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Premedication with cimetidine and metoclopramide

Effect on the risk factors of acid aspiration

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Summary

A randomised, double-blind, placebo-controlled parallel study was conducted in adult females to evaluate the efficacy and safety of a combination of cimetidine 300 mg orally and metoclopramide 10 or 20 mg intravenously in reducing pre-operative residual gastric volume and raising gastric pH. The effect of pre-operative metoclopramide on postoperative nausea and vomiting was also investigated. Oral cimetidine was given approximately 2–2.5 hours before, and intravenous metoclopramide either 15 or 30 minutes prior to induction of anaesthesia. The study showed that placebo-treated patients undergoing outpatient operations have an increased risk of acid aspiration because of high residual gastric volume and low pH and increased risk of serious pulmonary injury should acid aspiration occur. Metoclopramide 10 or 20 mg intravenously prior to induction of anaesthesia was effective in reducing the residual gastric volume significantly, but not in raising pH. The combination of cimetidine and metoclopramide, as well as cimetidine alone, reduced the risk factors of acid aspiration by raising gastric pH and reducing residual volume. No anti-emetic effect of metoclopramide was observed. Higher doses of metoclopramide (20 mg) produced significant side effects (flushing, dizziness, extrapyramidal side effects), but were only marginally more effective than 10 mg doses in reducing residual gastric volume.

Key words

Gastrointestinal tract; stomach, pH.
Histamine; H_2-receptor antagonist, cimetidine.
Pharmacology; metoclopramide.

Much has been written about the risk of acid aspiration during anaesthesia, and various methods have been suggested to reduce this hazard. Yet the aspiration of stomach contents still remains a major cause of anaesthetic mortality and morbidity.[1] Thus, continued research in this area is indicated.[2] The introduction of cimetidine (an H_2-receptor blocker) was undoubtedly a breakthrough in approaching the problem of acid aspiration during anaes-

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thesia.[3-10] Cimetidine, given at least 60–120 minutes before the induction of anaesthesia (either orally, intramuscularly or intravenously, predictably raises the gastric pH to a safer level.[7-10] However, it is claimed that a single dose of cimetidine does not always reduce residual gastric volume.[8,10] Undoubtedly, intragastric pH is a more important factor than volume in determining the consequences of aspiration,[11] but high residual gastric volume and consequent high intragastric pressure certainly can precipitate or facilitate regurgitation and aspiration.

Metoclopramide, a dopamine antagonist and anti-emetic, accelerates gastric emptying by increasing motility of the gastrointestinal tract and increasing lower oesophageal sphincter pressure.[12,13] At present, metoclopramide is commonly used in radiological procedures of the gastrointestinal tract,[14] as an anti-emetic after cancer chemotherapy,[15] and as a gastric prokinetic agent in diabetic gastroparesis.[16]

Our study examines whether a combination of cimetidine and metoclopramide would be more effective than either drug alone in reducing the accepted risk factors of acid aspiration, without causing additional side effects.

Methods

The study consisted of two separate and independent phases.

Phase 1

Eighty adult female patients (ASA Class 1 or 2) scheduled for outpatient laparoscopic examination or laparoscopic tubal cauterisation were randomly divided into four test groups. The institutional ethics committee approved the study and each patient gave written informed consent. All patients fasted for at least 10 hours before operation and no premedication other than the study drugs was given. The study medications were dispensed in a randomised double-blind fashion. The staff of the hospital pharmacy blinded the medication in identical containers (capsules and vials) and randomisation was done by a computer. Each patient received one capsule (placebo or cimetidine 300 mg) administered orally approximately 2 hours before operation, and an intravenous agent (placebo or metoclopramide 10 mg) approximately 15 minutes prior to induction of anaesthesia. The intravenous agents (2 ml) were injected over a period of 60 seconds. Lactose was used as placebo for oral medication and 0.9 percent sodium chloride was used as the placebo for intravenous medication. Group 1 patients received placebo orally and placebo intravenously, group 2 patients received placebo orally and metoclopramide intravenously, group 3 patients received cimetidine orally and metoclopramide intravenously, and group 4 patients received cimetidine orally and placebo intravenously (Table 1).

Anaesthetic management in all cases was standardised; pretreatment with tubocurarine (3 mg), induction with thiopentone (4–5 mg/kg), suxamethonium (1.5–2.0 mg/kg) tracheal intubation; anaesthesia was maintained with nitrous oxide, oxygen, a volatile anaesthetic agent (usually isoflurane), fentanyl (1–2 μg/kg), suxamethonium infusion and controlled ventilation. Immediately following tracheal intubation, a Salem sump gastric tube (16 or 18 SWG) was passed via the mouth; position was confirmed by auscultation of injected air and as much gastric juice as possible was aspirated after repeated changes in the position of the stomach tube and of the patient. The aspiration of the stomach content was done over a period of 20–30 minutes.

Table 1. Phase 1: Demography (mean, SEM)

Drug group	n	Age (years)	Height (inches)	Weight (lb)
1 Oral placebo + intravenous placebo	20	30.67 (1.44)	63.62 (0.62)	142.19 (7.09)
2 Oral placebo + intravenous metoclopramide 10 mg	20	27.95 (0.98)	64.67 (0.73)	136.76 (5.04)
3 Oral cimetidine 300 mg + intravenous metoclopramide 10 mg	20	32.60 (1.20)	63.95 (0.54)	136.50 (8.37)
4 Oral cimetidine 300 mg + intravenous placebo	20	32.75 (1.80)	64.75 (0.63)	130.85 (4.47)
		$p = 0.06$	$p = 0.52$	$p = 0.67$

Table 2. Phase 2: Demography (mean, SEM)

Drug group	n	Age (years)	Height (inches)	Weight (lb)
1 Oral cimetidine 300 mg + intravenous metoclopramide 10 mg	15	29.80 (1.27)	65.33 (0.65)	144.20 (6.42)
2 Oral cimetidine 300 mg + intravenous metoclopramide 20 mg	19	30.32 (1.28)	64.68 (0.60)	142.37 (7.08)
3 Oral cimetidine 300 mg + intravenous placebo	19	28.32 (1.06)	65.21 (0.84)	142.79 (5.75)
		$p = 0.46$	$p = 0.79$	$p = 0.98$

The pH of the collected juice was measured using a Corning pH meter and volume was measured accurately by syringe.

The incidence of pre-operative side effects such as dizziness or sedation, and postoperative side effects such as nausea, vomiting or drowsiness, were recorded following specific interrogation regarding presence or absence of the side effects.

Phase 2

An additional 53 adult female patients (ASA Class 1 or 2) scheduled for the same operation in the same operating room were studied after all the cases in Phase 1 were completed. Phase 2 study protocol was exactly the same as in Phase 1, except that there were three study groups and all patients received cimetidine 300 mg orally approximately 160 minutes beforehand, followed by either metoclopramide 10 mg or 20 mg or a placebo given 30 minutes before induction of anaesthesia rather than 15 minutes before, as was done in Phase 1 (Table 2). The study in Phase 2 was terminated before all the designated cases were completed because of the necessity of writing an abstract by a given deadline; hence, we have groups of unequal size.

Statistical analysis

Demographic data, time intervals after medications, residual gastric volumes and pH values obtained from each group were compared between groups in each Phase by the ANOVA one-way analysis of variance technique to test the null hypothesis. In the case of an overall significance, pairwise multiple comparisons were performed to find which groups accounted for that significance. The side effects (nausea, vomiting, dizziness, etc.) which occurred in each group were compared with those in other groups using the Chi squared statistic. A value of $p < 0.05$ was considered significant.

Results

Tables 1 and 2 show the demographic variables in Phases 1 and 2 respectively. There was no statistical difference between the groups studied during each phase. The actual time interval between the oral premedication and gastric suctioning and also between the intravenous premedication and gastric suctioning is shown in Table 3 (Phase 1) and Table 4 (Phase 2). As planned, the oral medication in Phase 1 was given

Table 3. Phase 1: actual time intervals (mean, SEM)

Drug group	Time interval between oral medication and gastric suction (minutes)	Time interval between intravenous medication and gastric suction (minutes)
1 Oral placebo + intravenous placebo	132.38 (8.77)	19.05 (1.81)
2 Oral placebo + intravenous metoclopramide 10 mg	142.86 (8.97)	17.62 (1.45)
3 Oral cimetidine 300 mg + intravenous metoclopramide 10 mg	149.75 (11.86)	18.25 (1.37)
4 Oral cimetidine 300 mg + intravenous placebo I.V.	137.00 (9.89)	18.00 (1.56)
	$p = 0.63$	$p = 0.93$

Table 4. Phase 2: actual time intervals (mean, SEM)

Drug group	Time interval between oral medication and gastric suction (minutes)	Time interval between I.V. medication and gastric suction (minutes)
1 Oral cimetidine 300 mg	152.00	32.33
+ intravenous metoclopramide 10 mg	(10.81)	(1.45)
2 Oral cimetidine 300 mg	160.79	34.21
+ intravenous metoclopramide 20 mg	(9.02)	(1.88)
3 Oral cimetidine 300 mg	161.32	35.79
+ intravenous placebo	(8.87)	(1.88)
	p = 0.76	p = 0.42

approximately 2–2.5 hours prior to the gastric suctioning and intravenous medication was administered approximately 15–20 minutes beforehand. In Phase 2, these were given approximately 2–2.5 hours and 30–35 minutes, respectively, prior to gastric suctioning. There was no statistical difference between the groups in this respect.

Table 5 shows the pH values (mean, SEM) and residual gastric volume (mean, SEM) in Phase 1 cases. When no active agent was given (group 1, placebo and placebo), the mean pH of the gastric juice was 2.03 (SEM 0.25) and the average gastric volume was 45.48 (SEM 5.73) ml. In group 2 (placebo and metoclopramide 10 mg), the average pH was still low (2.28, SEM 0.33), but the residual volume (24.10, SEM 3.4 ml) was significantly lower ($p < 0.001$) compared to group 1. Group 3 (cimetidine and metoclopramide) and group 4 (cimetidine and placebo) both had high pH (5.30, SEM 0.46 and 5.45, SEM 0.46, respectively), and both groups also had low residual volumes (17.65, SEM 3.07 and 17.90, SEM 3.0 ml, respectively). The pH values in groups 3 and 4 were significantly ($p < 0.001$) higher than both group 1 (placebo and placebo) and group 2 (placebo and metoclopramide). There was no significant difference between group 3 and 4 with respect to pH levels. Residual volumes in groups 3 and 4 were also significantly reduced ($p < 0.001$) compared to group 1 but not from group 2, group 3 and group 4 revealed no significant difference in volume aspirated.

Table 6 shows the mean pH and residual volume in the three groups in Phase 2. The mean pH was high in all the three groups (well over 5), and with no statistical difference between the groups. The residual volumes in all the three groups were low and ANOVA analysis demonstrated no difference between the groups. No patient showed any clinical sign of aspiration either in Phase 1 or in Phase 2.

Table 5. Phase 1: pH and volume of gastric juice (mean, SEM)

Drug group	pH of gastric juice	Residual volume (ml)
1 Oral placebo	2.03	45.48
+ intravenous placebo	(0.25)	(5.73)
2 Oral placebo	2.28	24.10*
+ intravenous metoclopramide 10 mg	(0.33)	(3.42)
3 Oral cimetidine 300 mg	5.30†*	17.65*
+ intravenous metoclopramide 10 mg	(0.46)	(3.07)
4 Oral cimetidine 300 mg	5.45†*	17.90*
+ intravenous placebo	(0.46)	(3.00)
	p = 0.001	p = 0.001

*$p < 0.001$ compared to group 1.
†$p < 0.001$ compared to group 2.

The only side effect encountered in Phase 1 (Table 7) was nausea and vomiting in a few cases in the postoperative period. Regardless of whether the patients received metoclopramide or not, the frequency of nausea and vomiting was very similar in all groups, with one exception. There was a statistical difference ($p < 0.05$) between group 2 and group 4 favouring placebo over metoclopramide. Therapy for nausea and vomit-

Table 6. Phase 2: pH and volume of gastric juice (mean, SEM)

Drug group	pH of gastric juice	Residual volume (ml)
1 Oral cimetidine 300 mg	5.36	16.73
+ intravenous metoclopramide 10 mg	(0.52)	(3.56)
2 Oral cimetidine 300 mg	5.81	14.79
+ intravenous metoclopramide 20 mg	(0.44)	(3.71)
3 Oral cimetidine 300 mg	5.60	23.95
+ intravenous placebo	(0.45)	(2.49)
	$p = 0.81$	$p = 0.11$

Table 7. Phase 1: side effects

Drug group	Nausea only	Nausea and vomiting	Therapy required	No side effects
1 Oral placebo + intravenous placebo	2/20	2/20	0/4	17/20
2 Oral placebo + intravenous metoclopramide 10 mg	0/20*	4/20*	1/4	17/20
3 Oral cimetidine 300 mg + intravenous metoclopramide 10 mg	2/20	2/20	0/4	16/20
4 Oral cimetidine 300 mg + intravenous placebo	5/20*	2/20*	1/7	13/20

*Chi squared statistics for group 2 versus group 4 = $p < 0.05$.

in was instituted when the signs and symptoms occurred more than twice.

In Phase 2 (Table 8), the frequency of nausea and vomiting in the three groups appeared very similar, although there was a statistical difference ($p < 0.05$) between group 2 and group 3, this time favouring metoclopramide over a placebo. Six patients out of 19 in Phase 2/group 2 (metoclopramide 20 mg) complained of transient flushing and dizziness soon after the intravenous medication, and one patient had extrapyramidal side effects (tonic contractions of ocular and facial muscles) which was treated promptly with diphenhydramine 25mg intravenously. One patient in group 1 (metoclopramide 10 mg) also complained of transient dizziness after the medication.

There was no difference between the groups in either Phase 1 or Phase 2 in the duration of recovery room stay or time to discharge.

Discussion

The incidence of morbidity and mortality from acid aspiration during elective operation is not known. However, the risk factors (low gastric pH, high residual volume and increased intragasric pressure) have been identified. Thus, in clinical practice, it is prudent to try to reduce these risk factors as much as possible, especially in patients who are known to be at higher risk of regurgitation (e.g. obese patients, anticipated difficult intubation, high anxiety). The patients who received no active treatment (Phase 1, group 1, placebo and placebo) had consistently low pH

Table 8. Phase 2: side effects

Drug group	Nausea only	Nausea and vomiting	Therapy required	Flushing and dizziness	Extra-pyramidal side effects	No side effects
1 Oral cimetidine 300 mg + intravenous metoclopramide 10 mg	4/15	2/15	3/6	1/15	0/15	8/15
2 Oral cimetidine 300 mg + intravenous metoclopramide 20 mg	3/19	1/19*	2/4*	6/19	1/19	8/19
3 Oral cimetidine 300 mg + intravenous placebo	3/19	5/19*	4/8*	0/19	0/19	11/19

*Chi squared statistics for group 2 versus group 3 = $p < 0.05$.

and high gastric volume. The results found in this control group are comparable to those reported in other published work.[3-11] It has been suggested that patients scheduled for outpatient operation have higher residual gastric volume and lower pH compared to inpatients,[17] and thus presumably are at higher risk for pulmonary injury if acid aspiration occurs, although these data have not been verified in other studies. By current standards, the untreated patients in our study are at higher risk of acid aspiration compared to the treated group.

We confirmed the results of Wymer and Cohen,[18] who found that metoclopramide 10 mg given intravenously 15 minutes before operation, significantly reduced the gastric fluid volume but did not alter the pH. We also confirmed the results obtained by Capan *et al.*[19] that there was no significant difference in the intragastric pH and volume between the groups who received cimetidine alone and those who received cimetidine and metoclopramide (10 mg). Was this because of an insufficient dose of metoclopramide (10 mg) or because sufficient time (more than 15 minutes) was not allowed after the administration of the medication? In Phase 2, we addressed these two issues and increased the dose of metoclopramide to 20 mg and allowed at least 30 minutes after the metoclopramide. ANOVA analysis indicated that residual gastric volume was marginally better in patients who had received metoclopramide 20 mg (compared to placebo), but not significantly so; however, the metoclopramide 20 mg group had an unacceptably high frequency of side effects, especially dizziness. There was no difference in results between metoclopramide given 15 minutes versus 30 minutes prior to induction of anaesthesia (Phase 1 versus Phase 2). We have not analysed our data on the basis of popularly accepted high risk factors viz. pH less than 2.5 plus gastric volume more than 25 ml, because we believe these numbers have not been scientifically corroborated as yet. Manchikanti *et al.*[20] recently concluded that oral administration of cimetidine and metoclopramide in combination may reduce the risk of acid aspiration syndrome because the combination modifies accepted risk factors. However, careful analysis of their results clearly showed that cimetidine alone, given at bedtime and mornings, worked just as well as the combination of cimetidine and metoclopramide to reduce the accepted risks (pH 2.5 and gastric volume 25 ml). We found similar results with a single dose of cimetidine given in the morning.

The anti-emetic effect of metoclopramide is not evident. This may be due to the short half life of metoclopramide,[12,21] and when given pre-operatively (especially intravenously), the anti-emetic effect may not extend to the postoperative period. Several other investigators[22-24] also showed that pre-operative metoclopramide is not an effective postoperative anti-emetic.

Thus, we conclude that unmedicated adult female patients scheduled for outpatient laparoscopic procedure have a large residual gastric volume and low pH. A single dose of cimetidine given orally at least 2 hours before induction of anaesthesia should significantly reduce the accepted risk factors (pH and volume) for acid aspiration and reduce the chance of significant pulmonary injury should acid aspiration occur. A pre-operative combination of cimetidine orally and metoclopramide intravenously also reduces the risk factors, but not any more than cimetidine alone. However, the combination may have an advantage because metoclopramide is known[25] to increase lower oesophageal sphincter tone and thus should prevent regurgitation.

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