Intramuscular cimetidine and ranitidine as prophylaxis against gastric aspiration syndrome - a randomized double-blind study

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Preoperative cimetidine 300 mg or ranitidine in 50 and 100 mg doses were administered intramuscularly to 120 patients in a randomized double-blind study. The volume and pH of gastric aspirate samples obtained after tracheal intubation and before extubation were measured. The pH of gastric aspirate was higher following ranitidine 100 mg than ranitidine 50 mg or cimetidine 300 mg at both intubation and extubation ($p = 0.006$). In addition, fewer patients tended to be "at risk" of pulmonary aspiration syndrome (pH $\leq$ 2.5) after ranitidine 100 mg than ranitidine 50 mg or cimetidine 300 mg.

Preoperative intramuscular ranitidine 100 mg was found to be suitable for use in protection against gastric aspiration syndrome.

Key words
HISTAMINE: cimetidine, ranitidine; COMPLICATIONS: aspiration prophylaxis.

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The risk of aspirating gastric contents during general anaesthesia has been recognized for well over 100 years. Mendelson[1] demonstrated in his animal experiments that the acidity of the aspirate was a major etiological factor in the development of aspiration pneumonitis. Subsequent studies[2,3] showed that the condition occurred when the pH of the gastric aspirate was below 2.5. Since the introduction of H_2 (histamine$_2$) receptor antagonists, preoperative administration of cimetidine has been used to decrease the risk of developing aspiration pneumonitis should aspiration of gastric contents occur. However, some patients are still found to have a gastric pH of less than 2.5 after cimetidine and thus are potentially at risk for the gastric aspiration syndrome.[4,5] The new H_2 blocker ranitidine has been compared with cimetidine (administered orally or intravenously), in terms of its effect on gastric pH and volume.[6,7] Ranitidine produced a higher mean pH than cimetidine and when administered intravenously resulted in fewer patients "at risk." The present randomized double-blind study was designed to compare the effect of preoperative intramuscular cimetidine and ranitidine on the volume and pH of gastric aspirate at the time of intubation and extubation. Patients were considered to be "at risk" for the pulmonary aspiration syndrome if gastric pH was 2.5 or less.

Methods

Institutional approval of the protocol was obtained and all patients gave written informed consent before entry into the study. The 120 patients studied

TABLE I Patient variables

	n	*Age (years)*	*Weight (kg)*	*Height (cm)*	*Number receiving premedication*
Cimetidine 300 mg	40	34.7±2.0	70.2±2.6	170.3±1.4	23
Ranitidine 50 mg	40	35.2±2.2	66.5±2.1	168.5±1.4	25
Ranitidine 100 mg	40	34.2±2.0	69.1±2.4	168.7±1.7	24

Patient values are expressed as means ±1 SEM for each study medication.

were ASA physical Status I or II, aged 18 to 70 years who were scheduled for elective surgery under general anaesthesia with endotracheal intubation. Patients were excluded from the study if they had gastrointestinal disease or were receiving medications likely to affect gastric motility or pH. Patients were randomly assigned, within blocks of six, to one of three treatment groups: Group I received cimetidine 300 mg, Group II ranitidine 50 mg, and Group III ranitidine 100 mg, all administered approximately one hour preoperatively by a nurse not involved with the anaesthetic. All patients were fasted for at least six hours and, if desired, were premedicated with oral diazepam 5–15 mg 1½ to 2 hours preoperatively. The presence of side effects, including pain at the site of intramuscular injection, was elicited by a questionnaire given to the patient immediately prior to induction of anaesthesia. After tracheal intubation, a 16 French gauge Salem oro-gastric tube was inserted. The gastric contents were aspirated using a 50 ml syringe by an anaesthetist unaware of which drug was used, at intubation and prior to extubation. The volume of aspirate was recorded and pH was measured using a Fisher Accumet 320 pH meter.

Patient variables were compared by analysis of variance, and gastric pH by the Mann-Whitney U test. The incidence of patients at risk, and exhibiting side effects, was compared by the Fisher Exact test. For the purpose of this study statistical significance was defined as $p < 0.05$.

Results

The treatment groups were similar with respect to age, weight, height (Table I) and duration of fasting time. Gastric juice could not be aspirated in eight patients at intubation and seventeen patients at extubation (Tables II and III).

The time interval between intramuscular drug administration and collection of gastric aspirate, and the volume of gastric aspirate were similar in all three groups at the time of intubation (Table II). The pH of gastric aspirate was higher following ranitidine 100 mg than either ranitidine 50 mg or cimetidine 300 mg ($p = 0.008$).

The results at extubation were similar except that the volume of gastric aspirate tended to be smaller and the pH higher than at intubation (Table III). Ranitidine 100 mg produced a higher mean pH ($p = 0.006$) than ranitidine 50 mg or cimetidine 300 mg.

Only one patient was "at risk" following ranitidine 100 mg (having a pH of 2.5 at intubation, 45 minutes after drug administration). However, at extubation 30 minutes later, the pH in this patient was 4.6. In the ranitidine 50 mg group two patients were "at risk" at intubation, with pH's of 2.1 and 2.3, the time from drug administration being 50 and 60 minutes respectively. In the cimetidine group four patients were "at risk" at intubation for up to 120 minutes after receiving the drug. At extubation none of the patients receiving ranitidine 100 mg were "at risk" compared to one patient in each of the ranitidine 50 mg and cimetidine 300 mg groups.

The incidence of side effects is summarized in Table IV. Drowsiness, headache and dizziness occurred with similarly low frequency in the three groups. However, there was significantly more pain at the injection site following cimetidine 300 mg than either ranitidine 50 mg or ranitidine 100 mg ($p = 0.006$).

TABLE II Findings at time of intubation*

	n	*Time (minutes)*	*Volume (ml)*	*pH*	*Number at risk*
Cimetidine 300 mg	38	73.8±4.5	8.6±1.3	5.4±0.3	4
Ranitidine 50 mg	37	76.6±4.5	7.4±1.3	5.6±0.2	2
Ranitidine 100 mg	37	79.7±4.6	8.9±1.0	6.3±0.2†	1

Time from administration of medication to gastric sampling, and volume and pH of gastric aspirate are expressed as means ±1 SEM. Patients at risk are those with a gastric pH ≤ 2.5.
*Eight patients were excluded because no sample could be obtained.
†$p = 0.008$ when compared with cimetidine 300 mg or ranitidine 50 mg.

TABLE III Findings at time of extubation*

	n	*Time (minutes)*	*Volume (ml)*	*pH*	*Number at risk*
Cimetidine 300 mg	33	142.9±9.7	4.9±0.8	5.87±0.3	1
Ranitidine 50 mg	33	132.6±8.0	5.4±0.9	5.92±0.3	1
Ranitidine 100 mg	37	149.9±7.5	4.7±0.7	6.57±0.17	0

Time from administration of medication to gastric sampling, and volume and pH of gastric aspirate are expressed as means ±1 SEM. Patients at risk are those with a gastric pH ≤ 2.5.
*Seventeen patients were excluded because no sample could be obtained.
†$p = 0.006$ when compared with cimetidine 300 mg and ranitidine 50 mg.

Discussion

The gastric aspiration syndrome continues to constitute a serious risk for general anaesthesia.[8–10] Many agents, including cimetidine, have been investigated to evaluate their ability to raise the pH of gastric aspirate above 2.5 at the time of intubation and thus decrease the morbidity and mortality associated with aspiration of gastric contents. However, preoperative cimetidine does not consistently increase gastric pH to greater than 2.5 and the percentage of patients at risk varies from ten per cent following 300 mg of cimetidine given intravenously[4] to 16 per cent when it is given orally.[5] Ranitidine, a new H_2 receptor antagonist which is more selective, potent, and longer acting than cimetidine, was therefore studied to determine whether it would be more effective than cimetidine in raising gastric pH.

In addition to a gastric pH level of 2.5 or less, a minimum gastric volume of 0.4 $ml \cdot kg^{-1}$ is often used to define patients at risk of severe pneumonitis in the event that gastric acid aspiration should occur.[11] However, in this study it was decided to define "risk" solely on the basis of the pH level,

TABLE IV Incidence of side effects

	n	*Pain*	*Drowsiness*	*Headache*	*Dizziness*
Cimetidine 300 mg	40	12*	6	1	0
Ranitidine 50 mg	40	2	5	1	0
Ranitidine 100 mg	40	2	5	1	1

*$p = 0.006$ when compared to ranitidine 50 and 100 mg.
The incidence of preoperative side effects as elicited by questionnaire are shown for each treatment group.

since the method of gastric aspiration employed may not accurately measure the total volume of gastric juice. A dye dilution method may have given a higher total volume but this would have invalidated the extubation sampling.[12]

The present study did not contain a placebo group since adequate data had been obtained from a previous study[6] and it was deemed unnecessary to include a further group of patients who would not receive active medication. Ranitidine is considered to be five to eight times more potent than cimetidine in inhibiting gastric secretion.[13] Thus ranitidine 50 mg is approximately equipotent to and ranitidine 100 mg is somewhat more potent than cimetitine 300 mg in this respect.

When comparing the results of the present study to our previous findings, ranitidine 100 mg administered intramuscularly at approximately one hour preoperatively raised the mean gastric pH to 6.3, a value similar to that found approximately one hour after intravenous ranitidine 80 mg (pH = 5.8), and two hours after oral ranitidine 150 mg (pH = 6.1).[6] One patient out of 37 (three per cent) was "at risk" at intubation following intramuscular ranitidine 100 mg, compared to one out of 20 (five per cent) following intravenous ranitidine 80 mg, or three out of 27 (11 per cent) following oral ranitidine 150 mg. Thus, intramuscular ranitidine 100 mg would appear as effective as intravenous ranitidine 80 mg and possibly more so than oral ranitidine 150 mg, particularly when considering the number of patients "at risk."

The incidence of side effects following intramuscular ranitidine was low and the drowsiness following cimetidine and ranitidine was probably related to premedication with diazepam. Similar numbers of patients received premedication in the three groups (Table I).

Interaction between cimetidine and diazepam has been noted in that prior administration of cimetidine may potentiate the sedative effects of diazepam possibly by inhibition of microsomal oxidative function in the liver.[14] Ranitidine is not considered to cause this potentiation because it does not inhibit microsomal oxidation.[15] However, in this study this interaction between cimetidine and diazepam was probably of little significance because the cimetidine was administered after the oral diazepam premedication.

Intravenous ranitidine 80 mg caused itching at the site of injection in 15 per cent of patients and oral ranitidine was associated with very few side effects.[6] Since intramuscular ranitidine 100 mg has a low incidence of side effects and is at least as effective as intravenous or oral ranitidine, it would appear to be the preferred route of administration, when clinically appropriate for protection against gastric aspiration syndrome.

In conclusion, intramuscular ranitidine 100 mg was significantly better than cimetidine 300 mg and ranitidine 50 mg in producing a higher mean pH and thus fewer patients at risk for developing aspiration pneumonitis. Both ranitidine 50 mg and ranitidine 100 mg produced fewer patients at risk, at the time of intubation, than did cimetidine 300 mg.

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Résumé

Dans une étude à double insu portant sur 120 malades, on a comparé les effets sur le volume et le pH du suc gastrique de la cimétidine 300 mg à ceux de la ranitidine à la dose de 50 et 100 mg administrée par voie intramusculaire avant l'intervention. Les mesures de volume et de pH gastrique ont été effectuées après l'intubation et avant l'extubation.

Le pH du suc gastrique était plus élevé à la suite de ranitidine 100 mg comparé à la ranitidine 50 mg ou la cimétidine 300 mg au moment de l'intubation et de l'extubation ($p = 0.006$). En outre, il y avait moins de patients jugés en risque "d'aspiration en puissance" ($pH \leq 2.5$) dans le groupe traité à la ranitidine 100 mg que dans le groupe ranitidine 50 mg ou cimétidine 300 mg.

Il apparaît donc que la ranitidine 100 mg administrée par voie intra-musculaire constitue un agent efficace de protection contre le syndrome d'aspiration gastrique.