Effects of single and repeated doses of omeprazole on gastric acid and pepsin secretion in man

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SUMMARY  The effects of omeprazole, a substituted benzimidazole, on gastric acid and pepsin secretion have been studied in twelve healthy subjects. From six to eight hours after a single oral dose of 30 mg, there was a 66% reduction in basal acid output, and a 71·2% reduction in pentagastrin stimulated acid output. A single dose of 60 mg produced a 91·7% reduction in basal acid output and a 95·3% reduction in pentagastrin stimulated acid output. After seven days treatment with 30 or 60 mg daily, there was almost 100% inhibition of both basal and pentagastrin stimulated acid output. Omeprazole did not significantly affect pepsin secretion which is in keeping with its proposed mode of action, as an inhibitor of the H⁺/K⁺-ATPase enzyme on the secretory membrane of the parietal cell. There were no side effects after omeprazole either with single or repeated dosing.

The substituted benzimidazoles are new agents which are potent inhibitors of gastric acid secretion. They act by selective, non-competitive inhibition of the H⁺/K⁺-ATPase enzyme in the parietal cell.1 This enzyme is the active transport mechanism for hydrogen ion secretion in the stomach. Although one of these agents, omeprazole, has been shown to suppress basal and pentagastrin stimulated acid secretion after a single dose,2 little is known about its effects after repeated dosing. In addition, previous studies have used a buffered suspension of the drug2 as it is partially inactivated by gastric acid, or have looked at its acid inhibitory effect 24 hours after a dose.3

We have studied the effects of two different doses of omeprazole on basal and pentagastrin stimulated acid and pepsin secretion after a single dose and after seven days of treatment. Capsules of enteric-coated omeprazole granules were used, and the effects studied around the time of expected maximum acid inhibition.

Methods

Subjects
Twelve healthy male subjects, mean age 25·2 years (range 19–34 years) were studied. None had any past medical history of note or was on any medication. All subjects gave informed written consent to the study which was approved by the research and ethical committee of the Greater Glasgow Health Board, Northern District.

Subjects were randomly allocated to one of two groups. Each received one dose of placebo followed after three to five days by either 30 mg or 60 mg of omeprazole orally as a single daily dose for seven days. Subjects attended the Clinical Pharmacology Research Laboratory on three occasions during the study: day 0 (placebo); day one (first dose omeprazole) and day seven (seventh dose omeprazole). The study design was identical on each occasion. Subjects arrived fasted at around 0830 hours and were given capsules containing enteric-coated omeprazole granules or placebo. A standard light breakfast was given 15 minutes after drug administration and the subject remained fasted for the remainder of the study day. At around 1415 hours (or 5½ hours postdose) a size 16 FG vented naso-gastric tube was passed and its position checked by means of a water recovery technique.4 From 1430 until 1530 hours – that is, from six to seven hours postdose – gastric juice was aspirated continuously and collected as four 15 minute samples for measurement of basal acid output. During the next hour, each subject received an intravenous infusion of pentagastrin (1·2 μg/kg/h), and gastric juice was
continuously aspirated and collected as four 15 minute samples for determination of plateau acid output.

Basal acid output was defined as the acid produced in the second half of the basal hour multiplied by a factor of two, and plateau acid output as the acid produced in the two consecutive highest 15 minute periods of the second hour multiplied by a factor of two. An intravenous infusion of pentagastrin was used to give a constant rate of stimulation, and the dose selected was designed to give a near maximal stimulus without producing systemic side effects. Acid output was determined by titration to pH 7.0 with 0.1M sodium hydroxide. A small aliquot of gastric juice was taken from each sample for estimation of pepsin secretion by the method of Berstad. Results are expressed as mean ± standard deviation. Statistical comparisons were made using the Mann-Whitney U test.

Results

Basal and pentagastrin stimulated acid output after placebo were similar in the two groups. A single dose of 30 mg produced a 66% reduction in basal acid output, and a 71.2% reduction in plateau acid output (p<0.01). The volume of gastric juice was reduced by 30.8% in the basal hour (p<0.05) and by 47.1% in response to pentagastrin (p<0.01). Basal pepsin secretion was not significantly altered although there was an apparently significant (p<0.05) rise in pepsin secretion in the pentagastrin stimulated hour. After seven days of omeprazole 30 mg daily, basal acid output was reduced by 99.8% (p<0.05) and plateau acid output by 98.4% (p<0.01) when compared with values following placebo. Five of the six subjects produced no acid in the basal hour and three remained achlorhydric in reponse to pentagastrin. The volume of gastric juice at the end of the seven day course was reduced by 54.9% (p<0.01) and 79.2% (p<0.01) in the basal and pentagastrin stimulated hours respectively. There were no significant changes in pepsin secretion either basally or after pentagastrin (Table 1).

A single 60 mg dose of omeprazole had a much greater effect on acid output reducing basal acid output and plateau acid output by 91.7% (p<0.05) and 95.3% (p<0.01) respectively. Volumes of gastric juice secretal in the basal and pentagastrin stimulated hours were reduced by 59.2% (p<0.01) and 79.5% (p<0.01) respectively. There was no significant change in pepsin secretion. After seven days treatment with omeprazole 60 mg daily, basal acid output was reduced by 99.1% (p<0.01) and plateau acid output by 99.0% (p<0.01). Volumes of gastric juice were reduced by 62.3% (p<0.01) in the basal hour and by 83.8% (p<0.01) in the pentagastrin stimulated hours. Pepsin secretion did not significantly change (Table 2).

No side effects were encountered with omeprazole. Each subject kept a diary for the duration of the study in which they were asked to note any adverse events and none was recorded. Subjects were also specifically asked about side effects on each of the three study days and, again, none was reported. Standard biochemical and haematological indices were measured before inclusion in the study, and were repeated within five days of completion of the study. No drug related abnormalities were found.

Discussion

These data show that omeprazole, in doses of 30 or 60 mg daily, is a potent inhibitor of gastric acid secretion, when this is assessed around the time of expected maximum effect. It has no significant effect

| Basal | | Stimulated |
|-------|-------|-------|-------|
|       | Acid output (mmol/h) | Pepsin output (mg/h) | Volume (ml) | Acid output (mmol/h) | Pepsin output (mg/h) | Volume (ml) |
| Placebo | 4.30 +3.37 | 22.2 ± 16.4 | 99.7 ± 34.3 | 35.41 ± 5.45 | 5.4 ± 2.9 | 302.0 ± 42.7 |
|        | 1.53 ±1.91 | 17.8 ± 12.2 | 69.0 ± 22.6 | 10.24 ± 10.06 | 36.8 ± 46.1 | 159.7 ± 66.8 |
| Seventh dose | 5.01 ±0.02 | 5.2 ± 4.1 | 45.0 ± 12.0 | 0.58 ± 0.99 | 18.3 ± 18.8 | 62.7 ± 19.3 |

* p<0.05. † p<0.01
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Table 2  Acid and pepsin output and volume of gastric juice after placebo, first dose of 60 mg omeprazole and seventh dose of 60 mg omeprazole. (n=6; mean ± SD)

<table>
<thead>
<tr>
<th></th>
<th>Basal</th>
<th>Stimulated</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Acid output (mmol/h)</td>
<td>Pepsin output (mg/h)</td>
</tr>
<tr>
<td>Placebo</td>
<td>4.56</td>
<td>11.8</td>
</tr>
<tr>
<td></td>
<td>±3.19</td>
<td>± 7.5</td>
</tr>
<tr>
<td>First dose</td>
<td>0.38</td>
<td>13.1</td>
</tr>
<tr>
<td></td>
<td>±0.49*</td>
<td>±17.1</td>
</tr>
<tr>
<td>Seventh dose</td>
<td>0.04</td>
<td>6.0</td>
</tr>
<tr>
<td></td>
<td>±0.09†</td>
<td>± 5.2</td>
</tr>
</tbody>
</table>

* p<0.05.  † p<0.01

on pepsin secretion. This is consistent with the proposed mechanism and site of action of the drug.

Sixty milligrams of omeprazole produced a greater inhibitory effect than 30 mg after a single dose. This is in agreement with previous work which has shown a prolonged inhibition of gastric acid secretion which is dose-dependent. After seven days of treatment, there was no difference between the two dose levels with the majority of our subjects being achlorhydric – that is, pH of gastric juice >7.0, in the basal hour, and the response to pentagastrin being inhibited by around 99%. This would be consistent with an increasing response with time as a consequence of accumulation of the effect of omeprazole, which for a single dose normally exceeds 24 hours.

The reduction in the volume of gastric juice secreted after omeprazole was not of the same magnitude as the reduction in acid output. There was no concomitant reduction in pepsin secretion. These observations suggest that other components of the gastric secretion are relatively unaltered by omeprazole, and give further evidence for the drug’s highly specific site and mode of action. The lack of reduction in pepsin secretion is unlikely to be of clinical importance as pepsin would be biologically inactive in the absence of intragastric acid.

It is of considerable interest that the drug had no observed haematological, biochemical, or subjective side effects, despite its extremely powerful action on gastric acid secretion. Omeprazole has now been given to patients with the Zollinger-Ellison syndrome with good therapeutic effect and without side effects. Clearly, a degree of caution is necessary with any new agent, but clinical trials in patients with active peptic ulceration seem indicated. The optimum dose for ulcer healing remains to be found but our studies indicate that even 30 mg omeprazole daily produces a degree of inhibition of acid secretion in excess of that seen with H2 receptor antagonists. The H2 receptor antagonists do not have an increasing effect with time.

Although most of our subjects had basal achlorhydria after seven days treatment, we were assessing basal secretion around the time of the drug’s maximal inhibitory effect. Other workers have found degrees of acid inhibition of the order of 30% 24 hours after a single dose, and have commented that the acid inhibitory effect reached a peak after five days treatment. It seems unlikely, therefore, that prolonged periods of achlorhydria would occur on long term treatment.

Omeprazole is a powerful inhibitor of gastric acid secretion in man, and a potentially useful agent in peptic ulcer.

This work has been presented in part to the Medical Research Society in January 1983 (Clin Sci 1983; 64: 74p) and to the British Society of Gastroenterology in April 1983 (Gut 1983; 24: A498).

Capsules of omeprazole and placebo were supplied by Astra Pharmaceuticals.

References

3 Muller P, Dammann HG, Seitz H et al. Effect of


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