Effects of oral nizatidine on preoperative gastric fluid pH and volume in children

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Summary
We have studied the effect of oral nizatidine 6 mg kg⁻¹ in total on preoperative gastric fluid pH and volume in children. One hundred and four healthy children, aged 4-11 yr, were allocated randomly to four groups (n = 26): placebo administered at 21:00 and 06:30 the night before and on the day of surgery, respectively (placebo-placebo: control); nizatidine 6 mg kg⁻¹ at 21:00 and placebo at 06:30 (nizatidine-placebo); placebo at 21:00 and nizatidine 6 mg kg⁻¹ at 06:30 (placebo-nizatidine); and nizatidine 3 mg kg⁻¹ at 21:00 and 06:30 (nizatidine-nizatidine). Each child ingested a large volume of apple juice 3 h before estimated induction of anaesthesia. After induction of anaesthesia, pH and volume of gastric fluid obtained via an orogastric tube were measured. Mean pH in the placebo-nizatidine and nizatidine-nizatidine groups was significantly higher than that in the placebo-placebo group (5.7 (SEM 0.3), 6.0 (0.3) vs 1.8 (0.2), respectively) (P < 0.05). Mean pH in the nizatidine-placebo group was similar to that in the control group (2.3 (0.3) vs 1.8 (0.2)). The number of children with pH < 2.5 and volume > 0.4 ml kg⁻¹ in the nizatidine-nizatidine (0%) and placebo-nizatidine (4%) groups was reduced compared with the control (46%) or nizatidine-placebo (38%) group. These data suggest that oral nizatidine 6 mg kg⁻¹ in total, if given at one dose on the morning of the day of surgery or in two equal doses at bedtime before surgery and on the morning of surgery, may have a role in the prophylaxis of acid aspiration syndrome. Further studies are needed to determine the optimal dose and safety of the drug in children. (Br. J. Anaesth. 1994; 73: 600-604)

Key words
Anaesthesia, paediatric. Gastrointestinal tract, volume. Gastrointestinal tract, pH.

General anaesthesia in children carries a risk of pulmonary aspiration of gastric contents [1]; the incidence is higher than in adults [2, 3]. The severity of lung damage after gastric fluid aspiration is determined often by the pH and volume of the fluid aspirated [4, 5]. Many investigators have shown that a high percentage of paediatric patients who come to the operating room have a gastric fluid volume > 0.4 ml kg⁻¹ and pH < 2.5, regardless of the fasting interval [6-10]. Patients who fulfils these criteria are believed to be at increased risk of developing aspiration pneumonitis [11, 12]. Several pharmacological attempts have been made successfully to reduce the risk of lung damage by decreasing gastric acid secretion in paediatric surgery [1, 9, 10, 13-17]. Histamine H₂ receptor antagonists, including cimetidine, ranitidine and famotidine, have been advocated for use in the preoperative period to modify gastric contents before induction of paediatric anaesthesia [9, 10, 13-17].

Nizatidine is a new, potent H₂ receptor antagonist [18, 19]. The drug has been used orally in the treatment of peptic ulceration and reflux oesophagitis [20-23]. The use of nizatidine as effective premedication to increase gastric fluid pH and decrease volume has been reported in adults undergoing gynaecological laparoscopy [24]. We have conducted a controlled, randomized, prospective study to evaluate the efficacy of preoperative oral nizatidine 6 mg kg⁻¹ in total, in controlling gastric fluid pH and volume in children. To make this assessment, we used three different timings of administration of the drug: at bedtime before surgery, on the morning of the day of surgery and a combination of the two timings.

Patients and methods
After obtaining institutional approval and informed consent from the parents of all children, we examined the effects of oral nizatidine on gastric fluid volume and pH in 104 otherwise healthy children (ASA I), aged 4-11 yr, undergoing elective ophthalmological, dermatological or otoaryngological surgery as inpatients. Patients with gastrointestinal disease, patients 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 one of four groups as follows (n = 26 for each group): placebo administered orally at 21:00 and 06:30 the night before and on the day of surgery, respectively (placebo-placebo: control); nizatidine 6 mg kg⁻¹ at 21:00 and placebo at 06:30 (nizatidine-placebo); placebo at 21:00 and nizatidine 6 mg kg⁻¹ at 06:30 (placebo-nizatidine); and nizatidine 3 mg kg⁻¹ at 21:00 and 06:30 (nizatidine-nizatidine). Each child ingested a large volume of apple juice 3 h before estimated induction of anaesthesia. After induction of anaesthesia, pH and volume of gastric fluid obtained via an orogastric tube were measured. Mean pH in the placebo-nizatidine and nizatidine-nizatidine groups was significantly higher than that in the placebo-placebo group (5.7 (SEM 0.3), 6.0 (0.3) vs 1.8 (0.2), respectively) (P < 0.05). Mean pH in the nizatidine-placebo group was similar to that in the control group (2.3 (0.3) vs 1.8 (0.2)). The number of children with pH < 2.5 and volume > 0.4 ml kg⁻¹ in the nizatidine-nizatidine (0%) and placebo-nizatidine (4%) groups was reduced compared with the control (46%) or nizatidine-placebo (38%) group. These data suggest that oral nizatidine 6 mg kg⁻¹ in total, if given at one dose on the morning of the day of surgery or in two equal doses at bedtime before surgery and on the morning of surgery, may have a role in the prophylaxis of acid aspiration syndrome. Further studies are needed to determine the optimal dose and safety of the drug in children. (Br. J. Anaesth. 1994; 73: 600-604)

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Performing the aspiration was unaware of the Trendelenburg and in both lateral decubitus positions with the child in the supine, reverse aspiration with a 50-ml syringe. Aspirations were of air. Gastric fluid samples were obtained by gentle over the epigastrium during introduction of 5-10 ml stomach, and its position verified by auscultation Argyle Salem Sump catheter was inserted into the stomach, and its position verified by auscultation. No patient experienced coughing, laryngospasm or vomiting during induction. Although gastric fluid was obtained from all children, the volume was sufficient for pH determination in only 81 of the 104 samples. In the remainder, an insufficient quantity of gastric aspirate precluded measurement; these small quantities of gastric fluid were assigned a residual volume of 0 ml. Gastric fluid volume was greater in the control and nizatidine-placebo groups than with the other two regimens (fig. 1). The placebo-nizatidine and nizatidine-nizatidine groups had similar gastric volumes. It is noteworthy that these groups had a gastric volume of almost 0.4 ml kg⁻¹ which gastric pH was similar (fig. 1). These two groups had a higher gastric fluid pH than the other two groups. The placebo-nizatidine and nizatidine-placebo groups had similar gastric regimens (fig. 1). The placebo-nizatidine and nizatidine-placebo groups had similar gastric regimens (fig. 1). The placebo-nizatidine and nizatidine-placebo groups had similar gastric regimens (fig. 1). The placebo-nizatidine and nizatidine-placebo groups had similar gastric regimens (fig. 1). The placebo-nizatidine and nizatidine-placebo groups had similar gastric regimens (fig. 1). The placebo-nizatidine and nizatidine-placebo groups had similar gastric regimens (fig. 1). The placebo-nizatidine and nizatidine-placebo groups had similar gastric regimens (fig. 1).

### Results

There were no significant differences between the four groups in age, weight or volume of fluids ingested (table 1).

Although gastric fluid was obtained from all children, the volume was sufficient for pH determination in only 81 of the 104 samples. In the remainder, an insufficient quantity of gastric aspirate precluded measurement; these small quantities of gastric fluid were assigned a residual volume of 0 ml. Gastric fluid volume was greater in the control and nizatidine-placebo groups than with the other two regimens (fig. 1). The placebo-nizatidine and nizatidine-nizatidine groups had similar gastric volumes. It is noteworthy that these groups had a gastric volume of almost 0.4 ml kg⁻¹, that is near the cut-off value for risk of aspiration pneumonitis. These two groups had a higher gastric fluid pH than did the control and nizatidine-placebo groups, in which gastric pH was similar (fig. 1).

### Table 1  Patient data (mean (SEM or range)) and dosing schedule in the four groups (P = placebo, N = nizatidine). No significant differences between groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Dosing schedule</th>
<th>P-P</th>
<th>N-P</th>
<th>P-N</th>
<th>N-N</th>
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<tr>
<td></td>
<td></td>
<td>P</td>
<td>P</td>
<td>P</td>
<td>P</td>
</tr>
<tr>
<td></td>
<td>21:00 night before surgery</td>
<td>P</td>
<td>N</td>
<td>P</td>
<td>N</td>
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<tr>
<td></td>
<td>06:30 morning of surgery</td>
<td>P</td>
<td>P</td>
<td>P</td>
<td>P</td>
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<tr>
<td>n</td>
<td></td>
<td>26</td>
<td>26</td>
<td>26</td>
<td>26</td>
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<tr>
<td>Age (yr)</td>
<td></td>
<td>6.8 (4-11)</td>
<td>6.9 (4-10)</td>
<td>6.7 (4-10)</td>
<td>7.2 (4-11)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td></td>
<td>23 (0.8)</td>
<td>23 (0.7)</td>
<td>22 (0.7)</td>
<td>25 (0.8)</td>
</tr>
<tr>
<td>Volume of apple juice ingested (ml kg⁻¹)</td>
<td>9.8 (0.1)</td>
<td>9.9 (0.1)</td>
<td>9.8 (0.1)</td>
<td>9.9 (0.1)</td>
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</tbody>
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Figure 1 Effect of nizatidine on preoperative gastric fluid volume and pH (mean, SEM). Group A = control (placebo-placebo), group B = nizatidine-placebo, group C = placebo-nizatidine and group D = nizatidine-nizatidine. * P < 0.05 vs control group; † P < 0.05 vs nizatidine-placebo (B) group.

Figure 2 Number of patients with both gastric pH < 2.5 and volume > 0.4 ml kg⁻¹. Group A = control (placebo-placebo), group B = nizatidine-placebo, group C = placebo-nizatidine and group D = nizatidine-nizatidine. * P < 0.05 vs control group; † P < 0.05 vs nizatidine-placebo (B) group.

Discussion

Acid aspiration prophylaxis before surgery is generally believed to be unnecessary in healthy children presenting for surgery [1]. However, its use might be considered in patients where airway difficulties are anticipated [1]. Children with trauma may be another group of patients who may benefit because these patients are likely to have delayed gastric emptying, and even prolonged fasts will not be helpful in all patients [32]. H₂ antagonists have been studied as acid aspiration prophylaxis in otherwise healthy children presenting for routine surgery. Cimetidine [14], famotidine [13] and ranitidine [17] have been shown to increase the pH of gastric fluid. However, to the best of our knowledge, the use of nizatidine as premedication in children has not been reported. In the present study, we used ASA I children. This population was chosen to ensure a safe approach to the initial evaluation of the effects of nizatidine.

Consistent with a previous report in adults [24], we have shown in children that preoperative nizatidine effectively increased gastric pH and decreased gastric volume. As reduction in gastric volume is not a consistent feature in studies of H₂ antagonists [13, 14, 17], the ability of nizatidine to decrease gastric volume may be an advantage over other H₂ antagonists. However, mean gastric volume in children receiving nizatidine remained at 0.4 ml kg⁻¹, the cutoff value for risk of aspiration pneumonia [1]. Thus the effectiveness of nizatidine as premedication is probably mainly as a result of an increase in gastric pH rather than a decrease in gastric volume.

Nizatidine is a highly selective H₂ receptor blocking drug which is as potent as ranitidine and is characterized by high bioavailability (71%) compared with ranitidine (50%) and a short time to peak plasma concentrations (within 2 h) after an oral dose [18, 33]. Rebound increases in gastric secretion after discontinuation of nizatidine seem to occur less frequently than with ranitidine [34]. Nizatidine does not interfere with drug metabolism by binding to cytochrome P450 [35] and it does not influence male or female hormone function, or fertility [18, 36, 37]. Unlike cimetidine, no interactions have been observed in humans with warfarin [38], lignocaine [39], diazepam [35], chlorzoxazone [40], lorazepam [40], metoprolol [41] or theophylline [40]. Nizatidine has no effect on secretion of gastric mucus [42].

These characteristics may be advantageous.

The rationale for using nizatidine 6 mg kg⁻¹ as a total dose in the present study was based on the following data from other laboratories and our preliminary studies. Nizatidine has an accepted place in clinical practice for treatment of reflux oesophagitis and peptic ulcer [20–23]. For this purpose, oral administration of nizatidine 300 mg day⁻¹ (equivalent to 6 mg kg⁻¹ for 50-kg adults) is advocated in adults
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[20–23]. No major adverse effects were observed in these reports. However, the dose used in the present study may have been inappropriate because of different morphological and pharmacokinetic factors from those in adults; further studies are therefore needed to establish the dose–response relationship of nizatidine.

The timing of administration of nizatidine (2 h before anaesthesia in the placebo–nizatidine and nizatidine–nizatidine groups) was chosen because the t1/2 max of nizatidine is 1–2 h after oral administration of 150–300 mg [18, 43] and the onset of the gastric antisecretory effect of nizatidine is obvious within 0.5–1 h after a single oral dose of 300 mg [44–48]. This onset is more rapid than other H₂ antagonists. Compared with other H₂ blockers, nizatidine has a shorter duration of antisecretory effect (approximately 8 h after 150 mg or 300 mg) [47, 48]. This pharmacokinetic characteristic may be responsible for our observations that a single dose of oral nizatidine 6 mg kg⁻¹ on the morning of surgery could reduce the number of children considered at risk of aspiration pneumonitis although the same dose at bedtime before surgery failed to increase gastric pH and decrease gastric volume: the night dose may be ineffective and superfluous. The results in the nizatidine–nizatidine group suggest that 3 mg kg⁻¹ in the morning is as effective as the larger dose (placebo–nizatidine 6 mg kg⁻¹).

Blind aspiration, as used in the present study, is a common method of measuring volume of gastric contents [49–51]. Although constant manual aspiration with a syringe consistently yields greater recovery of gastric fluid than techniques that use wall suction or intermittent aspiration [52], it does not completely empty the stomach which therefore results in underestimation of gastric fluid volume [53]. In addition, both the functional division of the stomach into antral and fundal sacs [54] and the physical characteristics of the orogastric tube [52] may interfere with the accuracy of blind aspiration.

To minimize these errors, we aspirated manually via a large-bore, multi-orifice orogastric tube which was repositioned several times with the patient in first the supine and reverse Trendelenburg positions and then in the left and right lateral decubitus positions.

The rate of gastric emptying depends on several variables, including volume of ingested fluids [55]. As a large volume of ingested clear fluid increases gastric pressure more than a small volume, and a greater intragastric pressure results in greater gastric emptying [56], it is evident that a large volume would result in faster gastric emptying. Thus the children in the present study were required to ingest a large volume of apple juice (approximately 10 ml kg⁻¹) during the fasting period to increase the rate of gastric emptying.

In conclusion, we have shown that oral nizatidine 6 mg kg⁻¹ administered on the morning of surgery or 3 mg kg⁻¹ at bedtime and the same dose on the morning of surgery, increased preoperative gastric fluid pH and decreased gastric volume in children and thereby reduced the number of children considered at risk for aspiration pneumonitis. Oral nizatidine may be useful in children undergoing surgery who have airway difficulties which are considered to increase the risk of aspiration pneumonitis. Further studies are required to evaluate the effectiveness of the drug in these paediatric patients, and the optimal dose, timing and safety of the drug in children.

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