The comparative efficacy of cimetidine and ranitidine in controlling gastric pH in critically ill patients

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The comparative efficacy of intravenous cimetidine and ranitidine in controlling gastric pH in 100 intensive care unit patients was assessed in a double blind, prospective, randomized study. The total number of gastric pH determinations and the number of pH determinations with pH less than five were recorded. Patients received either cimetidine or ranitidine via continuous infusion, with dosage adjustments for patients with renal insufficiency. Antacids were administered each time the gastric pH was less than five. There was no difference overall in the number of patients who had at least one gastric pH determination < pH 5. There was however, a larger proportion of patients with ≥10, ≥15, ≥20 and ≥25 per cent of gastric pH determination < pH 5 in the cimetidine group than in the ranitidine group. This difference was statistically significant for ≥25 per cent. The drugs were well tolerated. Ranitidine was as effective as cimetidine and possibly more so in controlling gastric pH.

Key words

GASTROINTESTINAL TRACT: gastric pH, cimetidine, ranitidine; HISTAMINE-2 RECEPTOR ANTAGONISTS: cimetidine, ranitidine.

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The use of cimetidine, a histamine-2 (H_2) receptor antagonist, and antacids to increase gastric acid pH and reduce the risk of stress ulceration is well documented.[1-3] While some studies have shown antacids to be superior to cimetidine[4-5] others have stated that cimetidine is equally efficacious.[1,3] Proponents of the use of cimetidine have cited equal efficacy, convenience (versus hourly titration of antacid) and reduced incidence of adverse effects when compared to high dose antacids as the reasons for its widespread use.[1,3]

However, cimetidine is a less than ideal agent in the critically ill, especially because of central nervous system toxicity and the potential for drug interactions.[6-8] Ranitidine, a recently released H_2 receptor antagonist, may offer an advantage over cimetidine since it does not result in the same degree of neurological toxicity nor interfere with drug metabolism in therapeutic doses.[9] Ranitidine may also be effective when cimetidine has failed.[10] Based on these potential advantages, it seemed appropriate to compare intravenous cimetidine and intravenous ranitidine in the control of gastric pH.

Methods

From July 13, 1983 to January 7, 1984, 100 patients admitted to the Surgical Intensive Care Unit (SICU) who underwent randomization within 12 hours of admission to the unit were entered into the study, providing no exclusion criteria were present. Specific exclusion criteria were: known hypersensitivity to cimetidine or ranitidine; previous upper gastrointestinal surgery; previous history/evidence of pre-existing peptic ulcer disease; severe liver disease; haemorrhagic diathesis; moderate pre-existing re-

TABLE I Drug doses related to renal function

Creatinine clearance	*Cimetidine dose*	*Ranitidine dose*
>1 ml/sec	1200 mg/day	
0.2–1.0 ml/sec	900 mg/day	
<0.2 ml/sec	600 mg/day	
>0.2 ml/sec		300 mg/day
≤0.2 ml/sec		150 mg/day

nal insufficiency (serum creatinine ≥ 260 $mmol \cdot L^{-1}$); prior use of an H_2 receptor antagonist or antacids within 24 hours; age less than 12 years; pregnant or nursing women; previous history of pyloric stenosis, oesophageal stricture, oesophageal ring, scleroderma, hiatus hernia or atrophic gastritis; a body weight < 40 kg or > 90 kg. Informed consent was obtained from the patient or next of kin. The protocol was reviewed and accepted by the University and Hospital Research and Ethics Committees.

Patients were randomly allocated, by selecting the next consecutive number box, to receive either cimetidine 300 mg intravenously over 20 minutes followed by a continuous intravenous infusion of 50 mg per hour (1200 mg daily) or ranitidine 50 mg intravenously over 20 minutes followed by a continuous infusion of 12.5 mg per hour (300 mg daily). Syringes of the drug were prepared and boxes containing these drug kits (for first 24-hour period) were stored in the SICU. These kits were prepared by the Department of Pharmacy with neither the SICU staff nor the patient having knowledge of which drug the kit contained. The Pharmacy Department was responsible for supplying subsequent solutions of appropriate drug and any necessary dosage alterations. Patients with mild pre-existing renal insufficiency or who developed renal insufficiency while on study received reduced doses as indicated in Table I.

A nasogastric tube was inserted and gastric pH was measured every four hours using a commercially available pH sensitive tape (Colourphast®) commencing at time 0. Thirty ml of antacid (Gelusil Extra Strength®) was administered via the nasogastric tube if the pH was less than five. Routine blood work including serum electrolytes, BUN and creatinine were measured daily. Liver function tests were done on the day of admission and the day of discharge. Thyroid function tests were done on admission and one week later. All patients had continuous EKG monitoring and an assessment of the Glascow Coma Scale daily. The patients were continued in the study until one of the following events occurred:

1 The patient received a full seven days of therapy.
2 The patient was started on oral or nasogastric feedings.
3 The patient experienced a major gastrointestinal bleed defined as appreciable or continued appearance of blood either fresh or altered blood in the nasogastric secretions or melena stools associated with a drop in haemoglobin of 20 $g \cdot L^{-1}$ or more.
4 The patient developed an adverse effect of significant magnitude to preclude continuation of the study.
5 The patient expired.

The number of pH readings < pH 5 and total number of pH readings were recorded. Patients were deemed eligible for analysis only if they completed 36 hours in the study and had at least nine gastric acid determinations. Differences between means were analyzed by an unpaired t-test. Differences between proportions were measured by Chi square analysis. The level of $p < 0.05$ was considered significant.

Results

Of the original 100 patients entered in the study 71 (38 of the cimetidine group and 33 of the ranitidine group) were included in the final analysis. The 17 patients not included for analysis in the ranitidine group were excluded for the following reasons: nine improved and were transferred from the SICU in less than 36 hours, three died within 36 hours, two were started on tube feedings, two were excluded for an inadequate number of samples and one was excluded because of body weight < 40 kg. The 12 patients in the cimetidine group not included for analysis were excluded for the following reasons: seven improved and were transferred in less than 36 hours, two died within 36 hours, one was excluded for an inadequate number of samples, one was excluded because of body weight > 90 kg and one because of the drug infusion being inadvertently turned off for a period of 12 hours. The demographic data are shown in Table II. The two groups were comparable with respect to age, sex and hours in the study.

When patients who failed to have gastric pH

TABLE II Demographic data

	Cimetidine group (n = 38)	*Ranitidine group (n = 33)*
Age (years)	39.1 ± 19.4	41.3 ± 21.1
Sex (M/F)	24/14	19/14
Length of study time (hours)	81.8 ± 36.1	91.7 ± 82.0
Primary diagnosis		
Vascular	3	6
Craniofacial surgery	4	4
Trauma	11	8
Closed head injury ± trauma	11	7
Neurosurgical/spinal cord trauma	5	5
Acute respiratory failure	1	1
Sepsis	0	1
Other (myocardial infarction, seizures, CVA)	3	0

controlled were placed in risk groups one through five depending on the number of risk factors present, there was no significant difference between the groups (Table III) even though there were five patients in the cimetidine group with five risk factors but only one in the ranitidine group with five risk factors. There were no patients who had more than five of the seven risk factors. The seven risk factors for stress ulceration included sepsis, respiratory failure, major operative procedures, renal failure, hypotension, multiple trauma, head injury and spinal cord injury. Data were not specifically analyzed within each of the risk groups because of the small numbers in each group. There was no statistical correlation between the number of risk factors and the inability to control gastric pH ($r = -0.038$).

Table IV reports the outcome of patients with respect to mortality and evidence of gastrointestinal bleed. Mortality rates between the groups were comparable. There were no clinically significant gastrointestinal haemorrhages. One patient in the cimetidine group and two patients in the ranitidine group had microscopic bleeding. This difference between groups was not statistically significant.

TABLE III Presence of risk factors

Number of risk factors	*Cimetidine group (n = 38)*	*Ranitidine group (n = 33)*
1 or 2	17	17
3	10	11
4 or 5	11	5

TABLE IV Outcome of patients

	Cimetidine (n = 38)	*Ranitidine (n = 33)*
Mortality	7/38 (18.4%)	6/33 (18.2%)
Evidence of bleed	1/38	2/33

After excluding the first aspirate obtained at time 0, 27 of the 38 patients (71.1 per cent) receiving cimetidine had a pH <5 on at least one occasion while 22 of 33 patients (66.7 per cent) receiving ranitidine had a pH <5 on at least one occasion (p = NS). There were a number of patients in both groups who were completely controlled with these agents. Subsequent analysis of the data and division of the patients into groups based on the percentage of gastric pH determinations of <5 revealed the information summarized in the Figure. Poor control

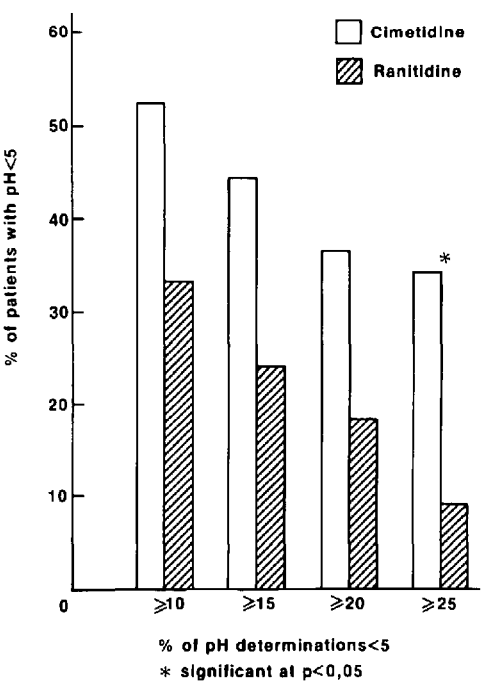

FIGURE Number of pH readings less than five as a percentage of total number of pH readings.

was arbitrarily defined as greater than 25 per cent of gastric pH's <5. Thirteen of 38 patients in the cimetidine group (31.6 per cent) and three of 33 patients in the ranitidine group (9.1 per cent) were poorly controlled. This is statistically significant, with fewer patients receiving ranitidine poorly controlled ($p < 0.05$). In addition, 13 of the 38 in the cimetidine group (34.2 per cent) versus four of 33 patients receiving ranitidine (12.1 per cent) had, on at least one occasion, consecutive pH determinations which were less than five. This approached but did not reach statistical significance ($\chi^2 = 3.60$) ($p < 0.06$).

Using the Glascow Coma Scale to assess neurological function eight of 38 patients (21.1 per cent) in the cimetidine group and one of 33 patients (3.0 per cent) in the ranitidine group had a reduction in neurological function from the first to the last day of the study (p = NS). Furthermore, it was difficult to ascertain the neurological effects of the drugs due to the frequent use of pancuronium, diazepam and morphine and possible disease related deterioration.

Adverse effects

Both agents were well tolerated. Four of 38 patients in the cimetidine group (10.5 per cent) who had two serum aspartate aminotransferase levels determined had at least a two-fold increase in these levels. Three of these were above the normal range. Six of forty (15 per cent) of all patients who received ranitidine, including patients who were excluded (see above), who had two serum aspartate aminotransferase determinations performed, had at least a two-fold increase in these levels. Three of these were above the normal range. Clinical hepatotoxicity was not present in any of these patients. In addition, three patients receiving cimetidine developed adverse events. In only one case in which a patient developed diarrhoea was the drug felt to be implicated. One patient developed renal failure (thought to be an operative complication) and one patient developed a decreasing level of consciousness and reduced platelet count, felt to be due to sepsis. Two patients in the ranitidine group had adverse events. One patient who deteriorated neurologically was also receiving lidocaine and developed sepsis and renal failure. The second patient developed a rash on her face. She was receiving high dose corticosteroids at the time. In neither case was the study drug felt to be implicated.

Discussion

The administration of ranitidine by continuous infusion was at least as effective as cimetidine in our population in controlling gastric pH. When poor control was arbitrarily chosen as ≥25 per cent of pH determinations uncontrolled, there was a statistically significant difference between the cimetidine and ranitidine groups with fewer patients who received ranitidine being poorly controlled. The end-point of control of gastric pH was chosen rather than gastrointestinal bleeding, because of the already low and seemingly decreasing incidence of gastrointestinal bleeding secondary to gastric erosions.[4,11] To select an infrequent occurrence such as gastrointestinal haemorrhage as our end point would have necessitated a much larger study population. Our strict exclusion criteria, including severe hepatic dysfunction and renal disease, eliminated many patients from the study who were at high risk of stress ulceration. This was done so that the groups would be more homogeneous. In addition, recent information indicates that dosing adjustments of cimetidine may be needed in patients with hepatic disease and that they may be more prone to CNS toxicity.[12] For this ethical reason, as well as to maintain the double-blind format, we chose to exclude these patients from entry into the study.

The continuous intravenous infusion method of administration was chosen because of ease of administration and preliminary data which indicates that this route may be more efficacious than when the drug is administered intermittently.[13,14] Several recent reports have cited that following abrupt discontinuation of cimetidine, there may be episodes of gastrointestinal bleeding.[15–17] Whether hyperacidity can occur following short-term continuous infusions of either cimetidine or ranitidine is unknown but we suggest careful monitoring of gastric pH after discontinuation of the infusion.

We selected a relatively large daily dose of ranitidine (300 mg) for comparison with cimetidine. This dose was chosen for several reasons. First, the dose of 300 mg compared with 1200 mg of cimetidine is in keeping with the data that indicate that ranitidine is 4–10 times more potent than cimetidine and to date has had little dose related toxicity.[9] Secondly, this dose of ranitidine was similar to the dose that was used in another placebo controlled trial.[18] And thirdly, recent investigations have established a correlation between cimetidine

serum concentration and gastric pH[19] and better control of gastric pH with larger doses of cimetidine.[5] Although no trials in the critically ill have been performed to establish if the same association between concentration and effect occur it was anticipated that larger doses of ranitidine would result in better control of gastric pH.

Many risk factors have been identified for the development of stress ulceration including respiratory failure, sepsis, peritonitis, major operative procedures, burns, trauma, renal failure and hypotension.[20] Severe head injury has also been reported to be associated with gastrointestinal haemorrhage secondary to hyperacidity.[21] Our data support this finding. Seven of the 12 cimetidine failures and one of the three ranitidine failures had either severe closed head injury or had undergone a neurosurgical procedure. In addition, two patients with spinal cord injuries, both in the ranitidine group, were poorly controlled. As has been reported by others, spinal cord injury may be associated with gastrointestinal bleeding secondary to hyperacitity.[22] In two patients admitted with sepsis or who became overtly septic (positive cultures, haemodynamic alterations) gastric pH was poorly controlled. Others have reported that sepsis may be associated with lack of control of pH and that neither antacid nor cimetidine is effective in this group.[23]

We were unable to show a correlation between the total number of risk factors and the ability to control gastric pH. Hastings *et al.*[20] were able to show a correlation between the number of risk factors and bleeding but did not address the question of risk factors and gastric pH. The presence of low gastric pH is only one of three potential factors that may contribute to gastrointestinal bleeding. The other two factors are back diffusion of acid and decreased perfusion of gastric mucosa as described by Skillman[24] and may account for this lack of association.

The decline in neurological status in 21.2 per cent of patients receiving cimetidine versus only three per cent of patients receiving ranitidine was not statistically significant. As mentioned earlier, it was not possible to distinguish between deleterious drug effect and the effects of other therapies or disease states. The failure to demonstrate a difference may be due to other potential complicating therapies as well as the fact that cimetidine's central nervous system toxicity is most problematic in patients with severe hepatic and renal disease.[2] These patients were excluded from our study and dosing adjustments were made for patients with moderate renal disease.

We advocate the stabilization of haemodynamic and respiratory abnormalities as early as possible. Further, we feel that the early administration of adequate nutrition, enterally or parenterally, is of utmost importance. At present, we administer ranitidine parenterally via continuous infusion in total parenteral nutrition (TPN) solution[25] at a dosage of 100 mg per 24 hours. This dosage is sufficient to control the gastric pH of most patients. If it is not effective, a dose of ranitidine or 200 mg or more is instituted. We use the lower dose initially as the data on the dosing of ranitidine is limited.

We have concerns regarding gastric hypersecretion following discontinuation of continuous high dose ranitidine and therefore advocate close monitoring of patient's gastric pH after discontinuing an infusion of ranitidine or switching to intermittent therapy.

Our study indicates that ranitidine is as effective and possibly more effective than cimetidine. This, however, only becomes apparent and significant when poor control of pH, defined as greater than 25 per cent of pH readings less than five, is used as the criteria for the definition of superior efficacy for ranitidine. As previously stated, ranitidine is four to ten times as potent as cimetidine and we chose to use the lower end of the spectrum and assume ranitidine to be only four times as potent as cimetidine. We do, however, feel that ranitidine is a superior agent because of its lack of interference in the metabolism of other drugs used in the critically ill. Ranitidine is well tolerated but the most effective regimen remains to be defined. We must emphasize that upon discontinuation of the drug or when switching from continuous infusion to intermittent injection that patients be monitored closely to assess the development of possible gastric hypersecretion.

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References

1 *McElwee HF, Sirenek KR, Levine BA.* Cimetidine affords protection equal to antacids in prevention of stress ulceration following thermal injury. Surgery 1979; 86: 620–6.

2 *Freston JW.* Cimetidine. Ann Intern Med 1982; 97: 573–80.

3 *Khan F, Parakh A, Patel S, Chitkura R, Rehman M, Goyal R.* Results of gastric neutralization with hourly antacids and cimetidine in 320 intubated patients with respiratory failure. Chest 1981; 79: 409–12.

4 *Priebe JH, Skillman JJ, Bushnell LS, Long PC, Silen W.* Antacid versus cimetidine in preventing acute gastrointestinal bleeding. N Engl J Med 1980; 302: 426–30.

5 *Stothert JC, Simonowitz DA, Dellinger EP et al.* Randomized prospective evaluation of cimetidine and antacid control of gastric pH in the critically ill. Ann Surg 1980; 192: 189–74.

6 *Kimelblatt BJ, Cerra FB, Calleri G, Berg MJ, McMillen MA, Schentag JJ.* Dose and serum concentration relationships in cimetidine-associated mental confusion. Gastroenterology 1980; 78: 791–5.

7 *Freston JW.* Cimetidine. Ann Intern Med 1982; 97: 728–34.

8 *Feely J, Wilkinson GR, McAllister CB, Wood AJJ.* Increased toxicity and reduced clearance of lidocaine by cimetidine. Ann Intern Med 1982; 96: 592–4.

9 *Brogden RN, Carmine AA, Heel RC et al.* Ranitidine: a review of its pharmacology and therapeutic use in peptic ulcer disease and other allied diseases. Drugs 1982; 24: 267.

10 *Danilewitz M, Tim LO, Hirschowitz B.* Ranitidine suppression of gastric hypersecretion resistant to cimetidine. N Engl J Med 1982; 306: 20–2.

11 *Spenney JG, Hirschowitz BI.* Cimetidine for prevention of acute gastrointestinal bleeding (letter). N Engl J Med 1981; 303: 108.

12 *Schentag JJ, Cerra FB, Calleri GM, Leising ME, French MA, Bernhard H.* Age, disease and cimetidine disposition in healthy subjects and chronically ill patients. Clin Pharmacol Ther 1981; 29: 737–43.

13 *Russel JA, Ostro M, Soldin SJ, Mahon WA.* Pharmacokinetics and pharmacodynamics of intravenous cimetidine in the ICU. Abstract. Presented at Royal College of Physicians and Surgeons Conference Annual Meeting, Calgary, 1983.

14 *Moore RA, Feldman S, Treuting J, Bloss R, Dudrick SJ.* Cimetidine and parenteral nutrition. J Parenter Enter Nutr 1981; 5: 62–3.

15 *Wallace WA, Orr CME, Bearn AR.* Perforation of chronic peptic ulcers after cimetidine. Br Med J 1977; 2: 685–6.

16 *Gill MJ, Saunders JB.* Perforation of chronic peptic ulcers after cimetidine. Br Med J 1977; 2: 1149.

17 *Hoste P, Ingels J, Elewant A, Bartier F.* Duodenal perforation after cimetidine. Lancet 1978; 1: 666.

18 *Vandenberg B, VanBlankenstein M.* The prevention of stress induced upper gastrointestinal bleeding by ranitidine in critically ill patients. *In*: Misiewicz JJ, Wormsley KC, eds. The clinical use of ranitidine. Oxford: Medicine Publishing Foundation 1982; 263: 8.

19 *Pancorbo S, Bubrick MP, Chin TWF, Miller KW, Onstad G.* Cimetidine dynamics after repeated intravenous injection. Clin Pharmacol Ther 1984; 35: 50–4.

20 *Hastings PR, Skillman JJ, Bushnell LS, Silen W.* Antacid titration in the prevention of acute gastrointestinal bleeding: a controlled randomized trial in 100 critically ill patients. N Engl J Med 1978; 298: 1041–5.

21 *Gudeman SK, Wheeler CB, Miller JD, Halloran LG, Becker DP.* Gastric secretory and mucosal injury response to severe closed head injury. Neurosurgery. 1983; 12: 175–9.

22 *Epstein N, Hood DC, Ransohoff J.* Gastrointestinal bleeding in patients with spinal cord trauma. J Neurosurg 1981; 54: 16–20.

23 *Martin LF, Max MH, Polk Jr HC.* Failure of gastric pH control by antacids or cimetidine in the critically ill: a valid sign of sepsis. Surgery 1980; 88: 59–68.

24 *Skillman JJ, Silen W.* Stress ulceration in the acutely ill. Ann Rev Med 1976; 27: 9–22.

25 *Walker SE, Bayliff CD.* Stability of ranitidine hydrochloride in total parenteral nutrition solution. In Press. Am J Hosp Pharm 1986.

Résumé

L'efficacité relative d'un traitement intraveineaux à la cimetidine et ranitidine dans le contrôle pH gastrique est étudiée chez 100 patients des soins intensifs. Cette étude prospective est à double insu et randomisée. Le nombre total des mesures du pH gastrique ainsi que le nombre des mesures du pH inférieur à cinq était enregistré. Les patients ont reçu soit de la cimetidine soit de la ranitidine en perfusion continue avec des ajustements de dosage pour les patients en insuffisance rénale. Des antacides ont été administrés chaque fois que le pH gastrique était inférieur à cinq. Il n'y avait aucune différence dans le nombre de patient qui ont présenté au moins un seul pH gastrique inférieur à cinq. Il y avait cependant une grande proportion de patients dans le groupe cimetidine pour qui les déterminations d'un pH gastrique inférieur à cinq étaient de ≥10, ≥15, ≥20, et ≥25 pour cent. Cette différence entre les deux groupes n'était statistiquement significative que pour les déterminations ≥25 pour cent. Les médicaments étaient bien tolérés. La ranitidine était aussi efficace que la cimétidine et possiblement plus dans le contrôle du pH gastrique.