Randomized Prospective Evaluation of Cimetidine and Antacid Control of Gastric pH in the Critically Ill

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One hundred forty-four critically ill patients admitted to an intensive care setting were randomly assigned to cimetidine or antacid treatment groups. Gastric pH was monitored hourly. One hundred twenty-three (85%) patients demonstrated a fall in pH to <4 and were considered to require prophylaxis. Prophylaxis was considered adequate if the measured pH could then be maintained at ≥4. Fifty-eight patients received antacids alone, the average requirement being 41 cc/hour. Sixty-five patients received cimetidine. Seventeen (26%) of the cimetidine prophylaxis patients failed to raise their pH and were then placed on hourly administration of antacid with successful elevations of pH to ≥4 in all cases on an average supplementary dose of 53 cc/hour. Risk factors, including sepsis, hypotension, head injury, respiratory failure, degree of trauma, and age, were not statistically different in the two treated groups. Using these same criteria, responders to cimetidine could not be differentiated from nonresponders. All patients were protected from significant stress bleeding while on this study. Significant complications of either treatment were minimal. Antacids offered consistent protection against gastric acidity and were 100% effective. A routine schedule of 300 mg every six hours of cimetidine was effective in only 47% of patients, and the maximum dose of cimetidine was effective in only 74% of patients. Hourly measurement of intragastric pH is required for monitoring the response to prophylaxis of stress bleeding in severely ill patients.

THE PREVENTION OF STRESS ulceration and subsequent bleeding in critically ill or traumatized patients is the end point of prophylaxis.[15] Maintenance of gastric pH to greater than or equal to 3.5 is thought to be an effective means of achieving this end point.[24] Morbidity and mortality secondary to stress ulceration has been documented following multiple trauma, sepsis, renal failure, head injury, and burns.[1,3,19,26] Proponents of prophylaxis have advocated the use of H_2 receptor antagonists or antacids.[4,6,7,14]

Cimetidine, a recently developed H_2 blocking histamine analog, has been proposed as a safe, reliable, and easily administered agent which lowers gastric acidity and therefore might prevent development of stress ulceration.[2,11] Sporadic reports have shown its effectiveness and advocated its use as a prophylactic agent.[9,12,13,18,25] Our group has reported that cimetidine is not 100% effective, and suggested that careful monitoring should be performed if it is to be administered to critically ill patients.[16] Alternatively, several reports have demonstrated the effectiveness of high dose antacids in the prevention of stress bleeding.[5,17,23]

This study was organized in an attempt to determine the relative effects on gastric pH of the administration of cimetidine and antacids in a prospective, randomized fashion.

Methods

One hundred ninety consecutive patients who were admitted to the Harborview Medical Center Surgical Intensive Care Unit (SICU) between October, 1978 and July, 1979 were incorporated into this study. All patients admitted to the intensive care unit with a diagnosis of gastrointestinal hemorrhage or those who failed to follow the outlined protocol were excluded from the study. One hundred forty-four patients were therefore available for analysis. All patients in this study were judged on clinical criteria to require the insertion of a nasogastric tube or have a gastrostomy prior to the randomization. Each patient remained NPO for the duration of the study. Patients underwent hourly monitoring of intragastric pH using pH sensitive paper. If the pH < 4 the patient was randomized to receive either cimetidine or antacid. The randomization process was based on a random number table in a blinded fashion.

Cimetidine was administered using an initial dosage level of 300 mg every six hours and was continued

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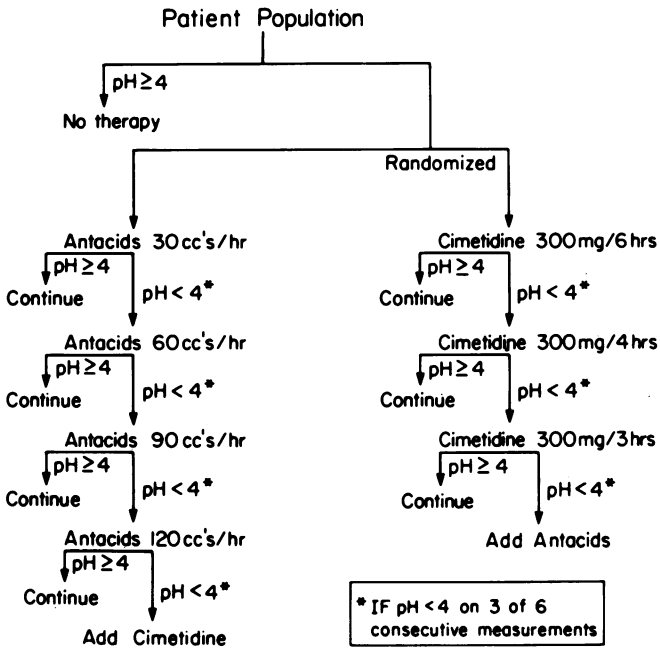

FIG. 1. Schematic representation of study protocol.

at this rate if the intragastric pH $\geq$ 4. If this pH was not achieved, the frequency of drug administration was increased to every four hours, and then to every three hours. The criteria for failure at a given dose was a pH < 4 for three out of six consecutive hourly measurements. The maximum dose was 2400 mg per 24 hours. Any patient who failed all three dosage levels then had antacid added to the cimetidine regimen according to the antacid protocol.

Patients admitted to the antacid therapy group, either by randomization or by failure of cimetidine, were treated with 30 cc of Mylanta II®* every hour via the nasogastric or gastrostomy tube. The tube was subsequently clamped for 30 minutes and then placed on suction for 30 minutes. If the pH < 4 at the end of three of six consecutive hourly time periods, the amount of Mylanta II was increased to 60 cc/hour. Similarly, if pH control failed at this level, the amount of antacid was increased to 90 cc/hour and finally 120 cc/hour if required. Any patient who required more than 120 cc/hour of antacid then had cimetidine added to the protocol. Any patient developing severe diarrhea (defined as greater than four loose stools per day) while on Mylanta II underwent substitution of the antacid with Alternagel.®†

All studies continued until the patient no longer required gastric decompression or was discharged from the intensive care unit as a result of improvement or death. Day-to-day clinical management was performed by an attending physician independent of the study protocol. A flow sheet depicting the study protocol is shown in Figure 1.

Prophylaxis failure was defined as a pH < 4 on three of six consecutive hourly measurements of gastric pH. Prophylaxis failure was also defined as the development of significant gastrointestinal bleeding requiring blood transfusions. Gastrointestinal bleeding was recorded if melena occurred or bright red bleeding from the nasogastric tube was found which would not clear with iced saline lavage.

All patients underwent hourly guiac measurements of their gastric aspirate. Due to the high rate of positivity (>90%) this was not considered as a criteria for significant gastric bleeding.

The major categories of patient illness or risk factors which were noted on admission of the patient to the intensive care unit or which developed while on the study were: 1) Abdominal trauma defined as an injury requiring laparotomy. 2) Major cardiovascular disease or heart failure diagnosed in those patients admitted to the intensive care unit following a myocardial infarction or in those who experienced arrhythmias requiring therapy. Myocardial trauma was also present in two patients. 3) The development of respiratory failure was defined as the requirement for mechanical ventilation with P/F ratio (Pa_{O_2}/FI_{O_2}) of less than 200. 4) The criteria for sepsis were one or more positive blood cultures associated with a clinical picture suggesting sepsis, sepsis proven by abdominal exploration or autopsy; exploration of a wound found to have necrotizing fascitis. 5) Neurologic injury consisted of an alteration in mental status for greater than 12 hours associated with an open or closed head wound. 6) Orthopedic injuries were considered as major risk factors when a long bone, pelvic, or spinal fracture was present. 7) Vascular injury was recorded as a risk factor only in the presence of an aortic injury or major vascular injury threatening the loss of an extremity. 8) Renal failure was defined as a serum creatinine value greater than 3 mg/dl on two successive occasions 24 hours apart. 9) Hepatic failure was defined as serum bilirubin greater than 5 mg/dl associated with hepatic enzyme elevation. 10) An addiction to alcohol or drug abuse was also used as a major risk factor. 11) Metastatic carcinoma or neoplasm receiving radiation or chemotherapy was also recorded as a major risk factor. 12) Any patient was considered significantly hypotensive if he sustained a blood pressure of less than 90 Torr for a

* Stuart Pharmaceuticals, Wilmington, Delaware.
† Wyeth Laboratories, Philadelphia, Pennsylvania.

period of greater than 30 minutes. 13) A prior history of gastric ulceration or peptic ulcer disease was also considered a possible risk factor.

In 14 randomly selected patients undergoing cimetidine therapy blood samples for determination of cimetidine blood levels were obtained and determined using the method of Randolph.[20]

Statistical analysis was performed using chi square analysis and Fischer's exact test.

Results

One hundred forty-four patients were included in this study. Fifty-eight patients were randomized to the antacid treatment group and 65 patients were randomized to the cimetidine therapy group. Forty-six patients were not included in these results because they met protocol criteria for less than 24 hours. Twenty-one patients required no therapy because of persistent pH ≥ 4. Forty-eight (74%) cimetidine recipients had the expected elevation of pH ≥ 4. Seventeen (26%) failed despite maximum dosage of cimetidine. All failures with cimetidine had antacids added and responded successfully. No failure of antacid therapy was seen in this study and therefore no patients crossed over from the antacid therapy group into the cimetidine therapy group.

Table 1 compares the antacid randomized group to the cimetidine randomized group. No significant difference exists between the groups in relation to the previously mentioned risk factors. Similarly, the two groups are quite comparable in age and sex ratio.

TABLE 1. *Comparison of Antacid and Cimetidine Prophylaxis Groups (No Significant Differences)*

	Antacid	Cimetidine
Number	58	65
Length of time studied	59.7 hrs	58.1 hrs
Age (average)	47	43
Sex		
male	41 (70.7)	48 (73.9)
female	17 (29.3)	17 (26.1)
Abdominal trauma	38 (65.5)	38 (58.5)
Cardiovascular disease	14 (24.1)	15 (23.1)
Respiratory failure	38 (65.5)	45 (69.2)
Sepsis	17 (29.3)	18 (27.7)
Neurologic injury	18 (31.0)	20 (30.8)
Orthopedic injury	25 (43.1)	29 (44.6)
Vascular injury	8 (13.8)	9 (13.8)
Renal failure	3 (5.2)	3 (4.6)
Hepatic failure	5 (8.6)	7 (10.7)
Addiction	14 (24.1)	17 (26.2)
Carcinoma	1 (1.7)	4 (6.1)
Hypotension	29 (50.0)	37 (56.9)
Ulcer history	9 (15.5)	6 (9.2)
Death	13 (22.4)	6 (9.2)

Numbers in parentheses indicate per cent.

TABLE 2. *Dosage Levels of Prophylaxis of Antacids and Cimetidine to Maintain pH ≥ 4*

Antacid 58 Patients		Cimetidine 65 Patients	
Dosage*	Number of Patients	Dosage schedule†	Number of Patients
30 cc/hr	40 (70)	Every 6 hours	22 (33.8)
60 cc/hr	14 (24)	Every 4 hours	22 (33.8)
90 cc/hr	1 (1)	Every 3 hours	4 (6.2)
120 cc/hr	3 (6)		
Failed	0	Failed	17 (26.2)

Numbers in parentheses indicate per cent.

* Average dosage for successful patients per hour: 41.4 cc/hr.

† Average dosage for successful patients on cimetidine per 24 hours: 1530 mg.

The twenty-one patients who maintained a gastric pH ≥ 4 required no prophylaxis and will not be dealt with further in this paper.

All patients responded to antacid therapy. Forty patients (70%) responded to 30 cc every hour to maintain gastric pH at the desired level. Only three patients required 120 cc per hour to maintain this level. The average dosage of Mylanta II for all patients combined was 41.4cc/hour. Of all patients receiving cimetidine, 34% responded to 300 mg every six hours. An additional 40% of the patients responded to administration at a dosage level of every four or every three hours. The average successful dose of cimetidine was 1530 mg/24 hours. A comparison of dosage responses to antacid and cimetidine is shown in Table 2. Cimetidine failure occurred in 17 patients (26%), who are classified as cimetidine nonresponders, despite an average dose of 2224 mg/24 hours. Two of these patients had the addition of antacid prior to obtaining maximal cimetidine doses (protocol error). The average antacid dose required for maintenance of gastric pH ≥ 4 in the cimetidine failure group was 53 cc/hr.

In an effort to characterize the cimetidine failures we examined the incidence of risk factors in this group (Table 3). Although there is a trend toward more hypotension ($p < .087$) and respiratory failure ($p < .067$) in this group, these are not statistically significant values. There was a larger number of females who failed to respond to cimetidine ($p < .05$).

Significant upper gastrointestinal bleeding, requiring transfusion occurred in only one patient. This patient was originally randomized to the cimetidine therapy group after sustaining a skull fracture with multiple orthopedic injuries. He required progressively increasing doses of cimetidine without achieving adequate control. At a dosage level of 2400 mg/24

TABLE 3. *Comparison of Cimetidine Responders and Nonresponders*

	Cimetidine Responders	Cimetidine Nonresponders (Failures)	Significance (p)
Number	48 (73.8)	17 (26.2)	
Age (average)	40	45	NS
Sex			
male	39 (81.2)	9 (52.9)	0.05*
female	9 (18.8)	8 (47.1)	
Abdominal trauma	30 (62.5)	8 (47.1)	NS
Cardiovascular disease	11 (22.9)	4 (23.5)	NS
Respiratory failure	30 (62.5)	15 (88.2)	0.067
Sepsis	14 (29.2)	4 (23.5)	NS
Neurologic injury	15 (31.2)	5 (29.4)	NS
Orthopedic injury	21 (43.8)	8 (47.1)	NS
Vascular injury	6 (12.5)	3 (17.6)	NS
Renal failure	3 (6.2)	0	NS
Hepatic failure	5 (10.4)	2 (11.8)	NS
Addiction	15 (31.2)	2 (11.8)	NS
Carcinoma	3 (6.2)	1 (5.9)	NS
Hypotension	24 (50.0)	13 (76.5)	0.087
Ulcer history	5 (10.4)	1 (5.9)	NS
Death	5 (10.4)	1 (5.9)	NS

Numbers in parentheses indicate per cent.

hours, the patient began to bleed through the nasogastric tube (36 hours after admission), and blood loss was estimated to be 600 cc's. At this time, his gastric pH was 1. Blood transfusion, iced saline lavage, and control of his gastric pH with 90 cc's/hour of Mylanta II resulted in cessation of hemorrhage. The patient went on to recover, maintained on antacids and cimetidine.

Of the 75 patients receiving antacids (antacid group plus cimetidine failures on antacid), five developed significant diarrhea (6.6%) which required changing of the antacid to Alternagel with resolution of the diarrhea. No significant episode of diarrhea was noted in the cimetidine treatment group. Twenty-seven (36%) of the 75 patients receiving antacid had an arterial pH of greater than 7.5 on one or more occasions during the study. This finding was noted in five (7.7%) of the 65 patients receiving cimetidine. Alteration in mental status was noted in one patient in the cimetidine therapy group. This reverted to normal after discontinuance of the drug. No difference between the degree of thrombocytopenia or of neutropenia in the antacid and cimetidine treatment groups was noted.

The serum half-life of cimetidine in 14 random traumatized patients was 2.5 ± 0.7 hours (mean $\pm$ SD) compared with 13 normal patients receiving cimetidine whose half life was 1.8 ± 0.8 hours. The β half-life was significantly prolonged in the traumatized patients ($p < .05$). Table 4 correlates serum cimetidine levels with simultaneously measured intragastric pH. In cimetidine responders gastric pH varied directly with serum cimetidine levels, up to a pH of 4. Some patients only responded at levels up to 2 mg/L, levels higher than this did not greatly affect the pH.

Discussion

The mechanism of stress ulceration following severe trauma or critical illness is not well understood. Factors associated with development of ulceration include gastric acidity, increased mucosal permeability, decreased or abnormal production of mucus, altered mucosal blood flow, and biliary reflux.[8,21,22] The major emphasis in the prophylaxis of gastrointestinal ulceration or bleeding has been directed at reduction of gastric acidity. This has been accomplished either by the use of intragastric antacid solutions or by the use of intravenous cimetidine.[4,5,18,24] Antacids reduce gastric pH by direct neutralization of acid. On the other hand, cimetidine decreases gastric pH by blocking the H_2 receptor site present in the stomach and reducing acid output. Previous reports suggest that cimetidine serum levels of 0.5 mg/L are sufficient to reduce acid output by over 50% and raise gastric pH ≥ 4.[10] Herrmann found that cimetidine or antacids were effective in maintaining gastric pH > 4 in 12 of 12 acutely ill patients over a 12 hour period. While acid output was not measured in this study, pH was. Thus we cannot say whether the levels of cimetidine achieved significantly lowered acid output in the population of ICU patients. It is clear, however, that whatever output reduction was achieved was insufficient to raise the pH consistently over 4. Since the concentration of acid appears to be more important than the amount as a determinant of stress ulceration, cimetidine may not be an ideal agent for prevention under these circumstances. In this study only eight of 17 patients with cimetidine blood levels ≤ 1.5 mg/L raised the gastric pH to 4 or more. Following a 300 mg dose of cimetidine blood levels ≥ 1.5 mg/L were obtained for only two hours. This data may suggest that cimetidine in traumatized

TABLE 4. *Correlation of Drug Levels with pH Control*

Drug Level mg/L	Number of Determinations	Number with pH ≥ 4	Per Cent ≥ 4
≤ 0.5	3	1	33
$0.5 < X < 1.0$	8	4	50
$1.0 < X < 1.5$	6	3	50
$1.5 < X < 2.0$	7	5	71
≥ 2.0	10	9	90

patients should be given by continuous infusion instead of in pulsed doses. It has also been suggested that cimetidine tends to increase mucosal blood flow, and to exert a cytoprotective effect.[12]

Whatever the mechanism, both cimetidine and antacids have been shown to reduce the incidence of stress ulceration and bleeding. In a previous group of unrandomized patients we have observed that cimetidine was only 76% effective in raising gastric pH $\geq$ 4 in the traumatized patient.[16] This study performed in a prospective, randomized fashion confirms this finding. Approximately one-quarter of the patients who received cimetidine in this series did not respond with a consistent increase of intragastric pH despite the administration of maximal doses. As suggested in Table 3, the cimetidine nonresponders were more predominantly female and possessed a trend towards more hypotension and respiratory failure than their counterparts in the cimetidine responding group. Although the combined risk factors and mortality were not significantly different in these two groups the drug resistance which they manifested might suggest that they were more ill in some way than the cimetidine responders. The higher incidence of females present in this group raises the possibility of a relationship between nonresponding and circulating estrogens, although this was not measured. However, sepsis was not directly related to the inability to respond to cimetidine, one patient who was undergoing continuous pH monitoring via an indwelling probe became severely septic and unresponsive to cimetidine therapy. This situation rapidly changed, however, when an intra-abdominal abscess was drained (Fig. 2). As shown in Figure 2, a marked response in intragastric pH was noted and cimetidine treatment became successful.

Comparison of the antacid and cimetidine groups are remarkably similar (Table 1). A slight trend is however noted with a greater number of deaths recorded for the antacid treated group (13 deaths) versus for the cimetidine group (6 deaths). Comparison of the mode of death between these two groups shows no difference. With the exception of a ruptured aortic aneurysm, all patients died of multisystem failure, sepsis, adult respiratory distress syndrome or cerebral trauma. No deaths resulted from antacid complications.

Antacid therapy using Mylanta II was found to be 100% effective. Although this method of prophylaxis is more time consuming from the nursing standpoint, and tended to promote diarrhea and alkalosis to a greater extent, the average daily pharmacy cost to each patient was found to be $4.60. Cimetidine, on the other hand, was only effective 75% of the time at an average daily cost of $21.60 for each patient.

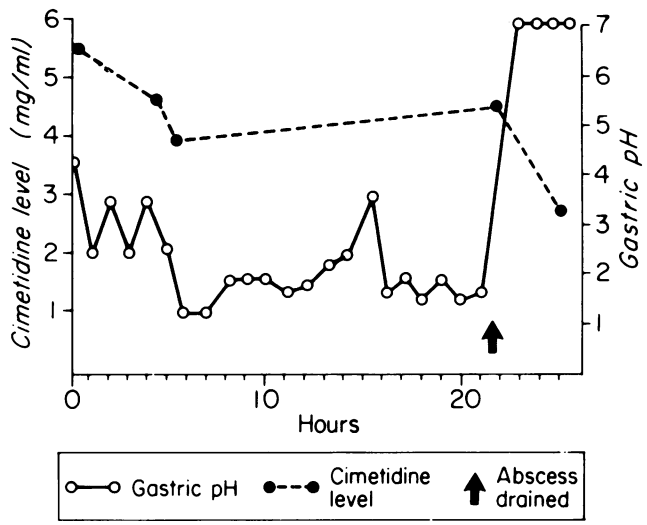

FIG. 2. Graphic representation of Cimetidine blood levels and gastric pH in a septic patient. Inadequate pH control is obtained with constant Cimetidine infusion at eight times the suggested minimum effective dose until drainage of an intra-abdominal abscess.

The results of this study suggest that antacids combined with continuous monitoring of intragastric pH is a more effective and cheaper mode of prophylaxis than cimetidine.

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