Ranitidine suspension or famotidine resoriblette and gastric fluid volume and pH

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We studied the effect of two new formulations of H_2-receptor antagonists on gastric fluid pH and volume. Forty-five healthy, elective adult in-patients in three study groups, 15 in each, were premedicated using oral diazepam 10 mg with 100 ml of a dose of water soluble suspension of ranitidine 300 mg with sodium citrate/bicarbonate, or a resoriblette of famotidine 40 mg, or placebo. Gastric fluid samples were obtained by blind aspiration after anaesthesia induction, 50–70 min from premedication, and again 90 min from premedication. After a mean period of 60 min from ingestion the patients medicated with H_2-antagonists had higher gastric juice pH than those in the control group (1.5 (1.1–6.3), median (range)) ($P < 0.0001$) for ranitidine (6.8 (4.1–7.8)), $P < 0.01$ for famotidine (3.9 (1.5–7.6)); $P < 0.05$ ranitidine vs famotidine). Recovered volumes were similar for the groups (median 3–4 ml, range 0–50 ml). None of the H_2 patients had pH < 3.5 and volume ≥ 0.3 ml · kg^{-1} ($P < 0.05$ vs placebo). In second aspirations, taken 90 min from premedication, the group differences from control in pH persisted. Famotidine patients had the lowest volumes ($P < 0.05$ vs controls); yet one famotidine patient had a pH < 2.5 and volume ≥ 0.3 ml · kg^{-1}. It is concluded that, at the moment of oral anxiolytic premedication, ranitidine-buffer suspension effectively reduced gastric juice acidity, whereas famotidine resoriblette failed to increase reliably gastric pH in 50–90 min.

Les auteurs étudient les effets de deux préparations antagonistes des récepteurs H_2 sur le pH et le volume gastriques. Quarante-cinq adultes bien portants hospitalisés sont répartis en trois groupes de quinze et reçoivent du diazépam 10 mg en prémédication suivi d'une suspension de ranitidine 300 mg dans 100 ml d'eau avec du bicarbonate/citrate de sodium ou un comprimé de famotidine 40 mg ou un placebo. Les échantillons de liquide gastrique sont obtenus par aspiration à l'aveugle après l'induction, 50 à 70 minutes après le prémédication et une fois de plus 90 minutes après la prémédication. Après un délai moyen de 60 minutes de l'ingestion, les patients qui ont reçu un antagoniste H_2 ont un pH gastrique plus élevé que ceux du groupe contrôle (1,5 (1,1–6,3), médiane (écart)) ($P < 0,0001$) pour la ranitidine (6,8 (4,1–7,8)), $P < 0,01$ pour la famotidine (3,9 (1,5–7,6)); $P < 0,05$ ranitidine vs famotidine). Le volume aspiré était le même pour les groupes (médiane 3–4 ml, écart 0–50 ml). Aucun des patients H_2 n'avait un pH < 3.5 et un volume $\geq 0,3$ ml · kg^{-1} ($P < 0,05$ vs placebo). A une deuxième aspiration réalisée 90 min après la prémédication, les différences de pH entre les groupes comparativement aux contrôles persistent. Les patients sous famotidine ont les volumes les plus bas ($P < 0,05$ vs contrôles); toutefois un patient du groupe famotidine avait un pH < 2,5 et un volume $\geq 0,3$ ml · kg^{-1}. Les auteurs concluent qu'au moment de la prémédication orale anxiolytique, la suspension de ranitidine tamponnée réduit avec efficacité l'acidité gastrique, alors que la préparation de famotidine ne réussit pas à augmenter de façon constante le pH gastrique en 50–90 min.

Key words
HISTAMINE: ranitidine, famotidine;
GASTROINTESTINAL TRACT: intragastric pH and volume;
COMPLICATIONS: aspiration, acid gastrointestinal reflux.

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Timely administration[1] or repeated dosing[2] of the oral H_2-receptor antagonists ranitidine or famotidine have provided effective prophylaxis against gastric acid aspiration. However, to be effective, the timing of administration is crucial, and this may necessitate intravenous administration.[1] An oral formulation producing a rapid and reliable effect would be attractive, because nurses are often not licensed to give *iv* drugs. Such a formulation might also enable simultaneous administration of an oral sedative premedicant and improve flexibility of the surgical list.

Two modern formulations of H_2-receptor antagonist have been registered for use in patients with gastroduodenal ulcers. A water soluble suspension of ranitidine (Zantac® effervescent granules, Glaxo) mixed with sodium citrate and sodium bicarbonate (1230 mg of each per 300 mg ranitidine) gives rapid relief of gastritis symptoms. A lingual or buccal resoriblette of famotidine (Pep-

cidin Rapitab®, MSD) dissolves rapidly in mouth, though its effect is dependent upon absorption of the swallowed drug, rather than on absorption through the oral mucosa. Our study aimed to answer, whether these two formulations administered one hour before induction of anaesthesia, would reduce gastric acidity.

Methods

The Ethic Committee of the institute approved the study protocol. Forty-five informed, consenting ASA 1-2 patients, aged 18-60 yr, scheduled for elective surgery and general anaesthesia participated in the study. Symptoms of, or medication for, any gastrointestinal disease, >20% overweight, and abdominal surgery were exclusion criteria. The patients were randomized to receive either ranitidine (Group R), famotidine (Group F) or placebo (Group C = control) preparations. (Table I).

The patients were fasted after midnight. In each group, the patients received a diazepam tablet, 10 mg, which was washed down with the ranitidine suspension, or a placebo suspension, and followed by a resoriblette, applied between tongue and buccal mucosa. The patients were taught to apply the resoriblette correctly at the preanaesthetic visit using a placebo sample, and they were instructed to swallow the remaining saliva after the resoriblette had dissolved. The dosing was targeted to occur 60 min preceding anaesthesia induction to allow 50-70 min until the first aspiration. The Group C patients received 100 ml glucose in water suspension, the volume, colour, taste, and pH (5.8) of which paralleled that of the active ranitidine preparation (pH 6.4). Thereafter, they received an oral placebo resoriblette resembling active famotidine. The Group R patients received a powder of ranitidine (Zantac®, Glaxo), 300 mg, suspended in 100 ml water, and a placebo resoriblette. The Group F patients received a resoriblette of famotidine (Pepcidin®, MSD), 40 mg, after the placebo suspension.

Following three minutes preoxygenation, anaesthesia was induced using propofol and fentanyl. A rapid sequence tracheal intubation was facilitated by succinylcholine without mask ventilation. Vecuronium was used to provide further muscle relaxation, and anaesthesia was maintained with enflurane in nitrous oxide 70% and oxygen, supplemented with fentanyl. A 25 French gauge (Ch 25) multiorificed orogastric tube was inserted until its tip met firm resistance. The tip position was confirmed by epigastric auscultation of 5 ml injected air. Thereafter the gastric contents were evacuated carefully using a 50 ml syringe while an assistant compressed the epigastrium three times in each of the following positions: (1) supine, (2) slight (about 15°) left lateral tilt, (3) 15° head-down tilt added, (4) tilting to the right, (5) head-down tilt off, and (6) repeated supine. The tube was drawn out while applying suction, and, after emptying, sited again in the oesophagus. At 90 min from the premedication it was reinserted to the original depth, and a second sample was aspirated (without positioning or epigastric pressure), primarily for the determination of pH.

TABLE I Clinical characteristics of the study groups

Group	*Control (n = 15)*	*Ranitidine (n = 15)*	*Famotidine (n = 15)*
Sex (F/M)	11/4	13/2	12/3
Age (yr)	51 ± 5	46 ± 9	45 ± 9
Weight (kg)	72 ± 11	71 ± 12	70 ± 14
Height (cm)	170 ± 9	169 ± 7	168 ± 9
Smoking (+/−)	5/10	6/9	5/10
Premedication to (min)			
- First aspiration	61 ± 6	59 ± 4	60 ± 8
- Second aspiration	91 ± 1	91 ± 2	91 ± 1
Propofol (mg)	151 ± 24	154 ± 26	148 ± 20
Fentanyl given till second sampling (μg)	130 ± 41	110 ± 51	123 ± 59

Values are mean ± SD, or number.

The pH was immediately determined using indicator paper (Acilit®, Art 9531, Merck, Germany), and later with a digital pH meter (Knick GWB pH-Meter 761 Calimatic, Knick, Germany). The results were in good agreement and the pH meter readings were chosen for analysis. When there was insufficient volume (<0.5 ml) for analysis with the electronic pH meter, the pH results obtained with indicator paper were discarded, due to uncertainty whether the fluid was gastric juice, mucus or saliva. For statistical purposes, negative aspirations were tabulated as zero ml. Patients were considered "at risk" for gastric acid aspiration, if they had pH < 2.5 and volume ≥ 0.3 mg $\cdot$ kg^{-1}.

The demographic variables and time intervals were analyzed using ANOVA and Dunnet's test. The pH results were compared using Mann-Whitney U test. Frequencies were computed from contingency tables. $P < 0.05$ indicated the level of statistical significance.

Results

Premedication times were equal among the groups (Table I). At 60 min, compared with Group C, pH was higher in group R ($P < 0.0001$) and Group F ($P < 0.01$), and the numbers of patients with pH < 2.5 were less ($P < 0.0001$, and <0.05, respectively) (Table II). The volumes of gastric contents were similar. Volumes of <0.5 ml were obtained in three patients in each group. Compared with four patients in Group C, none of the patients was "at risk" after premedication with ranitidine or famotidine ($P < 0.05$). This difference validated also at a pH limit <3.5 ($P < 0.05$).

The pH differences prevailed in the 90 min aspirations

TABLE II Gastric juice pH and volume

Group	*Control*	*n*	*Ranitidine*	*n*	*Famotidine*	*n*
First aspiration (50–70 min)						
pH: median	1.5	12	6.8*	12	3.9*†	12
(range)	(1.1–6.3)		(4.1–7.8)		(1.5–7.6)	
pH < 2.5	11	12	0*	12	5*	12
Volume (ml): median	3	15	4	15	4	15
(range)	(0–50)		(0–45)		(0–23)	
Patients at risk‡	4	15	0*	15	0*	15
Second aspiration (90 min)						
pH: median	1.9	13	6.6*	11	6.7*	11
(range)	(1.4–6.4)		(4.2–7.8)		(1.8–7.8)	
pH < 2.5	7	13	0*	11	3	11
Volume (ml) median	10	15	5	15	2.5*	15
(range)	(0–31)		(0–28)		(0–28)	
Patients at risk‡	1	15	0	15	1	15

Values are median and range, or number.
*Significantly different from Control Group.
†Significantly different from Ranitidine Group.
‡pH < 2.5 and volume ≥ 0.3 ml · kg^{-1}.

between Group R and Group C ($P < 0.001$), or Group F and Group C ($P < 0.01$). In four cases in Group C and in one case in Group F, pH increased from below to above 2.5. Group F patients had lower volumes than those in Group C ($P < 0.05$), but the difference lost statistical significance, if the volumes were indexed to weight. One patient both in Groups C and F appeared to be "at risk," whether the pH limit was set at <2.5 or <3.5.

Discussion

Applying conventional risk limits for pH and volume, a third of the control patients were "at risk" for gastric acid aspiration during induction of anaesthesia. Ranitidine-buffer suspension effectively and rapidly raised pH, whereas the pH increase after famotidine resoriblette was unsatisfactory.

Proposals towards more stringent safety criteria for pH (>3.5), and more liberal limits for volume have been recently suggested.[3] If the pH value 3.5 had been adopted in the present study, it would not have affected the proportions of patients "at risk." There is no evidence to assume that the number of patients "at risk" would have further reduced had the first sampling interval been 90 min. Blind gastric aspiration, when properly performed, has been shown to be nearly as precise as gastroscopic suction in evacuation of the gastric contents.[4] As the main proportion of the relatively more acidic gastric contents was aspirated at 60 min, the 90 min samples mainly represent the juice produced between the two samplings. Possibly, the second sample would have been more acidic, and occasionally more voluminous, had the first evacuation not taken place. Fentanyl might have prohibited gastric motility slightly, and retarded the propulsion of the remnant juice not caught at 60 min. However, in a true-to-life situation opioids are generally used during anaesthesia or even as premedicants. In previous studies, the doses of opioids have often remained vaguely defined, and in occasional studies anticholinergic premedication has been in use.

The interval between H_2-receptor antagonist administration and gastric juice sampling has rarely been accurately controlled in previous reports, which makes it difficult to make comparisons between studies. Information on the rapidity of the drug effect has been gained using continuous pH monitoring: intravenous ranitidine 50 mg raised gastric juice pH (from an initial mean value of 3.5) by one pH unit in 20 min, and by one and a half pH unit in 60 min.[5] Doses of 50 or 100 mg *iv* increased gastric pH from 1.5 to 3.5 in 40–50 min.[6] Both results were obtained during anaesthesia. Unfortunately, even timely (>90 min pre-induction) *iv* ranitidine does not guarantee absolute protection against acid regurgitation during operations prone to provoke regurgitation, as evidenced using a continuous oesophageal pH-monitoring.[7] Peak serum concentrations of ranitidine were attained one to three hours after oral ingestion, and none of 32 patients were at risk (pH < 2.5, vol > 25 mL) 3.5 hr after ingestion.[8] The present results with ranitidine suspension compare favourably with the above findings, possibly owing to the fact that ranitidine suspension is furnished with sodium citrate and bicarbonate.

None of eighty patients was at risk (pH < 2.5, vol > 25 ml), after receiving famotidine 20 mg *po* at least

two hours,[9] or *im* at least one hour before induction.[9,10] Further, oral famotidine 20 or 40 mg results in a prophylaxis rate (pH >2.5) of about 90% following a minimum interval of 60 min.[11] The failure rate after famotidine resoriblette was unexpectedly high. The finding may result because the formulation acts through gastric absorption, and not through oral mucosal penetration. In accordance with previous observations,[9,10] famotidine appeared to reduce gastric volume rapidly, though the effect has not been affirmed consistently.[1,11] This propensity reduces the number of patients "at (the theoretic) risk," even if pH is considered to be more decisive for pulmonary damage.[3]

It is concluded that after 50–70 min, a water suspension of ranitidine (-citrate-bicarbonate) provides reliable reduction of gastric acidity in healthy adults. Its clinical effect in subjects with an increased risk for gastric acid aspiration, such as obstetric, paediatric, day-case, morbidly obese, trauma, and hyperacidity, cannot be predicted from this study. A resoriblette of famotidine fails to produce a clinically acceptable rate of de-acidification, even though the low gastric volume reduces the risk of dangerous acid aspiration.

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