

Dose-Response Effects of Intravenous Ranitidine on Gastric pH and Volume in Outpatients

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The dose-response effects of intravenous ranitidine given 45 min to 5 h earlier on gastric pH and volume were evaluated in six groups of 25 outpatients, each undergoing elective surgery under general anesthesia. Patients in Group 1 received no ranitidine and served as controls. Patients in Groups 2-6 received ranitidine intravenously in incremental doses of 0.5 mg · kg⁻¹ body weight from 0.5 mg to 2.5 mg (Group 2, 0.5 mg; Group 3, 1.0 mg; Group 4, 1.5 mg; Group 5, 2.0 mg; and Group 6, 2.5 mg). Ninety-six per cent of patients in the control group (Group 1) had gastric pH ≤ 2.5 while 36% of the patients had gastric content volumes ≥ 25 ml with pH ≤ 2.5. Ranitidine, in incremental doses of 0.5-2.5 mg · kg⁻¹ body weight, caused a significant reduction of gastric acidity and volume. The ED₅₀ of ranitidine producing a gastric pH > 2.5 was 0.36 mg · kg⁻¹, and the ED₉₅ was 0.98 mg · kg⁻¹ body weight. The ED₉₅ of ranitidine producing a gastric volume < 25 ml was 1.96 mg · kg⁻¹. At the dose of 1.5 mg · kg⁻¹ of ranitidine, 100% of the patients had gastric contents with pH > 2.5. The proportion of patients with volume < 25 ml was 68% with ranitidine, 0.5 mg · kg⁻¹, and gradually increased to 100% with 2.5 mg · kg⁻¹ body weight. It is concluded that a significant number of outpatients are at risk for aspiration of acid gastric contents and that this risk is lowered by preoperative administration of ranitidine. (Key words: Complications: aspiration; pneumonitis. Gastrointestinal tract: gastric pH, volume; stomach. Histamine, antagonists: ranitidine. Lung: aspiration. Pharmacology, premedication: ranitidine.)

PULMONARY ASPIRATION OF acidic gastric contents continues to draw attention in the anesthesia literature.^{1,2} In recent years, the emphasis has been on decreasing the acidity and volume of gastric contents.³⁻⁶ Ranitidine is a highly selective H₂-receptor antagonist that has been shown to reduce gastric acidity.³⁻⁶

A gastric pH lower than 2.5 and gastric volume of 0.4 ml · kg⁻¹ or approximately 25 ml are generally considered to be critical factors for the development of pulmonary injury in adults.⁷⁻⁹ Analyses of gastric fluid after induction of anesthesia in nonobese adult outpatients undergoing elective surgery have demonstrated a significant proportion of patients to be at potential risk of acid as-

piration syndrome.^{6,10,11} The optimal dose of intravenous ranitidine to raise the gastric pH higher than 2.5 and reduce volume to less than 25 ml has not been evaluated. Thus, the purpose of this prospective investigation was to examine the dose-response relationship of intravenous ranitidine (0.0-2.5 mg · kg⁻¹ body weight) on pH and volume of gastric contents in outpatients.

Materials and Methods

One hundred and fifty adult outpatients receiving general anesthesia for elective surgery were studied. All patients were healthy and none had gastrointestinal disorders. This study was approved by the Institutional Review Committee and informed consent was obtained from all the patients. Patients were randomly assigned into six groups of 25 each. Patients in Group 1 received no ranitidine and served as the control. Patients in Groups 2-6 received ranitidine intravenously in incremental doses of 0.5 mg · kg⁻¹ body weight from 0.5-2.5 mg (Group 2, 0.5 mg; Group 3, 1.0 mg; Group 4, 1.5 mg; Group 5, 2.0 mg; and Group 6, 2.5 mg · kg⁻¹). Ranitidine was diluted with 50 ml of saline and was administered over a period of 10-15 min into the intravenous infusion 45 min to 5 h prior to induction of anesthesia. All the patients (Groups 1-6) were premedicated with diazepam, 5 mg, and hydroxyzine, 100 mg, with a sip of water 45-120 min prior to induction of anesthesia. All the patients were observed for any local or general adverse reactions.

Following satisfactory induction of anesthesia with sodium thiopental, a no. 18 Salem sump tube was passed into the stomach, and all available gastric contents were aspirated into a mucus trap. The position of the gastric tube was verified by insufflation of air through the gastric tube with simultaneous auscultation over the epigastrium. The pH was determined in the laboratory by a Corning® pH meter with an Ag/AgCl combination electrode.

Patients with gastric pH ≤ 2.5 or volume ≥ 25 ml were defined to be at risk of aspiration. Risk factors were analyzed in combination and independently. Statistical analyses performed were analysis of variance (ANOVA) and chi-square tests. One-way ANOVAs with Duncan's multiple range follow-up tests were used to test the significance of differences among the means of the six groups. Overall, 6 × 2 chi-square tests of independence with 2 × 2 chi-square follow-up tests were used to test the significance of differences between the proportions at risk in the six

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TABLE 1. Patient Characteristics, Fasting Periods, and Time Interval from Ranitidine Administration

	Number of Patients	Sex Distribution (M/F)	Age* (yr)	Height* (cm)	Weight* (kg)	Fasting Period* (h)	Time from Ranitidine to Sampling* (min)
Group 1 (no ranitidine)	25	12/13	33.5 ± 2.8	170.3 ± 1.4	67.0 ± 2.6	13.50 ± 0.85	—
Group 2 (ranitidine 0.5 mg · kg ⁻¹ iv)	25	15/10	37.2 ± 2.5	173.2 ± 2.3	74.2 ± 3.0	12.70 ± 0.49	75.8 ± 8.4
Group 3 (ranitidine 1.0 mg · kg ⁻¹ iv)	25	16/9	35.7 ± 2.9	175.0 ± 2.8	74.9 ± 3.0	12.26 ± 0.45	75.5 ± 8.3
Group 4 (ranitidine 1.5 mg · kg ⁻¹ iv)	25	11/14	36.0 ± 3.0	172.7 ± 1.8	69.7 ± 2.6	12.48 ± 0.48	82.8 ± 6.4
Group 5 (ranitidine 2.0 mg · kg ⁻¹ iv)	25	15/10	36.3 ± 2.8	174.1 ± 2.1	74.3 ± 2.9	13.22 ± 0.56	97.4 ± 8.7
Group 6 (ranitidine 2.5 mg · kg ⁻¹ iv)	25	13/12	32.2 ± 3.1	173.2 ± 1.7	73.8 ± 2.6	13.28 ± 0.42	108.6 ± 6.5
Direction and significance of values	NS	NS	NS	NS	NS	NS	6 > 4 = 2 = 3

NS = not significant.

* Values are mean ± SEM.

groups. Results were considered statistically significant if *P* values were less than 0.05.

Results

Statistical information concerning patient characteristics, fasting periods, and drug administration for the six groups is presented in table 1. Sex distribution, age, height, weight, and fasting period were similar in all the groups. There were small but significant differences among the five groups receiving ranitidine with respect to the time from administration of ranitidine to gastric sampling (*P* < 0.05).

GASTRIC pH

There were significant differences among the six groups with respect to mean pH (*P* = 0.0001) (table 2). The five ranitidine groups (Groups 2–6) had significantly higher mean pH than the control group (Group 1) (*P* < 0.05). The group receiving 1.5 mg · kg⁻¹ of ranitidine (Group 4) had a significantly higher mean pH than the group receiving 1.0 mg · kg⁻¹ (Group 3), which had significantly higher mean pH than the group receiving 0.5 mg · kg⁻¹ (Group 2) (*P* < 0.05). The groups receiving 2.0 mg · kg⁻¹ and 2.5 mg · kg⁻¹ of ranitidine (Groups 5 and 6) had significantly higher mean pH than the group receiving 0.5 mg · kg⁻¹ (Group 2) (*P* < 0.05), but did not differ significantly from the groups receiving 1.0 mg · kg⁻¹ and 1.5 mg · kg⁻¹ (Groups 3 and 4).

The six groups differed significantly in terms of pro-

portion of patients with pH ≤ 2.5 (*P* = 0.0001). The five ranitidine groups had significantly fewer patients with pH ≤ 2.5 than the control group (*P* < 0.05). Groups 3–6 receiving 1.0 mg · kg⁻¹ or more of ranitidine had significantly fewer patients with pH ≤ 2.5 than Group 2 receiving 0.5 mg · kg⁻¹ of ranitidine (*P* < 0.05), while Groups 3–6 did not differ significantly from each other. Similar results were obtained for the proportion of patients with pH ≤ 1.8. The six groups did not differ significantly in terms of proportion of patients with pH ≤ 1.5. The ED₅₀ to achieve pH > 2.5 was 0.36 mg · kg⁻¹ and the ED₉₅ was 0.98 mg · kg⁻¹ body weight.

GASTRIC VOLUME

The six groups differed significantly with respect to mean gastric volume (*P* = 0.0001) (table 3). The ranitidine group receiving 0.5 mg · kg⁻¹ (Group 2) did not differ significantly from the control group (Group 1), but the other four ranitidine groups (Groups 3–6) had significantly lower mean volume than the control group (Group 1) (*P* < 0.05). Group 6 had significantly lower mean volume than Group 2 (*P* < 0.05), but Groups 3–6 did not differ significantly.

The six groups differed significantly in terms of proportion of patients with gastric volume ≥ 25 ml (*P* = 0.0017). The three groups receiving the lowest ranitidine doses (Groups 2–4) did not differ significantly from the control group (Group 1), but the two groups (Groups 5 and 6) receiving the highest doses had significantly fewer patients with volume ≥ 25 ml than the control group

TABLE 2. Gastric pH Characteristics

	pH		Patients with pH ≤ 1.5	Patients with pH ≤ 1.8	Patients with pH ≤ 2.5
	Mean ± SEM	Range			
Group 1 (no ranitidine)	1.82 ± 0.07	1.28–2.73	4 (16)	14 (56)	24 (96)
Group 2 (ranitidine 0.5 mg · kg ⁻¹ iv)	4.67 ± 0.46*	1.55–7.85	0 (0)	1 (4)*	8 (32)*
Group 3 (ranitidine 1.0 mg · kg ⁻¹ iv)	5.94 ± 0.35*	2.02–8.20	0 (0)	0 (0)*	1 (4)*
Group 4 (ranitidine 1.5 mg · kg ⁻¹ iv)	6.83 ± 0.18*	4.70–8.52	0 (0)	0 (0)*	0 (0)*
Group 5 (ranitidine 2.0 mg · kg ⁻¹ iv)	6.38 ± 0.24*	3.39–8.00	0 (0)	0 (0)*	0 (0)*
Group 6 (ranitidine 2.5 mg · kg ⁻¹ iv)	6.61 ± 0.19*	3.63–8.00	0 (0)	0 (0)*	0 (0)*
Direction and significance of values	1 < 2 < 3 < 4 1 < 2 < 5 = 6		NS	1 > 2 = 3 = 4 = 5 = 6	1 > 2 > 3 = 4 = 5 = 6

NS = not significant.
Numbers in parentheses are percentages of patients.

* Ranitidine groups differed significantly from control group (Group 1), $P < 0.05$.

(Group 1) and Group 2 ($P < 0.05$). Groups 3–6 did not differ significantly.

The dose–response curve for the control group (Group 1) and the five ranitidine groups (Groups 2–6) depicting the relationship between the proportion of patients with volume < 25 ml and ranitidine dose showed a gradual increase from 64% with volume < 25 ml for the 0.0 mg · kg⁻¹ group (control) to 100% for the 2.5 mg · kg⁻¹

group (Group 5). The ED₉₅ was 1.96 mg · kg⁻¹ body weight.

COMBINED RISK OF pH AND VOLUME

The six groups differed significantly in terms of the proportion of patients with both pH ≤ 2.5 and volume ≥ 25 ml ($P = 0.0001$) (table 3). The group receiving the smallest dose of ranitidine (Group 2) did not differ sig-

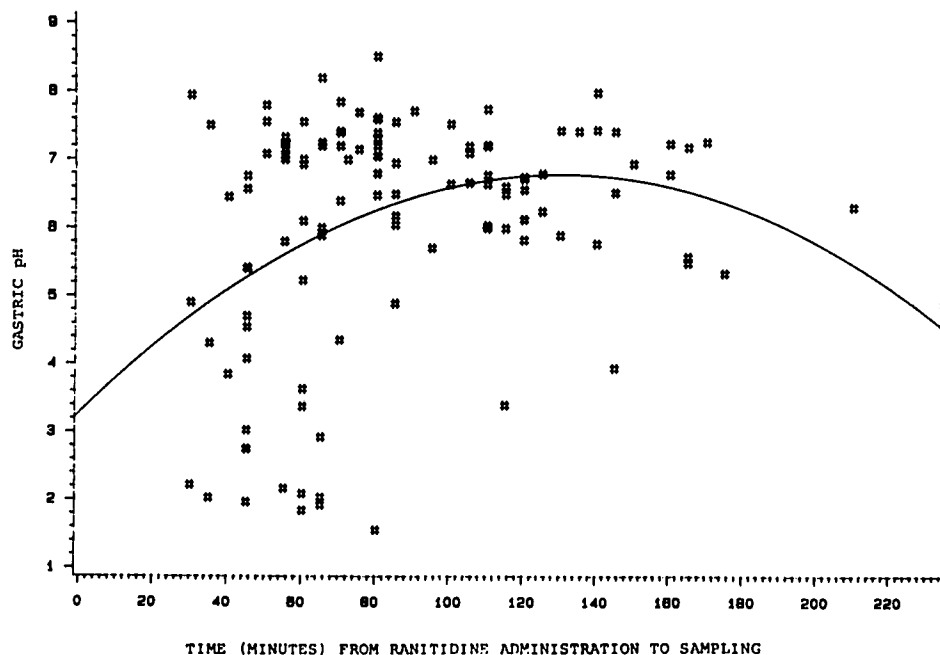
TABLE 3. Gastric Volume Characteristics

	Volume (ml)		Patients with Volume ≥ 25 ml	Patients with Volume ≥ 25 ml with pH ≤ 1.5	Patients with Volume ≥ 25 ml with pH ≤ 1.8	Patients with Volume ≥ 25 ml with pH ≤ 2.5
	Mean ± SEM	Range				
Group 1 (no ranitidine)	26.0 ± 4.7	8–100	9 (36)	2 (8)	7 (28)	9 (36)
Group 2 (ranitidine 0.5 mg · kg ⁻¹ iv)	19.7 ± 4.3	2–85	8 (32)	0 (0)	1 (4)	6 (24)
Group 3 (ranitidine 1.0 mg · kg ⁻¹ iv)	10.9 ± 1.9*	2–37	3 (12)	0 (0)	0 (0)*	1 (4)*
Group 4 (ranitidine 1.5 mg · kg ⁻¹ iv)	10.8 ± 2.1*	2–40	4 (16)	0 (0)	0 (0)*	0 (0)*
Group 5 (ranitidine 2.0 mg · kg ⁻¹ iv)	10.0 ± 2.4*	2–60	1 (4)*	0 (0)	0 (0)*	0 (0)*
Group 6 (ranitidine 2.5 mg · kg ⁻¹ iv)	7.23 ± 0.9*	2–18	0 (0)*	0 (0)	0 (0)*	0 (0)*
Direction and Significance of values	1 > 3 = 4 = 5 = 6 2 > 6		1 = 2 > 5 = 6	NS	1 > 3 = 4 = 5 = 6	2 > 4 = 5 = 6 1 > 3 = 4 = 5 = 6

NS = not significant.
Numbers in parentheses are percentages of patients.

* Ranitidine groups significantly different from control group (Group 1), $P < 0.05$.

FIG. 1. Relationship of gastric pH to time interval from ranitidine administration to gastric sampling. Polynomial regression showing an increase in pH with increasing time interval up to 2 h with a small decrease subsequent to 2 h.

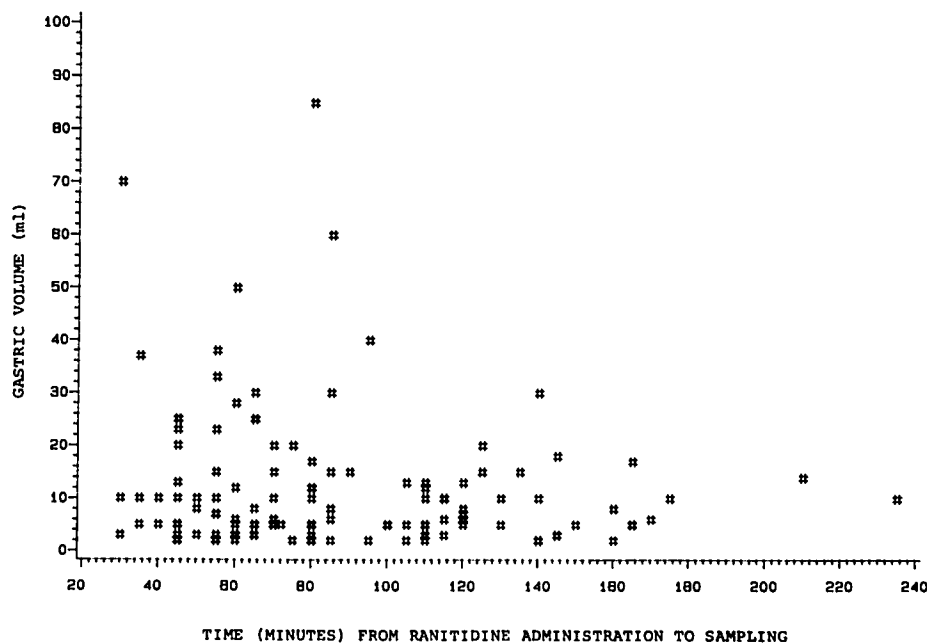


nificantly from the control group (Group 1), but the other four ranitidine groups (Groups 2-6) had significantly fewer patients with both $pH \leq 2.5$ and volume ≥ 25 ml than did Group 1 ($P < 0.05$). Groups 3-6 did not differ significantly. Similar results were obtained for the proportion of patients with both $pH \leq 1.8$ and volume ≥ 25 ml. The six groups did not differ significantly in terms of proportion with both $pH \leq 1.5$ and volume ≥ 25 ml.

OPTIMAL TIME INTERVAL

There was a large increase in pH with increasing time from ranitidine administration to gastric sampling up to approximately 2 h and a small decrease subsequent to 2 h (fig. 1) ($P < 0.05$). In contrast, there was no effect of time from ranitidine administration to gastric sampling on gastric volume (fig. 2).

FIG. 2. Relationship of gastric volume to time interval from ranitidine administration to gastric sampling, indicating no significant correlation between gastric volume and time interval.



SIDE EFFECTS

Side effects following intravenous administration of drugs were noted only in two patients in the intravenous ranitidine groups (<2%). Localized itching and rash at the site of infusion lasting approximately 10–15 min was seen in one patient while the other patient developed a rash approximately 5–10 cm around the infusion site, with localized burning and generalized itching lasting for 10–15 min. In both instances these symptoms started at the completion of the infusion.

Discussion

Regurgitation with subsequent pulmonary aspiration of gastric contents is a recognized hazard of anesthesia.^{1,2} It is generally agreed that highly acidic gastric contents with *pH* 1.0–1.5, in small volumes, are capable of producing severe pulmonary injury and death in animals.^{7,8,12} Recent data from aspirates with various combinations of *pH* and volume in rats demonstrated that the volume of 0.4 ml · kg⁻¹, considered as a potential risk, may well be beyond the critical value if associated with a *pH* < 1.4, while aspirates with higher *pH* of >1.8 were associated with far fewer deaths even at volumes exceeding 1–2 ml · kg⁻¹.¹²

H₂-receptor antagonists cimetidine and ranitidine are potent inhibitors of gastric acid secretion.¹³ Ranitidine appears to be as effective as cimetidine in the treatment of a variety of acid-peptic disorders and acid-aspiration prophylaxis during general anesthesia, and offers the advantage of a more prolonged period of protection with presumably fewer side effects.^{3-6,13,14}

Studies with intravenous or intramuscular ranitidine either 50 mg or 100 mg in patients undergoing elective surgery demonstrated a gastric *pH* > 2.5 in 88–100% of patients and a gastric volume of <25 ml in 87–96% of patients.^{4,5} However, these results were not significantly different than those following 300 mg of cimetidine (iv or im). In adults the recommended parenteral dose of ranitidine is 50 mg, and the recommended oral dose is 150 mg.¹³ Due to the high variability of bioavailability of ranitidine (40–88%), the intravenous dose equivalent to 150 mg oral ranitidine is 60–132 mg or 0.86–1.89 mg · kg⁻¹ in an adult weighing 70 kg. In our study we have evaluated the effects of intravenous ranitidine dosage from as low as 0.5 mg to as high as 2.5 mg · kg⁻¹.

Preoperative intravenous ranitidine increased *pH* and reduced the volume of gastric contents. Reduction of gastric acidity was seen at the lowest dosage examined, *i.e.*, 0.5 mg · kg⁻¹, and at a dosage of 1.0 mg · kg⁻¹, intravenous ranitidine increased the proportion of patients with gastric *pH* > 2.5 to 96%, while 1.5 mg · kg⁻¹ raised this proportion to 100%. Ranitidine also reduced the volume of gastric juice, but significant volume reductions (<25 ml) were

observed only at the higher doses (2.0–2.5 mg · kg⁻¹). In other words, ranitidine has less effect on reducing gastric volume than on raising gastric *pH*.

A pitfall in this study is the technique employed for the collection of gastric contents, as the exact location of the gastric tube at the time of the aspiration of gastric contents is not known and consequently all the contents may not be obtained. Hence, gastric contents collected by this technique may not accurately represent the total volume of gastric contents. Measurement of gastric contents by dye dilution yields consistently higher gastric volumes than collection by aspiration through a gastric tube and is presumed to be more accurate.¹⁰ However, in this study, any error in the estimation of gastric contents should be consistent across all the groups. Therefore, comparisons of group means and proportion of patients at risk are not biased by the use of this technique and most likely would underestimate the potential risk of acid pneumonitis. In addition, to avoid criticism of technical problems associated with the measurement of gastric volume, we have analyzed risk factors independently for *pH* and volume.

The results in this study and other studies suggest that a significant proportion of outpatients undergoing elective surgery are at risk for aspiration pneumonitis, as 96% of the patients in the control group (Group 1) have gastric *pH* ≤ 2.5, and 36% have gastric contents ≥ 25 ml with *pH* ≤ 2.5. Ranitidine in dose ranges from 0.5 to 2.5 mg · kg⁻¹ body weight administered intravenously reduced these risk factors markedly. Ranitidine 1.0 mg · kg⁻¹ body weight reduced the proportion of patients with gastric *pH* ≤ 2.5 to 4%, while 1.5 mg · kg⁻¹ reduced this proportion to 0%. Because there is no evidence that gastric-content volume in itself poses a potential risk, raising the gastric *pH* to safe levels is likely to provide adequate protection. This may be achieved by administration of 1.0–1.5 mg · kg⁻¹ of ranitidine intravenously or intramuscularly. Parenteral ranitidine may have some advantages over parenteral cimetidine, as cardiovascular side effects are less and the longer duration of action of ranitidine extends protection into the recovery period.¹³⁻¹⁵ An additional advantage may be its potential effect on the lower esophageal sphincter because a dose-related increase in lower esophageal sphincter pressure following intravenous bolus injection of ranitidine 0.5 to 1.0 mg · kg⁻¹ body weight was reported in healthy volunteers.^{**} However, these findings were questioned by another group of investigators.¹⁶ Parenteral ranitidine does not appear to have any special advantages over oral ranitidine because 150 mg and 300 mg of ranitidine administered orally at least 90 min prior to induction of anes-

** Bertaccini G, Molina E, Bobbie P, Foggi E: Ranitidine increases lower esophageal sphincter pressure in man. *Ital J Gastroenterol* 13: 147–150, 1981.

thetia raised gastric $pH > 2.5$ in 88–100% of the patients.^{3–6} Intravenous ranitidine is indicated in patients when there is inadequate time for preparation of the patient with oral ranitidine or cimetidine.

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