The role of H₂ receptor antagonist premedication in pregnant day care patients

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In a randomised study of 132 pregnant outpatients, the effect on gastric volume and pH of oral premedication with a single dose of an H₂ antagonist was investigated. Either cimetidine 400 mg (n = 33), or ranitidine 150 mg (n = 33), were given 90 to 120 minutes before scheduled surgery. Mean pH was significantly higher in cimetidine (5.0) and ranitidine (5.2) groups, and mean volume was significantly lower in cimetidine (13.2 ml) and ranitidine (11.1 ml) groups compared with 66 untreated patients (pH 1.6, volume 22.1 ml). A gastric pH ≤ 2.5 was found in 97 per cent of unpremedicated patients and 35 per cent of these patients also had a gastric volume ≥ 25 ml. Eighty-three per cent of patients received their premedication within 75–200 minutes of surgery. Patients premedicated within that range had a significantly lower incidence of either a gastric pH ≤ 2.5 or a volume ≥ 25 ml (p < 0.01). Both cimetidine and ranitidine significantly reduced the number of patients with these risk factors. Four patients, however, in the cimetidine group had both a pH ≤ 2.5 and a volume ≥ 25 ml. Pharmacological manipulation of the gastric environment does not prevent aspiration and clearly cannot be substituted for careful airway management and vigilance on the part of the anaesthetist. However, premedication of pregnant outpatients with a single, oral dose of an H₂ antagonist is a simple, inexpensive, safe and effective way of reducing the risk of a severe aspiration pneumonitis.

Key words

ANAESTHESIA: outpatient; HISTAMINE H₂ RECEPTOR BLOCKERS: cimetidine, ranitidine; PNEUMONIA: aspiration; PREMEDICATION: histamine H₂ receptor blockers, cimetidine, ranitidine.

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Pulmonary damage due to aspiration of gastric contents remains a major cause of anaesthetic-related morbidity and mortality.^{1,2} Outpatients are considered to be a high risk group, since they have been shown to have increased gastric volumes compared with inpatients.³ Pregnancy is also considered to increase the risks of gastric regurgitation although patients presenting for first trimester abortions do not have increased gastric volumes or acidity when compared to nonpregnant female outpatients.⁴ The hormonally induced changes in gastrointestinal smooth muscle sphincter tone, the intra-abdominal pressure changes caused by the lithotomy or Trendelenberg positions, and surgical manipulation all increase the risk of intraoperative gastric regurgitation.

Results from animal studies support the concept that aspiration of very acidic fluid markedly worsens the severity of the resultant pneumonitis.⁵ Pharmacological modification of the gastric environment has attracted much attention in recent years in an effort to minimise this risk. H₂ receptor antagonists have been shown to be effective in reducing acidity and gastric volumes in inpatients; however, outpatients present a particular problem because many advocated methods require intravenous or multiple dose administration.^{6,7}

The aim of this study was to evaluate the effectiveness of premedication with a single oral dose of cimetidine or ranitidine given 90–120 minutes before scheduled surgery. Patients in the first trimester of pregnancy requiring therapeutic abortion were studied because of their special risk factors and because the use of oral H₂ receptor antagonist premedication has not been previously reported in this group of outpatients.

Methods

After approval of the study protocol by the institutional ethics committee and after informed patient consent, 132 outpatients presenting for first trimester therapeutic abortion were studied. Details of patient age, weight, gestation, smoking history, fasting interval and history of recent vomiting or symptoms of reflux were recorded after arrival of the patients in the day care holding area.

Patients were randomly allocated to either treatment or nontreatment groups: Group 1 patients ($n = 66$) received no premedication (control); Group 2 ($n = 33$) received cimetidine 400 mg and Group 3 ($n = 33$) received ranitidine 150 mg orally with 10 ml of water to aid swallowing, 90–120 minutes before scheduled surgery. No other premedication was used. All patients starved from midnight until surgery which was performed during a separate elective afternoon operating list. Patients with known gastrointestinal disease and patients receiving any medication known to affect gastric secretion were excluded.

Anaesthesia was induced with fentanyl $2 \mu\text{g}\cdot\text{kg}^{-1}$ and thiopentone $4\text{--}7 \text{ mg}\cdot\text{kg}^{-1}$, and maintained with 70 per cent N_2O in oxygen, with increments of thiopentone (25 mg) as required. No other drugs were administered. At the end of surgery, an #18 Salem Sump orogastric tube was introduced into the stomach, and its position confirmed by auscultation for insufflated air. Gastric contents were aspirated with the patient in three different positions – lithotomy with Trendelenburg tilt, supine, and left lateral – to facilitate maximal emptying. The pH of the aspirate was measured using a calibrated Radiometer PHM82 pH meter.

Data were analysed using one-way analysis of variance and Student's t -test. Chi-square analysis (with Yates's correction applied where appropriate) was used to compare patient characteristics between groups and to compare the proportions of patients in the three groups with $\text{pH} \leq 2.5$, volume $\geq 25 \text{ ml}$, or a combination of both risk factors. Correlation between these characteristics and measured gastric volumes and acidity was sought using linear regression analysis. Patients in whom no gastric contents were aspirated were excluded from statistical comparisons between and within the premedication groups. Differences were considered significant when $p < 0.05$. Both mean pH and hydrogen ion (H^+) concentration are reported.

TABLE I Patient characteristics (mean $\pm$ SEM)

	<i>n</i>	Age (yrs)	Weight (kg)	Gestation (weeks)
Group 1 (no premed)	66	22.8 ± 0.6	58.4 ± 1.2	9.4 ± 0.2
Group 2 (cimetidine)	33	23.3 ± 0.9	59.1 ± 1.4	8.8 ± 0.2
Group 3 (ranitidine)	33	23.8 ± 0.9	57.9 ± 1.5	9.2 ± 0.3

Results

There were no significant differences between the three groups of patients with regard to age, weight, gestation, incidence of smoking, fasting interval, history of vomiting or reflux or premedication interval (Tables I, II).

Mean pH was significantly higher ($p < 0.001$) in the cimetidine (5.0) and ranitidine (5.2) groups compared with the control group (1.6) (Table III). The differences between mean H^+ concentrations in treated vs untreated patients were also significant ($p < 0.001$). Significantly fewer ($p < 0.001$) patients receiving cimetidine (18.5 per cent) or ranitidine (16.1 per cent) had a gastric $\text{pH} \leq 2.5$ compared with controls (96.9 per cent) (Figure). One patient in Group 1, six patients in Group 2 and two patients in Group 3 had no gastric aspirate despite confirmation of the sump tube position.

Mean gastric volumes were also significantly lower ($p < 0.001$) in the cimetidine (13.2 ml) and ranitidine (11.1 ml) groups compared with the control group (22.1 ml) (Table IV). Treatment with cimetidine or ranitidine reduced the incidence of a gastric volume $\geq 25 \text{ ml}$ from 34.8 per cent

TABLE II Fasting and premedication intervals (mean $\pm$ SEM (Range))

	Fasting interval (hours)	Premedication interval (minutes)
Group 1 (no premed) $n = 66$	16.7 ± 0.3 (7–22)	—
Group 2 (cimetidine) $n = 33$	17.2 ± 0.3 (14–23)	105.0 ± 6.1 (60–195)
Group 3 (ranitidine) $n = 33$	17.4 ± 0.4 (12–24)	113.2 ± 8.4 (60–210)

FIGURE Comparisons of risk factors in treatment and non-treatment groups.

TABLE III Gastric acidity characteristics

	pH			H ⁺ Conc Mean $\pm$ SEM (nmol·L ⁻¹)
	Mean $\pm$ SEM	Range	Median	
Group 1 (no premed) n = 65	1.6 $\pm$ 0.1	1.0-3.3	1.4	3.56 $\pm$ 0.26 $\times 10^7$
Group 2 (cimetidine) n = 27	5.0 $\pm$ 0.4*	1.4-7.4	5.8	0.29 $\pm$ 0.12 $\times 10^7$ *
Group 3 (ranitidine) n = 31	5.2 $\pm$ 0.3*	1.6-7.4	6.3	0.22 $\pm$ 0.10 $\times 10^7$ *

*p < 0.001 vs Group 1.

(Group 1) to 12.1 per cent ($p < 0.05$) and 9.1 per cent ($p < 0.02$) respectively (Figure).

Whereas 34.8 per cent of unpremedicated patients had both a pH ≤ 2.5 and a volume ≥ 25 ml, 12.1 per cent of the cimetidine ($p < 0.05$ vs control), and none of the ranitidine ($p < 0.001$ vs control) patients fell into this "high risk" category (Figure).

There was no difference between the cimetidine and ranitidine groups with respect to pH, H⁺ concentration, or the incidence of pH ≤ 2.5 , volume ≥ 25 ml or both critical pH and volume criteria ($p > 0.05$).

Premedication intervals were similar in both treatment groups (Table II). Eighty-three per cent of patients received their premedication within 75-

TABLE IV Gastric volume characteristics

	Mean $\pm$ SEM (ml)	Range (ml)
Group 1 (no premed) n = 65	22.1 $\pm$ 1.5	0-65
Group 2 (cimetidine) n = 27	13.2 $\pm$ 2.4*	0-70
Group 3 (ranitidine) n = 31	11.1 $\pm$ 1.5*	0-36

*p $\leq$ 0.001 vs Group 1.

200 minutes before actual surgery. Premedication outside that range produced a significantly higher incidence of either a pH $\leq$ 2.5 or volume $\geq$ 25 ml (p < 0.005).

Gastric volume and acidity were uninfluenced by weight, gestation, duration of fast, smoking history or history of vomiting or gastric reflux.

Discussion

Aspiration of gastric contents continues to feature prominently in reviews of anaesthetic-related deaths.^{1,2} Even if the aspirated fluid has been strained of particulate matter and neutralised to a pH of 5.9, it produces a chemical pneumonitis; however, mortality after aspiration increases markedly when large volumes or highly acidic contents are aspirated.^{8,9} Given the disadvantages of antacid treatment,¹⁰ it is not surprising that recent research has focussed on alternative methods of gastric environment manipulation.

Numerous studies have testified to the efficacy of H₂ receptor antagonists in raising gastric pH and, less reliably, reducing volume in obstetric and general surgical patients.¹¹ Their use has been advocated in other "high risk" patients.¹² Most anaesthetists would accept that parturients and the morbidly obese¹³ are at increased risk because of hormonal and/or mechanical factors. Outpatients are often included in the "at risk" category – presumably because of their lack of a supervised fasting period. However, although Ong and co-workers³ found increased gastric volumes in outpatients compared with inpatients, Manchikanti and Roush¹⁴ found no difference between inpatients and outpatients with respect to mean pH, volume, or the percentage of patients with pH < 2.5 and volume

> 25 ml. Similarly, there seems to be no difference in this regard between pregnant and non-pregnant outpatients.⁴

In this study, 97 per cent of fasting, unpremedicated pregnant outpatients had a pH $\leq$ 2.5, and 35 per cent also had volumes in excess of 25 ml. Since an aspiration method of measurement will tend to underestimate the true gastric volume,³ the numbers of patients at risk may be even greater. These high percentages must be contrasted with the extremely low incidence of aspiration syndrome in pregnant outpatients.¹⁵

Premedication of pregnant outpatients with a single oral dose of cimetidine or ranitidine produced a significant reduction in the number of patients with large volumes of highly acid gastric contents. Despite concern about the demonstrated effects of cimetidine on hepatic drug metabolism,¹⁶⁻¹⁸ and both cimetidine and ranitidine on hepatic blood flow,^{19,20} there are no reported adverse clinical interactions with anaesthetic drugs following a single, oral dose of either drug. Treatment with one dose of oral cimetidine produces no clinically significant enhancement of morphine-induced respiratory depression in volunteers.²¹ Caution, however, should be used in patients who may be sensitive to narcotics or sedatives.

There is no currently available method of prophylaxis which will eliminate the possibility of pulmonary damage following aspiration of gastric contents. The method outlined in this study is inexpensive, simple and is suited to use in day care surgery. Timing of premedication is important and patients scheduled first in the morning may occasionally present difficulties. It should also be noted that cimetidine and ranitidine have not been approved for use during pregnancy.

H₂ receptor antagonists do not prevent aspiration of gastric contents into the lung from occurring. Skillful technique and vigilance on the part of the anaesthetist cannot be substituted, and the anaesthetised patient must always be considered at risk from regurgitation and possible aspiration. However, premedication of outpatients in the first trimester of pregnancy with a single, oral dose of an H₂ antagonist is a simple and effective way of reducing the risk of severe aspiration pneumonitis.

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Résumé

Dans une étude faite au hasard sur 132 patientes gravides, hospitalisées le jour même de l'opération, l'effet sur le volume gastrique et le pH d'une prémédication orale avec une dose unique d'un antagoniste H₂ a été investigué. La cimetidine 400 mg (n = 33), ou la ranitidine 150 mg (n = 33), ont été données de 90 à 120 minutes avant la chirurgie. Le pH moyen était significativement plus haut dans le groupe cimetidine (5.0) que le groupe ranitidine (5.2). Le volume moyen était significativement plus bas dans le groupe cimetidine (13.2 ml) et le groupe ranitidine (11.1 ml) comparés à un groupe témoin de 66 patientes non traitées où le pH était de 1.6 et le volume de 22.1 ml. Un pH gastrique ≤ 2.5 a été trouvé chez 97 pour cent des patientes non prémédiquées et 35 pour cent de celles-là avaient un volume gastrique aspiré ≥ 25 ml. Quatre-vingt-trois pour cent des patientes ont reçu leur prémédication entre 75 et 200 minutes avant la chirurgie. Les patientes prémédiquées dans les limites de ce temps ont eu une incidence significativement plus basse soit du pH gastrique ≤ 2.5 ou du volume ≥ 25 ml ($p < 0.01$). La cimetidine et la ranitidine ont diminué significativement le nombre des patientes pouvant présenter ces facteurs de risque. Quatre patientes cependant, dans le groupe cimetidine, avaient un pH ≤ 2.5 et un volume ≥ 25 ml. Les manipulations pharmacologiques du milieu gastrique ne préviennent pas l'aspiration et de toute évidence ne peuvent remplacer la vigilance de l'anesthésiste et le bon maintien des voies aériennes. Cependant la prémédication des patientes enceintes se présentant à l'hôpital le jour même de la chirurgie avec une dose orale unique d'un antagoniste H₂ est simple, non coûteuse, sécuritaire et efficace pour diminuer les risques d'une pneumonie d'aspiration sévère.