The effect of omeprazole on gastric emptying in patients with duodenal ulcer disease

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The effect of a single oral dose of omeprazole (90 mg) on gastric emptying was assessed with a dual isotope scintigraphic technique in eight patients with a history of duodenal ulcer disease. Omeprazole had no significant effect on solid or liquid gastric emptying. The bioavailability ($AUC_{0-2\text{ h}}$) of omeprazole in all patients was greater than that required for total suppression of acid secretion. No adverse clinical or laboratory effects were observed.

Keywords omeprazole gastric emptying duodenal ulcer

Introduction

Omeprazole is a substituted benzimidazole which inhibits basal and stimulated gastric acid secretion in animals (Larsson *et al.*, 1983) and humans (Lind *et al.*, 1983). This effect may be due to non-competitive inhibition of an H^+ , K^+ -ATPase which functions as a 'proton pump' in the secretory membrane of the parietal cell (Fellenius *et al.*, 1981).

Preliminary data from animal experiments have demonstrated that omeprazole delays gastric emptying in rats after oral, but not intravenous, administration of a high dose (400 $\mu\text{mol/kg}$ p.o. and 80 $\mu\text{mol/kg}$ i.v.; Larsson & Carlsson, 1981). Since the plasma concentrations of omeprazole were similar following administration by either route, a local rather than a systemic effect was suggested. The potential impact of omeprazole in peptic ulcer therapy (Gustavsson *et al.*, 1983) suggested the necessity to investigate its effect on gastric emptying in humans. Radionuclide methods are now widely applied to the non-invasive measurement of gastric emptying of both solid and liquid meal components (Horowitz *et al.*, 1982) and in this study we have used a radionuclide technique (Collins *et al.*, 1983) to evaluate the effect of a single oral dose of omeprazole (90 mg) on gastric emptying in patients with duodenal ulcer disease.

Methods

Eight male patients 34–60 years of age (median 51.5) with duodenal ulcer disease in remission were included in the study. The diagnosis of duodenal ulcer had previously been established in all patients by endoscopy. No patient was receiving any anti-ulcer medication or experiencing gastrointestinal symptoms at the time of entry. Written informed consent was obtained and the study protocol was approved by the Research Review Committee of the Royal Adelaide Hospital.

Each patient participated in two experiments, arranged in random order and separated by at least seven days, in which a single oral dose of omeprazole (90 mg of an encapsulated, uncoated granulate) or placebo was administered at 08.00 h, under double-blind conditions and after an overnight fast. 300 ml of a 160 mmol/l sodium bicarbonate solution was administered in divided doses before, together with and for 30 min after drug administration, to avoid acid degradation of omeprazole (Lind *et al.*, 1983).

An indwelling venous cannula was used to obtain blood samples (5 ml) for assay of omeprazole at 08.00, 08.15, 08.30, 08.45, 09.00, 09.30 and 10.00 h. Plasma omeprazole concentrations were measured with a chromatographic technique (Mihaly *et al.*, 1983) and the area

under the plasma omeprazole concentration-time curve from 0 to 2 h ($AUC_{0-2\text{ h}}$) was calculated by the trapezoidal rule.

Gastric emptying was measured with a dual isotope scintigraphic technique (Collins *et al.*, 1983), commencing at 10.00 h and continuing for at least 2 h. The solid meal was a 100 g ground beef hamburger containing *in vivo* labelled ^{99m}Tc chicken liver (Meyer *et al.*, 1976) and the liquid meal was 150 ml of 10% dextrose in water containing ^{133m}In -DPTA. The patient was seated and a posteriorly positioned scintillation camera was used for data acquisition. From the histograms for the solid and liquid components of the meal (expressed as percent remaining within the stomach *vs* time) several parameters were derived. For the solid component these were the lag period before food left the stomach, the time for 50% emptying (t_{50}) and the average rate of linear emptying (expressed as %/min). For the liquid component, the t_{50} and the amount of tracer remaining at 10 min after ingestion were obtained. The amount of liquid remaining at 10 min after ingestion was used as an index of the early phase of liquid emptying (Colmer *et al.*, 1973). Safety evaluations included blood pressure and pulse rate recordings at 08.00, 08.30, 09.00 and 12.00 h on each study day and a thorough clinical examination and haematological/biochemical blood screen before the first and after the second study.

Gastric emptying data were analysed using Student's two-tailed *t*-test for paired data and changes in cardiovascular parameters were analysed using two-way analysis of variance. A *P* value of less than or equal to 0.05 was considered significant in all analyses.

Results

All patients tolerated the study well and no adverse symptoms or unwanted laboratory effects were observed. Both blood pressure and pulse rate tended to fall slightly during the experiment in all patients, on both study days (Figure 1). The changes in blood pressure were not significant. The small fall in pulse rate was statistically significant 60 min after administration of omeprazole ($P < 0.05$), relative to the value obtained in the placebo group at the same time.

As has been reported previously (Collins *et al.*, 1983), a large interindividual variation in gastric emptying rates was observed. In all subjects solid emptied more slowly than liquid and was characterised by a lag period, followed by an emptying phase which approximated a

Figure 1 Pulse rate and systolic/diastolic blood pressure recorded during gastric emptying measurements in eight patients (mean $\pm$ s.e. mean) given oral omeprazole (90 mg, ■) or placebo (□) together with bicarbonate buffer. * $P < 0.001$ relative to pre-dose values, ** $P < 0.001$ relative to pre-dose and $P < 0.05$ relative to placebo.

linear pattern. The emptying of liquid was non-linear, with a slope that decreased with time and approximated a monoexponential pattern. Omeprazole had no significant effect on parameters of solid or liquid emptying as assessed by Student's *t*-test ($P > 0.1$) and 95% confidence limits (Table 1).

The plasma omeprazole concentrations also showed large interindividual variations. The mean AUC was $12.9 \pm 2.3 \mu\text{mol l}^{-1} \text{ h}$ (range 4.5–20.6) and the time of peak plasma concentration ($C_{\text{max}} = 11.3 \pm 1.4 \mu\text{mol/l}$) varied between 30 and 240 min (the latter being a second peak in one patient), with a median value of 30 min. As all patients had significant plasma concentrations of omeprazole at the end of the sampling period, the $AUC_{0-2\text{ h}}$ represents a considerable underestimation of the total AUC , and therefore bioavailability of omeprazole administered at this dose. There was no correlation between the $AUC_{0-2\text{ h}}$ and parameters of either liquid or solid emptying.

Table 1 Solid and liquid gastric emptying in eight patients (mean $\pm$ s.e. mean) given oral omeprazole (90 mg) or placebo

	Placebo	Omeprazole
Solid lag period (min)	18 $\pm$ 2	21 $\pm$ 4
Solid 50% emptying time (min)	72 $\pm$ 7	82 $\pm$ 10
Solid linear emptying time (%/min)	0.8 $\pm$ 0.1	0.8 $\pm$ 0.1
Retention of liquid at 10 min (%)	61 $\pm$ 4	69 $\pm$ 5
Liquid 50% emptying time (min)	14 $\pm$ 3	18 $\pm$ 3

Discussion

The results of this study indicate that oral administration of a single 90 mg dose of omeprazole is well tolerated and has no significant effect on gastric emptying of solids or liquids. A small (but statistically non-significant) trend towards a delay in emptying of liquids and solids is seen in the mean values (Table 1). The large interindividual variation in gastric emptying rates and the limitations on the number of patients who can be studied by this technique increase the possibility of a type II error. However the size of the trend is small, and unlikely to be of clinical significance, particularly in view of the large dose of omeprazole used. The observation of AUC values in all patients which were substantially greater than those necessary for total suppression of pentagastrin-stimulated acid secretion (Lind *et al.*, 1983) indicates that the antisecretory effects of omeprazole would be maximal (and total) during the period of the gastric emptying study. The dosage and formulation of omeprazole used in this study facilitated rapid absorption of a large dose, administered in a way that ensured contact with the gastric mucosa. Therefore any direct (local) effects of omeprazole, or an effect secondary to inhibition of acid secretion should have been identified in this situation.

A deficiency of all radionuclide gastric emptying methods is that only the emptying of the marker is assessed and the effects of dilution by gastric secretion are not quantified. A reduction in gastric secretion may theoretically result in an apparent increase in the gastric emptying rate which could offset a drug-induced delay. However, no change in the early phase of liquid emptying was detected (when the volume of meal-stimulated gastric secretion would be minimal) and solid emptying is largely independent of the volume of intragastric liquid (Meyer, 1979). It is therefore unlikely that a reduction in gastric secretion in the omeprazole treated group contributed to the observed results.

Intraduodenal pH has been demonstrated to

influence gastric emptying (Hunt & Knox, 1972) and any antisecretory drug will reduce duodenal acid load, while also modifying gastrin and secretin release, which might in turn alter gastric emptying. Despite these theoretical possibilities, studies on the influence of H₂-receptor antagonists (Scarpignato *et al.*, 1982) and alkali (Deering *et al.*, 1979) on gastric emptying in humans have shown no consistent effect, and support our conclusion that elevation of intragastric pH does not influence gastric emptying. It is therefore unlikely that the bicarbonate buffer (which was given to controls as well as omeprazole groups and would largely be emptied before the start of the emptying study) obscured any drug effect. For clinical use omeprazole will be formulated in enteric coated granules (and not administered with bicarbonate), but the high plasma concentrations achieved in the present study make any effect on gastric emptying unlikely.

The delay in gastric emptying due to omeprazole which was reported in the rat, and identified as being of local origin (Larsson & Carlsson, 1981) may reflect species differences or have resulted from the increased osmolality of the gastric contents (Hunt, 1983) which would have accompanied oral administration of such a large dose of omeprazole.

The findings of a recent study suggest that omeprazole at doses of 20–60 mg/day induces healing of duodenal ulcer more rapidly and in a higher frequency than has been observed with other available drugs (Gustavsson *et al.*, 1983). The safety of omeprazole remains to be established in large scale clinical investigations, but it is of interest to note that oral administration of a large dose in this study was not associated with any adverse effects. The small reduction in pulse rate observed after omeprazole administration was significant, but was matched by consistent (but non-significant) reductions after placebo administration. Such findings have not previously been reported and some relationship to the experimental procedure must be suspected.

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