Gut, 1989, **30**, 1173–1178

Double blind multicentre* comparison of omeprazole 20 mg once daily *versus* ranitidine 150 mg twice daily in the treatment of cimetidine or ranitidine resistant duodenal ulcers

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SUMMARY **The purpose of the present study was to compare omeprazole 20 mg once daily and ranitidine 150 mg twice daily in healing duodenal ulcers unhealed by previous treatment with cimetidine ≥0·8 g or ranitidine ≥0·3 g daily for at least six weeks. In a double blind multicentre trial, 151 patients were randomly assigned to either omeprazole or ranitidine. Clinical assessments and endoscopies were carried out at two and four weeks. Patients characteristics were similar in both groups. Statistical analysis (χ^2 test) did not show any significant difference in healing rate (p>0·20) irrespective of the method of calculation. On an 'intent-to-treat' analysis (n=151), healing was: omeprazole 46·6%, ranitidine 43·3% at day 15 and omeprazole 70·7%, ranitidine 68·4% at day 29; and among the patients who completed treatment, healing was: omeprazole 48·3%, ranitidine 46·3% at day 15 (n=125; 95% confidence interval of the difference – 17 to 21) and omeprazole 79·6%, ranitidine 75·4% at day 29 (n=115; 95% confidence interval of the difference – 13 to 21). After a further four weeks treatment with omeprazole, healing occurred in 16/20 (80%) who still had active disease at day 29. Patients on omeprazole and on ranitidine experienced similar decrease in day time and night time epigastric pain and in heartburn. Multivariate analysis (logistic regression) did not indicate any influence on age, sex, smoking and alcohol habits, previous drug administered, duodenitis and duodenal erosions on the healing rate. In this model, healing rate was not significantly influenced by previous treatment duration (p=0·09 at day 15 and p>0·2 at day 29) but was significantly influenced by ulcer size (p=0·04 at day 15 and p=0·02 at day 29). Forty one patients complained of adverse events: 19 on omeprazole (four trial withdrawals), 22 on ranitidine (three trial withdrawals).**

Conventional dose of histamine H_2 receptor antagonists heal between two thirds and four fifths of duodenal ulcers at one month and more than 90% at two months.[1] Reasons for therapeutic failures remain unclear but inadequate control of acid secretion is one of the possible causes.[1] Omeprazole is a potent and long acting antisecretory drug. A dose of 20 mg daily has been repeatedly shown to be more efficient in duodenal ulcer healing than cimetidine (0·8 or 1 g daily) or ranitidine (300 mg daily) at two weeks and at four weeks.[2-4] Compared with cimetidine 1200 mg daily, the superiority of omeprazole 20 mg daily did not reach statistical significance at four and six weeks but a trend toward more rapid ulcer healing and more rapid relief of symptoms was observed.[5] Moreover,

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Accepted for publication 14 November 1988.

several studies have suggested that omeprazole 20 mg daily was as effective as a 40 mg daily dose.[2,6] We therefore conducted a study to compare the effectiveness and safety of omeprazole 20 mg once daily with ranitidine 150 mg twice daily for the treatment of duodenal ulcers 'resistant' to a previous course of at least six weeks' duration with histamine H_2-receptor antagonists given at conventional doses.

Methods

PATIENTS

Eighteen centres in France participated in the study. Outpatients aged 18 years and over were admitted if they had an endoscopy proved unhealed duodenal ulcer with a crater ≥5 mm in diameter at the end of a continuous treatment of at least six weeks with cimetidine ≥0·8 g daily or ranitidine ≥300 mg daily. Patients were excluded if they had any of the following: coexistent gastric, prepyloric, or pyloric canal ulcer, had previously undergone ulcer surgery other than oversewing of a perforation; complication of peptic ulcer disease; concomitant treatment with non-steroidal anti-inflammatory drugs or anticoagulants; pregnancy or lactation; severe coexistent disease, or any condition which contraindicated the use of omeprazole or ranitidine.

The study was double blind using a double dummy technique. Patients were allocated at random to receive either ranitidine 150 mg twice daily and placebo omeprazole once daily or omeprazole 20 mg once daily (morning) and placebo ranitidine twice daily. Stratification was performed for each centre. Each blister pack contained two tablets and one capsule (two tablets of ranitidine and one capsule of placebo omeprazole or one capsule of omeprazole and two tablets of placebo ranitidine). The day for each blister and each dose and its timing were clearly indicated. All patients received 40 Maalox tablets (neutralising capacities 18 mmol per tablet) for pain relief. No other antiulcer treatment was allowed. In the four days before starting drug therapy, patients had a physical examination and a laboratory screen was carried out. Detailed information on duration and age of dyspeptic symptoms, duration and severity of current episode, type and duration of previous drug therapy, previous ulcer complication, and social habits were recorded. The presence of pain in the last week before entry to the study was noted. A diary card was used to record day and night pain. Two visits were planned: on day 15±3 for endoscopy, symptoms and adverse events recording and on day 29±3 for endoscopy (only for patients unhealed at day 15), physical examination, laboratory screen, symptoms and adverse events recording. The patients were instructed to return immediately if any problem arose. Patients with ulcers unhealed after four week treatment were offered a further four week open treatment with omeprazole (20 mg). Healing was defined as the complete disappearance of the ulcer crater regardless of the persistence of erosion or of duodenitis. Patients were asked to return all unused tablets, which were then counted to ascertain treatment compliance.

STATISTICAL ANALYSIS

Healing rates were calculated in two ways: first, based on the number of patients who were randomised to receive treatment ('intent to treat' analysis); second, based on the number of patients who completed the treatment. The statistical tests used for analysis were the χ^2 test to assess healing and pain relief and paired t test and analysis of variance to analyse changes in laboratory values. The 95% confidence interval of healing rates in the two treatment groups and of the differences between them were calculated. Results were considered statistically significant when p value was <0·05. The number of patients planned for the study (n=150) gave a test power of at least 80% to detect a true difference between the two treatments exceeding 25 percentage points (two sided test at the 5% significance level).

Multivariate analysis by logistic regression was performed in order to test influence as prognostic factors of study drugs, tobacco, alcohol, sex, age, previous treatment, type and duration of previous treatment, ulcer size, association with duodenal erosion, or erythematous duodenitis.

Table 1 *Comparison of patients in the two treatment groups*

	Omeprazole	*Ranitidine*
Patients (n)	75	76
Male/female	61/14	62/14
Mean age (SD) (years)	42·4 (14·6)	44 (14·5)
Smokers %	48	50
Alcohol %	33	38
Mean length of ulcer history in years (range)	6 (0–30·2)	6·6 (0·1–33·5)
Mean duration (SD) of previous H_2-receptor antagonist treatment (wk)	15·8 (20·3)	21·8 (35·8)
Previous antiulcer medication ranitidine/cimetidine	41/34	49/27
Pre-entry endoscopy ulcer size		
≤10 mm	65	65*
>10 mm	10	10
Erythematous duodenitis	37	33
Duodenal erosions	10	23
Ulcer shape round-oval	47	42
linear	13	18
salami	15	15
unknown	0	1

*Endoscopic data missing in one patient.

Table 2 *Healing rate at day 15 and day 29*

	Day 15		*Day 29*	
	Omeprazole	*Ranitidine*	*Omeprazole*	*Ranitidine*
Healing calculated on 'intent to treat'				
Patients (n)	75	76	75	76
Healed/unhealed	35/33	33/41	53/13	52/21
Missing data	7	2	9	3
Healing %	46·6	43·3	70·7	68·4
Healing calculated on patients completing the study				
Patients (n)	58	67	54	61
Healed/unhealed	28/30	31/36	43/11	46/15
Healing %	48·3	46·3	79·6	75·4
95% confidence interval in each treatment group	36 to 62	34 to 59	66 to 89	53 to 86
95% confidence interval of the difference between the two treatment groups	−17 to 21		−13 to 21	

Results

A total of 151 patients from 18 centres entered the study. The number of patients per centre was six to 12. The main patient characteristics in the two groups (omeprazole n=75, ranitidine n=76) were similar regarding age, sex ratio, proportion of smokers and alcohol users, length of ulcer history, ulcer size, and ulcer shape (Table 1). The mean duration of earlier treatment was somewhat longer in the ranitidine group and there was also an over representation of patients with ranitidine as previous treatment in this group. There were also more patients with duodenitis and with duodenal erosions in the ranitidine group. Where there was an imbalance all variables were tested as possible factors in the multivariate analysis of healing. Thereby the comparison between treatment groups was adjusted with regard to differences in these variables.

HEALING (Table 2)

Patients whose ulcers did not heal or who were withdrawn from the study for any reason were considered as treatment failures in the intention – to – treat analysis. At day 15 analysis, 13 patients (eight omeprazole, five ranitidine) were excluded for violation of inclusion criteria, three patients (omeprazole) were withdrawn because of side effects, seven patients were lost to follow up (five omeprazole, two ranitidine) and three patients (one omeprazole, two ranitidine) were excluded because of 'out of time' visit. At day 29 analysis, two other patients (ranitidine) were withdrawn because of side effects; five others (four omeprazole, one ranitidine) were lost to follow up and three (three ranitidine) were excluded because of 'out of time' visit.

The healing rate was similar in both treatment groups irrespective of the method of calculation. By the 'intent to treat' analysis, the healing rate (based on 151 patients) was at day 15: omeprazole 46·6%, ranitidine 43·3% and at day 29: omeprazole 70·7% and ranitidine 68·4%. In patients who completed the study, it was at day 15: omeprazole 48·3% (95% confidence interval (CI) 35–62), ranitidine 46·3% (95% CI 34–59) and at day 29: omeprazole 79·6% (95% CI 66–89), ranitidine 75·4% (95% CI 63–86). The 95% confidence interval of the difference between the two treatment groups were – 17 to 21 at day 15 and – 13 to 21 at day 29.

FACTORS INFLUENCING ULCER HEALING

Multivariate analysis by logistic regression showed that tobacco, alcohol, sex, age, previous medication (ranitidine or cimetidine), duodenitis, and duodenal erosions had no statistically significant influence on ulcer healing at day 15 or at day 29. The effect of the study drugs (omeprazole or ranitidine), ulcer size (diameter ≤10 mm or >10 mm) and duration of previous H_2-receptor antagonist treatment (≤eight weeks or >eight weeks) are given in Table 3. Only ulcer size proved to significantly influence healing rate, larger ulcers healing significantly less than smaller ones (p=0·04 and p=0·02 at day 15 and at day 29 respectively) (Figs. 1, 2).

Table 3 *Multivariate analysis test* of individual factors in the model ('per protocol analysis')*

	Day 15		*Day 29*	
Factor	χ^2	*p Value*	χ^2	*p Value*
Study drug	0·02	0·20	0·42	0·20
Ulcer size	4·30	0·04	5·70	0·02
Duration of previous treatment	2·95	0·09	0·51	0·2

*A low p value for a χ^2 difference indicates a significant effect of the factor tested.

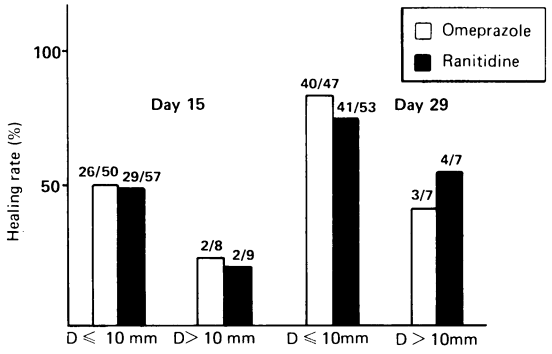

Fig. 1 *Influence of ulcer size (⩽10 mm in diameter or >10 mm in diameter on healing in the two treatment groups. There was no significative difference between the two treatment groups.*

HEALING RATE AT DAY 57

Twenty patients with ulcers unhealed after four weeks' treatment were then given an open treatment with omeprazole for a further four weeks. Healing occurred in 16 (80%): five of eight had previously been allocated to omeprazole treatment and 11 of 12 to ranitidine.

PAIN RELIEF (Fig. 3)

Of the 125 patients who recorded pain in their diary, less than half had daytime epigastric pain, about one third had night time epigastric pain and very few had heartburn on entry to the trial. Most patients became asymptomatic by day 15 and there was no difference in the proportion of patients with residual symptoms in the two treatment groups.

ADVERSE EVENTS AND WITHDRAWALS

Both drugs were well tolerated. Nineteen patients on omeprazole (25%) and 22 patients on ranitidine (29%) had adverse events recorded during study.

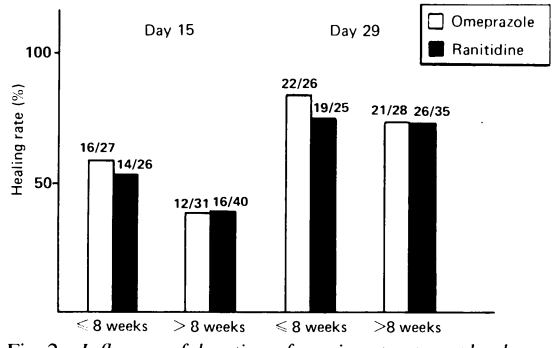

Fig. 2 *Influence of duration of previous treatment by the H_2-blockers (⩽eight weeks or >eight weeks) on healing in the two treatment groups. There was no significative difference between the two treatment groups.*

Gastrointestinal disorders were the most common adverse side effects on both drugs (n=12 on omeprazole and n=13 on ranitidine): anorexia, nausea, and vomiting, flatulence, belching, and diarrhoea. Other adverse effects were headache, somnolence, asthenia, sweating, palpitation, joint pain, back pain, cutaneous eruption. Finally, four patients on omeprazole were withdrawn: headache and fever in one, nausea asthenia and headache in one, cutaneous eruption in one, acute appendicitis in one. Three patients on ranitidine were withdrawn: diarrhoea in two and headache in one. No adverse event could be clearly related to drug therapy.

COMPLIANCE

For a two week period, each patient received 16 capsules (omeprazole or placebo-omeprazole) and 32 tablets (ranitidine or placebo-ranitidine). Among the patients who completed the trial, the number of tablets or capsules returned could be evaluated at day 15 in 50 of 58 in the omeprazole group and in 52 of 67 in the ranitidine group, at day 29 in 43 of 54 in the omeprazole group and in 47 of 61 in the ranitidine group. At day 15, the mean number of returned capsules was 3·4 (range 0–8) and the mean number of returned tablets was 3·2 (range 0–8). At day 29, the mean number of returned capsules was 2·6 (range 0–7) and the mean number of returned tablets was 3·6 (range 0–16).

Antacid consumption was apparently low in the two treatment groups. Unfortunately, it could not be precisely assessed as one third of patients did not return the antacid tablets and as several investigators probably noted the number of tablets consumed instead of the number of tablets returned.

HAEMATOLOGY AND BIOCHEMISTRY

No abnormality which could be attributed to the drugs was seen in either treatment group.

Discussion

To our knowledge, this is the first double blind randomised study comparing omeprazole and ranitidine in patients with duodenal ulcer unhealed by histamine H_2-receptor antagonist therapy for at least six weeks. The most important finding was that a further four week course of treatment with either omeprazole 20 mg once daily or ranitidine 150 mg twice daily was able to heal most of the ulcers: (between 66% and 89% for omeprazole and 63% and 86% for ranitidine).

Moreover, with both drug regimens rapid and almost complete pain relief was observed in the patients initially symptomatic. No significant adverse event was observed.

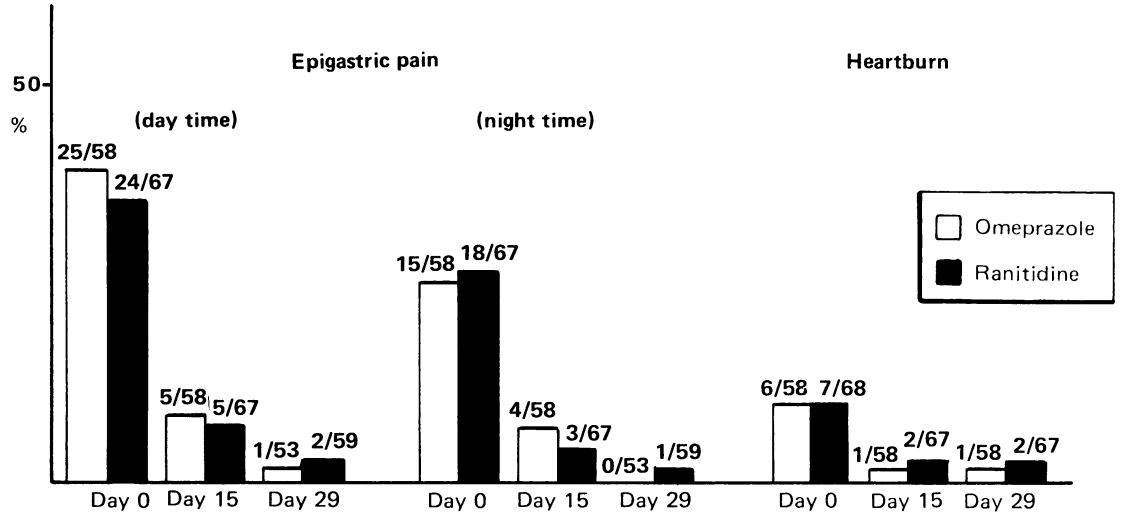

Fig. 3 *Pain reduction in the two treatment groups (percentage of patients with moderate or severe symptoms). There was no difference between the two treatment groups.*

The high healing rate in the ranitidine group was rather unexpected. It must be noted that it was higher than in other studies in which ranitidine had been given for four to six weeks to patients with an ulcer 'resistant' to cimetidine 1 g daily.[7-9] The relatively short period of previous treatment (six weeks) as compared with three months in some other studies[10,11] cannot account for good results in the present one: in a French comparative trial of cimetidine *v* ranitidine with similar inclusion criteria and which included a large number of patients, ranitidine 150 mg *bid* was shown to heal 70% of ulcers at six weeks. Moreover, multivariate analysis of prognostic factors in our study showed that duration of previous treatment did not significantly influence healing. A possible cause of high healing rate with ranitidine was that most patients (86%) had small ulcer (≤10 mm in diameter). Multivariate analysis indeed proved that ulcer size had a major influence on healing. Finally, we feel that compliance of patients to the drug could have been better during the trial than during previous treatment. Results obtained with ranitidine 150 mg twice daily in the present study confirm the previous statement by Bardhan[10] that continuing the H_2 blocker regimen unchanged is an option to be considered in patients with refractory duodenal ulcer.

Although the healing rate with omeprazole 20 mg was high (48·3% at two weeks and 79·6% at four weeks), it was not superior to that obtained with ranitidine 150 mg twice daily, which could appear surprising at first sight. There is some evidence from data from different groups who studied the two drugs separately[12-15,17] and from a recently published comparative study[18] that omeprazole 20 mg is more effective than ranitidine 300 mg in reducing 24 hour gastric acidity. The higher rate of duodenal ulcer healing with omeprazole 20 mg in comparative trials with ranitidine 300 mg[2-4] was considered to result from a better control of gastric acid secretion. As observed in several pHmetric studies, however,[16,18] not every patient responds to omeprazole 20 mg daily by a profound decrease in 24 hour intragastric acidity and some patients respond better to ranitidine 150 mg twice daily.[18] Moreover, analysis of pHmetric data suggested that the global superiority of omeprazole was the result of a better control of daytime acidity but not of nocturnal acidity.[12-16,18] Several authors showed that the resistance to conventional doses of H_2 blockers was mainly related to a poor control of nocturnal acidity.[19,20] It could therefore be anticipated that the same percentage of healing failure would be observed in patients treated by two drugs having similar effects on nocturnal acidity. Tytgat *et al*[21] recently reported results supporting this hypothesis. Omeprazole 40 mg daily was given as an open treatment to 11 patients with refractory duodenal ulcers. Healing was rapid and complete in every case but recurrence was observed in some patients during maintenance therapy with 20 mg daily. Increasing the dose to 40 mg permitted to heal the ulcer again and was required in some patients to avoid ulcer relapse.

In conclusion, the results of the present study confirm that three fourths of socalled 'resistant' duodenal ulcers can be healed by prolonging antisecretory therapy with omeprazole or ranitidine at

standard dosage for four weeks. One fourth of patients probably requires more efficient antisecretory treatment, however, which could be obtained with omeprazole 40 mg. Further studies are needed to assess usefulness of 24-hour gastric pH measurements to select the adequate posology of omeprazole in individual patients.

Part of this study has been presented at the Jubilee Meeting of the British Society of Gastroenterology held in London on 15–18 September 1987 and was published in abstract form (*Gut* 1987; **28:** A1341).

References

1 Wormsley KG. Duodenal ulcers which do not heal rapidly. *Br Med J* 1984; **289:** 1095.
2 Classen M, Damman HG, Domschke W, *et al.* Omeprazole heals duodenal, but not gastric ulcers more rapidly than ranitidine. Results of two German multicenter trials. *Hepatogastroenterology* 1985; **32:** 243–5.
3 Bardhan KD, Bianchi-Porro G, Bose K, *et al.* A comparison of two different doses of omeprazole versus ranitidine in treatment of duodenal ulcers. *J Clin Gastroenterol* 1986; **8:** 408–13.
4 Bigard MA, Isal JP, Galmiche JP, Ebrard F, Bader JP. Efficacité comparée de l'oméprazole et de la cimétidine dans le traitement de l'ulcère duodénal en poussée évolutive. Essai thérapeutique contrôlé multicentrique français. *Gastroenterol Clin Biol* 1987; **11:** 753–7.
5 Archambault AP, Pare P, Bailey RJ, *et al.* Omeprazole (20 mg daily) versus cimetidine (1200 mg daily) in duodenal ulcer healing and pain relief. *Gastroenterology* 1986; **94:** 1130–4.
6 Meyric-Thomas J, Misiewicz JJ, Trotman IF, *et al.* Omeprazole in duodenal ulceration: acid inhibition, symptom relief, endoscopic healing, and recurrence. *Br Med J* 1984; **289:** 525–8.
7 Brunner G, Losgen H, Harke U. Ranitidine in the treatment of cimetidine resistant ulcerations of the upper intestinal tract. In: Misiewicz JJ, Wormsley KG, eds. *The clinical use of ranitidine.* Oxford: Medicine Publishing Foundation, 1982: 254–6.
8 Quatrini M, Basilisco G, Bianchi PA. Treatment of 'cimetidine resistant' chronic duodenal ulcers with ranitidine or cimetidine: a randomised multicentre study. *Gut* 1984; **25:** 1113–7.
9 Etude coopérative. Efficacité de la ranitidine et de la cimétidine dans le traitement de l'ulcère duodénal ou gastrique résistant à un traitement initial par la cimétidine. Essai thérapeutique contrôlé multicentrique. *Gastroenterol Clin Biol* 1985; **9:** 147–52.
10 Bardhan KD. Refractory duodenal ulcer. *Gut* 1984; **25:** 711–7.
11 Bianchi-Porro G, Parente F, Lazzaroni M. Tripotassium dicitrato bismuthate (TDB) versus two different dosages of cimetidine in the treatment of resistant duodenal ulcers. *Gut* 1987; **28:** 907–11.
12 Walt RP, Male PJ, 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* 1982; **22:** 49–54.
13 Galmiche JP, Vallot T, Mayeur S, *et al.* Effet de la ranitidine sur le pH gastrique chez le sujet sain. Intérêt de l'enregistrement continu sur 24 Heures pour le choix du fractionnement optimal d'une dose thérapeutique. *Gastroenterol Clin Biol* 1982; **6:** 352–9.
14 Walt RP, Gomes M de FA, Wood EC, Logan LH, Pounder RE. Effect of daily oral omeprazole on 24 hour intragastric acidity. *Br Med J* 1983; **287:** 12–4.
15 Naesdal J, Bodemar G, Walan A. Effect of omeprazole, a substituted benzimidazole, on 24-H intragastric acidity in patients with peptic ulcer disease. *Scand J Gastroenterol* 1984; **19:** 916–22.
16 Sharma BK, Walt RP, Pounder RE, Gomes M de FA, Wood EC, Logan LH. Optimal dose of oral omeprazole for maximal 24 hour decrease of intragastric acidity. *Gut* 1984; **25:** 957–64.
17 Hemery P, Galmiche JP, Roze C, *et al.* Low-dose omeprazole effects on gastric acid secretion in normal man. *Gastroenterol Clin Biol* 1987; **11:** 148–53.
18 Lanzon-Miller S, Pounder RE, Hamilton MR, *et al.* Twenty four-hour intragastric acidity and plasma gastrin concentration before and during treatment with either ranitidine or omeprazole. *Aliment Pharmacol Therap* 1987; **1:** 239–51.
19 Gledhill T, Buck M, Paul A, Hunt RH. Effect of no treatment, cimetidine 1 g/day, cimetidine 2 g/day and cimetidine combined with atropine on nocturnal gastric secretion in cimetidine non-responders. *Gut* 1984; **25:** 1211–6.
20 Galmiche JP, Tranvouez JL, Denis P, *et al.* L'enregistrement nocturne du pH gastrique permet-il de prévoir la réponse thérapeutique des ulcères duodénaux sévères traités par ranitidine? *Gastroenterol Clin Biol* 1985; **9:** 583–9.
21 Tytgat GNJ, Lamers CBHW, Hammeeteman W, Jansen JMBJ, Wilson JA. Omeprazole in peptic ulcers resistant to histamine H_2-receptor antagonists. *Aliment Pharmacol Therap* 1987; **1:** 31–8.