

Effects of single-dose oral ranitidine and sodium citrate on gastric pH during and after general anaesthesia

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The effects on gastric pH of the H₂-receptor antagonist ranitidine (R) with 0.3 molar (M) sodium citrate (SC) as an oral effervescent and those of plain SC were studied in 25 patients scheduled for elective surgery. Following induction of general anaesthesia, the gastric contents were evacuated via a nasogastric tube, and a pH electrode was placed in the stomach. Then, eight patients received R 300 mg plus SC dose (Group R300), ten received R 150 mg plus SC dose (Group R150), and seven received 50 ml SC alone (Group SC). The drugs were administered orally in a double-blind fashion, and the gastric pH was recorded continuously over a period of 24 hr. Mean (range) baseline pH values were 1.2 (0.8–1.8), 1.3 (1.0–1.8), and 1.2 (0.9–1.6) in the R300, R150, and SC groups, respectively ($P = NS$ among groups). These values increased to 7.0 (6.2–7.5), 6.9 (6.3–7.3), and 4.9 (1.9–7.3), respectively, at emergence from anaesthesia ($P < 0.05$ for R300 vs SC and R150 vs SC). Two minutes after administration of R300 and R150, a mean (range) gastric pH of 6.8 (5.8–7.5), and 5.6 (1.2–7.0), respectively, was reached, and remained above 2.5 for 14 hr ($P = NS$). Plain SC increased the gastric pH within two minutes to a mean of 6.8 (6.7–7.0), and maintained it above 2.5 for six hours ($P < 0.05$ for R300 vs SC at 8, 10, 12, and 14 hr after induction). We conclude that both the combination of R plus SC, and SC alone are rapidly effective in neutralizing gastric acid when administered orally after induction of anaesthesia. However, the effectiveness of plain SC is shorter-lived, and if maintenance

of gastric pH above 2.5 for longer than six hours is needed, the R plus SC combination should be administered.

On a étudié chez 25 patients programmés pour une chirurgie non urgente, les effets sur le pH gastrique d'un antagoniste des H₂ récepteurs, la ranitidine (R) additionnée de citrate de sodium (CS) 0,3 molaire (M) effervescent, per os et ceux du CS seul. Après l'induction de l'anesthésie générale, le contenu gastrique est évacué par une sonde nasogastrique et une électrode à pH placée dans l'estomac. Ensuite, huit patients reçoivent 300 mg de R avec CS (Groupe R300), dix patients reçoivent 150 mg de R avec CS (Groupe R150) et sept patients reçoivent 50 ml de CS seul (Groupe CS). Ces médicaments sont administrés oralement en double aveugle, et le pH gastrique est enregistré continuellement pendant 24 h. Les valeurs moyennes de base du pH (écart) sont de 1,2 (0,8–1,8), 1,3 (1,0–1,8) et 1,2 (0,9–1,6) respectivement dans les groupes R300, R150 et CS ($P = NS$ entre les groupes). Les valeurs s'accroissent respectivement de 7,0 (6,2–7,5), 6,9 (6,3–7,3) et 4,9 (1,9–7,3), au réveil de l'anesthésie ($P < 0,05$ pour R300 vs CS et R150 vs CS). Deux min après l'administration de R300 et R150, on atteint respectivement des valeurs moyennes (écart) du pH gastrique de 6,8 (5,8–7,5), et de 5,6 (1,2–7,0), qui restent au-dessus de 2,5 pendant 14 h ($P = NS$). Le CS seul augmente le pH gastrique dans les 2 min à une valeur moyenne de 6,8 (6,7–7,0) et le maintient au-dessus de 2,5 pendant 6 h ($P < 0,05$ pour R300 versus CS à 8, 10, 12 et 14 h après l'induction). Nous concluons qu'autant la combinaison de R avec CS que le CS seul sont rapidement efficaces pour neutraliser l'acidité gastrique lorsqu'ils sont administré après l'induction de l'anesthésie. Cependant, l'efficacité du CS seul est de plus courte durée, et si le maintien du pH gastrique au-dessus de 2,5 est nécessaire pour plus de 6 h, on devrait administrer la combinaison de R et de CS.

Key words

AGENTS: ranitidine, sodium citrate;

GASTRIC pH: continuous monitoring, general anaesthesia.

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Since early reports of aspiration pneumonitis in the obstetrical population, anaesthetists have been concerned

with this rare but serious and potentially preventable complication. As early as 1862, Balfour described the first case of aspiration of gastric contents.¹ In 1946, Mendelson published a review of the syndrome, which eventually would bear his name.² His studies have shown that the severity of the pneumonitis is due to the acidic nature of the aspirated material. Values for gastric pH and volume, derived from animal models, are only a guideline in humans; they are considered to be a pH less than 2.5³ to 3.5,⁴ with a gastric volume of less than 0.4 ml · kg⁻¹ to 0.6–0.8 ml · kg⁻¹.⁶ Among the various prophylactic measures that have been investigated to reduce pulmonary injury following aspiration of gastric contents, are the administration of non-particulate antacids (sodium citrate) and H₂-receptor antagonists (ranitidine). Sodium citrate may be administered prior to emergency surgery because of its immediate onset of antacid action.^{7,8} Intravenous (*iv*) ranitidine, 50 mg, increases gastric pH to above 4 for at least 13 hr,⁹ but its delayed onset of about 30 min after *iv* administration¹⁰ or 90 min following oral intake¹¹ makes this compound unsuitable for prophylaxis against aspiration pneumonitis in emergency surgery.

A new formulation of effervescent ranitidine tablets has been developed recently. This combines ranitidine, 150 or 300 mg, with sodium citrate, 0.3 M, as effervescent excipient providing an immediately available hydrochloric acid neutralizing capacity.

The goal of this investigation was to compare the 24-hour gastric pH profiles of sodium citrate and those of effervescent ranitidine containing sodium citrate with regard to the ability to maintain a gastric pH above that associated with development of pulmonary aspiration syndrome, usually a pH above 2.5. This investigation was carried out in healthy patients undergoing non-emergency surgery, after suctioning of intragastric contents.

Methods

Twenty-five adult female patients, ASA class I-II, aged between 20 and 76 yr, with no previous history of gastrointestinal surgery or upper gastrointestinal disease, and scheduled for lower abdominal surgery, were investigated. Patients with a body weight 20% above or below the ideal were excluded from the study. Informed consent was obtained in all cases, and the study was approved by the institutional review board.

For each patient, calibration of a gastric pH electrode was accomplished in commercial buffer solutions of pH 7.00, 4.01, and 1.68 at room temperature, and was corrected to 37°C; a pH electrode drift of less than 0.1 units over ten minutes was considered acceptable. A miniature combined reference glass electrode connected to a pH

TABLE Patient demographics

	<i>Age (years)</i>	<i>Weight (kg)</i>	<i>Height (cm)</i>
Ranitidine 300 (<i>n</i> = 8)	56 ± 6	69 ± 10	155 ± 13
Ranitidine 150 (<i>n</i> = 10)	53 ± 5	70 ± 9	162 ± 3
Sodium citrate (<i>n</i> = 7)	37 ± 3	59 ± 2	158 ± 2

recorder (Gastrograph Mark III, Medical Instruments Corp. Solothurn, Switzerland) that stores pH values at six-second, and prints them at eight-minute intervals, as advanced transnasally for continuous intragastric pH monitoring. The electrode's proper position was verified by the sudden steep pH decrease at the gastro-oesophageal junction. Patients' intragastric pH profiles were monitored and recorded for 24 hr following induction of general anaesthesia and into the postoperative period. The three drug solutions were prepared as 50 ml solutions; the ranitidine plus sodium citrate solution (0.3 M) was prepared by dissolving an effervescent tablet in 50 ml of water. The drug solutions were then labeled and were administered to enrolled patients in a random, double-blind fashion.

All patients fasted for 8–12 hr before anaesthesia to ensure the absence of particulate matter. Surgery was started between 8–9 a.m., and the anaesthetic technique was standardized: premedication consisted of midazolam 5 mg *im* 45 min before anaesthesia. Thiopentone 4–6 mg · kg⁻¹ *iv* was given for induction of anaesthesia, followed by succinylcholine 1.5 mg · kg⁻¹ to facilitate orotracheal intubation. Enflurane plus 70% N₂ in O₂ was administered for maintenance of anaesthesia. Following tracheal intubation, a nasogastric tube was inserted, and all available gastric contents were evacuated.

After intragastric placement of the glass pH electrode, eight patients received 50 ml ranitidine 300 mg containing 0.3 M sodium citrate (Group R300), ten patients received 50 ml ranitidine 150 mg containing 0.3 M sodium citrate (Group R150), and seven patients received 50 ml 0.3 M sodium citrate alone (Group SC). The drugs were administered via the nasogastric tube immediately after induction of general anaesthesia (Table).

Statistical methods first used the Shapiro-Wilkerson test to document normal distribution of data. Patients' demographics and the gastric pH values at induction and emergence from anaesthesia were compared with analysis of variance (ANOVA) and unpaired *t* test, while all other non-parametric data were compared with multi-group Kruskal Wallis and the Mann-Whitney U tests, with Bonferroni adjustment for multiple comparisons. In all cases statistical significance was defined at the *P* < 0.05 level.

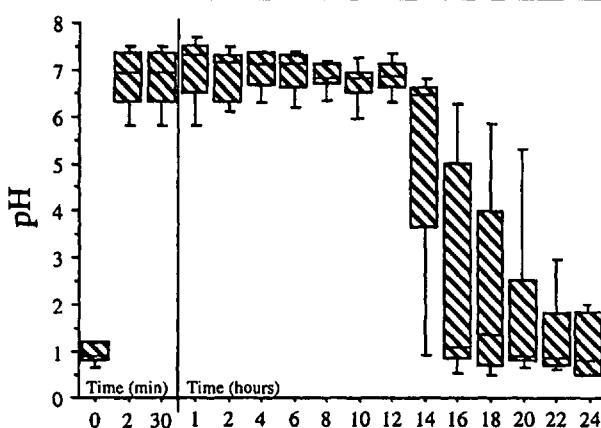


FIGURE 1 Time-course of gastric pH following administration of effervescent ranitidine 300 mg plus sodium citrate. The striped boxes represent the 25th-75th percentiles, the line represents the median, and the Ts and inverted Ts represent the 10th-90th percentiles.

Results

Patients in Group SC were younger than in the other two groups ($P < 0.05$). The gastric pH (mean \pm standard error of the mean, SEM) at intubation in groups R300, R150, and SC was 1.2 ± 0.1 (range of 0.8–1.8), 1.3 ± 0.1 (1.0–1.8), and 1.2 ± 0.1 (0.9–1.6), respectively; these values increased to a pH of 7.0 ± 0.2 (6.2–7.5), 6.9 ± 0.1 (6.3–7.3), and 4.9 ± 0.7 (1.9–7.3), respectively, at emergence from anaesthesia. There were statistically, though not clinically, significant differences between groups R300 and SC ($P = 0.012$) and between groups R150 and SC ($P = 0.011$) with regard to pH at emergence from anaesthesia. Following administration of effervescent ranitidine/sodium citrate combination, a mean gastric pH of 6.8 (range of 5.8–7.5; Group R300) and 5.6 (1.2–7.0, Group R150) was reached within two minutes ($P = \text{NS}$). The gastric pH remained >2.5 for 14 hr following both ranitidine dosages (Figures 1 and 2; $P = \text{NS}$ for duration of $\text{pH} > 2.5$). Sodium citrate increased the gastric pH to a mean of 6.8 (6.7–7.0) within two minutes of administration, but the duration of acid neutralization was shorter: the pH returned to <2.5 after six hours ($P < 0.05$ for Group SC vs Group R300 at 8, 10, 12, and 14 hr postoperatively; Figure 3).

Discussion

Aspiration pneumonitis, although a potentially deadly complication, is not common in modern anaesthetic practice. Because of its low overall incidence, large-scale prospective studies are needed to define the impact of any risk factor or intervention on outcome. One of the largest studies of anaesthetic outcome examined more than 185,000 anaesthetics.¹² The overall incidence of aspiration was found to be 4.7 per 10,000 anaesthetics; mortality

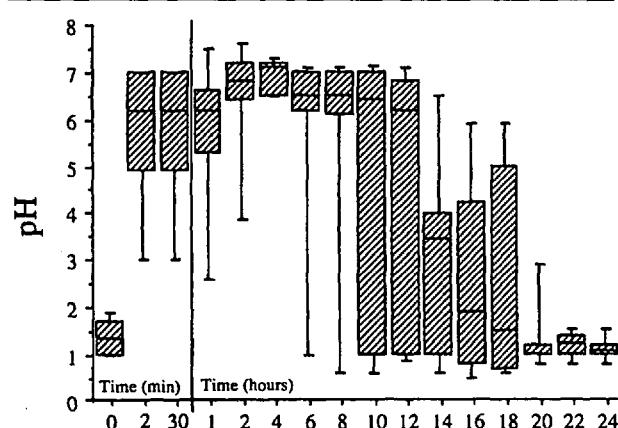


FIGURE 2 Time-course of gastric pH following administration of effervescent ranitidine 150 mg plus sodium citrate. The striped boxes represent the 25th-75th percentiles, the line represents the median, and the Ts and inverted Ts represent the 10th-90th percentiles.

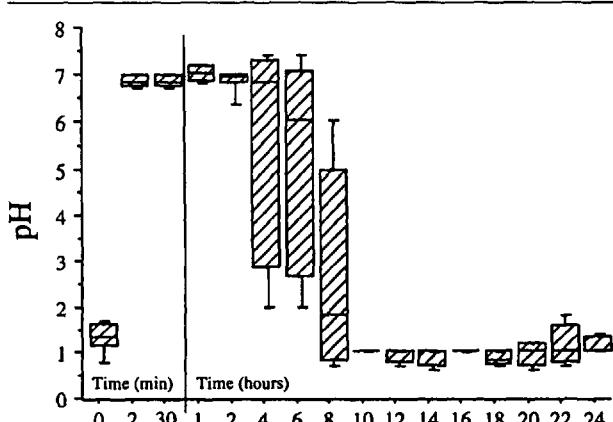


FIGURE 3 Time-course of gastric pH following administration of plain sodium citrate. The striped boxes represent the 25th-75th percentiles, the line represents the median, and the Ts and inverted Ts represent the 10th-90th percentiles.

was 5%, with the highest rate occurring in patients who were in poor physical condition preoperatively. A multicentre, prospective study in France from 1978 through 1982 reported 27 cases of pulmonary aspiration in more than 198,000 patients for an overall incidence of 1.4 per 10,000 anaesthetics.¹³ Of note, 14 of these 27 cases of aspiration described in this investigation occurred in the postoperative period. Recently, a large, retrospective study of over 172,000 anaesthetics found the risk of aspiration to vary from a low of 1:9200 (elective ASA I patients) to a high of 1:343 (emergency ASA IV and V patients).¹⁴ In this study, the risk of pulmonary aspiration was 1:7,956 in elective ASA I-II patients, and none of these patients developed serious pulmonary com-

plications. However, mortality increased to 1:4700 in patients with comorbid diseases (ASA IV-V). Of all instances of pulmonary aspiration, the majority (35.9%) occurred during tracheal extubation, while 32.9% occurred during laryngoscopy.¹⁴

Ranitidine is a highly selective H₂-receptor antagonist, which, when given orally, generates profound and sustained inhibition of gastric acid secretion.¹⁵ Plain ranitidine, 300 mg po, gave the most consistent reduction in gastric acid pH when administered 90 min before surgery.¹¹ The duration of action (i.e., the maintenance of a pH > 2.5) of 300 mg and 150 mg po doses has been shown to be 10–16 hr, and 2–7 hr, respectively.^{16,17} In the present investigation, the effervescent combination of ranitidine, 150 and 300 mg, plus sodium citrate was effective not only in increasing the gastric pH to above 2.5 within two minutes of administration, but also maintained the acid neutralization for a minimum of 14 hr.

Studies of the effects of sodium citrate on gastric pH have been conflicting: 0.3 M sodium citrate, 15 ml po, was found to be effective in increasing gastric pH to more than 2.5 by some investigators,¹⁸ but not by others.¹⁹ Given orally prior to surgery, the drug's effect lasted 60–180 min.^{18,20} Gastric pH values were shown to increase for a short (< 60 min)²¹ or long (58–195 min)²⁰ interval with 30 ml of the agent. The varying success may in part be due to poor mixing between gastric contents and the relatively small volume (15 ml) of antacid.²² Two studies using continuous measurements of intragastric pH in pregnant women at term have shown that sodium citrate neutralizes acid immediately, but the critical factor influencing its duration of action is gastric emptying.^{7,8} Opioid analgesics, which delay gastric emptying, prolong the effectiveness of sodium citrate. As all our patients received fentanyl both on induction of anaesthesia and intraoperatively, this might explain the prolonged duration of action in some of the patients investigated. Similar to the combination of ranitidine plus sodium citrate, 50 ml plain sodium citrate reliably increased the gastric pH to >2.5 within two minutes of administration in all our patients. The duration of action, however, was limited to six hours, making the agent an effective prophylactic at induction of general anaesthesia, and, in surgical procedures less than six hours, at emergence. In the prolonged postoperative period, however, when the majority of cases of pulmonary aspiration might occur,^{13,14} the drug is less useful in the prevention of aspiration pneumonitis.

Interestingly, despite the small number of patients in our groups, two treatment failures were observed: two minutes after drug administration, one patient in the R150 group had a gastric pH of 1.2, and remained at this pH for >120 min. Furthermore, one patient in the SC group had a gastric pH of 1.9 at emergence from

anaesthesia. No failure were observed in the R300 group of patients.

In conclusion, both sodium citrate and the combination of effervescent ranitidine plus sodium citrate induce a rapid increase in gastric pH and maintain the gastric pH > 2.5 for at least 14 hr when administered orally after induction of general anaesthesia. Although the findings of our study (in only 25 patients) are not directly applicable to unfasted, ASA III-V patients undergoing emergency surgery, the results nevertheless provide an insight to the effectiveness, onset time, and duration of gastric acid neutralization and inhibition provided by the combination of an antacid plus an H₂-receptor antagonist. These data support the claim that such a therapeutic combination may decrease the likelihood of pulmonary aspiration syndrome upon induction or emergence from anaesthesia, especially when a combination of ranitidine 300 mg plus effervescent sodium citrate is used.

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