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Omeprazole inhibition of nocturnal gastric secretion in patients with duodenal ulcer

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1 We studied the effect of single 08.00 h doses of omeprazole or placebo on gastric acid secretion during the following night, 14 to 23 h after administration, in seven male subjects with duodenal ulcer. The drug was given orally, double-blind, in randomized order.

2 Omeprazole 20 mg, 40 mg and 80 mg reduced mean total overnight acid output by 43%, 73% and 91% respectively and median pH increased from 1.4 with placebo to 1.6, 3.1 and 7.0 respectively. The inhibitory effect was maintained throughout the study period. No clinical side effects or abnormalities of laboratory screening tests were seen.

3 Omeprazole is well tolerated and administration at 08.00 h produces prolonged dose related inhibition of acid output during the following night.

Keywords nocturnal gastric secretion omeprazole duodenal ulcer

Introduction

Patients with duodenal ulcer often suffer nocturnal pain, and studies of 24 h pH show that it is during the night, when the stomach is empty and gastric contents are unbuffered, that the duodenum is exposed to highly acidic conditions for many hours (Watkinson, 1951). Excessive night time gastric secretion has been implicated in the pathogenesis of duodenal ulcer (Dragstedt, 1967) and the control of nocturnal secretion with bedtime doses of H_2-receptor antagonists has been successful in preventing ulcer recurrence (Burland *et al.*, 1980). Thus reduction of nocturnal acid secretion is of critical importance in the treatment of duodenal ulcer.

Omeprazole is one of the potent new class of gastric anti-secretory compounds, the substituted benzimidazoles. These appear to act by selective inhibition of the $H^+ + K^+$-ATPase proton pump within the parietal cells (Fellenius *et al.*, 1981). Omeprazole inhibits basal and pentagastrin stimulated gastric acid secretion and has a prolonged effect: 24 h after administration of single 20 mg or 40 mg doses (in a buffered suspension to avoid acid degradation of the drug), pentagastrin stimulated acid secretion was inhibited by 26% and 48% respectively (Lind *et al.*, 1983). This long duration of action raises the possibility of a once a day treatment regimen and an enteric coated formulation has been developed for clinical use (Muller *et al.*, 1983). We therefore investigated in patients with duodenal ulcer disease the effects of single morning doses of enteric coated omeprazole on gastric acid secretion during the following night.

Methods

The subjects were seven male patients with endoscopically diagnosed duodenal ulcer disease, in symptomatic remission at entry to the study. Their median age was 54 years (range 34–58), median weight 83 kg (range 67–105 kg), and three were smokers. Their history of ulcer disease ranged in duration from 5–30 years (median 20 years) but none had undergone gastrointestinal surgery or had other noteworthy disease. Previous acid secretory tests at various times had found basal acid outputs

ranging from 3.1–12.1 mmol/h (median 4.7 mmol). No patient received any other antisecretory drug in the 2 weeks before the study.

The study protocol was approved by the Research Review Committee of the Royal Adelaide Hospital and by the Australian Commonwealth Department of Health. Written informed consent was given by each patient.

Each patient was studied on four occasions at weekly intervals. Single doses of omeprazole 20 mg, 40 mg or 80 mg, or placebo were given in randomized order under double-blind conditions. The medication, formulated as enteric coated granules within four hard gelatin capsules, was administered at 08.00 h with a standard breakfast. The patients then left the hospital for a routine day's activity, but were asked not to smoke or eat after 14.00 h. They returned for a standard light meal at 18.30 h, then fasted until a 14 French gauge naso-gastric sump tube was passed under fluoroscope control at 21.30 h. The patients were positioned in bed in the left lateral decubitus position and at 22.00 h the gastric contents were aspirated and discarded. Gastric secretion was collected from 22.00 h to 07.00 h the next day by constant mechanical suction combined with intermittent manual aspiration. The gastric aspirate was pooled in hourly samples and frozen for determination of volume, pH and total titratable acidity (by titration to pH 7) 48 h later.

Patients were examined each week and a check list of possible adverse events recorded. Routine ECG, haematological, biochemical and urine tests were carried out before and 7 days after the study.

Two way analysis of variance was applied to the data on acid output, and Wilcoxon's matched pairs signed ranks test was used to assess the statistical significance of changes in volume, hydrogen ion concentration, acid output and median pH. The degree of inhibition produced by each dose was expressed as a percentage: i.e.

$$\frac{\text{placebo} - \text{treatment response}}{\text{placebo response}} \times 100\%$$

and applied to either the mean total nine hour acid output or hourly, as a percentage of the corresponding placebo hour. There was considerable variation in baseline (placebo) acid output between patients, and the treatment responses were therefore also expressed as a percentage inhibition for each individual.

Results

All doses of omeprazole reduced acid output and increased intragastric pH (Figure 1). Total nocturnal acid output during the 9 h decreased from a mean of 33.01 mmol with placebo to 18.93 mmol (−43%), 9.06 mmol (−73%) and 2.99 mmol (−91%) after 20 mg, 40 mg and 80 mg omeprazole respectively. All reductions were statistically significantly different from placebo ($P < 0.01$) and from each other.

After ingestion of placebo, acid output tended to decline after 01.00 h, a finding consistent with the circadian rhythm of gastric secretion. Following each dose of omeprazole acid output tended to fall progressively throughout the 9 h study period with no apparent recovery of acid output towards the end of the period (Figure 1). This prolonged inhibition, when expressed hourly as a percentage of the corresponding placebo control hour, tends to increase progressively during the night. The 20 mg, 40 mg and 80 mg doses of omeprazole produced respectively 19%, 57% and 85% inhibition of acid output between 22.00–23.00 h and 64%, 81% and 99% inhibition of the final hourly aspiration (06.00–07.00 h).

Table 1 shows the total overnight acid output for individual patients after placebo treatment and the degree of inhibition produced by the three doses of omeprazole. There was considerable interindividual variation in spontaneous acid secretion and no clear relationship of this to individual drug responsiveness was found.

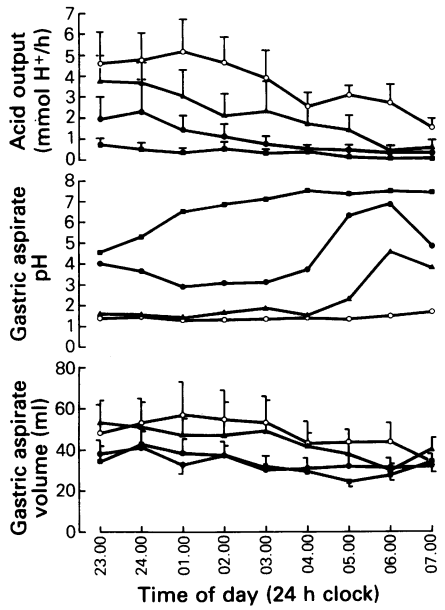

Figure 1 Nocturnal gastric acid output (mean ± s.e. mean), gastric aspirate pH (median values) and volume (mean ± s.e. mean) following placebo (○), omeprazole 20 mg (▲), omeprazole 40 mg (●) or omeprazole 80 mg (■).

Intragastric pH

The pH of the gastric aspirates also increased in a dose related manner following omeprazole. Median pH values of all the individual hourly aspirates increased from 1.4 following placebo to 1.6, 3.1 and 7.0 with omeprazole 20 mg, 40 mg and 80 mg respectively. No patient had an aspirate with pH greater than 4 following placebo while after omeprazole 20 mg, three patients achieved neutrality at some stage during the study and 35% of the aspirates had a pH of 4 or more. Omeprazole 40 mg produced neutrality (pH > 7) in four patients and pH greater than 4 in 49% of aspirates, and following omeprazole 80 mg all seven patients became neutral and 78% of the aspirates had a pH above 4. Figure 1 shows the time course of pH changes, with a progressive increase during the night, but a slight fall in pH in the last hour of collection following the 20 mg and 40 mg doses.

Secretory volume

Omeprazole reduced the volume of secretion, but to a lesser extent than hydrogen ion concentration or acid output (Figure 1). The mean volume of overnight secretion decreased by 8%, 29% and 31% following omeprazole 20 mg, 40 mg and 80 mg respectively, with only the effect of 40 mg and 80 mg doses reaching statistical significance.

Adverse effects

The patients tolerated the study well with only slight disturbance of sleep. No unwanted symptoms or signs were attributed to omeprazole. Clinical and laboratory screening revealed no abnormalities. Statistical analysis of haematological and biochemical screening tests showed small reductions within the normal range in haematocrit (47.4% to 45.5%), and serum calcium (2.48 mmol/l to 2.40 mmol/l), of no apparent clinical significance.

Discussion

A single oral dose of omeprazole given at 08.00 h, 14 h before the start of overnight secretory testing, produced a profound dose dependent inhibition of nocturnal gastric secretion in patients with duodenal ulcer disease. Individual patient responsiveness to the drug showed considerable variation and was unrelated to the spontaneous level of acid secretion (after placebo) which therefore has no value in predicting the response to the drug. Nevertheless in each of the patients the 80 mg dose produced profound inhibition of total nocturnal acid output, ranging from 82%–100%, and all achieved neutrality at some stage, in five of them for most of the night. The duration of action of omeprazole was clearly prolonged, with no recovery of acid output during the study period which extended from 14–23 h after administration of the drug. The apparent increase in inhibition (as a percentage of baseline) during the 9 h is related to the decline in baseline (placebo) acid output, and an increase in omeprazole activity cannot be inferred.

These results may be compared with our previous study of the effect of cimetidine, placebo and SK & F 93479 on nocturnal gastric secretion (Hetzel *et al.*, 1982). Cimetidine 400 mg given at 22.00 h inhibited acid output from 23.00 h–07.00 h by 89%. Median pH of all hourly aspirates following placebo in that study was 1.5, similar to the median pH of 1.4 in the

Table 1 Total overnight acid output in each patient following placebo, and percentage inhibition of this by omeprazole 20 mg, 40 mg, and 80 mg

Patient	*Acid output (placebo) (mmol/9 h)*	*Percentage inhibition by omeprazole*		
		20 mg	*40 mg*	*80 mg*
1	30.8	33%	85%	97%
2	16.0	45%	92%	100%
3	38.2	17%	38%	82%
4	24.8	92%	99%	100%
5	72.7	20%	59%	87%
6	16.1	43%	81%	80%
7	32.4	94%	96%	99%
Group mean	33.0	49%	79%	92%

present study. Cimetidine 400 mg produced a median pH of 5.8 in the aspirates 2–9 h after administration, an effect midway between that found with omeprazole 40 mg and 80 mg in the current study. Omeprazole was of course administered at 08.00 h in the present study and showed little sign of diminishing effect through the night, while in both our own studies and those of others (Longstreth *et al.*, 1976) the effect of cimetidine 400 mg tends to wane from 05.00 h onwards.

The present findings are in broad agreement with those obtained with omeprazole in other single dose experiments on basal and stimulated acid secretion in healthy volunteers. For example pentagastrin stimulated acid secretion measured 1–4 h after omeprazole 20 mg, 40 mg, 60 mg or 80 mg was inhibited by 35%, 65%, 90% and 99% respectively (Lind *et al.*, 1983). Repeat testing 24 h following the 20 mg and 40 mg doses found significant reductions of 26 ± 12% and 48 ± 9% respectively, and the 40 mg dose continued to produce significant inhibition of 34 ± 7% on the third day and 18 ± 4% on the fourth day. Studies on peptone meal stimulated gastric acid secretion found a dose dependent reduction by omeprazole 30 mg, 60 mg and 90 mg of 42%, 80% amd 92% respectively (Londong *et al.*, 1983).

Repeated daily doses of omeprazole have produced an increasing inhibitory effect on basal or pentagastrin stimulated acid secretion with maximal effects seen after 5 days (Lind *et al.*, 1983; Muller *et al.*, 1983). Thus it is not surprising that a small dose of omeprazole, 30 mg given daily for 1 week, produced profound reduction of 24 h intragastric acidity in nine duodenal ulcer patients (Walt *et al.*, 1983). Median pH of all hourly samples rose from 1.4 before treatment to 5.3 after treatment. Unfortunately the order of testing was not randomized in that study and repetition of the test procedure itself may have contributed some of the reduction.

In conclusion, omeprazole is a potent, well tolerated and long acting inhibitor of nocturnal gastric acid secretion, and appears suitable for once daily administration.

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References

Burland, W. L., Hawkins, B. W. & Beresford, J. (1980). Cimetidine treatment for the prevention of recurrence of duodenal ulcer: an international collaborative study. *Postgrad. med. J.*, **56**, 173–176.

Dragstedt, L. R. (1967). Gastric secretion tests. *Gastroenterology*, **52**, 587–589.

Fellenius, E., Berglind, T., Sachs, G., Olbe, L., Elander, B., Sjostrand, S. E. & Wallmark, B. (1981). Substituted benzimidazoles inhibit gastric acid secretion by blocking ($H^+ + K^+$)ATPase. *Nature*, **290**, 159–161.

Hetzel, D. J., Bartholomeusz, F. D. L. & Shearman, D. J. C. (1982). Inhibition of nocturnal acid secretion by SK & F 93479 in patients with duodenal ulcer. *IRCS Med. Sci.*, **10**, 800–801.

Lind, T., Cederberg, C., Ekenved, G., Haglund, U. & Olbe, L. (1983). Effect of omeprazole—a gastric proton pump inhibitor—on pentagastrin stimulated acid secretion in man. *Gut*, **24**, 270–276.

Londong, W., Londong, V., Cederburg, C. & Steffen, H. (1983). Dose-response study of omeprazole on meal stimulated gastric acid secretion and gastrin release. *Gastroenterology*, **85**, 1373–1378.

Longstreth, G. F., Go, V. L. W. & Malagelada, J. R. (1976). Cimetidine suppression of nocturnal gastric secretion in active duodenal ulcer. *New Engl. J. Med.*, **294**, 801–804.

Muller, P., Dammann, H. G., Seitz, H. & Simon, B. (1983). Effect of repeated, once daily, oral omeprazole on gastric secretion. *Lancet*, **i**, 66.

Walt, R. P., Gomes, M. de F. A., Wood, E. C., Logan, L. H. & Pounder, R. E.(1983). Effect of daily oral omeprazole on 24 hour intragastric acidity. *Br. med. J.*, **287**, 12–14.

Watkinson, G. (1951). A study of the changes in pH of gastric contents in peptic ulcer using the 24 hour test meal. *Gastroenterology*, **18**, 377–390.

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