Basal, sham feed and pentagastrin stimulated gastric acid, pepsin and electrolytes after omeprazole 20 mg and 40 mg daily

J N THOMPSON, J A BARR, N COLLIER, J SPENCER, A BUSH, L COPE,
R J N GRIBBLE, AND J H BARON

From the Department of Surgery, Royal Postgraduate Medical School, and Department of Medicine, St Charles Hospital, London

SUMMARY Gastric secretion was measured in nine patients with duodenal ulcer before, and after treatment for four weeks with omeprazole 20 mg or 40 mg daily. Basal acidity and acid output were affected variably by 20 mg, but inhibited totally by 40 mg daily. Sham feed stimulated acid output was reduced by 20 mg daily and completely inhibited by 40 mg daily. Maximal pentagastrin stimulated acid output was halved by 20 mg omeprazole daily and 84% inhibited by 40 mg daily. The reduction in acidity was always greater than the reduction of volume. Pepsin output after pentagastrin was little altered but with the reduced secretory volume pepsin concentrations were increased by both doses. The major cause of reduced aspirated acid output after omeprazole is decreased secretion of the primary acid component of the parietal cell by the proton pump H^+K^+ ATPase. Duodenogastric alkaline reflux is, however, markedly increased after omeprazole and is an additional factor in the resultant hypoacidity or even anacidity after this drug.

Substituted benzimidazoles such as omeprazole probably block the proton pump H^+K^+ ATPase in the parietal cell,^{1,2} and are among the most powerful and sustained inhibitors of maximal gastric secretion.³⁻⁵ There are only limited data on the effects in man of omeprazole on basal interdigestive,³ or sham feed stimulated⁶ gastric secretion, and few or no data on the effect of omeprazole on volume, acidity, electrolytes and pepsin. We report here such studies in patients with duodenal ulcer who were part of a multicentre open dose finding study of omeprazole given for four weeks.⁷

Reduction in aspirated acid after treatment with omeprazole has usually been attributed to inhibition of acid production by this drug without consideration of factors of gastric emptying into, and reflux back from, the duodenum. A marker will allow for loss of secretion from stomach to duodenum so that data can be expressed as corrected volume and outputs of acid and pepsin. After acid component has been secreted by the parietal cell it may be partly or wholly neutralised by alkali secreted by the

stomach or refluxed from the duodenum which has been estimated by the Hobsley formula from the sodium output in the gastric aspirate on the assumption that primary parietal component contains 5.7 mmol/l sodium.⁸ Any changes in intragastric potassium are not relevant to these calculations. Changes in gastric acidity after omeprazole are interpreted in terms of the postulated H^+K^+ exchange of the proton pump at the luminal surface of the parietal cell. Reduction in gastric acidity has been attributed to back diffusion of acid from lumen through mucosa. This mechanism is both controversial and incalculable. Any such back diffusion through undamaged mucosa will be minimal and will not be considered further here.

Methods

PATIENTS

Nine patients (median age 52 years, range 26-63 years) presenting consecutively with symptomatic and endoscopically demonstrated duodenal ulcers gave informed consent to these studies, which were approved by the local ethical committees. There were eight men and one woman. None had received

Address for correspondence: Dr J H Baron, Department of Surgery, Royal Postgraduate Medical School, Hammersmith Hospital, London W12 0HS.

Received for publication 2 November 1984

any treatment for their ulcers in the previous fortnight except with antacids. Four patients were randomly allocated to take a single oral dose of omeprazole 20 mg each morning for four weeks, and the other five took 40 mg in the same way.

Before starting omeprazole, and 24 hours after the last dose, gastric secretion studies were carried out with corrections for gastroduodenal loss by infusing phenol red as a marker, and for duodenal reflux from the sodium output using the Hobsley formulae.^{10 11}

Gastric secretion was aspirated continuously, collected in 10 minute fractions for 30 minutes basal, for 60 minutes after sham feed and for 90 minutes during the intravenous infusion of a maximal dose (6 $\mu\text{g/kg/h}$) of pentagastrin. In the sham feed test the patient chewed and then spat out a toasted ham sandwich during a 10 minute period. Each mouthful was well chewed and then spat out. The mouth was washed out with water to minimise swallowing of food particles. This chew, spit, and rinse was repeated for 10 minutes after which gastric secretion was aspirated continuously for another five 10 minute periods.

The volume of each sample was measured to the nearest 0.5 ml. The pH and titratable acidity were measured by titration with 0.01 M NaOH to pH 7 with an Autoburet titrator. Pepsin was assayed by an Autoanalyzer with haemoglobin as substrate.¹² Sodium and potassium concentrations were measured by Autoanalyzer. Bicarbonate concentrations (by Autoanalyzer) and tryptic activity (by pH stat automatic titrator and p-tosyl-L-arginine methyl ester) were determined in anacid samples, and in four patients chloride concentrations (by Autoanalyzer) were measured also.

Acid secretion was expressed in mmol/h by doubling the basal 30 minute output and tripling the 'plateau' output in the highest two consecutive ten minute outputs after the sham feed and during the pentagastrin infusion. Volumes and outputs of acid and pepsin were then corrected for gastroduodenal loss from the phenol red measurements and gastric acid parietal component calculated as Hobsley's V_G from the sodium measurements. In one of the four patients who took 20 mg omeprazole daily the total phenol red recovery was unsatisfactory in one test so that his corrected results are omitted.

Differences before and after omeprazole were expressed as the mean percentage change and analysed with the Mann-Whitney U test.

Results

ENDOSCOPY

All but one patient (taking 40 mg daily) had

complete healing of the duodenal ulcer at repeat endoscopy after four weeks treatment with omeprazole.

BASAL SECRETION (Fig. 1)

With 20 mg omeprazole daily there were variable changes in acidity but little change in corrected volume or acid output. Acidity and acid output were totally inhibited in two, almost completely inhibited in one, and markedly increased in the other patient. After 40 mg omeprazole, however, daily basal acidity and thus basal acid output were totally inhibited in every patient; corrected volume was reduced by about one third.

SHAM FEEDING

With 20 mg omeprazole daily there was negligible change in volume, but a two-thirds reduction in acidity and thus acid output. Omeprazole 40 mg daily reduced corrected volume by about one-fifth but acidity, and thus acid output, was almost totally (98%) inhibited.

PENTAGASTRIN STIMULATED SECRETION

After omeprazole 20 mg daily corrected volume was reduced by one-fifth, acidity by two-fifths and thus acid output was halved. With 40 mg omeprazole corrected volume was halved, acidity reduced by two-thirds with corrected acid output reduced by a mean of 84%.

PEPSIN

After omeprazole pepsin concentration and corrected outputs in basal and sham feed secretions were about halved with slightly greater reductions after the larger dose. Corrected pepsin outputs after pentagastrin were little altered by either dose of omeprazole, so that with the reduced secretory volume the mean pepsin concentrations increased by two-thirds after both doses.

PARIETAL COMPONENT

The changes in gastric acid parietal component have been calculated as Hobsley's V_G . After 20 mg daily omeprazole basal V_G , like corrected acid output, showed no consistent change; however, the mean percentage reductions of V_G after sham feeding (10%) and pentagastrin (25%) were markedly less than the mean percentage inhibitions of corrected acid output (63% after sham feed and 47% after pentagastrin). These discrepancies were even more marked after the higher 40 mg dose of omeprazole when the mean percentage reductions in V_G after basal, sham feed and pentagastrin were 49, 38, and 56% compared with 100, 98, and 84 mean percentage inhibitions of corrected acid outputs.

Fig. 1 Basal, sham feed and pentagastrin stimulated secretion before and after 20 mg and 40 mg omeprazole for four weeks. Results in the nine patients are shown together with the mean percentage change and the significance of the difference for each measurement. * = $p < 0.05$; ** = $p < 0.01$ by Mann-Whitney U.

An alternative approach to the reduction in acid output is by the Hunt¹³ comparison with change in chloride output in these patients in whom chloride was measured. These two changes were positively and significantly correlated (Fig. 2) and the regression slope for this relationship was 0.80 mmolH⁺/mmol Cl⁻, a value close to the slope anticipated for a change in acid secretion due entirely to a change in parietal cell secretion, 0.85 mmol H⁺/mmol Cl⁻, assuming parietal component contains 155 mmol H⁺/l and 170 mmol Cl⁻/l Hunt¹³ further assumed that were acidity to be decreased from an increase in gastric secretion of bicarbonate (which is secreted with chloride) then the fall in acid output would be accompanied by a rise in output of chloride, and a negative slope; this was not found.

DUODENOGASTRIC REFLUX

Reflux of alkaline duodenal contents into the stomach neutralises a proportion of gastric acid. This reflux, as calculated by the Hobsley sodium output formula was increased by omeprazole; reflux into basal and pentagastrin stimulated secretion was about doubled (+113 and +122%) after 20 mg daily, and more than doubled and almost trebled after 40 mg of omeprazole daily (+138 and +192%). The reduction in acid output after omeprazole can be attributed in part to increased alkaline admixture, with concentrations of bicarbonate as high as 23 mmol/l in anacid samples (pH as high as 8.7). The

Fig. 2 Correlation of acid and chloride changes after omeprazole plotted as change of secretion/10 min for the highest 10 min basal, sham fed and pentagastrin stimulated acid outputs before and after omeprazole 20 mg (two subjects) and 40 mg (two subjects): four subjects, 12 data points. Decreased H⁺ mmol = 1.33 + 0.80 mmol decreased Cl⁻: $r = 0.93$, $p < 0.001$. The lower line represents the relation expected if the changes were due solely to changes in parietal secretion (see Hunt).¹³

source of alkali must have been in part from pancreatic secretion because these alkaline gastric aspirates always had measurable tryptic activity. There may have been a small and invisible contribution from bile which may contain bicarbonate in a concentration up to 25 mmol/l. The contributions of duodenal and gastric mucosal bicarbonate are not calculable.

CATION EXCHANGE

After sham feed and pentagastrin the almost total inhibition of acidity was accompanied by marked increases in potassium concentrations in some patients (Fig. 3). Mean plateau potassium concentrations increased after omeprazole 20 mg/d for four weeks from 8.8 to 11.4 mmol/l (after sham feed) and 11.0 to 18.5 mmol/l (after pentagastrin) and from 11.6 to 15.2 mmol/l (sham feed) ($p < 0.05$) and from 16.0 to 20.4 mmol/l (pentagastrin) after omeprazole 40 mg/d.

Discussion

In these studies omeprazole 20 and 40 mg daily for four weeks produced reductions in observed maximal acid outputs (54 and 84%) comparable with previous series³⁻⁵ which were little changed when the data were corrected for gastroduodenal loss (47 and 84%). The dose related reductions of phenol red corrected basal acid output (totally inhibited in half the patients after 20 mg, and in every patient after 40 mg daily) are comparable with the complete inhibition of basal acid output after 30 and 60 mg daily previously reported.³ The dose related mean reductions in corrected acid output after sham feed (63 and 98%) were also greater than those after pentagastrin (47 and 84%), presumably because sham feed is only a submaximal stimulus comparable to another vagal stimulant, insulin.¹⁴ The markedly smaller mean reductions in pentagastrin (53%) and sham feed stimulated (54%) acid outputs found by Konturek *et al*⁶ after omeprazole 48 mg were presumably because of their use of a single intragastric dose instead of the chronic dosage for at least five days needed to elicit maximum inhibition.⁴

The reductions in titratable acidity were always greater than those in corrected volume, so that aspiration of the stomach after treatment with omeprazole still yields considerable quantities of juice but of low or even zero acidity. These changes cannot be explained with any certainty because there may be more than one effect of the drug.

The major cause of the reduced aspirated acid output after omeprazole is a decrease in secretion of the primary parietal component. The positive Hunt regression of chloride and acid reduction (Fig. 2)

Fig. 3 Gastric secretion (basal and after sham feeding and pentagastrin $6 \mu\text{g/kg/h}$) before (—) and after (---) 28 days of ormeprazole 40 mg daily in a man with duodenal ulcer.

also suggests a reduction of hydrochloric acid secretion, rather than a simple neutralisation by sodium bicarbonate. The constant of 1.33 mmol/10 min in the regression equation suggests, however, some neutralisation by a chloride containing bicar-

bonate secretion, the most likely source of which is reflux into the stomach of alkaline duodenal content rather than from secretion of bicarbonate from non-parietal cells of the gastric mucosa. This reflux has been estimated by the Hobsley formula and

shown to be about double the control after 20 mg, and almost treble after 40 mg, omeprazole daily. The Hobsley formula is based on the assumption that the sodium concentration of pure acid parietal component is negligible and that the sodium content of gastric aspirate is almost entirely from duodenal reflux; the Hobsley calculations would clearly be invalid in samples after omeprazole if this intracellular inhibitor of H^+K^+ ATPase altered sodium fluxes: there are no theoretical pointers or experimental data on this issue. Some of this alkaline juice must be pancreatic in origin because of the tryptic activity detected in alkaline samples of gastric secretion after omeprazole: duodenal mucosa and bile may be additional elements contributing to the bicarbonate in the duodenal juice. The mean percentage reductions of pentagastrin stimulated V_G by the Hobsley formula after 20 mg and 40 mg omeprazole of 25 and 56% are markedly less than the 47 and 84 mean percentage reductions of corrected acid output. This discrepancy between reductions of V_G and of acid output is remarkably similar to the difference after intravenous cimetidine, 50% vs 70%.¹⁵ The increased reflux seen in our patients after omeprazole and in patients after cimetidine is presumably because of the effects of the drugs. It is conceivable that reflux might be increased by alterations in or near the pylorus after healing of the ulcer. We know of no published data on this point, and the only one of our patients whose duodenal ulcer did not heal after omeprazole showed the same increase in calculated reflux as in those other patients whose ulcers did heal.

The high potassium concentrations occasionally seen in gastric aspirates when pentagastrin stimulated acid was suppressed by omeprazole (Fig. 3) are in the same 20–30 mmol/l range which have been seen in dogs with gastric fistulae, both after omeprazole¹⁶ and after another substituted benzimidazole, picoprazole.¹⁷ This rise in gastric juice potassium is probably a parietal cell effect rather than spurious from salivary contamination¹⁸ because the dogs given picoprazole had Komarow oesophagostomies which divert saliva.¹⁷ Mucosal K^+ fluxes have also been seen when omeprazole was applied to the isolated guinea pig mucosa.¹⁶ These results are therefore compatible with the hypothesis that omeprazole inhibits gastric acid by an effect on the H^+K^+ ATPase of the parietal cell proton pump involving H^+ transport, and possibly also an exchange of H^+ for K^+ .¹⁷

Omeprazole is not known to have any action on the chief cells¹⁹ or indeed on any other cell in the body except the parietal cell. The pepsin concentrations and corrected outputs in basal secretion and after sham feeding were about halved, and the

proteolytic effects of these concentrations of pepsin would be minimal at the high pH often found in basal and sham feed stimulated gastric juice after omeprazole seen both in this study and in 24 hour studies including basal, interdigestive, and nocturnal secretion.²⁰

Corrected pepsin outputs after pentagastrin were little altered by either dose of omeprazole. The corrected secretory volume was, however, reduced (see above) so that with both doses the mean pepsin concentrations were increased by two-thirds. pH values below 3.5 occasionally occur during omeprazole therapy²⁰ so that pepsin could be proteolytic in these circumstances. The biological effect of this increased pepsin concentration taken together with the reduced acidity and acid output is uncertain.

We are most grateful to Sister Leela Francis-Reme, and Mr Kang Li for their skilful performance and analysis of these secretion tests. We wish to thank Astra Pharmaceuticals for supplying the omeprazole and for their support.

References

- 1 Fellenius E, Berglinth T, Sachs G, *et al.* Substituted benzimidazoles inhibit gastric acid secretion by blocking ($H^+ + K^+$) ATPase. *Nature* 1981; **290**: 159–61.
- 2 Olbe L, Haglund U, Leth R *et al.* Effects of substituted benzimidazole (H 149/194) on gastric acid secretion in humans. *Gastroenterology* 1982; **83**: 193–8.
- 3 Howden CW, Forrest JAH, Reid JL. The effects of omeprazole on gastric secretion in man. *Clin Sci* 1983; **64**: 74p.
- 4 Lind T, Cederberg C, Ekenved G, Haglund U, Olbe L. Effect of omeprazole – a gastric proton pump inhibitor on pentagastrin stimulated acid secretion in man. *Gut* 1983; **24**: 270–6.
- 5 Muller P, Dammann H-G, Seitz H, Simon B. Effect of repeated, once daily, oral omeprazole on gastric secretion. *Lancet* 1983; **1**: 66.
- 6 Konturek SJ, Kweiczen N, Obtulowicz W, Kopp B, Oleksy J. Action of omeprazole (a benzimidazole derivative) on secretory responses to sham feeding and pentagastrin and upon serum gastrin and pancreatic polypeptide in duodenal ulcer patients. *Gut* 1984; **25**: 14–8.
- 7 Co-operative Study. Omeprazole in duodenal ulceration: acid inhibition, symptom relief, endoscopic healing, and recurrence. *Br Med J* 1984; **289**: 525–8.
- 8 Hobsley M. Pyloric reflux: a modification of the two-component hypothesis of gastric secretion. *Clin Sci* 1974; **47**: 131–41.
- 9 Baron JH. *Clinical tests of gastric secretion. History, methodology and interpretation.* London: Macmillan Press, 1978.

- 10 Faber RG, Russell RCG, Royston CMS, Whitfield P, Hobbsley M. Duodenal reflux during insulin-stimulated secretion. *Gut* 1974; **15**: 880–4.
- 11 McCloy RF. A basal-insulin-pentagastrin gastric secretion test. Appendix to Baron JH. *Clinical tests of gastric secretion. History methodology and interpretation*. London: Macmillan Press, 1978; 212–7.
- 12 Vatie J, Cheret AM, Bonfils S. Le dosage automatique de l'activite protéolytique du suc gastrique. *Biol Gastroenterol* 1968; **1**: 15–29.
- 13 Hunt JN, Smith JL, Jiang CL, Kessler L. Effect of synthetic prostaglandin E₁ analog on aspirin-induced gastric bleeding and secretion. *Dig Dis Sci* 1983; **28**: 897–902.
- 14 Utley RJ, Carter DC. The effect of a single dose of omeprazole on insulin induced gastric secretion in healthy subjects. *Br J Surg* 1983; **70**: 295.
- 15 Suleiman S, Whitfield PF, Parkin JV, Nwabunike TO, Hobbsley M. Reduction of acid secretion induced by cimetidine is less than it seems. [Abstract]. *Gut* 1980; **21**: A450.
- 16 Larsson H, Ryberg B, Karlsson A, Carlsson E, Sundell G. Omeprazole interferes with gastric mucosal potassium flow during histamine stimulated secretion. *Scand J Gastroenterol* 1982; **17**: suppl 78, 274.
- 17 Hirschowitz BI, Fong J. Effects of KC1 and insulin on benzimidazole-inhibited canine gastric secretion. *Am J of Physiol* 1983; **245**: G739–744.
- 18 Okosdinossinian EK, El Munshid HA. Composition of the alkaline component of human gastric juice – effect of swallowed saliva and duodeno-gastric reflux. *Scand J Gastroenterol* 1977; **12**: 945–50.
- 19 Fryklund J, Wallmark B, Larsson H, Helander HF. Effect of omeprazole on gastric secretion on H⁺, K⁺-ATPase and in pepsinogen – rich cell fractions from rabbit gastric mucosa. *Biochem Pharmacol* 1984; **33**: 273–80.
- 20 Walt RP, Wood EC, Logan LH, Gomes MFA, Pounder RE. Effect of daily oral omeprazole on 24 hour intragastric acidity. *Br Med J* 1983; **287**: 12–14.