Comparison of pirenzepine, ranitidine, and pirenzepine–ranitidine combination for reducing preoperative gastric fluid acidity and volume in children

N. MAEKAWA, K. NISHINA, K. MIKAWA, M. SHIGA AND H. OBARA

Summary
We conducted a two-part controlled study to evaluate the efficacy of preoperative oral pirenzepine (muscarinic receptor antagonist known to inhibit gastric secretion), ranitidine, and the combination pirenzepine–ranitidine in controlling gastric fluid pH and volume in 210 ASA I children, aged 2–14 yr, undergoing elective surgery. In the first part of the study (n = 90), the proportion of children considered at risk for aspiration pneumonitis was reduced with pirenzepine 25 mg (P < 0.05) but not with 12.5 mg. In the second part of the study, the other 120 children were allocated randomly to one of four groups: pirenzepine 25 mg with placebo; ranitidine 75 mg with placebo; pirenzepine 25 mg with ranitidine 75 mg; and placebo and placebo. These medications were administered 1 h before anaesthesia. After tracheal intubation, volume and pH of the gastric fluid aspiration via a multi-orifice orogastric tube were measured. Pirenzepine 25 mg decreased gastric fluid volume (P < 0.05) but failed to increase gastric pH. Ranitidine 75 mg increased gastric pH (P < 0.05) but failed to decrease fluid volume. The pirenzepine–ranitidine combination reduced gastric fluid acidity and volume (P < 0.05). (Br. J. Anaesth. 1998; 80: 53–57)

Keywords: pharmacology, pirenzepine; antacids, ranitidine; complications, aspiration; gastrointestinal tract, pH; gastrointestinal tract, volume; gastrointestinal tract, antimuscarinics

Paediatric general anaesthesia is associated with a risk of pulmonary aspiration gastric contents1 and the incidence of this complication is higher than in adults.2 Many children arriving in the operating theatre have been shown to have a gastric fluid volume > 0.4 ml kg⁻¹ and a pH < 2.5, regardless of the fasting interval.3 6 Patients who fulfill these criteria are believed to be at increased risk of developing aspiration pneumonitis.7 Several pharmacological interventions have proved successful in reducing the risk of lung damage by controlling gastric acid secretion, including H₂ histaminergic receptor antagonists and proton pump inhibitors.1 3 6 8–13

Pirenzepine, a selective M₁ muscarinic receptor antagonist,14 has been used extensively as an oral treatment for peptic and stress ulcers in adults.15–17 The successful use of this drug in children with peptic ulcer18 19 or for prevention of stress ulcer after paediatric cardiac surgery has been reported.20 Pirenzepine i.v. before surgery in adults has been shown to reduce gastric secretion before anaesthesia.21 22 However, there are no data on the efficacy of preoperative pirenzepine in controlling gastric fluid pH and volume in children.

Thus, the first aim of this study was to examine if preoperative oral pirenzepine reduces gastric fluid at induction of anaesthesia in paediatric patients. In adults undergoing surgery, concomitant use of pirenzepine and a H₂ receptor antagonist was superior to pirenzepine alone.22 23 Therefore, the second aim of this study was to ascertain if a combination of pirenzepine and a H₂-receptor antagonist is more effective than each drug given alone in paediatric anaesthesia. We used ranitidine at a dose thought to be acceptable in children.6 24

Patients and methods
The study comprised two parts. Both were approved by the local Ethics Committee and parental informed consent was obtained for all children.

PATIENTS AND GROUP ASSIGNMENT
In part I, we examined the effects of pirenzepine on gastric fluid pH and volume in 90 healthy, ASA I children, aged 3–14 yr, undergoing elective (ophthalmological, otological, orthopaedic or urological) surgery. Patients with gastrointestinal disease, obese children who were more than 20% heavier than their ideal body weight and those receiving medications known to affect gastric fluid composition or gastric emptying were excluded. The children were allocated randomly to receive one of three medications (n = 30 in each group): placebo (group P₀), pirenzepine (Gastrozepin, Boehringer Ingelheim Japan, Kawanishi, Japan) 12.5 mg (group P₁₂.₅) and pirenzepine 25 mg (group P₂₅). These medications were administered orally 60 min before induction of anaesthesia.

After confirmation of the effectiveness of pirenzepine 25 mg in reducing the number of children thought to be at risk of aspiration pneumonitis in part I of the study, we conducted part II to compare
the efficacy of pirenzepine, ranitidine and the combination pirenzepine–ranitidine in 120 children (2–14 yr). Inclusion and exclusion criteria were identical to those in part I. Patients were allocated randomly to one of four treatments (n = 30 in each group): placebo and placebo (group C), pirenzepine 25 mg and placebo (group P), ranitidine (Zantac, Glaxo-Sankyo, Tokyo, Japan) 75 mg and placebo (group P), and pirenzepine 25 mg and ranitidine 75 mg (group P-R). These medications were also given orally 60 min before induction of anaesthesia.

## Patient characteristics (mean (SD) or range)

<table>
<thead>
<tr>
<th>Group</th>
<th>Part I</th>
<th>Part II</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>7.5 (5–14)</td>
<td>7.1 (3–12)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>28 (4.0)</td>
<td>28 (4.1)</td>
</tr>
<tr>
<td>Clear fluids ingested</td>
<td>12/6/2</td>
<td>15/14/1</td>
</tr>
<tr>
<td>Volume (ml kg⁻¹)</td>
<td>6.3 (2.0)</td>
<td>6.2 (2.1)</td>
</tr>
</tbody>
</table>

### Table 1

<table>
<thead>
<tr>
<th>Type (tea/water/apple juice)</th>
<th>12/6/2</th>
<th>15/14/1</th>
<th>16/12/2</th>
<th>13/17/0</th>
<th>15/14/1</th>
<th>14/13/3</th>
<th>17/11/2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume (ml kg⁻¹)</td>
<td>6.3 (2.0)</td>
<td>6.2 (2.1)</td>
<td>6.8 (2.1)</td>
<td>6.4 (2.2)</td>
<td>6.2 (2.1)</td>
<td>6.6 (2.4)</td>
<td>6.8 (2.3)</td>
</tr>
</tbody>
</table>

### STATISTICAL ANALYSIS

Comparison of data between groups was made using one-way analysis of variance and Bonferroni correction for multiple comparisons of parametric data, while the Kruskal–Wallis rank test was used for non-parametric data. Differences between risk factors for the pulmonary acid aspiration syndrome were tested for significance using the chi-square test. P < 0.05 was regarded as statistically significant. Thirty patients in each group were sufficient to detect a difference of 0.7 between groups in gastric volume and pH at a significance level of 0.05 (= α), with a power of 0.85.²⁵

### RESULTS

There were no differences between the seven groups in age, weight or type or volume of clear fluids ingested (table 1). Although gastric fluid was obtained from all children, the volume was sufficient for pH determination in 77 of the 90 samples and in 97 of the 120 samples in parts I and II, respectively. In the remainder, a very small quantity of gastric fluid remained in the gastric tube and could not be aspirated into the syringe. Such an insufficient quantity of gastric aspirate precluded measurements; these small quantities of gastric fluid were arbitrarily regarded as a residual volume of 0 ml. None of the children had particulate matter in the gastric aspirates. Adverse side effects (eruption, headache, diarrhoea or fever) related to pirenzepine or ranitidine were not observed before surgery.

### PART I

As shown in figure 1, gastric fluid volume was less with pirenzepine 25 mg. The lower dose of pirenzepine failed to affect fluid volume significantly. Pirenzepine failed to decrease gastric fluid acidity significantly, regardless of dose. However, pirenzepine 25 mg significantly reduced the proportion of children considered at risk.

### PART II

Pirenzepine alone and the combination pirenzepine–ranitidine significantly decreased gastric fluid volume but ranitidine alone did not. In contrast, ranitidine alone and pirenzepine–ranitidine increased significantly gastric fluid pH whereas pirenzepine alone did...
M3). M1 receptors are found in ganglia and various pharmacologically into three subtypes (M1, M2 and M3). The number of children deemed at risk to zero.

Comitant use of pirenzepine and ranitidine reduced the proportion of children with a gastric fluid pH < 2.5 and gastric fluid volume > 0.4 ml kg⁻¹. Concomitant use of pirenzepine and ranitidine reduced the number of children deemed at risk to zero.

Discussion

Gastric secretion is regulated by nervous and hormonal mechanisms. Nervous regulations act through the parasympathetic fibres of the vagus nerves, and hormonal regulation takes place mainly in response to gastrin. Receptors for histamine, acetylcholine and gastrin, all of which are stimulants for secretion of gastric acid, have been identified on the parietal cells of the stomach. 

Muscarinic cholinergic receptors are classified pharmacologically into three subtypes (M1, M2 and M3). M1 receptors are found in ganglia and various secretory glands, M2 receptors predominate in the myocardium and also appear to be found in smooth muscle, and M3 receptors are located in smooth muscle and secretory glands. Pirenzepine has a high affinity for M1 receptors with low affinity for M3 receptors. The drug is thought to inhibit secretion of gastric juice mainly by blocking binding of acetylcholine to M1 or M3 receptors, although the precise mechanism is unknown. Although pirenzepine also combines with M1 receptor on the ganglia of the vagus nerve, the nerve-mediated mechanism probably has less involvement in the anti-secretory action compared with antagonism of the gastric gland itself. The specificity for the muscarinic receptors contributes to the advantages of pirenzepine, with little effect on the heart (tachycardia), eye (mydriasis), bladder (disturbed urination) or gut (constipation). Although the M1 subtype is found in the central nervous system (CNS), central effects of pirenzepine are not seen because of its low lipid solubility and limited penetration into the CNS. The drug also inhibits secretion of gastrin, unlike omeprazole or H₂ receptor antagonists. Pirenzepine has been shown to reinforce protective factors against gastric ulcer by increasing the blood flow of the gastric mucous membrane and inhibiting reduction of gastric mucus production. These characteristics may also give the drug additional advantages.

The rationale for the timing and doses of pirenzepine in our study were based on data from others. Onset of the gastric anti-secretory effect of pirenzepine occurs within 60 min after a single oral dose. Pirenzepine has an accepted place in clinical practice for the treatment of severe gastritis and peptic ulcer in adults. For this purpose, pirenzepine 50–150 mg day⁻¹ (1–2 mg kg⁻¹ day⁻¹) given orally for several weeks of months is advocated. In adult studies, pirenzepine 0.5–1 mg kg⁻¹ day⁻¹ was used. No major adverse effects were observed. Although use of pirenzepine 50 mg may have been more effective, this large dose was not chosen to ensure safety in the initial evaluation of the effects of pirenzepine in this setting.

Reports on the effects of preoperative pirenzepine on gastric fluid in adults have been published. In all of these studies, premedication with i.v. pirenzepine successfully decreased gastric fluid volume. However, the effects on gastric fluid pH are conflicting. In several studies, pirenzepine failed to increase pH. Addition of other drugs (e.g. atropine or H₂ antagonists) to pirenzepine has been used successfully in adults to combat this drawback of pirenzepine. In this study, we observed phenomena similar to those in adult studies.

The efficacy of preoperative H₂ antagonists as acid aspiration prophylaxis has been demonstrated in children. However, the reduction in gastric fluid volume is not a consistent finding in studies of H₂ antagonists, including ranitidine. In our study, children who received ranitidine had gastric fluid volumes similar to those in the control group. The inability of H₂ antagonists to decrease gastric volume

**Figure 1** Gastric fluid analysis in part I of the study. Gastric fluid volume (A) and pH (B) are expressed as mean (SD). The percentage of children considered to be at risk of aspiration pneumonitis (C) (volume > 0.4 ml kg⁻¹ and pH < 2.5) is shown in parentheses above each column. Group P₀ = placebo, group P₁₂.₅ = pirenzepine 12.5 mg, group P₂₅ = pirenzepine 25 mg. *P < 0.05 compared with group P₀; †P < 0.05 compared with group P₁₂.₅.
may be a disadvantage compared with pirenzepine. However, because the risk of aspiration depends to a greater degree on gastric fluid pH, which is invariably increased by H₂ antagonists, than on volume, H₂ antagonists may be more suitable for prophylaxis than pirenzepine. In this study, we have shown that the pirenzepine–ranitidine combination reduced both gastric fluid volume and acidity, suggesting a potential use for this combination in clinical practice. However, these findings do not lead us to advocate this approach instead of rapid sequence induction in children at risk of aspiration pneumonitis.

In summary, we have shown that oral preoperative pirenzepine 25 mg (but not 12.5 mg) reduced gastric fluid volume in children but was ineffective in increasing gastric fluid pH to >2.5. In contrast, ranitidine 75 mg increased pH but failed to decrease volume. The combination of pirenzepine and ranitidine was superior to each drug alone for improvement in gastric fluid environment. In children who are at risk of aspirating gastric contents, the reduction in gastric fluid volume and acidity by this combined prophylactic intervention can reasonably be anticipated to provide protection against the occurrence of pneumonitis, should regurgitation and aspiration of gastric contents occur.

References
22. Murakawa T, Takagi H, Araki I, Kimura F, Kusuhita T, Kout H, Sato T, Hashimoto Y, Matsuki A. Effect of M1 blocker of H₂ blocker on gastric secretion during anaesthesia and