Gastric fluid volume and pH after nizatidine in adults undergoing elective surgery: influence of timing and dose

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We conducted a prospective, randomized, double-blind study to investigate the effect of oral nizatidine (150–600 mg), a new potent H_2 antagonist, on preoperative gastric fluid pH and volume in adults undergoing elective surgery. One hundred and seventy-five healthy adults (21–68 yr) were randomly allocated to seven treatment groups ($n = 25$): Placebo was administered at 21:00 and 06:30 the night before and on the day of surgery, respectively (0/0: control); nizatidine 150 mg at 21:00 and placebo at 06:30 (150/0); placebo at 21:00 and nizatidine 150 mg at 06:30 (0/150); nizatidine 150 mg at 21:00 and 06:30 (150/150); nizatidine 300 mg at 21:00 and placebo at 06:30 (300/0); placebo at 21:00 and nizatidine 300 mg at 06:30 (0/300); and nizatidine 300 mg at 21:00 and 06:30 (300/300). Each patient fasted overnight and took the drug and/or placebo with 20 ml water. After induction of anaesthesia, the pH and volume of gastric fluid obtained through an orogastric tube were measured. The mean pH of 0/150, 150/150, 300/0, 0/300, and 300/300 groups was higher than that of the control group ($P < 0.05$). Gastric volume in these groups was smaller than in the control ($P < 0.05$). The 150/0 group failed to decrease gastric fluid volume and increase pH. In the 300/0 group, the gastric

pH was lower than other regimens which effectively decreased gastric acidity ($P < 0.05$). The number of patients with a pH < 2.5 and a volume $> 0.4 \text{ ml} \cdot \text{kg}^{-1}$ in the 0/150, 150/150, 0/300, and 300/300 groups (0%) was less than in the control group (16%) ($P < 0.05$). These data suggest that oral nizatidine in a dose of $\geq 150 \text{ mg}$ given on the morning of surgery decreases preoperative gastric acidity.

Au cours de cette étude prospective, randomisée et à double aveugle, nous évaluons les effets de la nizatidine orale (150–600 mg), un nouvel antagoniste H_2 puissant, sur le volume et le pH gastriques d'adultes soumis à une chirurgie réglée. Des adultes bien portants au nombre de 175, âgés de 21 à 68 ans, sont répartis aléatoirement en sept groupes ($n = 25$): un placebo administré à 21 h la veille et à 6 h 30 le jour de la chirurgie (0/0: contrôle); nizatidine 150 mg à 21 h et placebo à 6 h 30 (150/0); placebo à 21:00 et nizatidine 150 mg à 6 h 30 (0/150); nizatidine 150 mg à 21 h et à 6 h 30 (150/150); nizatidine 300 mg à 21 h et placebo à 6 h 30 (300/0); placebo à 21 h et nizatidine 300 mg à 6 h 30 (0/300); nizatidine 300 mg à 21 h et 6 h 30 (300/300). Tous les patients sont gardés à jeun pour la nuit et prennent le placebo ou le médicament avec 20 ml d'eau. Après l'induction de l'anesthésie, le pH et le volume du liquide gastrique sont mesurés après aspiration par sonde oro-oesophagienne. Le pH moyen de 0/150, 150/150, 300/0, 0/300 et 300/300 est plus élevé que dans le groupe contrôle ($P < 0,05$). Dans ces groupes, le volume gastrique est aussi moindre que dans le groupe contrôle ($P < 0,05$). Dans le groupe 150/0 on ne note pas cette réduction de volume et cette augmentation de pH. Dans le groupe 300/0, le pH gastrique est plus bas que pour les autres groupes qui présentent tous une diminution significative de l'acidité gastrique ($P < 0,05$). Le nombre de patients avec un pH $< 2,5$ et un volume $> 0,4 \text{ ml} \cdot \text{kg}^{-1}$ dans les groupes 0/150, 150/150, 0/300 et 300/300 (0%) est moins élevé que dans le groupe contrôle (16%) ($P < 0,05$). Ces données suggèrent qu'un dosage $\geq 150 \text{ mg}$ de la nizatidine orale, administrée le matin de la chirurgie, diminue l'acidité gastrique préopératoire.

Key words

ANAESTHESIA, COMPLICATIONS: aspiration;
GASTROINTESTINAL TRACT: gastric fluid volume,
gastric pH;
PREMEDICATION: histamine-2 receptor antagonist,
nizatidine.

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Accepted for publication 5th April, 1995.

Aspiration of gastric contents is a cause of anaesthetic morbidity and mortality.¹ Many preoperative pharmacological attempts have been made to eliminate the risk of pulmonary aspiration by decreasing acidity and/or volume of the gastric fluid,²⁻⁴ but without guaranteed success.⁵ They include H₂-receptor antagonists such as cimetidine,² famotidine,³ and ranitidine.^{3,4} Nizatidine, a potent new H₂ antagonist,^{6,7} has been used orally in the treatment of peptic ulceration and reflux oesophagitis.⁸⁻¹² This highly selective H₂ receptor blocking drug is as potent as ranitidine and highly bioavailable (71%) compared with ranitidine (50%), and achieves peak plasma levels within two hours after an oral dose.^{6,13} However, data on the use of nizatidine as a premedicant are limited. We conducted a controlled, randomized, and prospective study to assess the effect of nizatidine in controlling gastric fluid pH and volume in adults. To make this assessment, we used three different doses (150, 300, and 600 mg in total) and timing of administration: at bedtime before surgery, on the morning of the day of surgery, and a combination of the two. In the current study, we used ASA physical status I inpatients to ensure a safe approach to the initial evaluation of nizatidine's effects.

Methods

Patients

After obtaining institutional approval and informed consent from all patients, we examined the optimal dose and timing of oral nizatidine on gastric fluid volume and pH in 175 otherwise healthy adults (ASA physical status I), aged 21–68 yr, undergoing elective surgery as inpatients. Patients with gastrointestinal disease, obese patients who were >20% ideal body weight, and those taking medication known to affect gastric fluid composition or gastric emptying were excluded.

The patients, who fasted overnight, were randomly assigned to one of seven regimens ($n = 25$ for each group) in which placebo or active medication was administered orally at 21:00 the night before surgery and at 06:30 on the day of surgery (Table I). Nizatidine is provided as a 150 mg capsule (Acinon®, Eli Lilly Japan, Kobe, Japan) in Japan. All doses were given with 20 ml water. No other premedication was prescribed. Fasting interval for fluids was ten hours.

Anaesthesia

In all cases, induction of anaesthesia was begun at 08:30. After preoxygenation with 100% oxygen by mask, anaesthesia was induced with thiamylal 5 mg · kg⁻¹ followed by vecuronium 0.2 mg · kg⁻¹. The lungs were carefully ventilated with 50% nitrous oxide, oxygen, and sevoflurane 3–4%, to avoid inflation of the stomach. After man-

ual ventilation of the lungs, the trachea was intubated and anaesthesia was maintained with 60% nitrous oxide, oxygen, and sevoflurane 2% (inspired). All inductions were uneventful and no patients had coughing, laryngospasm, or vomiting during the procedure.

Sample collection

Following tracheal intubation, a multiorifice 16-Fr Argyle Salem Sump® tube was inserted into the stomach. Placement of the orogastric tube within the stomach was verified by auscultation over the epigastrium during introduction of 10 ml air. Gastric fluid samples were obtained by gentle aspiration with a 50 ml syringe. We attempted to maximize returned volume by repeated aspiration with the tube rotated and withdrawn 10 cm and readvanced. Pressure was also applied over the epigastrium to ensure maximum emptying of the stomach. The investigator performing the aspiration was unaware of the patient's pre-anaesthetic medication. Gastric contents were visually inspected for particles and the volume was measured with a syringe. The pH of the gastric fluid was immediately determined by an independent observer using a pH meter (Horiba F-8L, Japan), which has a 0.01 pH units precision over the entire pH range. The electrode was calibrated using standard buffers at pH values of 2, 4 and 7.

Statistics

The age, weight, and gastric fluid pH and volume were recorded for each patient. Comparisons 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. Chi-square test was used for proportions of patients at risk of developing pulmonary acid-aspiration syndrome. $P < 0.05$ was deemed statistically significant.

Results

There were no differences in age or weight among the seven groups (Table I).

Gastric fluid was obtained from all patients enrolled in the study and its volume was sufficient for pH determination in 161 of 175 samples. In the remainder, the very small quantity of gastric fluid could not be aspirated into the syringe and precluded measurement. These small quantities of gastric fluid were arbitrarily regarded as a residual volume of 0 ml. Gastric fluid volume was smaller in the 0/150, 150/150, 300/0, 0/300, and 300/300 groups than in the control group, and the pH of these groups was higher than the control (Table II). The 150/0 group failed to decrease gastric fluid volume and increase pH. In the 300/0 group, the gastric pH was lower than that

TABLE I Randomized groups and demographic data of patients ($n = 25$ for each group) (mean $\pm$ SD)

Groups	Oral Medication		Age (yr)	Weight (kg)	Sex Male:female
	21:00 evening before surgery	06:30 morning of surgery			
0/0	Placebo	Placebo	47 $\pm$ 8	57 $\pm$ 7	14:11
150/0	Nizatidine 150 mg	Placebo	45 $\pm$ 7	59 $\pm$ 8	10:15
0/150	Placebo	Nizatidine 150 mg	44 $\pm$ 8	56 $\pm$ 8	12:13
150/150	Nizatidine 150 mg	Nizatidine 150 mg	46 $\pm$ 8	55 $\pm$ 7	13:12
300/0	Nizatidine 300 mg	Placebo	46 $\pm$ 7	56 $\pm$ 6	14:11
0/300	Placebo	Nizatidine 300 mg	47 $\pm$ 9	58 $\pm$ 6	13:12
300/300	Nizatidine 300 mg	Nizatidine 300 mg	45 $\pm$ 8	56 $\pm$ 8	15:10

TABLE II Gastric fluid analysis (mean $\pm$ SD (range))

Groups	Gastric fluid volume (ml)	pH	Volume > 25 ml pH < 2.5	Volume > 50 ml pH < 1.0
0/0	19 $\pm$ 17 (0-73)	2.7 $\pm$ 1.9 (0.8-7.2)	4/25 (16%)	2/25 (8%)
150/0	18 $\pm$ 19 (0-81)	3.5 $\pm$ 2.1 (1.0-7.1)	4/25 (16%)	2/25 (8%)
0/150	11 $\pm$ 10 (0-36)*	5.9 $\pm$ 1.8 (2.1-7.8)*†‡	0/25 (0%)*†	0/25 (0%)
150/150	10 $\pm$ 10 (0-36)*†	5.6 $\pm$ 1.6 (2.4-7.5)*†‡	0/25 (0%)*†	0/25 (0%)
300/0	11 $\pm$ 10 (0-42)*	4.1 $\pm$ 2.4 (1.2-8.0)*	1/25 (4%)	0/25 (0%)
0/300	9 $\pm$ 9 (0-29)*†	6.3 $\pm$ 1.7 (2.3-8.3)*†‡	0/25 (0%)*†	0/25 (0%)
300/300	9 $\pm$ 10 (0-34)*†	6.5 $\pm$ 1.7 (2.6-8.3)*†‡	0/25 (0%)*†	0/25 (0%)

* $P < 0.05$ vs 0/0 (control) group.† $P < 0.05$ vs 150/0 group.‡ $P < 0.05$ vs 300/0 group.

of other regimens which effectively decreased gastric acidity. Table II also shows the number of patients considered at risk for aspiration pneumonitis as defined by a gastric fluid pH of < 1 and a volume of > 0.8 ml $\cdot$ kg $^{-1}$ (recent criteria)¹⁴ or by a gastric fluid pH of < 2.5 and a volume of > 0.4 ml $\cdot$ kg $^{-1}$ (classical criteria).¹⁵ The "classical criteria" proposed by Roberts *et al.*¹⁵ are based on their unpublished data and animal experiments using rabbits.¹⁶ A relative recent experiment using rats shows that the sensitivity and specificity of these criteria are 56% and 79%, respectively.¹⁷ In contrast, the "recent criteria" were proposed on the basis of experiment using a primate model. The sensitivity of these criteria is as high as 100%, although the specificity is 60%.¹² Using classical criteria, the 150/0 and 300/0 groups had a similar proportion of high risk patients to that of the control group (16%, 4%, and 16% in the 150/0, 300/0, and control groups, respectively). The risk was decreased in the 0/150, 150/150, 0/300, and 300/300 groups (0%). However, according to the new criteria, there were no differences in the groups' proportion of high risk patients (0-8%). These results may be due to lower power of the study because of small sample size.

No patient had particulate matter in the gastric aspirate. No adverse effects (eruption, headache, and di-

arrhoea), considered to be related to nizatidine were observed.

Discussion

In the current study, we have shown the efficacy of oral nizatidine in decreasing gastric fluid volume and increasing gastric fluid pH in otherwise healthy adult inpatients. Although aspiration pneumonitis is now considered to be a rare complication of anaesthesia, the risk is thought to increase in some patients and conditions. Until recently, independently quoted risk factors include obesity¹⁸ (where 77% have a gastric volume > 25 ml and a pH < 2.5), late pregnancy,¹⁹ outpatients,²⁰ and those presenting for emergency surgery.²¹ However, Warner *et al.*, by reviewing 215,488 cases of general anaesthesia, have recently shown that these factors are not independent and that the most common predisposing condition is gastrointestinal obstruction.⁵ Other specific factors include lack of coordination of swallowing, depressed level of consciousness, previous oesophageal surgery, and a recent meal.⁵ In their report, no pulmonary aspiration was observed in patients undergoing 256 elective and 389 emergency Caesarean sections. Warner *et al.* also demonstrated that the majority of aspirations occurs during tracheal extubation and laryngoscopy. Gagging with vomiting during

these procedures has been shown to be more common than passive regurgitation. Pharmacological prophylaxis may not be of value if patients vomit because, even if a patient's stomach was empty at induction of anaesthesia, retrograde peristalsis may force the small intestinal contents back into the stomach which can then reach the pharynx as reflex relaxation of the lower and upper oesophageal sphincters occurs.²² Comparison of two recent reports by Maltby *et al.*^{23,24} revealed that the risk of acid aspiration is similar in outpatients and inpatients. The bioavailability of nizatidine and its pharmacokinetic behaviour in patients with these predisposing conditions are likely to differ from those of the healthy patients enrolled in the current study. Thus, our data may not be extrapolated to these patients, in whom further studies are required to assess the optimal dose and timing of administration.

The costs of nizatidine (150 mg capsule), ranitidine (150 mg tablet) and cimetidine (300 mg tablet) are \$1.50, \$2.80, and \$0.85, respectively. No study which compared the effects on preoperative gastric fluids properties among the three H₂ antagonists given as a premedicant has been conducted. Thus, the cost/benefit ratios of these drugs remain to be determined.

A rebound increase in gastric secretion on discontinuation of nizatidine seems to occur less frequently than with ranitidine.²⁵ Nizatidine does not interfere with drug metabolism by binding with cytochrome P-450,²⁶ nor does it influence male or female hormone function, or fertility.^{6,22,28} Unlike cimetidine, no interactions with warfarin,²⁹ lidocaine,³⁰ diazepam,²⁶ chlorodiazepoxide,³¹ lorazepam,³¹ metoprolol,³² or theophylline,³¹ all of which may be used in the perioperative period, have been observed in humans. Nizatidine has no effect on secretion of gastric mucus.³³ These characteristics may be advantages.

The rationale for using nizatidine 150 mg as a single dose in the current study was based on data from other laboratories. Nizatidine has an accepted place in clinical practice for the oral treatment of reflux oesophagitis and peptic ulcer at doses of 150–300 mg · day⁻¹.^{8–12} Major adverse effects were not observed in these reports. Furthermore, the timing of administration, two hours before anaesthesia, was chosen because T_{max} of nizatidine ranges between one or two hours after 150–300 mg *po*.^{6,34} and the onset of gastric anti-secretory effect is obvious within 0.5–1 hr after a single dose of 300 mg *po*.^{35–39} This onset is more rapid than after other H₂-antagonists. Compared with other H₂-blockers, nizatidine has a shorter duration of anti-secretory effect (approximately eight hours after 150 mg or 300 mg).^{38,39} The pharmacokinetic profile of the drug may be responsible for the conclusion that a single dose of oral nizatidine on the morning of surgery

could increase gastric pH and decrease gastric volume although the same dose at bedtime on the previous day failed to control the properties of the gastric fluid.

In conclusion, nizatidine given in a dose of at least 150 mg *po* on the morning of surgery decreased preoperative gastric acidity and gastric volume in adults undergoing elective surgery and thereby reduced the number of patients deemed at risk for aspiration pneumonitis according to classical criteria. Assessment by these criteria may lead us to use nizatidine 150 mg two hours before anaesthesia for acid aspiration prophylaxis, as a smaller dose of the drug is thought to present less potential risk for the occurrence of untoward side effects. However, further studies are required to evaluate the effectiveness of the drug for other high risk groups of aspiration pneumonitis such as those involving obesity and pregnancy.

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