Anesthesiology
65:684–687, 1986

Prophylactic Intravenous Cimetidine Reduces the Risk of Acid Aspiration in Morbidly Obese Patients

ARTHUR M. LAM, M.D., F.R.C.P.(C),* D. MICHAEL GRACE, M.D., D. PHIL, F.R.C.S.(C), F.A.C.S,†
FOSTER J. PENNY, M.D., F.R.C.P.(C),‡ WILLIAM C. VEZINA, M.D., F.R.C.P.(C)§

Morbidly obese patients are at risk of acid aspiration pneumonitis should regurgitation occur during induction of anesthesia because of the large residual volume of gastric fluid with a low *p*H. It has been postulated that obese patients may have delayed gastric emptying and that the prolonged distention of the stomach may stimulate increased production of acid by the parietal cells.[1]

The purpose of this study is to evaluate the effects of prophylactic intravenous cimetidine in two dose regimens *versus* saline premedication on the volume and acidity of gastric fluid in patients undergoing gastroplasty for morbid obesity. As part of the preoperative investigation in these patients, the gastric emptying half-time was determined using a radionuclide method to evaluate the hypothesis of delayed gastric emptying.

METHODS

The study was approved by the Health Sciences Standing Committee on Human Research of the University of Western Ontario. Patients scheduled for gastric stapling procedures for morbid obesity were studied. Morbid obesity is defined as 100 lb above the ideal weight.¶ All patients fasted for a minimum of 8 h before the operation. The patients were initially divided into two groups in a random fashion, with Group 1 receiving saline and Group 2 receiving cimetidine 600 mg by intravenous infusion (iv) over 10 min, 60–90 min before the operation. Because the optimal dose of cimetidine for acid aspiration prophylaxis has not been determined in morbidly obese patients, a third group of patients receiving cimetidine 300 mg iv was subsequently added. Of 34 patients studied, 13 received saline as preoperative medication, eight received cimetidine 300 mg iv and 13 received cimetidine 600 mg iv. No other premedication was given, and no patient was receiving drugs known to influence gastric acidity.

The gastric emptying half-time, performed between 2 and 5 days preoperatively, was determined using a radioactive tracer method.[2]

In all patients, oxygen was administered for 3 min prior to induction of anesthesia with sodium thiopental and succinylcholine, and a cuffed endotracheal tube was then inserted while cricoid pressure was applied. After stabilization of the general condition of the patient, a no. 18 modified nasogastric tube with extra orifices was inserted into the stomach and all gastric contents were aspirated for analysis of volume and *p*H. Complete aspiration was ascertained by the surgeon on entry into the peritoneal cavity, and any residual volume was retrieved with manual compression of the stomach by the surgeon. The volume and *p*H of the gastric fluid was immediately analyzed using a graduated cylinder and Corning® *p*H meter by a research assistant who was unaware of the nature of the premedication used. For statistical comparison, one-way analysis of variance and Student's *t* test with a Bonferroni correction were used for the volume of gastric fluid. Because of the concern that *p*H may not be normally distributed, the Kruskal-Wallis rank-sum test was used for the analysis of *p*H. In addition, because *p*H is a logarithmic number and its use in statistical computation has been debated,[3–5] the analysis was repeated using the actual hydrogen ion concentration. The influence of preoperative gastric emptying half-time on subsequent gastric volume and *p*H following cimetidine administration was assessed using the least-squares linear regression analysis. Chi-square analysis was used to compare the proportion of patients at risk of acid aspiration pneumonitis (risk is defined as *p*H of less than 2.5 and volume exceeding 25 ml) in the treatment groups with the control group. A P value of <0.05 was considered significant.

* Associate Professor, Department of Anaesthesia.
† Associate Professor, Department of Surgery.
‡ Assistant Professor, Department of Anaesthesia.
§ Assistant Professor, Department of Nuclear Medicine.

Received from the Departments of Anaesthesia, Surgery, and Nuclear Medicine, University Hospital and University of Western Ontario, London, Ontario, Canada. Accepted for publication July 28, 1986. Presented in part at the American Society of Anesthesiology Meeting, Atlanta, Georgia, 1983.

Address reprint requests to Dr. Lam: Department of Anaesthesia, University Hospital, P. O. Box 5339, Postal Stn. A., London, Ontario, Canada N6A 5A5.

Key words: Anesthesia complications: aspiration; obesity. Gastrointestinal tract: histamine antagonists; *p*H; stomach; volume. Pharmacology: cimetidine.

¶ Brodsky JB: Anesthesia for the morbidly obese patient. American Society of Anesthesiologists, 34th Annual Refresher Course Lectures 226–228, 1983.

RESULTS

There were no complications arising from the study. The three groups were similar in age, weight, height, and sex (table 1). In all patients aspiration was complete and no additional volume was retrieved with manual compression of the stomach. Because of variations of actual time of the operation from the scheduled time, not all patients received their premedication within the time period prescribed; four patients received it less than 60 min and three patients more than 90 min before the operation.

Gastric Emptying Half-time. The mean gastric emptying half-time ($t_{1/2}$) in the three groups ranged between 51 and 68 min, and the median $t_{1/2}$ ranged between 43 and 47 min (table 2). There was one patient in each group with a prolonged $t_{1/2}$ (exceeding 120 min), accounting for the difference between the mean and the median value. There were no significant differences among the groups. The female patients tended to have higher $t_{1/2}$ (67 ± 5 min (SEM), n = 26) compared with the male patients (46 ± 7 min (SEM), n = 8), but this difference was not statistically significant ($P = 0.2$, unpaired t test). The preoperative $t_{1/2}$ did not have any appreciable influence on the efficacy of cimetidine, as correlation between $t_{1/2}$ and gastric volume as well as *p*H following cimetidine administration yielded no statistically significant relationships.

Gastric Volume. The saline control group had a large residual volume of gastric fluid (40 ± 5 ml) at the time of anesthetic induction, with 77% having volumes exceeding 25 ml (tables 2 and 3). The administration of cimetidine significantly reduced the gastric volume to approximately one-half of the control value ($P < 0.005$) with no difference between the two treatment groups; the mean volume was 16 ± 4 ml in the cimetidine 300 mg group and 18 ± 4 ml in the cimetidine 600 mg group. In each treatment group there was one patient who had a gastric volume greater than 25 ml at the time of anesthetic induction (table 3), and in both cases the time from the administration of cimetidine to the time of induction was less than 60 min.

TABLE 1. Subject Data

	Control (n = 13)	Cimetidine 300 mg (n = 8)	Cimetidine 600 mg (n = 13)
Age (yr ± SD)	39 ± 8	38 ± 9	37 ± 8
Weight (kg ± SD)	141 ± 21	133 ± 24	137 ± 24
Height (cm ± SD)	167 ± 9	165 ± 8	170 ± 11
Sex (F/M)	9/4	7/1	10/3

*Gastric p*H. The mean gastric *p*H of the saline control group was 2.17 ± 0.32 and the actual H^+ concentration was 22.1 ± 6.30 × 10^{-3} mol/l. Eighty-five per cent of these patients had a gastric *p*H less than 2.5. Preoperative cimetidine administration significantly elevated the gastric *p*H to 5.85 ± 0.62 (300 mg group) and 5.85 ± 0.61 (600 mg group), and the percentage of patients with *p*H less than 2.5 was reduced to 19% in the treatment groups ($P < 0.001$, table 3).

Patients at Risk (with volume > 25 ml and p*H < 2.5).* Seventy-seven per cent of the patients in the control group were considered to be at risk of acid aspiration pneumonitis with gastric volume exceeding 25 ml and *p*H less than 2.5. In contrast, only two patients or 10% in the treatment groups fall into this category. Moreover, both these patients received their premedication of cimetidine less than 60 min prior to anesthetic induction (table 3).

DISCUSSION

The most critical factor in determining the severity of pulmonary lesions following aspiration of gastric content appears to be the acidity of the aspirate,[6] although a critical volume may also be important. In general, the higher the acidity, the less is the volume required to cause pulmonary damage.[7] Although the results from preliminary studies on the Rhesus monkey were never confirmed and

TABLE 2. Gastric Emptying and Gastric Content Data

	Value	Control (n = 13)	Cimetidine 300 mg (n = 8)	Cimetidine 600 mg (n = 13)
Preoperative* gastric emptying half-time ($t_{1/2}$ in min)	mean ± SEM	64 ± 11	51 ± 10	68 ± 11
	median	43	47	44
Volume of Gastric fluid (ml)	mean ± SEM	40 ± 5	16 ± 4†	18 ± 4†
*p*H of gastric fluid	mean ± SEM	2.17 ± 0.32	5.86 ± 0.62‡	5.85 ± 0.61§ (n = 12)
H^+ concentration of gastric fluid (mol/l × 10^{-3})	mean ± SEM	22.10 ± 6.30	1.42 ± 1.40†	2.20 ± 1.90†

* One patient in each group had infinite gastric emptying half-time and was arbitrarily assigned a $t_{1/2}$ of 120 min.

† Within analysis of variance, significantly different from the control group ($P < 0.005$).

‡ Kruskal-Wallis rank-sum test, significantly different from control ($P < 0.001$).

§ Gastric aspirate could not be obtained in one patient.

TABLE 3. Distribution of High-risk Groups

	Control		Cimetidine Groups	
	(n = 13)	(%)	(n = 21)	(%)
No. of patients with $pH < 2.5$	11	85	2	10*
No. of patients with volume > 25 ml	10	77	4	19*
No. of patients at risk (vol > 25 ml and $pH < 2.5$)	10	77	2	* 10

* Chi-square analysis, significantly different from control ($P < 0.001$).

no human data is available,[8] it is generally accepted that patients with gastric volumes greater than 25 ml and pH less than 2.5 at the time of anesthetic induction are at risk of acid aspiration pneumonitis.[8] The increased risk of aspiration in morbidly obese patients compared with nonobese patients was first reported by Vaughn *et al.* in 1975.[1] In their study, 75% of the obese patients had gastric volumes of more than 25 ml and pH less than 2.5. Our present study confirms their findings. They postulated that similar to obstetric patients at term, morbidly obese patients may be at increased risk because of delayed gastric emptying. Our findings however, do not support this theory because the mean gastric emptying half-times in our obese patients did not differ significantly when compared with healthy nonobese volunteers previously studied using a similar method.[9] However, there was one patient in each group who had delayed emptying.

Regardless of the pathophysiology, that morbidly obese patients pose significant risk at the time of anesthetic induction is beyond dispute. Not only are they at risk because of the large residual gastric volume with high acidity, but they are also prone to the complication of regurgitation because of potential airway problems secondary to their obesity. It is therefore logical to attempt to minimize this risk by decreasing the gastric volume and increasing gastric pH pharmacologically. The administration of antacid has been popular in the management of obstetric patients, but with recent demonstration that aspiration of particulate antacid may cause pulmonary damage,[10,11] this practice is no longer advisable. Clear liquid antacid may still be useful, but the theoretical increase in gastric volume also makes it less than ideal. Cimetidine, a histamine H_2-receptor antagonist, has been shown to be extremely effective in reducing gastric acidity.[12–17] Its effect on volume is more variable, with some studies showing a significant reduction and no reduction in others.[16,17] This appears to be dependent on the route of administration and the time interval between administration and specimen collection; intravenous administration appears to be more effective, and a minimum of 45 min is required for its effect to be demonstrated.[17]

While cimetidine is readily absorbed from the gastrointestinal tract, parenteral administration achieves a higher blood level faster than oral administration and therefore may shorten the time required to achieve its effect. Although the efficacy of cimetidine as a premedicant in obstetric patients has been extensively studied, there have been few studies carried out in morbidly obese patients. Wilson *et al.* have demonstrated that cimetidine 300 mg administered orally the night before and again the morning of surgery significantly reduced gastric acidity but did not decrease volume significantly compared with the two groups of patients receiving atropine or glycopyrrolate.[18] However, the control group who received no premedications had too few patients for comparison. As mentioned earlier, the intravenous route may be more effective than the oral route in reducing acidity and decreasing volume. In addition, prior to our study of gastric emptying half-time, we were unsure if morbidly obese patients had normal gastric motility and because cimetidine is largely absorbed in the small intestine,[19] we avoided oral administration. We therefore chose to administer cimetidine intravenously 60 to 90 min before the operation to allow optimal effect. Indeed, we observed not only that pH was increased, but also that volume was significantly reduced. Another possible explanation for the discrepancy in volumes in other studies was the method of collection. In most studies the gastric volume obtained by simple aspiration is at best an estimate of the actual gastric volume because there are no independent means to confirm complete evacuation. In contrast, in the present study the stomach was manually compressed by the surgeon on entry into the peritoneal cavity, and in no patient was additional volume obtained. The accuracy of volume determination was thus assured. Interestingly, in comparison to the study of Wilson *et al.* which used a similar method to confirm complete emptying of the stomach, gastric volumes were similar but pH values in our study were higher, suggesting that the advantage of the intravenous route, at least in obese patients, lies not with a greater reduction in volume, but with a greater reduction in acidity.

We also administered cimetidine in two dose regimens because the optimal dose of premedicant had not been previously studied in morbidly obese patients. There are theoretical advantages in administering a small dose of cimetidine should this prove to be as effective as a larger dose. Although the safety record of cimetidine has been confirmed in extensive clinical trials, it is now recognized that cimetidine can reduce hepatic blood flow as well as inhibit the microsomal enzyme activity and therefore may interfere with elimination of drugs such as oral anticoagulants,[20] propranolol[21] and benzodiazepines.[22] In our study 300 mg of cimetidine appears to be as effective as the 600 mg regimen. From this point of view the newer

H_2-receptor antagonist ranitidine is also appropriate because it causes little or no drug interaction and also has a longer duration of action.[23] Indeed, similar efficacy with oral ranitidine for this purpose in obese patients has recently been demonstrated by Manchikanti *et al.*[24] The slightly better results achieved in our study is possibly due to a more effective route of administration. Although the intravenous administration of cimetidine had been reported to cause bradycardia and asystole,[25] these complications were generally associated with rapid bolus administration to sick patients and have not been observed with slow infusion. Accordingly, in this study cimetidine was given by slow infusion and no side effects were reported.

Although one patient in each treatment group remained at risk of acid aspiration (with volume < 25 ml and $pH > 2.5$), yielding a similar incidence to the study by Wilson *et al.*,[18] in both patients the interval between administration of cimetidine and the time of anesthetic induction was less than 60 min. There was no patient in the treatment groups with a gastric pH of less than 2.5, provided 60 min had elapsed between the time of administration and time of anesthetic induction, and this may represent a theoretical advantage over oral administration. These two failures, nevertheless, emphasize the importance of timing of cimetidine premedication for acid aspiration prophylaxis. It also suggests that such a regimen may not be useful for management of patients undergoing emergency surgery because of the limitation of time. However, in elective surgery, the premedication regimen, in concert with normal precautions indicated for patients at risk of aspiration (application of cricoid pressure during endotracheal intubation), should improve the margin of safety for morbidly obese patients requiring general anesthesia.

In summary, our study indicates that, in morbidly obese patients, the intravenous administration of cimetidine 300 mg, 60 to 90 min preoperatively would significantly reduce the number of patients at risk of acid aspiration pneumonitis. Because of the potential untoward cardiac effects, the intravenous infusion should be given slowly over 10 min.

The authors thank Peter Lok for technical assistance and L. Nolan for preparation of the manuscript.

References

1. Vaughan RW, Bauer S, Wise L: Volume and pH of gastric juice in obese patients. ANESTHESIOLOGY 43:686–689, 1975
2. Vezina WC, Grace DM, Chamberlain MJ, Mowbray RD, Clare ME, Vanderwerf J, King ME, Carruthers SG: Gastric emptying before and after transverse gastroplasty for morbid obesity. Clin Nucl Med 11:308–312, 1986
3. Feinstein AR: On central tendency and the meaning of mean for pH values. Anesth Analg 58:1–3, 1979
4. Krause PD: Statistical analysis of pH data. Anesth Analg 57:143–144, 1978
5. Giesecke AH, Beyer CW, Kallus FT: More on interpretation of pH data. Anesth Analg 57:379–381, 1978
6. Teabeaut JR: Aspiration of gastric contents an experimental study. Am J Pathol 28:51–67, 1952
7. James CF, Modell JH, Gibbs CP, Kuck EJ, Ruiz BC: Pulmonary aspiration: Effects of volume and pH in the rat. Anesth Analg 63:665–668, 1984
8. Roberts RB, Shirley MA: Reducing the risk of acid aspiration during cesarean section. Anesth Analg 53:859–868, 1974
9. Champion MC, Sullivan SN, Chamberlain M, Vezina W: Naloxone and morphine inhibit gastric emptying of solids. Can J Physiol Pharmacol 60:732–734, 1982
10. Taylor G: Acid pulmonary aspiration syndrome after antacids. A case report. Br J Aneasth 47:615–617, 1975
11. Bond VK, Stoelting RK, Gupta CD: Pulmonary aspiration syndrome after inhalation of gastric fluid containing antacids. ANESTHESIOLOGY 51:452–453, 1979
12. Johnston JR, Moore J, McCaughey W, Dundee JW, Howard PJ, Toner W, McClean E: Use of cimetidine as an oral antacid in obstetric anesthesia. Anesth Analg 62:720–726, 1983
13. Hodgkinson R, Glassenberg R, Joyce TH, Coombs DW, Ostheimer GW, Gibbs CP: Comparison of cimetidine (Tagamet) with antacid for safety and effectiveness in reducing gastric acidity before elective cesarean section. ANESTHESIOLOGY 59:86–90, 1983
14. Maliniak K, Vakil AH: Pre-anesthetic cimetidine and gastric pH. Anesth Analg 58:309–313, 1979
15. Salmenpera M, Korttila K, Kalima T: Reduction of the risk of acid pulmonary aspiration in anaesthetized patients after cimetidine premedication. Acta Anaesthesiol Scand 24:25–30, 1980
16. Coombs DW, Hooper D, Colton T: Acid-aspiration prophylaxis by use of preoperative oral administration of cimetidine. ANESTHESIOLOGY 51:352–356, 1979
17. Coombs DW, Hooper D, Colton T: Pre-anesthetic cimetidine alteration of gastric fluid volume and pH. Anesth Analg 58:183–188, 1979
18. Wilson SL, Mantena NR, Halverson JD: Effects of atropine, glycopyrrolate and cimetidine on gastric secretions in morbidly obese patients. Anesth Analg 60:37–40, 1981
19. Finkelstein W, Isselbacher KJ. Cimetidine. N Engl J Med 2:992–996, 1978
20. Serlin MJ, Sibeon RG, Mossman S, Breckenridge AM, Williams JRB, Atwood JL, Willoughby JMT: Cimetidine: Interaction with oral anticoagulants in man. Lancet 2:317–319, 1979
21. Feely J, Wilkinson GR, Wood AJJ: Reduction of liver blood flow and propranolol metabolism by cimetidine. N Engl J Med 304: 692–695, 1981
22. Klotz U, Reimann I: Delayed clearance of diazepam due to cimetidine. N Engl J Med 302:1012–1014, 1980
23. McAuley DM, Moore J, McCaughey W, Donnelly BD, Dundee JW: Ranitidine as an antacid before elective Caesarean section. Anaesthesia 38:108–114, 1983
24. Manchikanti L, Roush JR, Colliver JA: Effect of preanesthetic ranitidine and metoclopramide on gastric contents in morbidly obese patients. Anesth Analg 65:195–199, 1986
25. Shaw RG, Mashford ML, Desmond PV: Cardiac arrest after intravenous injection of cimetidine. Med J Aust 2:629–630, 1980