from 1·4 to 2·4 during treatment.[3 4] This study showed that ranitidine 150 mg at night caused a decrease in acidity that was restricted to the night and early morning.

Duodenal ulceration is a chronic illness and many patients require maintenance treatment with an $H_2$-antagonist. It is reassuring that intragastric acidity was decreased for only 10 out of 24 hours after each maintenance dose of ranitidine 150 mg at night. For most of the day and during the evening the patients receiving maintenance treatment with ranitidine showed no change in intragastric acidity. The presence of normal concentrations of acid in the stomach for this prolonged period makes bacterial colonisation of the stomach unlikely during maintenance treatment.[5]

It may be relevant to the pathogenesis of duodenal ulceration that the short lived decrease in nocturnal acidity observed in this study is sufficient to prevent relapse of ulceration in most patients.

There is no report of the effect of maintenance treatment with cimetidine 400 mg at night on 24 hour intragastric acidity in patients with duodenal ulcers, but its effect may be even more transient than that of ranitidine.

1 Anonymous. *Zantac (ranitidine)*. Greenford: Glaxo Laboratories, April 1984. (Data sheet.)
2 Pounder RE, Williams JG, Milton-Thompson GJ, Misiewicz JJ. Effect of cimetidine on 24 hour intragastric acidity in normal subjects. *Gut* 1976;**17**:133-8.
3 Walt RP, Gomes MdeFA, Wood EC, Logan LH, Pounder RE. Effect of daily oral omeprazole on 24 hour intragastric acidity. *Br Med J* 1983;**287**:12-4.
4 Walt RP, Male P-J, Rawlings J, Hunt RH, Milton-Thompson GJ, Misiewicz JJ. Comparison of the effects of ranitidine, cimetidine and placebo on the 24 hour intragastric acidity and nocturnal acid secretion in patients with duodenal ulcer. *Gut* 1981;**22**:49-54.
5 Anonymous. Bacteria in the stomach. [Editorial.] *Lancet* 1981;ii:906-7.

(*Accepted 8 August 1984*)

**Academic Department of Medicine, Royal Free Hospital School of Medicine, London NW3 2PF**
I A SANTANA, MD, research fellow
B K SHARMA, MRCP, research fellow
R E POUNDER, MD, FRCP, senior lecturer in medicine
E C WOOD, PHD, clinical medical student
S MASTERS, SRN, research nursing sister
M TALBOT, junior technician

Correspondence to: Dr R E Pounder.

## Acceptance of viewdata for poisons information

We recently suggested that a viewdata system could present basic poisons information effectively and ease the work of poisons information services by facilitating the storage and retrieval of information and reducing the need for staff to answer telephone inquiries.[1] Since its inauguration at the beginning of April 1983, our viewdata system has been the information source used by staff of the Scottish Poisons Information Bureau to answer conventional telephone inquiries and by centres throughout Britain which obtained terminals for direct