COMPARATIVE TRIAL OF THE EFFECT OF RANITIDINE AND CIMETIDINE ON GASTRIC SECRETION IN FASTING PATIENTS AT INDUCTION OF ANAESTHESIA

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ABSTRACT

A comparative trial of the H_2-receptor antagonists, cimetidine and ranitidine, on gastric pH and volume, was conducted in 168 healthy patients coming to elective surgery. The drugs were administered in random fashion either intravenously (ranitidine 50 mg or 100 mg, cimetidine 300 mg or placebo) or orally (ranitidine 150 mg, cimetidine 300 mg or placebo). The patients received the drugs or placebo 45 minutes to five hours before operation. After induction of anaesthesia, a nasogastric tube was passed and the stomach contents were aspirated. The volume and pH were measured. Those patients receiving ranitidine 50 or 100 mg or cimetidine 300 mg intravenously had statistically significantly higher gastric pH compared to those receiving placebo, but up to eight percent of patients had a pH less than 2.5. Oral administration of cimetidine 300 mg or ranitidine 150 mg were also superior when compared to placebo. However, 25 per cent of the patients receiving oral cimetidine had a pH less than 2.5; cimetidine orally was statistically significantly inferior to ranitidine 100 mg given intravenously. We conclude that the intravenous use of either ranitidine or cimetidine is an acceptable method to decrease the acidity of gastric contents before induction of anaesthesia. Orally, ranitidine appears to be a better choice than cimetidine in the doses studied. Both ranitidine and cimetidine need to be given at least 45 minutes before induction of anaesthesia to be effective; therefore the use of these agents to decrease the risk of acid pulmonary aspiration syndrome by no means obviates the need for proper anaesthesia technique during induction of anaesthesia.

KEY WORDS: ANTACIDS, ranitidine, cimetidine; COMPLICATIONS, lung, acid aspiration, prophylaxis.

INTRODUCTION

PULMONARY ASPIRATION of gastric contents may be associated with induction of general anaesthesia and was first described in pregnant women by Mendelson in 1946.[1] Experimental studies in animals have shown that the severity of this complication is due to the acidic nature of the inhaled material and may also be related to the use of intermittent positive pressure ventilation in the treatment of the aspiration. It has been suggested that if the gastric pH can be raised above 2.5, or possibly even 3.5,[2] and the gastric volume can be reduced to less than 25 ml, then the pulmonary acid aspiration syndrome may be avoided. In the past the only practical method of raising the gastric pH has been by oral ingestion of antacids by patients before operation.[3] The regime needs to be applied rigorously and many patients find the taking of mist. magnesium trisilicate, the compound most frequently advocated, somewhat unpalatable. In addition, since no oral antacid has been shown to be totally effective, the usual measures to prevent regurgitation must also be employed.[4]

The recent introduction of H_2-receptor antagonists has led to a series of trials involving the first of these agents, cimetidine, which has been shown to raise gastric pH to the accepted value both by oral and intravenous dosing.[3,5] Ranitidine is a new H_2-receptor antagonist, currently undergoing limited clinical trials in Canada and differs from cimetidine by being a substituted amino alkyl furan without an imidazole ring. Studies in man have suggested that ranitidine is a more active H_2-receptor antagonist than cimetidine, being approximately 4 to 7 times more potent on a molar basis,[6,7] and is thought to have fewer side effects. The onset and duration of action of cimetidine and ranitidine are reported to be similar and the maximum gastric inhibitory effect of both drugs reaches peak effect 60 to 75 minutes after intravenous injection.[8]

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In the present study, cimetidine and ranitidine were given intravenously and orally and compared with a placebo (intravenous-0.9 per cent normal saline; oral-lactose tablet identical in formulation to ranitidine) with respect to inhibition of gastric secretion in fasting patients at induction of anaesthesia.

Methods

One hundred and sixty-eight (168) patients (ages 16 to 72 years), ASA class 1 and 2, were studied. Fifteen additional patients were excluded from the study because of the inability to obtain a gastric sample, either due to inadequate gastric volume with the gastric tube in place or inability to pass the tube into the stomach. All patients studied had a general anaesthetic requiring tracheal intubation for general surgical, orthopaedic, gynaecological or plastic surgical procedures. Written informed consent was obtained from each patient on the evening before operation and approval for the study was obtained from the Ethics and Research & Development Committees of the Foothills Hospital, Calgary. Exclusions from the study included any patient with a weight of less than 50 kilograms or more than 90 kilograms; any patient with kidney or liver disease; any patient with known sensitivities to H_2-receptor antagonists; any patient with gastrointestinal disease or who was already taking any antacid substance.

Patients were assigned randomly to one of seven groups of equal size (n = 24). The patients received either ranitidine 50 mg or 100 mg, cimetidine 300 mg or placebo as an intravenous agent, or ranitidine 150 mg, cimetidine 300 mg or a placebo orally. The groups were comparable with respect to age and type of surgery (Table I).

All patients had fasted at least eight hours before induction of anaesthesia. Each patient received diazepam 0.1 to 0.2 $mg \cdot kg^{-1}$ as oral premedication approximately two hours before induction of anaesthesia. The drugs studied were given intravenously through an indwelling catheter, 45 minutes to three hours before operation, or were given orally from one and one half to five hours preoperatively, the test drug being taken with a sip of water (less than 30 ml).

Induction of anaesthesia was accomplished with thiopentone 4 to 6 $mg \cdot kg^{-1}$ intravenously, followed by a neuromuscular blocking drug, either succinylcholine, pancuronium or d-tubocurarine. A nasogastric tube (#16 Salem sump) was inserted into the stomach immediately after induction of anaesthesia and the contents of the stomach were aspirated. The volume of the aspirate was measured using a graduated cylinder and the pH of the gastric fluid was measured using a Fisher Accumet pH meter, Model 750 with a standard combination pH electrode. All pH values were measured in triplicate and then averaged before statistical analysis using the Student's t test.

TABLE I

Group	ASA I	ASA II	Ages Range/Median	Male	Female
Intravenous Drugs					
A Ranitidine 50 mg	22	2	17–51 33	9	15
B Ranitidine 100 mg	24	0	18–56 31	8	16
C Cimetidine 300 mg	18	6	16–70 36	11	13
D Placebo	20	4	20–72 34	13	11
Oral Drugs					
E Ranitidine 150 mg	20	4	21–69 36	10	14
F Cimetidine 300 mg	21	3	19–67 33	12	12
G Placebo	20	4	18–71 33	9	15

Results

Intravenous Groups (Table II)

1. Ranitidine 50 mg (Group A) or 100 mg (Group B)

There was one patient in each group with a pH below 2.5 (4 per cent). One patient in group A and one in Group B had a volume in excess of 25 ml. No patient had both a pH less than 2.5 and a volume greater than 25 ml. There were two patients in each group with a pH less than 3.5 (8 per cent).

2. Cimetidine 300 mg (Group C)

Two patients had a pH less than 2.5 (8 per cent). One of these also had a volume greater than 25 ml. A total of two patients had a volume in excess of 25 ml. There were no additional patients with a pH less than 3.5.

TABLE II

Group	Number of Patients	Volume >25 ml	pH Range	pH < 2.5	pH < 3.5
Intravenous Drugs				Number (per cent)	
A Ranitidine 50 mg	24	1	1.407–8.264	1(4)	2(8)
B Ranitidine 100 mg	24	1	1.630–8.701	1(4)	2(8)
C Cimetidine 300 mg	24	2	2.121–8.260	2(8)	2(8)
D Placebo	24	4	1.116–7.709	18(79)	19(79)
Oral Drugs					
E Ranitidine 150 mg	24	1	1.508–8.512	2(8)	4(17)
F Cimetidine 300 mg	24	1	1.426–8.709	6(25)	7(29)
G Placebo	24	4	1.036–7.762	19(79)	21(87.5)

3. Placebo (Group D)

A total of eighteen patients (75 per cent) had a pH less than 2.5. Four patients had a measured volume in excess of 25 ml. These four patients also had a pH less than 2.5. One additional patient had a pH less than 3.5 (79 per cent).

There was no relationship between failure of either ranitidine or cimetidine to alter pH favourably and intravenous administration more than forty-five minutes before induction of anaesthesia. There was no statistically significant difference in pH between groups A and B, or between groups A or B and C. There was a statistically significant difference in pH values obtained when comparing ranitidine (Group A) vs. placebo (Group D) ($p < 0.001$); ranitidine (Group B) vs. placebo (Group D) ($p < 0.001$); cimetidine (Group C) vs. placebo (Group D) ($p < 0.001$), when given as intravenous agents.

Oral Groups (Table II)

1. Ranitidine 150 mg (Group B)

Two patients had a pH less than 2.5 (8 per cent) and in one of these patients, the measured volume exceeded 25 ml. Two additional patients had pH values less than 3.5 (17 per cent).

2. Cimetidine 300 mg (Group F)

Six patients (25 per cent) had a pH less than 2.5. Two of these patients also had a gastric volume greater than 25 ml. One other patient had a pH less than 3.5 (29 per cent).

3. Placebo (Group G)

Nineteen patients had a pH less than 2.5 (79 per cent). Four patients had a volume greater than 25 ml and in all of these the pH was less than 2.5. Two additional patients had a pH less than 3.5 (87.5 per cent).

There was no statistical difference between oral cimetidine (Group F) compared with oral ranitidine (Group E). However, compared to placebo (Group G), pH values in both H_2 receptor antagonist groups were statistically significantly higher ($p < 0.001$). Intravenous ranitidine (Group B) was statistically significantly better than cimetidine 300 mg orally (Group F) in raising gastric pH ($p < 0.01$). Treatment failures were not related to the timing of the oral doses.

It should be noted that the measured gastric volumes may underestimate the amount present in the stomach, as no attempt was made to define gastric volume accurately, other than the initial aspiration. A dilution method for defining gastric volumes has been described but was not employed in this study.[9]

Side effects before induction of anaesthesia were noted only in the intravenous ranitidine groups. Itching and/or burning at the site of injection was not uncommon, occurring in 11 out of 48 patients. This usually subsided within 10 to 15 minutes of injection. One patient developed a macular rash with no wheals after injection of ranitidine, but this disappeared without treatment within 15 minutes. Nausea was a common complaint in the postoperative period in all groups of patients and therefore is more likely related to the anaesthesia and surgical procedure rather than to any drugs which might have been given preoperatively.

Discussion

Patients at risk of acid aspiration pneumonitis include pregnant patients undergoing Caesarean section or other obstetrical surgical procedures, emergency patients in whom gastric emptying is often delayed and those patients who are morbidly obese.[10] In addition, patients coming for elective surgery who have been fasting, especially on an outpatient basis, may also be at risk.[9] Cimetidine is well established as a suitable premedicant to increase gastric pH and reduce gastric volume.[3,5,10–16] However, it may not be fully effective and needs to be given some time, probably at least three quarters of an hour, before induction of anaesthesia. In the field of obstetrics, there has been a general lack of knowledge of the effects of cimetidine on the foetus at term and it is only recently that studies of its use during pregnancy have been carried out without any adverse effects noted.[17,18]

In the present study, patients receiving either intravenous ranitidine (50 or 100 mg) or cimetidine (300 mg) at least three-quarters of an hour before induction of anaesthesia had gastric pH in the range where the risk of developing aspiration pneumonitis is considered to be slight. Although two of 48 in the ranitidine group and two of 24 in the cimetidine group had a pH lower than 2.5, it appears that intravenous administration of these drugs in fasting non-pregnant patients is an effective means of increasing gastric pH before anaesthesia and elective surgery. The intravenous dose of ranitidine was much less than the intravenous dose of cimetidine, showing the greater potency of ranitidine. In addition, the 50 mg intravenous dose of ranitidine was just as effective as 100 mg in altering gastric pH before induction of anaesthesia.

When given orally, ranitidine 150 mg appears to be more effective than cimetidine 300 mg; however the difference is not statistically significant. Oral ranitidine 150 mg is as effective in altering gastric pH when compared with intravenous ranitidine or cimetidine if given at least two hours before induction of anaesthesia.

Oral cimetidine was more effective in altering pH when compared to placebo, but it still left 25 per cent of patients with a pH of less than 2.5 when the drug was given between two and four hours before induction. Intravenous ranitidine 100 mg was better than oral cimetidine in raising gastric pH. The results of the present study are comparable with those reported recently by Johnson and his colleagues,[19] who showed that both cimetidine and ranitidine increase gastric pH significantly when compared to placebos.

Side effects have been reported with both intravenous and oral use of cimetidine.[20–24] Long-term cimetidine treatment has been shown to alter hepatic drug metabolism,[25] whereas ranitidine did not do so after short term continuous use; the possibility of prolonged anaesthetic drug effects in patients on cimetidine therapy must be kept in mind.[26,27] However, single doses of cimetidine have not been associated with any significant side effects; similarly, no side effects have been reported after single doses of ranitidine. However this may represent the limited use of a new drug, and it remains to be seen what the true incidence of side effects may be. In the present study, burning and itching were noted not uncommonly in patients given intravenous ranitidine, but these resolved spontaneously. It is possible that this could have been prevented by slower intravenous injection or by dilution.

We conclude that ranitidine is a suitable compound for increasing gastric pH above the range believed to be associated with the risk of aspiration pneumonitis; in addition, gastric volume is reduced and this may also play a part in reducing this risk. Ranitidine may be given either intravenously or orally and is effective by either route. When given intravenously, there appeared to be little difference between ranitidine and cimetidine in the doses used in this study. In contrast, the intravenous administration of ranitidine appeared to be more effective when compared to oral cimetidine. In most studies, a pH value over 2.5 is quoted as being desirable. However, if Crawford's[2] suggestion of a lower limit of 3.5 is accepted, then there appear to be some patients always at potential risk, whether given cimetidine or ranitidine in any dose range studied to date. In this respect, vigorous administration of antacids may be more effective.[28] In addition, when immediate induction of anaesthesia is required, the only means of altering gastric pH is by the use of oral antacids, since the minimum effective time for H_2 receptor antagonists, given either orally or intravenously, is 45 minutes. Finally, the use of any of these agents by no means obviates the need for skilled anaesthetists with adequate assistance and equipment, the use of the Sellick manoeuvre properly applied, and rapid tracheal intubation in those patients truly at risk of acid aspiration.

To date, we have only studied prepared

patients who are not at any known risk of aspiration pneumonitis. It may be that the H_2 receptor antagonist drugs react differently in patients who are at risk, such as emergencies, obstetrical patients and the morbidly obese. In addition, the alternative administration of H_2 receptor antagonists intramuscularly should be considered.[29]

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Résumé

Une étude comparative des antagonistes des récepteurs H2, la cimétidine et la ranitidine sur le pH et le volume gastrique a été réalisée sur 168 patients programmés pour une chirurgie réglée. Les médicaments ont été administrés de façon aléatoire soit par la voie intraveineuse (ranitidine 50 mg ou 100 mg, la cimétidine 300 mg ou placebo) soit par la voie orale (ranitidine 150 mg, cimétidine 300 mg ou placebo). Les patients ont reçu la drogue ou le placebo 45 minutes à cinq heures avant l'intervention. Après l'induction de l'anesthésie, une sonde nasogastrique a été mise en place et le contenu stomachal aspiré. On en a mesuré le pH et le volume. Les patients qui recevaient ranitidine 50 ou 100 mg ou cimétidine 300 mg par la voie veineuse avaient un pH plus élevé de façon significative que ceux qui avaient reçu le placebo mais huit pour cent avaient un pH de moins de 2.5: la cimétidine orale a été inférieure de façon significative à la ranitidine intraveineuse à la dose de 100 mg. Nous en concluons que l'administration intraveineuse de cimétidine ou ranitidine est une méthode acceptable pour diminuer le pH gastrique avant l'induction de l'anesthésie. Par la voie orale, la ranitidine nous a paru supérieure à la cimétidine aux doses utilisées. Les deux médicaments doivent être administrés au moins 45 minutes avant l'induction de l'anaesthésie pour être efficace; l'usage de ces médicaments pour diminuer le risque de l'aspiration pulmonaire n'exclut en aucune façon l'utilisation d'une technique anesthésique appropriée pour l'induction de l'anesthésie.