Single-dose intravenous H₂ blocker prophylaxis against aspiration pneumonitis: Assessment of drug concentration in gastric aspirate

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This placebo-controlled trial compared the effects of preoperative, intravenous cimetidine (300 mg) or ranitidine (50 mg) on gastric pH and gastric volume in 31 adult patients requiring general anesthesia. The elapsed time from drug administration to initial gastric sampling did not differ significantly between ranitidine (45 minutes), cimetidine (48 minutes), or placebo (52 minutes) treated patients. Ranitidine, but not cimetidine, significantly (P=0.02) increased gastric pH when compared with placebo. Gastric pH correlated (r=0.7, P=0.01) with cimetidine concentration in gastric fluid at induction.

Gastric pH was directly proportional to ranitidine concentration in gastric fluid at induction, but the correlation was weak (r=0.54, P=0.1). The H₂ blockers did not significantly alter gastric volume when compared with placebo. The number of patients with gastric pH<2.5 and gastric volume =>25 ml did not differ significantly between cimetidine (8%), ranitidine (10%), and placebo (22%). No clinical evidence of aspiration pneumonitis was found in our study patients.

Regurgitation of gastric contents with subsequent aspiration into the lungs contributes significantly to the morbidity of patients undergoing general anesthesia. Studies in animals show that the extent of pulmonary injury depends upon the amount and distribution of the aspirate, the acidity of the aspirate, and the presence of particulate and bacteria. Roberts and Shirley suggested that a patient “at risk” be defined as that patient with at least 25 ml of gastric fluid (0.4 ml/kg) with a pH below 2.5. Olsson and coworkers reported an incidence of aspiration pneumonitis confirmed by x-ray after anesthesia of 2.2 per 10,000 anesthetics, with a mortality of 0.2 per 10,000 inpatients.

Despite the low incidence of aspiration pneumonitis reported in recent literature, much attention is focused on aspiration pneumonitis prophylaxis. Antacids and anticholinergic agents have been used for prophylaxis, but these agents do not effectively decrease gastric volume, and they produce an inconsistent effect on gastric pH. Preoperative metoclopramide administration reduces gastric volume, but has a variable effect on pH.

The introduction of H₂ blockers led to a series of studies evaluating their effectiveness for aspiration pneumonitis prophylaxis. Multiple-dose, preoperative cimetidine regimens effectively control gastric pH at the time of induction. However, the reduction in gastric volume has been inconsistent. Ranitidine, a more potent H₂ blocker, effectively controls both gastric pH and volume after multiple-dose, preoperative administration. Following intravenous administration,
ranitidine promptly reduces gastric acidity; this effect persists for several hours. Cimetidine (300 to 400 mg) and ranitidine (50 mg) produce equivalent suppression of basal acid secretion following single-dose, intravenous administration in healthy volunteers. The onset of clinical effect (pH > 2.5) occurs within 30 minutes and peaks (pH 6.0) within one to two hours post-dose. These data suggest that single-dose, intravenous H₂-blocker administration would provide effective prophylaxis against aspiration pneumonitis. Such a regimen would be applicable in emergency surgery, where aspiration pneumonitis represents a more significant cause of morbidity and mortality.

This double-blind, placebo-controlled trial compared the effects of single-dose, preoperative, intravenous administration of cimetidine or ranitidine on gastric pH and gastric volume and evaluated the relationship between acid suppression and drug concentration in gastric fluid at induction of general anesthesia.

Methods

Patients 18 years of age or older, American Society of Anesthesiologist class I or II (ASA I-II), undergoing outpatient elective arthroscopic knee surgery or breast biopsy under general anesthesia, participated in the study. Patients were excluded from the study if they met any of the following criteria:
1. History of active peptic ulcer disease.
2. History of gastrointestinal surgery or stomach cancer.
3. Recent oropharyngeal surgery.
5. Pregnancy.
6. Known hypersensitivity to H₂ blockers.

Patients receiving anticholinergic agents, H₂ blockers, or antacids were also excluded from the study. The protocol was approved by the Institutional Review Board and written informed consent was obtained from all participants.

All patients were verbally instructed to fast after midnight on the night before surgery. Patients remained in a fasting state until their return to the anesthesia recovery room. Upon arrival to the preoperative suite, baseline vital signs (arm-cuff blood pressure, electrocardiogram, pulse, and respiratory rate) were recorded. Patients were randomly assigned to one of three treatment groups: (1) ranitidine HCl 50 mg in 20 ml of normal saline, (2) cimetidine HCl 300 mg in 20 ml of normal saline, or (3) placebo (20 ml of normal saline). The study medication was administered intravenously over a five-minute period 30 to 45 minutes before induction of anesthesia. Vital signs were recorded five minutes before and after drug administration.

Upon arrival at the operating room, baseline vital signs were obtained. All patients received a brief dose of 3 mg IV, fentanyl 100 μg IV, and methohexital 1.5 mg/kg IV followed by succinylcholine 1 to 1.5 mg/kg IV. Patients were intubated with a cuffed endotracheal tube. General anesthesia was maintained with a 70% nitrous oxide-oxygen mixture and isoflurane 0.5% to 1%.

The time of induction of anesthesia was noted and a nasogastric tube was inserted. A 60 ml syringe was used to aspirate the gastric fluid from the stomach. The volume of gastric fluid was measured with a graduated cylinder to the nearest 0.5 ml. A Corning M140 pH meter (Corning Scientific Instruments, Medfield, Massachusetts) with a standard pH electrode was used to measure pH. Two reference buffers, 4.0 pH and 10.0 pH (Corning Scientific Instruments) were used to calibrate the pH meter before each case. The pH electrode was removed from a distilled water container, wiped dry and placed in the sample. The pH was recorded to the nearest 0.01 units. Three pH determinations were made at 15-second intervals on each sample and the mean of the three readings was calculated.

Just prior to extubation, a new 60 ml syringe was used to obtain a second sample for volume and pH measurements, and the time of sampling was recorded. A minimum of 2 ml of fluid from each sample was placed in a test tube and frozen for subsequent quantitation of drug in the gastric juices. The liquid chromatographic assay described by Abdel-Rahim and associates was used to quantitate cimetidine in gastric fluid. Reverse phase high-performance liquid chromatography with ultraviolet detection was used to assay ranitidine in gastric fluid.

All patients were examined before discharge for any respiratory complications. Follow-up telephone interviews were done 24 hours after the procedure. Respiratory symptoms, if present, were recorded. The patients returned for medical evaluation if fever, purulent sputum, shortness of breath, or severe cough developed.

Statistical methods

A Mantel-Haenszel chi-squared test with two degrees of freedom was used for comparison between groups on variables expressed as percentages (origin, gender, current diseases, incidence of gastric volume => 25 ml, incidence gastric pH <= 2.5, and incidence of respiratory complaints). A Cochran-Mantel-Haenszel chi-squared test with two degrees of freedom was used to compare differences.
in smoking history. A general linear models procedure (F-test) was used to compare differences in age, weight, postintubation and preextubation gastric volume, postintubation and preextubation gastric pH, and time to postintubation and preextubation. Tukey's test was used for multiple comparisons. Linear regression analysis was used to evaluate the relationship between gastric pH and the concentration of cimetidine and ranitidine in gastric fluid at induction.

All P values were two-sided. Statistical significance was set at P<0.05.

**Results**

Thirty-five patients were enrolled in the study. Four patients were excluded from the study because of incorrect treatment assignments. Patient demographics and medical histories did not differ significantly between the three treatment groups (Table I). Three ranitidine-treated patients were excluded from further analysis because of protocol violations after enrollment in the study (two received local anesthesia, and one had a three-hour elapsed time to induction). One patient in the placebo group was excluded from further analysis because no gastric sample was recovered both postinduction and preextubation.

The elapsed time from drug administration to initial gastric sampling did not differ significantly between ranitidine (45 minutes), cimetidine (48 minutes), or placebo (52 minutes) treated patients. There was no significant difference in the elapsed time between drug administration and the second gastric sampling prior to extubation among the three treatment groups (98 minutes, 103 minutes and 114 minutes). More patients undergoing arthroscopic knee surgery (83%) had a gastric pH<=2.5 or a gastric volume=>25 ml at some time in the study when compared with patients undergoing breast biopsies (62%), but this difference was not statistically significant.

Gastric pH was significantly (P=0.02) higher in the ranitidine group when compared with the placebo group, both at induction and just prior to extubation (Table II). Cimetidine did not significantly alter pH when compared with placebo (Ta-

<table>
<thead>
<tr>
<th>Table I</th>
<th>Demographic characteristics of study groups</th>
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<tbody>
<tr>
<td>Variable</td>
<td>Ranitidine (N = 13)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>3 (23%)</td>
</tr>
<tr>
<td>Female</td>
<td>10 (77%)</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>28.77</td>
</tr>
<tr>
<td>Male</td>
<td>23.33</td>
</tr>
<tr>
<td>Female</td>
<td>30.40</td>
</tr>
<tr>
<td>Weight (#)</td>
<td>159.46</td>
</tr>
<tr>
<td>Male</td>
<td>173.33</td>
</tr>
<tr>
<td>Female</td>
<td>155.30</td>
</tr>
<tr>
<td>Origin</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>5 (38%)</td>
</tr>
<tr>
<td>Black</td>
<td>8 (62%)</td>
</tr>
<tr>
<td>Oriental</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Smoking History</td>
<td></td>
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<tr>
<td>None</td>
<td>6 (46%)</td>
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<tr>
<td>Cigarettes &lt; 1 pk/day</td>
<td>3 (23%)</td>
</tr>
<tr>
<td>Cigarettes ≥ pk/day</td>
<td>4 (31%)</td>
</tr>
<tr>
<td>Current Diseases</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>11 (85%)</td>
</tr>
<tr>
<td>Pulmonary Disease</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Heart Disease</td>
<td>1 (8%)</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>1 (8%)</td>
</tr>
<tr>
<td>Other Disease</td>
<td>1 (8%)</td>
</tr>
</tbody>
</table>

*General linear models procedure (F-test) used for means. Mantel-Haenszel chi-squared test with 2 degrees of freedom applied to percentages.
ble II). There was no significant difference in gastric pH between the cimetidine and ranitidine groups. There was no significant difference in gastric pH value between induction and preextubation periods. The mean gastric volume did not differ significantly between treatment groups either at induction or prior to extubation (Table II). The high risk combination of residual gastric volume $\geq 25$ ml and gastric pH $\leq 2.5$ was more common in the placebo group (22%) than in either the cimetidine (8%) or ranitidine (10%) groups, but these differences did not reach statistical significance.

There was a significant correlation ($r=0.7$, $P=0.01$) between gastric pH and cimetidine concentration in gastric juice at induction (Figure 1). Gastric pH was directly proportional to ranitidine concentration in gastric fluid at induction, but the correlation was weak ($r=0.54$, $P=0.1$) (Figure 2). There was no significant correlation between patient weight and either gastric pH or volume among any of the treatment groups.

Respiratory complaints (i.e., shortness of breath, severe cough, purulent sputum, or wheezing) were not noted during the recovery room evaluation or the 24-hour follow-up phone interview. No patient required a follow-up visit. All treatments were well tolerated. Transient bradycardia occurred during drug administration in one ranitidine-treated patient. One cimetidine-treated patient experienced nausea, vomiting, and diarrhea in the postanesthesia recovery room. One patient in the placebo group experienced a metallic taste shortly after drug administration.

### Table II

<table>
<thead>
<tr>
<th>Variable</th>
<th>Treatment</th>
<th>$P^*$</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Ranitidine ($N=10$)</td>
<td>Cimetidine ($N=12$)</td>
</tr>
<tr>
<td>Gastric pH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastric pH at induction</td>
<td>4.7 ± 0.82**</td>
<td>3.3 ± 0.64</td>
</tr>
<tr>
<td>Gastric pH preextubation</td>
<td>5.7 ± 0.87</td>
<td>4.1 ± 0.74</td>
</tr>
<tr>
<td>Gastric volume</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastric volume at induction</td>
<td>21.5 ± 5.7</td>
<td>14.2 ± 3.0</td>
</tr>
<tr>
<td>Gastric volume preextubation</td>
<td>10.3 ± 3.7</td>
<td>8.0 ± 2.4</td>
</tr>
</tbody>
</table>

*General linear models procedure (F-test) used for means. Mantel-Haenszel chi-squared test with 2 degrees of freedom applied to percentages. **Treatment means are significantly different (Tukey’s test—5% level).
Discussion

Aspiration of gastric contents is a serious but preventable complication of general anesthesia. The risk of acid aspiration is greater in obese patients, ambulatory surgical patients, pregnant patients, trauma patients, and patients with hiatal hernia or gastric outlet obstruction. Emotional strain and apprehension associated with the impending surgery may also disturb gastric motility and increase gastric acid secretion. Hydrochloric acid is most frequently responsible for the pathophysiological changes, morbidity, and mortality reported after accidental aspiration of gastric contents. In addition, histamine appears to play a direct role in acid-induced pulmonary injury.

Pharmacologic prophylaxis against acid aspiration is aimed at reducing gastric acid and volume. The ability of a drug to modify these factors does not guarantee that it will prevent aspiration pneumonitis. However, lowering both gastric acidity and gastric volume reduces the severity of pneumonitis.

Our data show that ranitidine produced the most pronounced gastric acid antisecretory effects. These findings are consistent with those of other investigators and may reflect ranitidine's potency at the H₂ receptor. Ranitidine is five to six times more potent than cimetidine at the H₂ receptor. The doses of ranitidine (50 mg) and cimetidine (300 mg) used in our study were equipotent.

Unfortunately, neither ranitidine nor cimetidine was able to significantly decrease gastric volume when compared with placebo. This finding is also consistent with previously published studies. The inconsistent effect of cimetidine and ranitidine on gastric volume may result from suboptimal dosing. Manchikanti and colleagues showed that ranitidine (0.5 to 2.5 mg/kg IV) produces a dose-dependent effect on gastric volume without any adverse effects. They found that at least 1.5 mg/kg IV of ranitidine was necessary in order to consistently reduce gastric volume at one hour post-dose. In our study, we used the FDA-approved dose for intravenous ranitidine (approximately 0.7 mg/kg for a 70 kg patient). The study by Dr. Manchikanti was published after we began our study.

After intravenous administration, the H₂ blockers distribute into stomach tissue where they exert their H₂ receptor blocking action on the parietal cells. Previous studies in trauma patients receiving stress ulcer prophylaxis have reported a significant correlation (r = 0.77, P<0.001) between gastric pH and cimetidine concentrations above 2 μg/ml in gastric fluid. We found a significant correlation between gastric pH at induction and cimetidine concentrations above 0.2 ng/ml of gastric fluid. Although gastric pH was directly proportional to ranitidine concentrations above 0.1 ng/ml of gastric fluid at induction, the correlation was weak. This may be the result of Type II error given the small sample size (n = 10).

Numerous studies have demonstrated that the H₂ blockers are beneficial in controlling gastric fluid pH and volume in patients requiring general anesthesia. Unfortunately, extrapolation of these findings is hindered by study design flaws (e.g., unknown medications on admission, differing preoperative regimens, inconsistent time of dosing, and heterogenous patient selection).

We excluded patients receiving drugs that could alter the risk of aspiration pneumonitis by affecting gastric secretion and/or motility. Anesthetic drugs were the same in all patients and are not a confounding factor in our study. The similar time interval between drug administration and gastric sampling in all three groups and our patients' low anesthetic risk (ASA I-II) reduced other possible biases in our study.

The results of recent studies evaluating the efficacy of aspiration pneumonitis prophylaxis have been questioned because these studies may have been biased by lack of control groups or a double-blinded observation. Our study design overcame these limitations and allowed us to assess the relative risk of acid aspiration in ambulatory patients undergoing elective arthroscopic knee surgery or breast biopsy procedures. Pulmonary aspiration is considered a potential risk if patients have 25 ml or more of gastric contents at a pH below 2.5. The number of patients with a high gastric volume and low gastric pH was similar in both groups of ambulatory surgery patients. Preoperative prophylaxis with H₂ blockers reduced gastric acidity, but did not significantly reduce the number of high risk patients with gastric volume > 25 ml and gastric pH<2.5 when compared with placebo.

Recent data suggest that gastric volumes above 0.4 ml/kg may be an independent risk factor for acid aspiration. A limitation of the gastric volume measurements in our study is that the exact location of the gastric tube is not known; therefore, the volume of gastric fluid collected by this technique may not accurately represent the total volume of gastric contents. In our study, any error in the estimation of gastric contents would be similar in all groups and would likely underestimate the potential risk for gastric aspiration.
Careful airway management and good anesthetic technique are the cornerstones of aspiration pneumonitis prophylaxis. Improvements in anesthetic agents and airway management have successfully reduced the incidence of aspiration pneumonitis to less than 3 in 10,000 cases. Prophylaxis with ranitidine reduces gastric acidity when compared with placebo and may reduce the severity of aspiration pneumonitis, but preoperative prophylaxis cannot replace good anesthetic technique.

REFERENCES


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ACKNOWLEDGEMENT

Support for this study was obtained by a grant from Glaxo Inc., Research Triangle Park, North Carolina.