EFFECT OF I.V. OMEPRAZOLE ON THE pH AND VOLUME OF GASTRIC CONTENTS BEFORE SURGERY

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Omeprazole, a substituted benzimidazole, is a new gastric antisecretory agent which, unlike H2-antagonists, inhibits the final common pathway of gastric acid secretion H+K+-ATPase [1]. The drug produces rapid, prolonged inhibition of this enzyme [2] and has been used orally in the treatment of recurrent peptic ulcer and Zollinger Ellison syndrome [3].

Omeprazole is a basic compound with a pKa of 3.97 [4]. It is inactivated by gastric acidity and must be given in enteric coated tablets. After absorption in the duodenum, it is cleared rapidly from plasma, but is concentrated selectively in the acidic environment of the gastric parietal cell, where it may remain for up to 24 h. I.v. omeprazole is distributed rapidly to the extracellular fluid volume, but omeprazole concentrations remain high in the parietal cells [5]. The drug is metabolized by the liver to inactive metabolites.

A single daily oral dose of 40 mg produced a consistent reduction of acid output, with a maximal effect at 6 h [6] and cumulative action. I.v. omeprazole seems less potent. A bolus of 80 mg followed by 40 mg every 8 h increased intragastric pH in patients with duodenal ulcer, but the effect was inconsistent [7]. There are no reports of the use of i.v. omeprazole before surgery as prophylaxis against the acid aspiration syndrome.

SUMMARY

Gastric pH and volume were measured in 87 patients who had received i.v. omeprazole (a new gastric antisecretory agent) 40 mg or placebo 1 or 3 h before surgery. Omeprazole increased the pH of gastric contents in the majority of patients. Administration 1 h before surgery produced greater gastric pH and smaller volume than administration 3 h before surgery. There was a reduction in the number of patients with a pH of less than 2.5 and a volume of 25 ml or more in the treated groups compared with the combined placebo groups. Omeprazole may have a role in prophylaxis against acid aspiration syndrome.

We have compared the effect of i.v. omeprazole 40 mg given 1 h or 3 h before surgery to patients undergoing general anaesthesia. This dose was chosen as it was likely to be effective in the majority of patients.

PATIENTS AND METHODS

This was a double-blind, parallel-group study. After Ethics Committee approval and informed written consent, 87 healthy patients (53 male) admitted for elective general, dental or E.N.T. surgery (requiring tracheal intubation) were allocated to one of four groups to receive omeprazole 40 mg or placebo given either 1 or 3 h before surgery. I.v. omeprazole was provided in a pack as a freeze dried sodium salt with an accompanying solvent of 10 ml of polyethylene glycol and phosphate buffer in water. This solution was administered via an indwelling i.v. cannula over 2.5 min. The placebo (mannitol) had an identical appearance and was reconstituted.
with the same solvent. Random allocation was based on a ratio of two treatment to one placebo.

Patients were aged 18-70 yr and had no clinical evidence of gastro-oesophageal disease, pyloric stenosis, renal, hepatic or cardiovascular disease. Further exclusion criteria included pregnancy, treatment with gastric antisecretory drugs and obesity (body mass index > 30).

All patients received temazepam 20 mg orally 1 h before surgery. Anaesthesia was induced with thiopentone and the trachea was intubated with a cuffed tube facilitated by administration of suxamethonium, vecuronium or alcuronium i.v. Anaesthesia was maintained with halothane, enflurane or isoflurane and nitrous oxide in oxygen. Spontaneous ventilation or IPPV was used as necessary. i.v. fentanyl or morphine was administered after induction of anaesthesia.

After stable anaesthesia had been established, assessments of intragastric pH and volume were made. A 16-French gauge oro- or nasogastric tube was passed and the location of the tip in the stomach was confirmed by auscultation over the epigastrium while 10 ml of air was injected into the tube. The gastric contents were aspirated before surgery with the patient supine and then in the left lateral position, and retained for measurement. Where no contents could be aspirated, phenol red solution 20 ml was inserted into the tube, the patient was turned, and the tube reaspirated to confirm successful placement in the stomach. Volume was estimated using the method described by George [8]. These patients were considered to have a volume of 0 ml and no data for pH were available.

The gastric tube was removed before recovery from anaesthesia. The pH of the gastric contents was measured with a Corning EEL model 10 pH meter and the result confirmed with pH indicator paper. The volume of aspirated contents was measured using a 10-ml syringe.

Data analysis

Data are expressed as mean (SD) or median and range. Comparisons between groups were made using Student's t tests for age, body mass index and time from injection to surgery. Chi-squared test was used to compare the sex ratio between groups.

Comparison was made between omeprazole (1 h) and placebo (1 h) and omeprazole (3 h) and placebo (3 h). Results were compared between the four groups with Fisher's exact test for treatment failure (defined as pH < 2.5 and volume > 25 ml). Non-parametric analysis of variance and Mann-Whitney U tests were used to compare gastric pH and volume. Overall statistical significance between groups was accepted at the 5% value.

RESULTS

Three patients (omeprazole treated) received an injection less than 50 min before surgery and were not considered in the 1-h group. The surgery of a further two treated patients was delayed by more than 1 h by unexpected changes in the operating schedules and these individuals were excluded. Thus the omeprazole 1-h group was smaller than intended.

No gastric contents could be aspirated in nine patients (seven treated). These patients were considered to have an empty stomach. In one control, the phenol red dye also could not be aspirated and this patient was excluded prospectively, on the grounds that successful placement in the stomach had not been achieved. The calculated gastric volumes were small in the majority of subjects.

The 1-h group received an injection 55-115 min before surgery and the 3-h group received an injection 150-245 min before surgery.

There were no significant differences between the groups with respect to age, body mass index, duration of surgery and surgical procedure. There was a significant preponderance of males in the omeprazole 1-h group. There was no difference in time to injection between controls and treated patients in the 1- and 3-h groups (table I).

The ranges of pH were similar in treated and 3-h control groups at induction of anaesthesia. All pH values in the 1-h control group were low (table II).

In the omeprazole 1-h group, four of 24 patients

| Table I. Patient data. * P < 0.05 compared with control 1-h |
|-------------------|-----------------|-----------------|
|                   | Age (yr) | Sex | Injection-sampling time (min) |
|                   | Mean (SD) | (M/F) | Mean (range) |
| Omeprazole        |          |      |                |
| 1 h (n = 24)      | 36.9 (12.8)| 18/6* | 74.5 (55-115) |
| 3 h (n = 29)      | 33 (13)   | 16/13 | 184 (150-245) |
| Placebo           |          |      |                |
| 1 h (n = 14)      | 35 (13.7) | 6/8  | 72.1 (55-110) |
| 3 h (n = 15)      | 34.5 (13.1)| 9/6  | 196 (153-230) |
TABLE II. pH and volume at induction (median (range)). Compared with placebo: ** P < 0.01; *** P < 0.001

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<thead>
<tr>
<th></th>
<th>pH</th>
<th>Volume (ml)</th>
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<td><strong>Omeprazole</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 h (n = 24)</td>
<td>6.15 (1.75-7.9)*****</td>
<td>2.75 (0-26)**</td>
</tr>
<tr>
<td>3 h (n = 29)</td>
<td>2.25 (1.6-6.9)*****</td>
<td>9.0 (0-42)</td>
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<tr>
<td><strong>Placebo</strong></td>
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<tr>
<td>1 h (n = 14)</td>
<td>1.65 (1.45-2.0)</td>
<td>18.0 (0-101)</td>
</tr>
<tr>
<td>3 h (n = 15)</td>
<td>1.60 (1.45-7.2)</td>
<td>10.5 (0-110)</td>
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had an intragastric pH of less than 2.5 (fig. 1). In three of four patients, the injection to sampling time was greater than 100 min and one of these subjects had a volume of gastric aspirate of 26 ml. In the omeprazole 3-h group, 15 of 29 had a pH less than 2.5 and two had a volume of 25 ml or more. A further two had volumes of 40 ml and 42 ml (pH 6.1 and 6.55, respectively) Twenty-five of the 27 control patients with gastric contents had a pH of less than 2.5 and nine of these had a volume in excess of 25 ml (fig. 1).

Intragastric pH and volume are shown in figure 2; the area enclosed by the dotted lines represents treatment failures. As there was no significant differences between the two placebo groups, their results were combined and are shown as one control group (n = 27) for clarity.

Table III shows patients who had an

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<th>pH &gt; 2.5</th>
<th>Volume &gt; 25 ml</th>
<th>Both</th>
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<td><strong>Omeprazole</strong></td>
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<tr>
<td>1 h (n = 24)</td>
<td>4</td>
<td>1</td>
<td>1*</td>
</tr>
<tr>
<td>3 h (n = 29)</td>
<td>15</td>
<td>4</td>
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<tr>
<td>1 h (n = 14)</td>
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<td>6</td>
<td>6</td>
</tr>
<tr>
<td>3 h (n = 15)</td>
<td>13</td>
<td>3</td>
<td>3</td>
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FIG. 1. pH of gastric contents in the groups.

FIG. 2. pH and volume of the gastric contents. The area within the broken line represents treatment failures.
intragastric pH of less than 2.5, a volume of 25 ml or more, or both.

**Adverse effects**

Two patients developed thrombophlebitis after surgery. One patient had received omeprazole and the other placebo. Both patients received the polyethylene glycol solvent. No other clinical or biochemical effects were noted.

**DISCUSSION**

In 25 of the 27 control patients with gastric contents, its pH was less than 2.5; in nine the gastric volume was large enough to constitute a risk. I.v. omeprazole 40 mg increased intragastric pH, but the results in the 1-h group were better than the 3-h group with respect to both pH and volume. Failures in this group occurred usually when injection to sampling time was greater than 100 min. At least some patients in all groups could be considered at risk.

There were a preponderance of males in the most successful (1-h) group. However, there was no evidence to suggest that differences in the data could be explained on sex difference alone. Treatment failures may have been a result of delayed gastric emptying or increased residual volume in the 3-h group. Clearly, many patients in the 3-h group had a small volume of acidic gastric contents, and it seems that these individuals had started secreting acid again.

To date, there are no other published studies of i.v. omeprazole in surgical patients, and although a large number of studies of i.v. H₂-antagonists have been carried out, comparison with the present study is difficult because of varying patient selection, time of administration and anaesthetic regimen, but the results for the omeprazole 1-h group appear to be similar to those obtained with i.v. ranitidine [9–12]. The reduction in gastric volume at 1 h is not a consistent feature of studies of H₂-antagonists.

The results of the omeprazole 3-h group, in which many patients had a low pH and a low volume, were surprising, as the drug causes irreversible enzyme inhibition [13]. I.v. omeprazole produces a 61% inhibition of maximally stimulated gastric acid output 90 min after administration and this effect is still present 24 h later [14]. Multiple administrations of omeprazole inhibit gastric acid output further [15]. When bound, omeprazole probably has a prolonged effect, but the amount bound, and thus the gastric acidity, may be subject to variability in pharmacokinetics. Omeprazole may require the presence of active enzyme to allow binding, and as the drug is eliminated rapidly it is possible that some enzyme inactive at the time of administration of a single dose of i.v. omeprazole becomes activated after the drug has been eliminated from the systemic circulation [14]. Oral omeprazole, which is absorbed slowly, may have an advantage in inhibiting enzyme activated later.

Despite omeprazole remaining in the parietal cells, a single i.v. dose does not abolish gastric acid secretion altogether. This may help to explain the data in the 3-h group. The tendency of some patients to sustain low gastric pH after i.v. omeprazole has been described previously [7]. Delayed gastric emptying and increasing residual volume may explain why some treated patients had a large volume. Nevertheless, the total number of patients at risk in the 3-h group was reduced compared with placebo. This reduction was not significant when compared with the placebo 3-h group alone.

The three patients who received omeprazole less than 50 min before surgery had a low pH, but in two of these, gastric contents aspirated at the end of surgery had a pH exceeding 2.5. Most failures in the omeprazole 1-h group occurred when surgery was delayed until more than 100 min had elapsed after injection. The best results occurred when induction of anaesthesia was between 50 and 100 min after injection. However, as it was difficult to predict the correct time of premedication, even in the 1-h group, data were obtained from many patients outside this apparently optimal injection to sampling time.

**REFERENCES**


