The effects of cimetidine and ranitidine with and without metoclopramide on gastric volume and pH in morbidly obese patients

A.M. Lam, MD FRCPC,
D.M. Grace MD DPHIL FRCSC,
P.H. Manninen MD FRCPC, C. Diamond BA

The efficacy of preanaesthetic intravenous cimetidine versus ranitidine with and without metoclopramide for acid aspiration prophylaxis was assessed in 60 morbidly obese patients in a double-blind manner. Group 1 patients received cimetidine 300 mg + saline. Group 2 patients received cimetidine 300 mg + metoclopramide 10 mg. Group 3 patients received ranitidine 100 mg + saline. Group 4 patients received ranitidine 100 mg + metoclopramide 10 mg. Gastric fluid was aspirated for analysis of volume and pH following induction of anaesthesia. All four premedication regimens were equally effective in reducing the gastric volume and acidity and the inclusion of metoclopramide had no additive effect. Although statistically not significant, two patients in the cimetidine groups remained at risk (volume > 25 ml and pH < 2.5) while no patients in the ranitidine groups remained so.

Key words

PHARMACOLOGY: cimetidine, ranitidine, metoclopramide; GASTROINTESTINAL TRACT: gastric pH, gastric volume; COMPLICATIONS: aspiration, obesity.

From the Departments of Anaesthesia and Surgery, University Hospital and University of Western Ontario, London, Ontario.

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Address correspondence to: Dr. A.M. Lam, Department of Anaesthesia, University Hospital, P.O. Box 5339, Postal Station A, London, Ontario N6A 5A5.

Despite increasing awareness of the risk of aspiration associated with the induction of general anaesthesia, regurgitation with subsequent aspiration and development of aspiration pneumonitis remains a serious complication.¹⁻³ Although theoretically all patients are predisposed to this complication, the morbidly obese patient is considered to be particularly at risk because of the large volume of gastric fluid high in acidity present at the time of induction of anaesthesia.⁴ Recognizing that the most important risk factor is the presence of a critical volume of gastric fluid with low pH, various premedication regimens have been designed to reduce this risk by neutralizing the gastric acidity and/or reducing the gastric volume.

Cimetidine, a H₂-receptor antagonist, has been shown to be effective in decreasing acidity with or without decreasing volume in a number of clinical studies in obstetric patients,⁵⁻⁸ outpatients⁹ and paediatric patients.¹⁰ In morbidly obese patients, Wilson *et al.* had demonstrated that preoperative oral cimetidine reduced gastric acidity significantly, but not gastric volume.¹¹ In contrast, our previous study showed that preoperative intravenous cimetidine is effective in reducing both volume and acidity in the gastric fluid.¹² More recent studies indicate that the effectiveness of cimetidine can be further improved with the addition of metoclopramide which promotes gastric emptying.¹³⁻¹⁵

This study was therefore undertaken to evaluate prospectively in a double-blind manner the relative effectiveness of cimetidine and ranitidine with and without metoclopramide for the purpose of acid

aspiration prophylaxis in the morbidly obese patient. As part of the preoperative workup, gastric emptying time was also determined using a radioactive tracer method.¹² This allowed comparison between the study groups and assessment of the influence of gastric emptying time on the effectiveness of the H_2 -receptor antagonists.

Methods

The study protocol was approved by the Human Ethics Committee of the University of Western Ontario and a written informed consent was obtained from each patient. Sixty patients scheduled to undergo gastropasty for morbid obesity were studied. Patients with known peptic disease or currently on histamine antagonists for gastrointestinal symptoms were excluded from the study. All patients had fasted a minimum of 8 hr prior to induction of anaesthesia. In a randomized manner, patients were assigned to one of four groups receiving respectively: (1) cimetidine 300 mg + saline, (2) cimetidine 300 mg + metoclopramide 10 mg, (3) ranitidine 100 mg + saline, (4) ranitidine 100 mg + metoclopramide 10 mg ($n = 15$ in each group). All premedications were given intravenously over 10 min and administered 60 to 90 min preoperatively according to the scheduled operating times. The premedication combinations were prepared by the Department of Pharmacy and the investigators were blinded to the exact combination of the premedication until the entire study was completed. No other premedication was given.

The gastric emptying half-time was determined by having the patient ingest a standard test meal consisting of a Technetium 99 m labelled egg salad sandwich and 100 ml water, with the patient in the supine position and with the head of the bed elevated. This was performed between three to seven days preoperatively. A computer interface gamma camera acquired images continuously at four frames per min for one hr. A 2 hr image was obtained when no significant gastric emptying had occurred. Gastric emptying with this test meal followed a linear curve for individuals of normal weight¹⁶ and morbidly obese subjects.¹⁷ The linear rate of emptying was determined and the time taken for the peak counts (y) to decrease to $y/2$ ($t_{1/2}$) was determined using the equation $y = mx + b$. Thus transient delay in onset of gastric emptying had no

effect of the $t_{1/2}$ calculation. This determination was not carried out in all patients.

All patients were preoxygenated for 3 min, induced with thiopentone and succinylcholine and intubated using a rapid sequence technique. Following stabilization of the patient's condition, a modified #18 nasogastric tube with extra orifices was inserted into the stomach and all gastric contents aspirated for analysis of volume and acidity. To ensure complete aspiration of gastric fluid, the stomach was inspected and manually compressed by the surgeon upon entry into the peritoneal cavity. Any extra volume thus retrieved was added to the original volume collected. The volume and pH were measured with a graduated cylinder and a Corning digital pH meter immediately following collection of the specimen. After the entire study was completed, the codes were broken and the results analyzed accordingly.

For comparison between groups, a one-way analysis of variance was used. Because of the concern that the pH may not be normally distributed in obese patients, Kruskal-Wallis rank-sum test was also used for analysis of pH. The actual hydrogen ion concentration was also used for statistical computation. For comparison within the cimetidine (Groups 1 and 2) and ranitidine groups (Groups 3 and 4), the Mann-Whitney rank sum test was used. The proportion of patients who remained at risk was compared with Fisher's exact test. A p value < 0.05 is considered significant.

Results

There were no complications arising from the study. The four groups were similar in age, weight and sex (Table I). Evacuation of the stomach was incomplete in nine patients and additional volumes ranging from 1 ml to 18 ml (mean 6 ml) were obtained during manual compression of the stomach. There was one patient each in Group 1 and Group 4 where no gastric content could be aspirated and the volume was therefore considered to be zero but the pH could not be measured. Because of the inability to accurately predict the precise operating time, not all patients received their premedication within the prescribed time; 24 patients (six in Group 1, seven in Groups 2 and 4, four patients in Group 3) received their premedication more than 90 mins before the operation. The mean time from adminis-

TABLE I Age, weight, height and sex distribution of the treatment groups

	Group 1 (C + S)	Group 2 (C + M)	Group 3 (R + S)	Group 4 (R + M)
Age ($\pm$ SD)	39 $\pm$ 9	44 $\pm$ 10	38 $\pm$ 11	37 $\pm$ 9
Weight (kg $\pm$ SD)	138 $\pm$ 23	137 $\pm$ 27	134 $\pm$ 21	121 $\pm$ 18
Height (cm $\pm$ SD)	157 $\pm$ 17	163 $\pm$ 10	166 $\pm$ 7	164 $\pm$ 7
Sex (f/m)	12/3	12/3	12/3	13/2

n = 15 in each group.

TABLE II Results

	Group 1 (C + S)	Group 2 (C + M)	Group 3 (R + S)	Group 4 (R + M)
Time elapsed from premedication (min $\pm$ SEM)	100 $\pm$ 9	110 $\pm$ 9	101 $\pm$ 8	111 $\pm$ 11
Preoperative† (mean gastric emptying $\pm$ SEM)	48 $\pm$ 13	43 $\pm$ 9	53 $\pm$ 9	63 $\pm$ 11
Half-time (median) ($t_{1/2}$ in min)	34	33	44	50
Volume of gastric fluid (ml $\pm$ SEM)	11 $\pm$ 3	17 $\pm$ 5	14 $\pm$ 2	14 $\pm$ 3
pH of gastric fluid (SEM)	6.84* $\pm$ 0.43	6.51 $\pm$ 0.52	6.76 $\pm$ 0.31	6.72* $\pm$ 0.48
H ⁺ conc. (mol/L $\times 10^{-3}$) of gastric fluid (SEM)	2.55 $\pm$ 2.5	1.52 $\pm$ 1.4	0.07 $\pm$ 0.1	0.81 $\pm$ 0.8

*n = 14 because one patient in each group had no gastric aspirate.

†Not performed in all patients. n = 12 in group 1, 13 in groups 2, 3 and 4.

TABLE III Number of patients with volume > 25 ml and pH < 2.5, by group

	Group 1 (C + S)	Group 2 (C + M)	Group 3 (R + S)	Group 4 (R + M)
No. of patients with pH < 2.5	1	1	0	1
No. of patients with vol > 25 ml	1	3	2	2
No. of patients "at risk" (vol > 25 ml and pH < 2.5)	1	1	0	0

tration of premedication to collection of specimen, however, was similar in all groups (Table II).

Gastric emptying half-time

This was determined in 51 of the 60 patients studied. Similar to our previous study,¹² the gastric emptying half-time was essentially normal in the obese patients studied (compared to nine healthy volunteers previously studied with a mean of 47 $\pm$ 4 mins),¹⁷ but with considerable variation, and there was one patient each in Groups 1, 3 and 4 who had very delayed gastric emptying with half-times exceeding 200 min. These outliers were excluded from the tabulated values because their inclusion would skew the means. Group 4 had the longest mean as well as median $t_{1/2}$, but the differences between the groups were not statistically significant (Table II).

Gastric volume

Gastric volumes were similar in all four groups (Table II). To evaluate the influence of metoclopramide, the saline groups (1 and 3) were combined to compare with the metoclopramide groups (2 and 4). The addition of metoclopramide to the H₂-receptor antagonists was not associated with any further reduction of volume. Similarly, there was no difference between the two H₂-receptor antagonists (Groups 1 and 2 versus 3 and 4). There were eight patients with gastric volume exceeding 25 ml and they distributed evenly between the cimetidine and the ranitidine groups (Table III). All eight patients received their premedication more than 100 min (range 100–180 min) before the collection of the gastric fluid. There was no correlation between the gastric emptying half-time and the subsequent gastric volume collected. Even in the

three patients with the very abnormal gastric emptying half-time the premedication regimens appeared to be effective.

Gastric pH

The gastric pH of all four groups were similar with no statistically significant differences between them. The addition of metoclopramide had no influence on gastric pH and the mean pH ranged from 6.51 in Group 2 to 6.84 in Group 1 (Table II). Two patients in the cimetidine groups and one patient in the ranitidine groups had gastric pH <2.5 (Table III). Again, no correlation between gastric emptying half-time and pH could be demonstrated.

Patients at risk

Defining "patients at risk" as those having gastric volume >25 ml and pH <2.5 at the time of anaesthetic induction, two patients remained at risk in the cimetidine groups whereas all patients were effectively protected in the ranitidine groups (Table III). This difference, however, was not statistically significant. Both patients in the cimetidine groups received their premedication 180 min before collection of gastric fluid. In contrast, three patients in the ranitidine groups who similarly received their premedication 180 min or more before sampling all had gastric pH exceeding 2.5.

Discussion

Although it has been demonstrated that the most important factor determining the severity of pulmonary lesions following aspiration of gastric contents is the acidity of the aspirate,¹⁸ and that the higher the acidity, the less is the volume required to cause the damage,¹⁹ the values of volume exceeding 25 ml and pH less than 2.5 are generally considered to be the critical factors predisposing the patient to this complication.²⁰ The increased risk of acid aspiration pneumonitis in obese patients was well documented by Vaughan *et al.* in 1975;⁴ 75 per cent of obese patients had gastric volume >25 ml and pH <2.5 at the time of anaesthetic induction. It is therefore important to minimize this risk by reducing the gastric volume and acidity in addition to the usual precaution taken for patients at risk of aspiration.

We previously demonstrated that intravenous cimetidine given 60–90 minutes preoperatively is an effective regimen, reducing both volume and

acidity.¹² Metoclopramide, a dopamine antagonist, promotes gastric emptying and increases the lower oesophageal sphincter tone, and has been shown to be useful in reducing the volume of gastric contents before induction of anaesthesia although it has no influence on gastric acidity.²¹ The combination of metoclopramide and a H₂-receptor antagonist thus appears to be an ideal combination for the purpose of acid aspiration prophylaxis. Indeed, limited studies in non-obese patients have substantiated this.^{13–15} However, the usefulness of this combination has not been studied carefully in obese patients who are more at risk than elective non-obese patients. Similarly, studies in non-obese patients suggest that the newer H₂-receptor antagonist ranitidine may be superior to cimetidine because of its longer duration of action.^{22–24} We therefore undertook this study to assess the relative effectiveness of cimetidine versus ranitidine and the merit of adding metoclopramide to the premedication regimen.

We chose to administer the drugs intravenously because the parenteral route appears to be more effective than the oral route.^{25,26} In addition, we are aware that some obese patients may have delayed gastric emptying and this may interfere with the absorption of the H₂-receptor antagonists. The determination of gastric volume was deemed accurate since the stomach was manually compressed by the surgeon and the additional volume retrieved was added to the original volume aspirated. This only occurred in nine instances. Because a high gastric volume and low pH in morbidly obese patients had been confirmed in our previous study,¹² a control group without premedication was not included as we did not feel this was ethically justifiable.

We found that all four premedication regimens were equally effective, reducing both the gastric volume and acidity compared to values obtained from a control group in the previous study ($p < 0.05$, one-way ANOVA and Dunnett's test).¹² The findings in gastric emptying half-time were similar to our previous observations;¹² the majority of the obese patients have normal gastric emptying half-time. It is interesting to note that the efficacy of the H₂-receptor antagonist in increasing pH and reducing volume was not affected even in those patients with abnormally delayed gastric emptying. The addition of metoclopramide did not make any difference, either in volume or acidity. Although this may seem initially surprising, the explanation

probably lies in the fact that the H₂-receptor antagonists were so effective that any effect that metoclopramide might have been masked.

Our results are at variance with two previous studies by Rao *et al.*¹⁴ and Solanki *et al.*,¹⁵ which both demonstrated that the combination of cimetidine-metoclopramide was superior to cimetidine alone in non-obese patients. Differences in study design and patient population may explain the variance. In Rao *et al.*'s study, the medications were administered orally, and since the oral route might not be as effective as the intravenous route, the additive effect of metoclopramide could be demonstrated. In contrast, Solanki *et al.* administered the medications intravenously and collected gastric aspirates at 30 as well as 60 min after the administration of the drugs. He observed that the difference between cimetidine and cimetidine-metoclopramide was only apparent at 30 min but not at 60 min. This suggests that the effect of cimetidine alone was less than optimal at 30 min, hence the additive effect of metoclopramide became apparent. This would be consistent with our present study, where no patient received the premedication less than 60 min before collection of the gastric fluid, and consequently the additive effect of metoclopramide could not be demonstrated.

Alternatively, the effect of metoclopramide may be dose-related and the dosage that we administered might be inadequate in the obese patient population. This explanation, however, is not supported by two separate studies in non-obese patients in whom Manchikanti *et al.* compared cimetidine with cimetidine-metoclopramide¹³ and ranitidine with ranitidine-metoclopramide,²⁷ and found no differences between the treatment groups.

Manchikanti *et al.* recently studied the combination of oral ranitidine and metoclopramide in morbidly obese patients and also observed no significant difference in gastric volume between the four treatment groups (two groups received ranitidine and two groups received ranitidine + metoclopramide).²⁸ However, the pooled mean of the ranitidine + metoclopramide groups was significantly less than that of the ranitidine groups. The different route of administration again may explain this variance from our present study. There was also no independent method to confirm complete aspiration of gastric contents in their study.

Similarly, we found no significant difference

between cimetidine and ranitidine, with or without the addition of metoclopramide. Although lack of significant difference does not prove equality of the four groups, examination of the results (Tables II and III) revealed that whatever difference existed, it was small and clinically unimportant. Nevertheless, we did observe that no patient in the ranitidine groups remained at risk (volume >25 ml and pH <2.5), whereas two patients in the cimetidine groups remained so.

Further scrutiny of the data suggested that this may be related to the relative duration of the two drugs. Because of the clinical nature of the study, the actual time of the operation was not rigidly controlled, consequently not all medications were administered in the prescribed time of 60–90 min preoperatively as planned. Both patients in the cimetidine group who remained at risk received their medications more than 100 min (105 and 180 min) before the time of sampling, whereas all patients in the ranitidine groups were rendered risk-free despite a similar incidence of long elapsed times. In addition to the longer duration of action, ranitidine also has other theoretical advantages; whereas cimetidine can cause important drug interactions secondary to reduction of hepatic blood flow²⁹ and inhibition of microsomal enzyme activity,³⁰ ranitidine is devoid of such undesirable effects.³¹

In summary, we conclude that both H₂-receptor antagonists, when given intravenously 60–90 min before the operation, are effective in reducing the risk of acid aspiration pneumonia in morbidly obese patients, and that the addition of metoclopramide does not afford any further protection. Furthermore, although we did not find any significant difference between cimetidine and ranitidine, because of its longer duration of action and the apparent lack of drug interaction, ranitidine appears to be the preferred premedicant for this purpose. Its use, however, does not prevent the occurrence of regurgitation and subsequent aspiration, therefore the usual precautions for patients at risk should still be followed.

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Résumé

L'efficacité de l'administration intraveineuse de cimétidine avant l'anesthésie versus la ranitidine avec ou sans métoclopramide pour la prophylaxie de l'aspiration bronchique était évaluée chez 60 patients obèses à double insu. Les patients du groupe I ont reçu de la cimétidine 300 mg + physiologique. Les patients du groupe II ont reçu de la cimétidine 300 mg + métoclopramide 10 mg. Les patients du groupe III ont reçu de la ranitidine 100 mg + physiologique. Les patients du groupe IV ont reçu de la ranitidine 100 mg + métoclopramide 10 mg. Le liquide gastrique était aspiré pour l'analyse du volume et du pH après induction de l'anesthésie. Tous les quatre régimes de prémédication étaient également efficaces à la réduction du volume gastrique et de l'acidité et l'addition de métoclopramide n'avait aucun effet additif. Même si statistiquement non significatif, deux patients du groupe cimétidine sont restés à risque (volume > 25 ml et pH < 2.5) alors qu'aucun patients du groupe ranitidine ne l'était.