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Omeprazole reduces preoperative gastric fluid acidity and volume in children

To explore the effects of oral omeprazole on preoperative gastric fluid pH and volume in children, 104 healthy in-patients aged 4–9 yr were randomly allocated to four groups ($n = 26$). Subjects in the Omeprazole-Omeprazole Group received two doses of omeprazole (20 mg per dose), those in the Placebo-Placebo Group, two doses of placebo, those in the Placebo-Omeprazole and Omeprazole-Placebo Groups, one dose each of the two preparations by mouth. For each treatment regimen, the first medication was administered at 9:00 p.m. on the night before surgery and the second at 5:30 a.m. on the morning of the day of surgery (three hours preoperatively). Children undergoing elective surgery were offered 10 ml · kg⁻¹ of apple juice three hours before induction of anaesthesia. After induction of anaesthesia and tracheal intubation, gastric fluid was aspirated through a large-bore, multiorifice orogastric tube and analyzed for pH and total fluid volume. The administration of omeprazole at bedtime before surgery increased gastric pH (3.3 ± 1.3 vs 2.0 ± 0.6 , $P < 0.05$) in comparison with placebo, as did two doses of omeprazole ($pH = 4.8 \pm 1.6$, $P < 0.05$). A single dose of omeprazole administration on the morning of the day of surgery failed to increase gastric pH. There was a reduction in the number of children with a $pH < 2.5$ and a volume > 0.4 ml · kg⁻¹ in the Omeprazole-Omeprazole and Omeprazole-Placebo Groups compared with the Placebo-Placebo or Placebo-Omeprazole Groups. Oral omeprazole 20 mg administered on the night prior to surgery will improve the gastric environment at the time of induction of anaesthesia, thus reducing the potential risk of pneumonitis, should the aspiration of gastric contents occur following the induction of

anaesthesia. These data also suggest that this drug, when administered in a single dose of approximately 1.0 mg · kg⁻¹ three hours before surgery, is ineffective in increasing gastric fluid pH to > 2.4 .

Cette étude évalue à la période préopératoire les effets de l'oméprazole oral sur le liquide et le volume gastriques des enfants. Cent quatre patients hospitalisés âgés de quatre à neuf ans sont répartis au hasard en quatre groupes ($n = 26$). Le groupe oméprazole-oméprazole reçoit deux doses d'oméprazole (20 mg par dose), le groupe placebo, deux doses de placebo, les groupes placebo-oméprazole et oméprazole-placebo, chacun une dose des deux préparations orales. La première médication est toujours administrée à 9.00 p.m. la veille de la chirurgie et la seconde à 5.30 a.m. le matin de la chirurgie (trois heures avant l'intervention). Les enfants programmés pour une chirurgie électorale peuvent boire 10 ml · kg⁻¹ de jus de pomme trois heures avant l'anesthésie. Après l'induction de l'anesthésie, le liquide gastrique est aspiré par une sonde orale de gros calibre à plusieurs orifices et analysé pour son pH et son volume total. L'oméprazole administré au coucher augmente le pH ($3,3 \pm 1,3$ vs $2,0 \pm 0,6$, $P < 0,05$) comparativement au placebo, ainsi que les deux doses d'oméprazole ($pH = 4,8 \pm 1,6$, $P < 0,05$). Une dose unique d'oméprazole administrée le matin de la chirurgie n'augmente pas le pH gastrique. On note une réduction du nombre d'enfants à $pH < 2,5$ et à volume $> 0,4$ ml · kg⁻¹ dans les groupes oméprazole-oméprazole et oméprazole-placebo comparativement aux groupes placebo-placebo et oméprazole-placebo. L'administration d'oméprazole 20 mg le soir qui précède la chirurgie améliore les conditions gastriques à l'induction de l'anesthésie pour ainsi diminuer le risque de pneumonite d'aspiration. Ces données suggèrent aussi que l'oméprazole administré en dose unique de 1,0 mg · kg⁻¹ trois heures avant la chirurgie n'augmente pas le pH gastrique à un niveau $> 2,4$.

Key words

ANAESTHESIA: paediatric;

COMPLICATIONS: aspiration;

GASTROINTESTINAL TRACT: gastric fluid volume, gastric pH;

PREMEDICATION: omeprazole.

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Omeprazole is a new potent gastric antisecretory agent which, unlike H₂-antagonists, inhibits the final common pathway of gastric acid secretion H⁺/K⁺-ATPase (proton pump).¹ The drug produces rapid and prolonged inhibition of this enzyme² and has been used orally in

the treatment of recurrent peptic ulceration, reflux oesophagitis, and Zollinger Ellison syndrome.³⁻⁵ Furthermore, successful use of omeprazole has been reported in children with reflux oesophagitis refractory to routine treatment with H₂-antagonists⁶ or familial G-cell hyperfunction.⁷ The drug has been recently reported to be effective as a premedicant by increasing gastric fluid pH and decreasing gastric fluid volume in adults.⁸⁻¹¹ We undertook the current prospective study to evaluate the efficacy of preoperative oral omeprazole in controlling gastric fluid pH and volume in children.

Methods

After institutional approval of the clinical investigation review board and parental informed consent of all children, we examined the effects of omeprazole on gastric fluid volume and pH in 104 otherwise healthy children (in-patients of ASA physical status I), aged 4-9 yr, undergoing elective surgery as in-patients. Patients with gastrointestinal disease, obese patients who were more than 20% heavier than their ideal body weight, and those taking medication known to affect gastric fluid composition or gastric emptying were excluded. The children were randomly assigned to one of four treatments as follows ($n = 26$ for each group): Omeprazole-Omeprazole, Placebo-Placebo (as a control group), Placebo-Omeprazole, and Omeprazole-Placebo; subjects in the Omeprazole-Omeprazole Group received two doses of omeprazole (20 mg per dose, Omepral®, Fujisawa, Japan), those in the Placebo-Placebo Group, two doses of placebo, those in the Placebo-Omeprazole and Omeprazole-Placebo Groups, one dose each of the two preparations by mouth. For each treatment regimen, the first medication was administered at 9:00 p.m. on the night before surgery and the second at 5:30 a.m. on the morning of the day of surgery.

Table I indicates these patients' profiles. Milk and solids were administered until 9:00 p.m. on the day before surgery. The patients were instructed to ingest a large volume of apple juice (10 ml · kg⁻¹) three hours before induction of anaesthesia (at 5:30 a.m. on the day of surgery).

Induction of anaesthesia in all cases was started at 8:30 a.m. After preoxygenation with 100% oxygen by mask, anaesthesia was induced with nitrous oxide (N₂O) 4 L · min⁻¹, oxygen 2 L · min⁻¹, and halothane in gradually increasing concentrations up to 1.5%. Infusion (lactated Ringer's solution) was started immediately after we confirmed loss of consciousness of children. Atropine 0.01 mg · kg⁻¹ *iv* was then administered through a three-way stopcock to prevent bradycardia and hypotension. After injection of atropine, halothane was increased to 2.5%. The lungs were ventilated taking care to avoid inflation

of the stomach. Tracheal intubation was facilitated by vecuronium bromide 0.1 mg · kg⁻¹ *iv*. All inductions were uneventful and no patients had coughing, laryngospasm, or vomiting during induction.

Following tracheal intubation, a 16-Fr Argyle Salem Sump® catheter was inserted into the stomach. Placement of the orogastric tube within the stomach was verified by auscultation over the epigastrium during introduction of 5-10 mL air. Gastric fluid samples were obtained by gentle aspiration with a 50 ml syringe by an investigator who was unaware of the patients pre-anaesthetic medication. Aspirations were attempted with the child held in supine, reverse Trendelenburg's, and both lateral positions to maximize gastric emptying. Pressure was applied over the epigastrium with the patient supine and then in the left and right lateral decubitus positions to ensure maximum emptying of gastric fluid. Gastric contents were visually inspected for particles and the volume of gastric contents was measured with the syringe. The pH of the gastric fluid was determined immediately using a pH meter (Horiba F-8L, Japan) which was calibrated using standard buffers at pH values of 4, 7, and 9. The pH meter has 0.01 pH units precision over the entire pH range. The gastric fluid pH was also determined using pH indicator paper (Aclit®, Merck, Germany and Advantec®, Toyo Roshii, Japan). After approximate gastric pH was estimated by Aclit® pH test paper, we could determine it more accurately at intervals of 0.1 using a series of Advantec® (CR, TB, BPB, BCG, CPR, and BTB), which covers a pH range from 0.4 to 9.6. In comparing the results of the different methods of testing gastric fluid properties used in the study, we found that, even for gastric aspirate pH levels <2.5, measurements obtained by the pH meter correlated well with values determined by the method of pH test paper ($r = 0.96$) (data not shown).

The age, weight, the volume of apple juice ingested, and gastric fluid pH and volume were recorded for each patient.

Comparisons of data between the groups were made using one-way analysis of variance and Bonferroni correction for multiple comparison of parametric data, while Kruskal-Wallis rank test was used for non-parametric data. The differences between the groups' risk factors for pulmonary acid-aspiration syndrome were tested for statistical significance by chi-square test. $P < 0.05$ was deemed statistically significant.

Results

There were no differences among the four groups with regard to age, weight, or volume of fluids ingested (Table I).

Although gastric fluid was obtained from all children

TABLE I Demographic data. Values are expressed as mean $\pm$ SD

Groups	Placebo- Placebo	Omeprazole- Placebo	Placebo- Omeprazole	Omeprazole- Omeprazole
<i>n</i>	26	26	26	26
Age (yr)	5.7 $\pm$ 1.5	5.9 $\pm$ 1.6	5.8 $\pm$ 1.5	6.1 $\pm$ 1.4
Weight (kg)	20 $\pm$ 3.9	21 $\pm$ 3.6	22 $\pm$ 4.0	22 $\pm$ 4.1
Volume of apple juice ingested (ml $\cdot$ kg ⁻¹)	9.9 $\pm$ 0.3	9.9 $\pm$ 0.3	9.8 $\pm$ 0.2	9.9 $\pm$ 0.3

TABLE II Gastric fluid analysis

	Placebo- Placebo	Omeprazole- Placebo	Placebo- Omeprazole	Omeprazole- Omeprazole
Gastric fluid volume (ml $\cdot$ kg ⁻¹)				
- mean $\pm$ SD	0.67 $\pm$ 0.56	0.23 $\pm$ 0.14*†	0.39 $\pm$ 0.19*	0.20 $\pm$ 0.10*†
- (range)	(0-3.0)	(0-0.47)	(0-0.82)	(0-0.46)
Gastric fluid pH				
- mean $\pm$ SD	2.01 $\pm$ 0.59	3.32 $\pm$ 1.28*†	2.49 $\pm$ 1.12	4.84 $\pm$ 1.55*†
- (range)	(0.8-3.8)	(0.9-7.2)	(0.9-6.7)	(2.4-7.3)
Gastric fluid volume $>$ 0.4 ml $\cdot$ kg ⁻¹ and gastric fluid pH $<$ 2.5	11/26 (42%)	3/26 (12%)*†	10/26 (38%)	1/26 (4%)*†

* $P < 0.05$ vs Placebo-Placebo (control) Group.† $P < 0.05$ vs Placebo-Omeprazole Group.

enrolled in the current study, the volume was sufficient for pH determination in only 80 of the 104 samples. In the remainder, a very small quantity of gastric fluid remained in the gastric tube and it 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. Gastric fluid volume was greater with the Placebo-Placebo (control) than with any of the other three regimens (Table II.) The Omeprazole-Placebo and Omeprazole-Omeprazole groups had lower volumes of gastric aspirate than the Placebo-Omeprazole group. In the former groups, gastric fluid volume was similar. The Omeprazole-Placebo and Omeprazole-Omeprazole groups had greater gastric fluid pH than did the Placebo-Placebo and Placebo-Omeprazole groups, which had similar gastric pH values (Table II).

Table II shows a number of children with gastric fluid volume greater than 0.4 ml $\cdot$ kg⁻¹ and gastric fluid pH less than 2.5. The control and Placebo-Omeprazole Groups had a similar proportion with a gastric pH $<$ 2.5 and gastric volume $>$ 0.4 ml $\cdot$ kg⁻¹ (Placebo-Placebo: 46% and Placebo-Omeprazole: 38%). In both groups where omeprazole was administered on the night before surgery, there was a difference in the proportion of subjects with the gastric pH less than 2.5 and gastric volume greater than 0.4 ml $\cdot$ kg⁻¹ (Omeprazole-Placebo: 11% and Omeprazole-Omeprazole: 4%).

No children had particulate matter in their gastric aspirates. No adverse side effects (rash, headache, diarrhoea, and fever) were observed.

Discussion

The onset of the gastric anti-secretory effect of omeprazole after a single oral dose occurs within two to six hours.^{12,13} Omeprazole has a prolonged effect (duration $>$ 24 hr)^{13,14} because it is concentrated selectively in the acidic environment of the gastric parietal cell, where it remains at high level for a long period of time.¹⁵ This pharmacological characteristic may account for our observation that oral omeprazole, even when given in a single dose at bedtime before surgery, effectively increased gastric pH and decreased gastric volume. Omeprazole, 20 mg orally taken the night before surgery and again on the morning of the day of surgery, increased gastric pH more consistently than a single dose of omeprazole at night before surgery. In contrast, a single 20 mg oral dose of omeprazole administered on the morning of the day of surgery (three hours before surgery) failed to improve the gastric aspirate environment. Although the reason for this failure is unknown, the rapid onset of omeprazole observed in adults may not hold true for children and three hours may be too short a time interval. Furthermore, these data suggest that omeprazole given in a single oral dose preoperatively is not suitable for ambulatory surgery patients who arrive two hours before

surgery for their premedication. In a previous adult study, a single oral dose of omeprazole was administered 279 min (mean) before induction of anaesthesia showed that the drug was effective in reducing gastric fluid volume and acidity.¹¹ Thus, omeprazole should have been administered to patients in the Placebo-Omeprazole Group more than three hours before induction of anaesthesia. However, a feeling of compassion toward children who are to be aroused from sleep at midnight to receive the premedication precluded us from giving them medication at such a time.

Although many studies of H_2 -antagonists have been carried out in children,¹⁶⁻²² their comparability with the current study is quite limited because of discrepancies in patient selection, time of administration and anaesthetic regimen used. However, since the reduction in gastric fluid volume is not a consistent finding in studies of H_2 -antagonists,¹⁸⁻²² the ability of omeprazole to decrease gastric volume may be an advantage of H_2 -antagonists. A rebound increase in gastric secretion following discontinuation of medication seems to occur less frequently with omeprazole than with cimetidine.²³ Omeprazole has little effect on haemodynamics.²⁴ These characteristics may also be advantages of the drug. Since H_2 -antagonists (cimetidine and ranitidine) given one to two hours before surgery have been demonstrated to increase gastric fluid pH in children successfully,²¹ these drugs may be more suitable for paediatric out-patients as a premedicant than omeprazole.

As the incidence of aspiration has been recently reported to be approximately 1:10,000,²⁵⁻²⁷ it is extremely unlikely that aspiration will occur in children who are not predisposed to regurgitation. Thus, prophylaxis of aspiration pneumonitis with omeprazole for otherwise healthy children may have fewer clinical implications. However, its use might be considered in cases where airway difficulties are anticipated.²⁸ 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 fasting will not be helpful in all cases.²⁹

The rationale for administration of omeprazole 20 mg per dose is based on the following data from other laboratories. Omeprazole has an accepted place in clinical practice for the treatment of severe reflux oesophagitis, recurrent peptic ulcer, and Zollinger Ellison syndrome in adults.³⁻⁵ For these purposes, oral administration of omeprazole at doses of 0.3–1.1 mg · kg⁻¹ · day⁻¹ (assuming a 70 kg adult) for several months is advocated.^{3-5,30} A single 0.6–1.1 mg · kg⁻¹ dose administered on the night before surgery in adults has been shown to be effective in reducing the number of patients at increased risk for acid aspiration syndrome.⁸⁻¹⁰ In three children (aged 8–15

yr) with reflux oesophagitis refractory to H_2 -antagonists, initial treatment with oral omeprazole 40 mg · day⁻¹ for several weeks and maintenance treatment with 20 mg · day⁻¹ for more than 24 mo were effective in ameliorating symptoms (retrosternal pain, haematemesis, and recurrent aspiration pneumonia) and endoscopic finding (ulcer formation) of this disease.⁶ Another prospective study in children (aged 5 mo–18 yr) with peptic oesophagitis has led to the conclusion that omeprazole at 20 mg · day⁻¹ for six to eight weeks is effective in reducing symptoms.³¹ Long-term treatment with oral omeprazole (20 mg · day⁻¹ for three years) in a child with severe peptic disease associated with antral G cell hyperfunction has been shown to result in symptom abatement and a return of laboratory values to normal.⁷ No adverse effects were observed in these reports. Omeprazole is a weak base (pKa = 4) and is inactivated rapidly in acid environments.³² Omeprazole is therefore formulated as an enteric coated tablet to enhance absorption from the small intestine. This characteristic of omeprazole precluded us from pulverizing the tablets. Furthermore, in the present study, doses of 0.7–1.5 mg · kg⁻¹ were used because 20 mg tablets are the only dosage form available in Japan. Thus, we studied the upper dose range of this medication. However, 10 mg tablets are available in some countries, where the effect of the optimal dose may be evaluated.

In conclusion, we have shown that oral omeprazole, 20 mg, administered on the night before surgery improved the gastric environment in children the following morning, whereas a single dose given three hours before surgery was ineffective. In subjects who are at risk of aspirating gastric contents, the reduction in volume of gastric fluid and the improvement of gastric pH may reduce the occurrence of pneumonitis, should regurgitation and aspiration of gastric contents occur.

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