Effect of ‘weekend therapy’ with omeprazole on basal and stimulated acid secretion and fasting plasma gastrin in duodenal ulcer patients

E G HEWSON, N D YEOMANS, P W ANGUS, A SHULKES, C W BROOK, R B SEWELL, AND R A SMALLWOOD

From the University of Melbourne Departments of Medicine (Gastroenterology) and Surgery, Austin Hospital, Melbourne, Victoria, Australia

SUMMARY The effect of intermittent dosage with omeprazole on basal and pentagastrin stimulated gastric acid secretion and fasting plasma gastrin was assessed in eight duodenal ulcer subjects who were in remission. Omeprazole (20 mg daily) was given for a three day ‘weekend’ each week for two months. Twenty four hours after the first and eighth weekend, basal and peak acid output were still markedly suppressed (>50%) compared with pretreatment. After the treatment free four days, however (just before the eighth weekend), peak acid output had returned to pretreatment values; basal acid output was still somewhat reduced (mean 3·6 mmol/l) but the difference from baseline was not statistically significant. Fasting plasma gastrin concentration increased slightly but significantly, from a baseline median of 17 pmol/l to 25 and 31 pmol/l respectively, 24 hours after the first and eighth weekends. All but two values (of 16) remained within the reference range. Before the fourth and eighth weekends, and again at 12 days and three months after treatment, gastrin values were not significantly different from baseline. Thus a ‘weekend therapy’ regimen with this long acting antisecretory compound produces substantial acid suppression, but for only part of the week, with modest and reversible changes in fasting plasma gastrin. It should therefore be suitable for efficacy testing for prevention of recurrence of peptic ulcer or reflux oesophagitis.

The gastric [H+ + K+] ATPase inhibitor, omeprazole, is very effective for the relief of symptoms and healing of peptic ulcer and of reflux oesophagitis. As with other presently available agents, however, relapse is common after treatment has ceased and the diseases are allowed to resume their natural course.

With the histamine H2-receptor antagonists, the strategy that has evolved for preventing recurrence has been maintenance therapy with a reduced dose. This may not be a suitable strategy with omeprazole, however, as the acid suppression achieved with low doses is unpredictable. In patients treated with 10 mg daily, some show little or no change in 24 hour gastric acidity, while in others it is suppressed by more than 90%.

A novel alternative approach would be to use omeprazole in full dosage (20 mg/d) in pulses, which would allow time in between periods of acid suppression for secretion to return to normal or near to normal. Because of omeprazole’s long duration of action, ‘weekend’ therapy of two or three days each week may provide a suitable regimen.

We have examined the effects on acid secretion of administering omeprazole for three days each week, to see if there is evidence of residual acid suppression at the end of the treatment free period and whether the acid inhibitory effect changes during two months of dosage. Because of recent evidence that near total acid suppression can induce fundic endocrine cell hyperplasia which is mediated by hypersecretion of...
gastrin, we have also assessed fasting plasma gastrin concentrations during and up to three months after the dosage period.

Methods

Subjects

Eight male subjects who had had a duodenal ulcer diagnosed by endoscopy within the previous two years took part. At the time of inclusion, all were in symptomatic remission and physical examination and baseline laboratory tests were normal. None had undergone ulcer surgery. Their mean age was 41 years (range: 26–52) and mean weight 72 kg (55–84). Two of the eight were regular smokers. Informed consent was obtained in writing from each patient and the study was approved by the Austin Hospital Ethical Review Committee.

Study design

The experimental design is indicated in Figure 1. During the week before the study, no antisecretory drugs were taken. The subjects then underwent eight weeks of ‘weekend therapy’ with omeprazole. This consisted of administration of omeprazole 20 mg orally, formulated as an enteric coated granulate in hard gelatin capsules, for three consecutive mornings (‘weekend’) each week.

Acid secretion (basal and pentagastrin stimulated) was measured immediately before the first omeprazole dose and 24 hours after the third daily dose, on the first and last ‘weekends’. Plasma was taken from the fasted subjects for gastrin assay before each of the acid secretory tests, as well as before the omeprazole dose at the start of weekend four. Further samples were taken 12 days and three months after the final weekend of dosage.

Subjects were questioned about any possible adverse effects at visits on the first, fourth, and final weekends and two weeks after cessation of treatment. Compliance was monitored by examining returned medication packages at each visit. Laboratory monitoring was done on entry, on the morning of the fourth weekend and on the final day of the eighth weekend; tests carried out included urine dipstick analysis, routine haematological indices (haemoglobin, leucocyte count, etc), and serum biochemistry analyses for electrolytes and renal and hepatic function.

Acid secretion studies

Subjects fasted overnight before each study. At approximately 0800 hours, a 12F Salem nasogastric sump tube (Argyle, USA) was placed in the most dependent part of the stomach, and its position checked by measurement of aspirate pH and by water recovery test. Resting contents were aspirated and discarded, after which gastric juice was collected by continuous mechanical suction supplemented by manual aspiration every five minutes. Basal secretion was collected for the first hour. Stimulated secretion was then collected in 15 minute aliquots for one hour after the subcutaneous injection of pentagastrin 6 μg/kg (ICI, Australia).

Volume and pH were recorded, and hydrogen ion concentration measured by titration to pH 7-0 with 0·1 M NaOH using an autoburette. Basal acid output (BAO) was calculated from the hydrogen ion output in the first hour, and peak acid output (PAO) was calculated (as usual) by summing the two highest consecutive 15 minute outputs in the postpenta-gastrin hour and converting this value to mmol/h.

Plasma gastrin measurement

Blood for plasma gastrin measurement was taken with subjects fasting, and prior to the passage of the nasogastric tube on days when acid studies were performed. Two samples were taken 5 minutes apart into lithium heparin tubes containing 300 kIU aprotinin (Bayer), and the plasma was separated and stored at –20°C until assayed. Gastrin concentration was determined by a radioimmunoassay13 with a detection limit of 2 pmol/l and a within assay coefficient of variation 2% at 30 pmol/l. All samples were run as a single batch (except for the final samples taken three months after treatment). Antiserum 1296 was used; this detects all C-terminal fragments longer than the pentapeptide.14 The upper limit of the reference range for this assay is 50 pmol/l. The duplicate samples for each patient differed by 2-4 (0-4) pmol/l (mean (SE)), and were meaned.

Statistical analyses

Acid outputs were normally distributed and are expressed as means and standard errors. The gastrin data were not normally distributed, therefore
medians and interquartile ranges (IQR) were calculated. Non-parametric tests of statistical significance were used throughout. Friedman's non-parametric two way analysis of variance was first applied to each set of data. When this indicated a probability less than 0.05 for the null hypothesis, the critical range test was used to disssout which values differed significantly from the baseline.

Results

ACID SECRETION
The individual values for BAO and PAO in the four secretion studies are shown in Figures 2 and 3. On the baseline day, BAO in the eight subjects was 7-6 (1·7) mmol/h (mean (SE)) and PAO was 48-4 (4·0) mmol/h. Twenty four hours after the first ‘weekend’ of omeprazole dosage, BAO and PAO were significantly inhibited – by 81 (13) and 72 (9)% respectively.

Immediately before the final ‘weekend’ – that is, five days after the last preceding omeprazole dose, mean BAO was 3-6 (1·2) mmol/h. This was about half the baseline mean, but the difference did not reach significance. At this time, PAO had returned to values similar to pretreatment (p>0·95, Friedman critical range).

Twenty four hours after the final ‘weekend’ of omeprazole treatment, BAO and PAO, were again markedly inhibited. There was no evidence of the development of further acid suppression as a result of the eight ‘weekends’ of dosage: acid outputs were similar at this time to those measured 24 hours after the first ‘weekend’.

Fig. 2 Basal acid output (BAO) for the eight subjects before and 24 hours after the first and eighth ‘weekends’ of omeprazole dosage. *p<0·05, **p<0·01 compared with PRE1 baseline (Friedman test+critical range test).

Fig. 3 Peak acid output (PAO) in the individual subjects. Significances as for Fig. 2.

PLASMA GASTRIN
The fasting plasma gastrin concentrations in individual subjects are indicated in Figure 4. Baseline measurements were within the reference range (<50 pmol/l) in all subjects, with the median 17 pmol/l and IQR 14–20 pmol/l.

Small but significant rises in plasma gastrin were observed in the samples taken 24 hours after the first (p<0·05) and eighth (p<0·01) weekends of dosage (Friedman test plus critical range test). At these times, median (and IQR) values were 25 (19–33) and 31 (27–35) pmol/l respectively, and values outside the reference range (51 and 82 pmol/l) were recorded in one (different) individual at each time. At the other sampling times – before weekends four and eight, and 12 days (weekend 10) and three months (weekend 20–22) after treatment – median values were not significantly different from baseline.

There was no significant correlation between the fasting gastrin concentrations and the corresponding BAO and PAO values in this group of patients. The mean difference between the gastrin concentrations in the duplicate samples at each visit was 2·5 pmol/l.

SAFETY MONITORING AND COMPLIANCE
No adverse symptoms were reported and no significant alterations in laboratory values occurred during the study, except for one subject who developed a neutrophil leucocytosis at the final weekend, considered to be secondary to an intercurrent bronchitis. As judged by returned medication packages, compliance was 100% by all subjects.

Discussion

This study was undertaken to develop a convenient maintenance dosage schedule with this long acting
drug, which might prevent the recurrence of acid peptic diseases yet avoid any putative adverse consequences of continuous acid suppression over long periods. Indications that it may be desirable to avoid near total achlorhydria in the long term come from reports of the development of enterochromaffin like (ECL) cell carcinoid tumours in rats treated with very high dose omeprazole for two years,\textsuperscript{15} and the recent recognition that ECL cell carcinoids occasionally occur in patients with pernicious anaemia.\textsuperscript{16}

Initially, the possibility that omeprazole stimulates ECL cell proliferation directly was mooted. It now seems likely, however, that the mediator of the ECL cell changes is gastrin. First, ECL cell hyperplasia can be induced in rats by other antisecretory (and gastrin raising) drugs such as ranitidine,\textsuperscript{12} and the omeprazole induced hyperplasia is prevented by antrectomy.\textsuperscript{12} Furthermore, ECL cell hyperplasia and ECL cell carcinoids have now been documented in patients with pernicious anaemia and the Zollinger-Ellison syndrome\textsuperscript{16-19} — both characterised by marked and sustained hypergastrinaemia.

The findings of the present study indicate that ‘weekend therapy’ with omeprazole 20 mg daily for three days per week is likely to result in substantial acid suppression for about half the week, but a return of acid secretion to normal or near normal before the next ‘weekend’. With regard to longterm effects, it is reassuring that the inhibition of peak acid secretion was much the same after the eighth weekend as the first. There was, therefore, no suggestion of an augmenting inhibition during two months’ dosage.

Nor was there any significant tachyphylaxis, which has been shown during continued therapy with histamine H\textsubscript{2}-receptor antagonists.\textsuperscript{20,21}

We chose to use a three rather than a two day ‘weekend’ for the present study for two reasons. First, inhibition of acid output increases over the first three to four days of dosage,\textsuperscript{22} so that the maximal effect attainable with a given dose would not be reached during a two day weekend. This increasing inhibition seems to be partly caused by an accumulation of pharmacological effect (because of long duration of action),\textsuperscript{23} and partly by an increase in the bioavailability of this acid labile drug as gastric acidity reduces.\textsuperscript{24} Second, as the half time of effect is about 24–36 hours,\textsuperscript{24} two days of dosing might be expected to reduce acid secretion by \( \geq \) 50% for only two to three days of seven — possibly not long enough to be effective in preventing ulcer or oesophagitis recurrence. Nevertheless, in our study there was a trend towards some residual inhibition of BAO at the end of the week. Sharma et al also found gastric acidity to be still reduced by 26% after a week without therapy.\textsuperscript{10} Hence the effects on acid secretion during the week of a two day pulse with omeprazole, perhaps at a higher dose than used here, are probably worth evaluating.

Our findings suggest that administration of omeprazole by the present regimen is only a mild stimulus to gastrin secretion. The modest increases at the end of the first and eighth weekends were similar to those found by several other groups after a few days to a few weeks of treatment.\textsuperscript{20,21,26} Although not statistically significant, there was a trend towards slightly higher values in our patients at the end of the two months’ therapy compared with the beginning, and a single patient showed a progressive rise during treatment (although only the final value exceeded the reference range). Because maintenance therapy to prevent peptic ulcer relapse is usually given for several years, it may therefore be prudent to examine the effect of ‘weekend therapy’ on plasma gastrin and acid secretion over a longer period, before concluding that substantial hypergastrinaemia or hypoclorhydria does not occur in occasional individuals at some later time. Such a study should also include ECL cell counting, because our postulate that cyclic modest rises of plasma gastrin are less likely than continuous rises to stimulate proliferation of these cells has not been tested.

To put the 80% increase in median plasma gastrin after the final treatment ‘weekend’ of this study into perspective, it should be noted that only one value at this time lay outside the reference range. It is particularly worthwhile to compare these gastrin increments with the increments reported after vagotomy and during maintenance treatment with
other antisecretory drugs. Jaffe et al. found that basal plasma gastrin concentration increased by 60% after selective or proximal vagotomy, while Korman et al. noted a 500% increase in patients with truncal vagotomy compared with unoperated ulcer controls. This has not been a universal finding, however: McGuigan and Trudeau found only a non-significant upward trend in gastrin in another vagotomy series. In duodenal ulcer patients given maintenance therapy with cimetidine, Hansky et al. showed a progressive increase in plasma gastrin concentration, with basal values increased by 40% and meal stimulated by 260% after six months. In contrast with the modest increases in plasma gastrin concentrations in patients receiving antisecretory drugs or subjected to vagotomy, the pernicious anaemia patients who were reported to develop ECL cell carcinoids all had gastrin concentrations higher than 1000 pmol/l.

We conclude that ‘weekend therapy’ with omeprazole produces substantial but intermittent suppression of acid, and only a mild and reversible rise of plasma gastrin during the week. We consider that this regimen is worth evaluating for efficacy in preventing the recurrence of peptic ulcer and reflux oesophagitis.

This work was supported in part by the National Health and Medical Research Council of Australia. Omeprazole was kindly donated by Astra (Australia). The technical assistance of Miss E Iliadis is gratefully acknowledged.

This work has appeared previously in abstract form (Gastroenterology 1987; 92: 1434).

References


