CLINICAL INVESTIGATION

A prospective study of simplified omeprazole suspension for the prophylaxis of stress-related mucosal damage

Phillips, Jeffrey O. PharmD, BCPS; Metzler, Michael H. MD, FCCM; Palmieri, Major Tina L. MD; Huckfeldt, Roger E. MD; Dahl, Nicola G. PharmD, BCPS

Critical Care Medicine: November 1996 - Volume 24 - Issue 11 - p 1793-1800

Abstract

Objectives

To determine the efficacy, safety, and cost of simplified omeprazole suspension in mechanically ventilated critically ill patients who have at least one additional risk factor for stress-related mucosal damage.

Design

Prospective, open-label study.

Setting

Surgical intensive care and burn unit at a university tertiary care center.

Patients

Seventy-five adult, mechanically ventilated patients with at least one additional risk factor for stress-related mucosal damage.

Interventions

Patients received 20 mL of simplified omeprazole suspension (containing 40 mg of omeprazole) initially, followed by a second 20-mL dose 6 to 8 hrs later, then 10 mL (20 mg) daily. Simplified omeprazole suspension was administered through a nasogastric tube, followed by 5 to 10 mL of tap water. The nasogastric tube was clamped for 1 to 2 hrs after each administration.

Measurements and Main Results

The primary outcome measure was clinically significant gastrointestinal bleeding determined by endoscopic evaluation, nasogastric aspirate examination, or heme-positive coffee ground material that did not clear with lavage, which was associated with at least a 5% decrease in hematocrit. Secondary efficacy measures were gastric pH measured 4 hrs after omeprazole was first administered, mean gastric pH after omeprazole was started, and the lowest gastric pH during omeprazole therapy. Safety-related outcomes included the occurrence rate of adverse events and pneumonia. No patient experienced clinically significant upper gastrointestinal bleeding after receiving omeprazole suspension. The 4-hr postomeprazole mean gastric pH was 7.1, the mean gastric pH after starting omeprazole was 6.8, and the mean lowest pH after starting omeprazole was 5.6. The occurrence rate of pneumonia was 12%. No patient in this high-risk population experienced an adverse event or a drug interaction that was attributable to omeprazole.

Conclusions

Simplified omeprazole suspension prevented clinically significant upper gastrointestinal bleeding and maintained gastric pH of >5.5 in mechanically ventilated critical care patients without producing toxicity.

(Crit Care Med 1996;24:1793-1800)

Key Words: gastrointestinal hemorrhage; omeprazole; intensive care units; mechanical ventilation; gastric mucosa; pH; prophylaxis

Patients with significant physiologic stress are at risk for stress-related gastric mucosal damage and subsequent upper gastrointestinal bleeding [1]. Risk factors that have been clearly associated with the development of stress-related mucosal damage are mechanical ventilation, coagulopathy, extensive burns, head injury, and organ transplant [2-6]. One or more of these factors are often found in critically ill, intensive care unit (ICU) patients. A recent cohort study challenges other risk factors previously identified, such as acid-base disorders, multiple trauma, significant hypotension, major surgery, multiple operative procedures, acute renal failure, sepsis, and coma [6]. Regardless of the risk type, stress-related mucosal damage results in significant morbidity and mortality. Clinically significant bleeding occurs in at least 20% of patients with one or more risk factors who are left untreated [7]. Of those patients who bleed, approximate 10% require surgery (usually gastrectomy), with a reported mortality rate of 30% to 50% [4,8]. Those patients who do not need surgery often require multiple transfusions and prolonged hospitalization. Prevention of stress-related upper gastrointestinal bleeding remains an important clinical goal.

In addition to general supportive care, the use of drugs to prevent stress-related mucosal damage is considered by many to be the standard of care [9]. However, general consensus is lacking about which drugs to use in this setting [7,10,11]. In two recent meta-analyses [12,13], antacids, sucralfate, and histamine-2-receptor (H_2)-antagonists were all found to be superior to placebo and similar to one another in preventing upper

gastrointestinal bleeding. Yet, prophylactic agents are withdrawn in 15% to 20% of patients in whom they are employed because of failure to prevent bleeding, or control pH [14-16], or because of adverse effects [10,17-20]. In addition, Smythe and Zarowitz [21] recently outlined the characteristics of an ideal agent for the prophylaxis of stress gastritis and concluded that none of the agents currently in use fulfill their criteria.

Omeprazole reduces gastric acid production by irreversibly inhibiting the hydrogen-potassium adenosine-triphosphatase of the parietal cell--the final common pathway for gastric acid secretion [22-24]. Because this drug maintains gastric pH control throughout the dosing interval and has a very good safety profile, it is a logical choice for stress ulcer prophylaxis. The absence of an intravenous or oral liquid dosage form in the United States, however, has limited the testing and use of omeprazole in the critical care patient population. In 1990, we used an extemporaneously prepared oral suspension of omeprazole to treat a patient who had developed clinically significant bleeding while receiving continuous-infusion cimetidine plus intragastric antacids. Subsequently, Barie et al. [25] described the use of omeprazole enteric-coated pellets administered through a nasogastric tube to control gastrointestinal hemorrhage in a critical care patient with multiple organ failure.

Our successful anecdotal experience led to the development and refinement of a dosage regimen for simplified omeprazole suspension of 40 mg, followed by a second 40-mg dose 6 to 8 hrs later, then a 20-mg daily dose administered at 0800 hrs. This regimen was subsequently tested in a small prospective evaluation of simplified omeprazole suspension for the prophylaxis of stress-related upper gastrointestinal bleeding [26]. The initial work led to this larger prospective evaluation. The objectives of this study were to determine the efficacy, safety, and cost of simplified omeprazole suspension in critical care patients who were clearly at risk for stress-related upper gastrointestinal bleeding. Rate of clinically significant bleeding and gastric pH control were the specific measures of efficacy. Safety considerations included occurrence of adverse events, drug interactions, and nosocomial pneumonia. The daily cost of care for simplified omeprazole suspension was calculated to provide a basis of comparison with other stress ulcer prophylaxis therapies.

MATERIALS AND METHODS

The study protocol was approved by the Institutional Review Board for the University of Missouri at Columbia.

Study Population.

All adult (>18 yrs old) patients admitted to the surgical intensive care and burn unit at the University of Missouri Hospital with an intact stomach, a nasogastric tube in place, and an anticipated ICU stay of at least 48 hrs were considered for inclusion in the study. To be included in the study, patients also had to have a gastric pH of <4, had to be

mechanically ventilated, and had to have one of the following additional risk factors for a minimum of 24 hrs after initiation of omeprazole suspension: head injury with altered level of consciousness; extensive burns (>20% body surface area); acute renal failure; acid-base disorder; multiple trauma; coagulopathy; multiple operative procedures; coma; hypotension for >1 hr; or sepsis. Sepsis was defined as the presence of invasive pathogenic organisms or their toxins in blood or tissues resulting in a systemic response that included two or more of the following: temperature of >38 degrees C or <36 degrees C; heart rate of >90 beats/min, respiratory rate of >20 breaths/min (or PaO_2 of <75 torr [<10 kPa]); white blood cell count of >12,000 or <4000 cells/mm^3; or >10% bands [27]. Patients in whom H_2-antagonist therapy had failed or who experienced an adverse event while receiving H_2-antagonist therapy were also included.

Patients were excluded from the study if they were receiving azole antifungal agents through the nasogastric tube; were likely to swallow blood (e.g., facial and/or sinus fractures, oral lacerations); had severe thrombocytopenia (platelet count of <30,000 cells/mm^3); were receiving enteral feedings through the nasogastric tube; or had a history of vagotomy, pyloroplasty, or gastroplasty. In addition, patients with a gastric pH of >4 for 48 hrs after ICU admission (without prophylaxis) were not eligible for participation. Patients who developed bleeding within the digestive tract that was not stress-related mucosal damage (e.g., endoscopically verified variceal bleeding or Mallory-Weiss tears, oral lesions, nasal tears due to placement of the nasogastric tube) were excluded from the efficacy evaluation and categorized as having nonstress-related mucosal bleeding. The reason for this exclusion is the confounding effect of nonstress-related mucosal bleeding on efficacy-related outcomes, such as the use of nasogastric aspirate inspection to define clinically significant upper gastrointestinal bleeding.

Study Drug Administration.

Simplified omeprazole suspension was prepared for administration by the patient's nurse using the following instructions: a) Empty the contents of one or two 20-mg omeprazole capsule(s) into an empty 10-mL syringe (with 20-gauge needle in place) from which the plunger has been removed (Omeprazole delayed-release capsules, Merck & Co, West Point, PA). b) Replace the plunger and uncap the needle. c) Withdraw 10 mL of 8.4% sodium bicarbonate solution, or 20 mL if 40 mg given (Abbott Laboratories, North Chicago, IL). The resultant preparation should contain 2 mg omeprazole/mL of 8.4% sodium bicarbonate. d) Allow the enteric-coated pellets of omeprazole to completely break down (approximate 30 mins, agitation is helpful). The omeprazole in the resultant preparation is partially dissolved and partially suspended. The preparation should have a milky white appearance with fine sediment and should be shaken before using. Do not administer with acidic substances.

We have performed a high-pressure liquid chromatography study that has demonstrated that this preparation of simplified omeprazole suspension maintains >90% potency for 7 days at room temperature. This preparation remains free of bacterial and fungal contamination for 30 days when stored at room temperature.

The initial dose of simplified omeprazole suspension was 40 mg, followed by a second 40-mg dose 6 to 8 hrs later, then a 20-mg daily dose administered at 0800 hrs (on the following day). Each dose was administered through the nasogastric tube. The nasogastric tube was then flushed with 5 to 10 mL of tap water and clamped for at least 1 hr. Omeprazole therapy was continued until there was no longer a need for stress ulcer prophylaxis (usually after the nasogastric tube was removed and the patient was taking water/food by mouth, or after the patient was removed from mechanical ventilation).

Primary Outcome Measures.

The primary outcome measure in this study was the rate of clinically significant stress-related mucosal bleeding, defined as endoscopic evidence of stress-related mucosal bleeding or bright red blood per nasogastric tube that did not clear after a 5-min lavage, or persistent Gastroccult (SmithKline Diagnostics, Sunnyville, CA)-positive coffee ground material for 4 consecutive hrs that did not clear with lavage (at least 100 mL) and produced at least a 5% decrease in hematocrit.

Secondary Outcome Measures.

The secondary efficacy measures were gastric pH, measured 4 hrs after omeprazole was administered, mean gastric pH after starting omeprazole, and lowest gastric pH during omeprazole administration. Gastric pH was measured immediately after aspirating gastric contents through the nasogastric tube. We used pH paper (pHydrion improved pH papers, Microessential Laboratory, Brooklyn, NY) to measure gastric aspirate pH. The pH range of the test strips was 1 to 11, in increments of 1 pH unit. Gastric pH was measured before the initiation of simplified omeprazole suspension therapy, immediately before each dose, and every 4 hrs between doses.

Other secondary outcome measures were occurrence rate of adverse events (including drug interactions) and pneumonia. Any adverse event that developed during the study was recorded. Pneumonia was defined using indicators adapted from the Centers for Disease Control and Prevention definition of nosocomial pneumonia [28]. According to these criteria, a patient who has pneumonia is one who has rales or dullness to percussion on physical examination of the chest, or has a chest radiograph that shows new or progressive infiltrate(s), consolidation, cavitation, or pleural effusion, and has at least two of the following present: new purulent sputum or changes in character of the sputum; an organism isolated from blood culture; fever or leukocytosis; or evidence of infection from a protective specimen brush or bronchoalveolar lavage.

Patients who met the criteria for pneumonia and were receiving antimicrobial agents for the treatment of pneumonia were included in the pneumonia occurrence rate figure. These criteria were also used as an initial screen before the first dose of study drug was administered to determine if pneumonia was present before the start of simplified omeprazole suspension.

Cost of Care Analysis.

A pharmacoeconomic evaluation of stress ulcer prophylaxis using simplified omeprazole suspension was performed. The evaluation included total drug cost (acquisition, preparation, and administration), actual costs associated with adverse events (e.g., psychiatry consultation for mental confusion), and costs associated with drug failure (e.g., clinically significant upper gastrointestinal bleeding). Total drug cost was calculated by adding the average institutional costs of omeprazole 20-mg capsules, 50-mL sodium bicarbonate vials, syringes, and needles; nursing time (drug administration, pH monitoring); pharmacy time (drug preparation, delivery, etc.); and disposal costs. Costs associated with clinically significant upper gastrointestinal bleeding included endoscopy charges and accompanying consultation fees, procedures required to stop the bleeding (e.g., surgery, hemostatic agents, endoscopic procedures), increased hospital length of stay (as assessed by the attending physician), and cost of drugs used to treat the gastrointestinal bleeding.

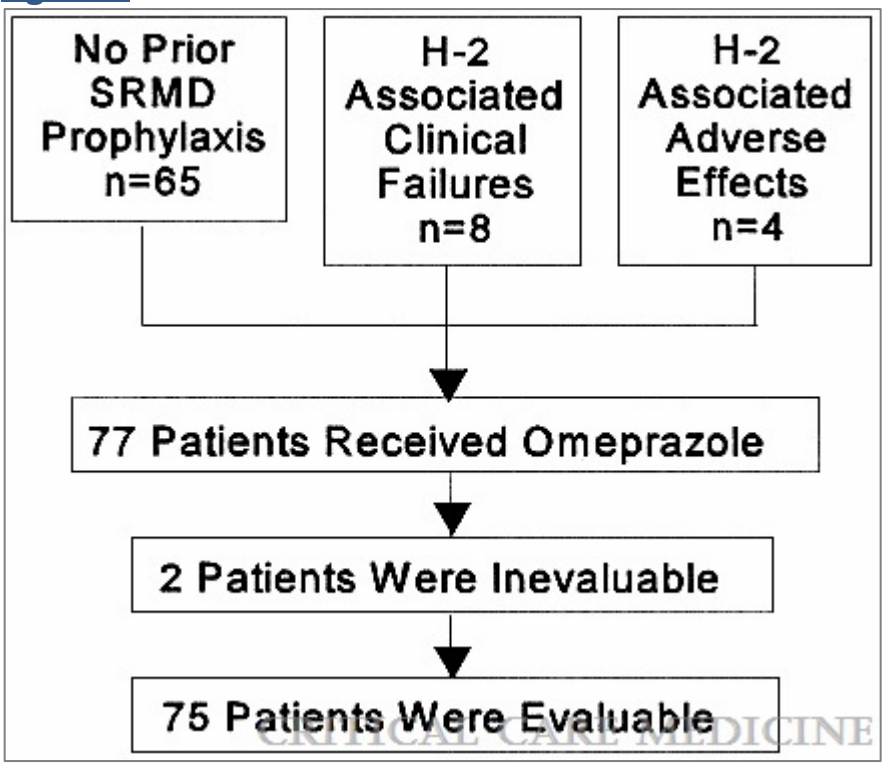
Statistical Analysis.

The paired t-test (two-tailed) was used to compare gastric pH before and after simplified omeprazole suspension administration and to compare gastric pH before simplified omeprazole suspension administration with the mean and lowest gastric pH value measured after beginning omeprazole.

RESULTS

Seventy-seven patients met the inclusion and exclusion criteria and received simplified omeprazole suspension Figure 1. Two patients were excluded from the efficacy evaluation because the protocol for omeprazole administration was not followed. In one case, the omeprazole enteric-coated pellets had not completely broken down before the administration of the first two doses, which produced an erratic effect on gastric pH. The gastric pH increased to >6 as soon as the patient was given a dose of simplified omeprazole suspension (in which the enteric-coated pellets of omeprazole had been allowed to completely break down).

Figure 1:



Overall patient enrollment scheme. SRMD, stress-related mucosal damage; H-2, histamine type 2.

The reason for the second exclusion was that nasogastric suctioning was not turned off after the omeprazole dose was administered. This oversight resulted in a transient effect on gastric pH. The suction was turned off with subsequent omeprazole doses, and control of gastric pH was achieved. Two patients were considered efficacy failures because omeprazole failed to maintain adequate gastric pH control on the standard omeprazole 20 mg/day maintenance dose. When the omeprazole dose was increased to 40 mg/day (40 mg once/day or 20 mg twice/day), gastric pH was maintained at >4 in both patients. These two patients were included in the safety and efficacy evaluations, including the gastric pH analysis. After the two patients were declared efficacy failures, their pH values were no longer followed for study purposes.

The ages of the remaining 75 patients ranged from 18 to 87 yrs; 42 patients were male and 33 were female. All patients were mechanically ventilated during the study. Table 1 shows the frequency of risk factors for stress-related bleeding that were exhibited by the patients in this study. The most common risk factors in this population were mechanical ventilation and major surgery. The range of risk factors for any given patient was 2 to 10, with a mean of 3 +/- 1 (SD). Five patients enrolled in the study had developed clinically significant bleeding while receiving continuous infusions of ranitidine (150 mg/24 hrs) or cimetidine (900 mg/24 hrs). In all five cases, the bleeding subsided and the gastric pH increased to >5 within 36 hrs after initiating omeprazole

therapy. Three patients were enrolled after having developed two consecutive gastric pH values of <3 while receiving an H_2-antagonist (in the doses outlined above). In all three cases, gastric pH increased to >5 within 4 hrs after omeprazole therapy was initiated. Four other patients were enrolled in this study after experiencing confusion (n = 2) or thrombocytopenia (n = 2) during H_2-antagonist therapy. Within 36 hrs of switching therapy, these adverse events resolved.

Table 1:

Mechanical ventilation	75
Major surgery	61
Multiple trauma	35
Head injury	16
Hypotension	14
Renal failure	14
Sepsis	14
Multiple surgery	12
Acid-base disorders	10
Coma	4
Liver failure	2
Burn	2

Risk factors present in patients in this study (n = 75)

Stress-Related Mucosal Bleeding and Mortality.

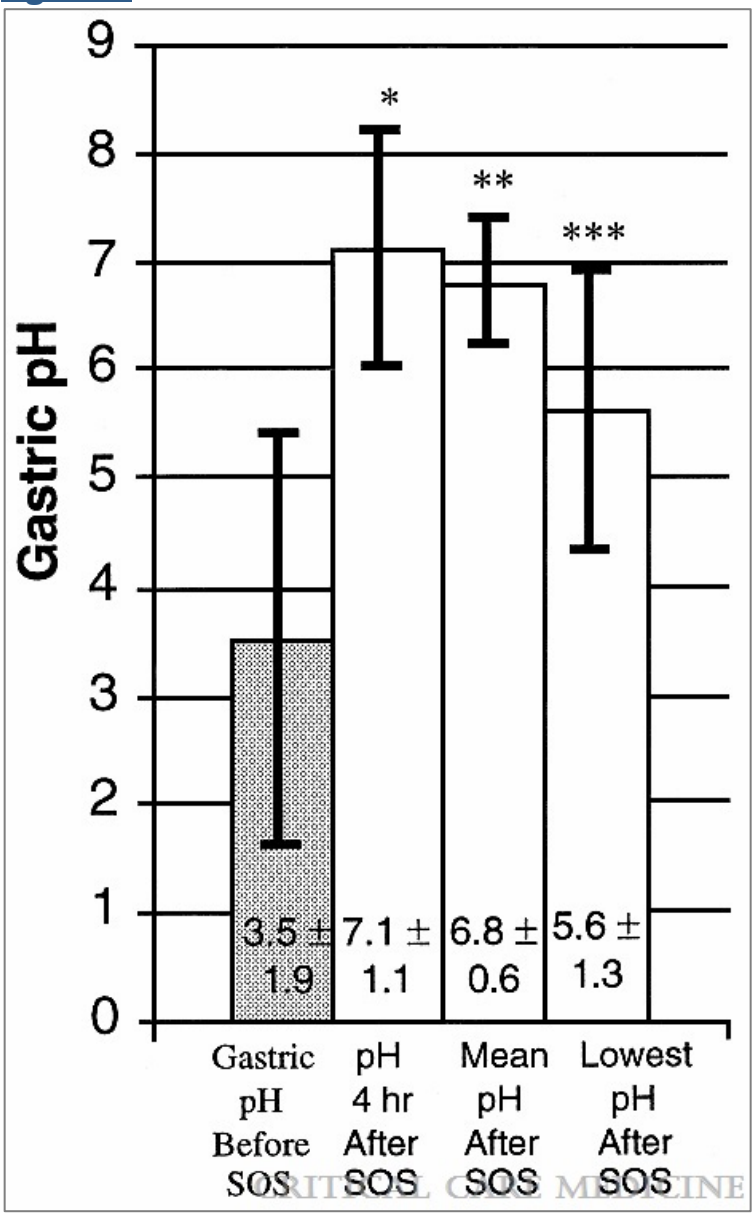
None of the 65 patients who received simplified omeprazole suspension as their initial prophylaxis against stress-related mucosal bleeding developed overt or clinically significant upper gastrointestinal bleeding. In four of the five patients who had developed upper gastrointestinal bleeding before study entry, bleeding diminished to the presence of occult blood only within 18 hrs of starting omeprazole suspension; bleeding stopped in all patients within 36 hrs. The overall mortality rate in this group of critically ill patients was 11%. No death was attributable to upper gastrointestinal bleeding or the use of simplified omeprazole suspension.

Gastric pH.

The mean +/- SD preomeprazole gastric pH was 3.5 +/- 1.9. Within 4 hrs of omeprazole administration, gastric pH increased to 7.1 +/- 1.1 Figure 2; this difference was statistically significant ($p < .001$). The differences between pre-omeprazole gastric pH

and the mean and lowest gastric pH measurements during omeprazole administration (6.8 +/- 0.6 and 5.6 +/- 1.3, respectively) were also statistically significant (p < .001).

Figure 2:



Gastric pH before and after simplified omeprazole suspension (SOS). Values are mean +/- SD. *p < .001 (pH before vs. 4 hrs after); **p < .001 (vs. mean pH after SOS); ***p < .001 (vs. lowest pH after SOS), by two-tailed paired t-test.

Safety.

Simplified omeprazole suspension was well tolerated in this group of critically ill patients. Only one patient with sepsis experienced an adverse event that may have

been drug related--thrombocytopenia. However, the platelet count continued to decrease after omeprazole was stopped. The platelet count then returned to normal despite reinstitution of omeprazole therapy. Of note, one patient on a jet ventilator continuously expelled all liquids placed in her stomach up and out through her mouth, and thus, was unable to continue on omeprazole. No clinically significant drug interactions with omeprazole were noted during the study period. Metabolic alkalosis is a potential concern in patients receiving sodium bicarbonate. However, the amount of sodium bicarbonate in simplified omeprazole suspension is small (approximate 12 mEq/10 mL), and metabolic alkalosis was not a problem in this population.

Pneumonia.

Pneumonia developed in nine (12%) patients receiving simplified omeprazole suspension. Pneumonia was present in an additional five patients before the start of omeprazole therapy.

Pharmacoeconomic Evaluation.

The average length of treatment was 9 days. The cost of care data are listed in Table 2. There were no costs to add from toxicity associated with simplified omeprazole suspension. Since two of 75 patients required 40 mg of simplified omeprazole suspension daily to adequately control gastric pH, the acquisition/preparation cost should reflect the extra drug required for these two patients. The additional 20 mg of omeprazole with vehicle (needed in 2/75 patients) adds approximately eight cents per day to the cost of care for each of the 75 patients. Therefore, the daily cost of care for simplified omeprazole suspension in the prophylaxis of stress-related mucosal bleeding was $11.12.

Table 2:

		Per Day	Total
Omeprazole (day 1)			
Product acquisition cost	40 mg load × 2 (5.87/dose)	11.74	11.74
Ancillary product	Materials for solution preparation	0.41	0.41
Miscellaneous	Syringe, needle, waste disposal	0.20	0.40
SOS preparation time (R.N.)	6 mins to prepare 100-mg vial	2.00	4.00
R.N. time ($20/hr)	21 mins/day (includes pH monitoring)	7.00	7.00
Omeprazole (days 2 to 9)			
Product acquisition cost	20 mg/day	2.93	23.47
Ancillary product	Materials for solution preparation	0.41	0.82
Miscellaneous	Syringe, needle, waste disposal	0.20	1.60
SOS preparation time (R.N.)	6 mins	2.00	4.00
R.N. time ($20/hr)	18 mins/day (includes pH monitoring)	6.00	48.00
Two of 75 patients required 40 mg of simplified omeprazole solution/day (days 2 to 9)			0.65
No additional cost for adverse effects or for failure			
Total			100.09
Simplified omeprazole solution cost/day ($)			11.12

SOS, simplified omeprazole solution; RN, registered nurse.
[a]The average length of treatment was 9 days. Cost of care was calculated from these data.

Pharmacoeconomic evaluation of omeprazole, cost of care[a]

DISCUSSION

Stress ulcer prophylaxis has become routine therapy in ICUs in most hospitals [29,30]. Controversy remains regarding pharmacologic intervention to prevent stress-related bleeding in critical care patients [31]. It has been suggested that the occurrence rate and risk of gastrointestinal bleeding has decreased in the last 10 yrs and drug therapy may no longer be needed [6,13,32]. This reasoning is not supported by a recent placebo-controlled study. Martin et al. [7], conducted a prospective, randomized, double-blind, placebo-controlled comparison of continuous-infusion cimetidine and placebo for the prophylaxis of stress-related mucosal damage. The study was terminated early because of excessive bleeding-related mortality in the placebo group. It appears that the natural course of stress-related mucosal damage in a patient at risk who receives no prophylaxis has not changed significantly. In the placebo group, 33% of patients developed clinically significant bleeding, 9% required transfusion, and 6% died with bleeding-related complications. In comparison, 14% of cimetidine-treated patients developed clinically significant bleeding, 6% required transfusions, and 1.5% died with bleeding-related complications; the difference in bleeding rates between treatment groups was statistically significant. This study [7] clearly demonstrated that continuousinfusion cimetidine reduced morbidity in critical care patients. Although these data were used to support the approval of continuous-infusion cimetidine by the Food and Drug Administration for stress ulcer prophylaxis, H_2-antagonists, in our opinion, fall short of being the optimal pharmacotherapeutic agents for prevention of stress-related mucosal bleeding.

Another controversy surrounding stress ulcer prophylaxis is which drug to use. In addition to the various H_2-antagonists, antacids and sucralfate are other treatment options for the prophylaxis of stress-related mucosal damage. An ideal drug in this setting should possess the following characteristics: prevent stress ulcers and their complications, be devoid of toxicity, lack drug interactions, be selective, have minimal associated costs (such as personnel time and materials), and be easy to administer [21].

Some authors [21] have suggested that sucralfate is possibly the ideal agent for stress ulcer prophylaxis. Randomized, controlled studies support the use of sucralfate [33-36], but data on critical care patients with head injury, trauma, or burns are limited. In addition, a recent study comparing sucralfate and cimetidine plus antacids for stress ulcer prophylaxis reported clinically significant bleeding in 3 (6%) of 48 sucralfate-treated patients, one of whom required a gastrectomy [35]. In the study performed by Driks and co-workers [36] that compared sucralfate to conventional therapy (H_2-antagonists, antacids, or H_2-antagonists plus antacids), the only patient whose death was attributed to stress-related upper gastrointestinal bleeding was in the sucralfate arm.

H_2-antagonists fulfill many of the criteria for an ideal stress ulcer prophylaxis drug. Yet, clinically significant bleeds can occur during H_2-antagonist prophylaxis [7,12,37], and

adverse events are not uncommon in the critical care population [10,17-20]. One reason proposed for the therapeutic failures of H_2-antagonist therapy is a lack of pH control throughout the treatment period [14]. Although the precise pathophysiologic mechanism(s) involved in stress ulceration are not clearly established, the high concentration of hydrogen ions in the mucosa [38] or gastric fluid in contact with mucosal cells appears to be an important factor. A gastric pH of >3.5 has been associated with a lower occurrence rate of stress-related mucosal damage and bleeding [3,5,39,40]. Several studies [14-16] have shown that H_2-antagonists, even in maximal doses, do not reliably or continuously increase intragastric pH above commonly targeted levels (3.5 to 4.5). This unreliability is true especially when used in fixed-dose bolus regimens [14-16]. In addition, gastric pH values tend to trend downward with time when using a continuous infusion of H_2-antagonists, which may be the result of tachyphylaxis [14,41]. Omeprazole has been shown [42] to reduce acidity more effectively than H_2-antagonists, and pH control is maintained for at least 24 hrs after the dose. The mean gastric pH in our study was 6.8 and the lowest gastric pH (mean) after beginning prophylaxis with omeprazole was 5.6. The predictable and sustained pH control that omeprazole provides may prove to be an advantage over H_2-antagonists [32].

The initial reports of increased frequency of pneumonia in patients receiving stress ulcer prophylaxis with agents that increase gastric pH has influenced the pharmacotherapeutic approach to management of critical care patients. However, several recent studies [29,43-45], a meta-analysis [30], and a closer examination of the studies that initiated the increased pH-associated pneumonia hypothesis [32] cast doubt on a causal relationship. The relationship between pneumonia and antacid therapy is much stronger than for H_2-antagonists. The shared effect of antacids and H_2-antagonists on gastric pH seems an irresistible common cause explanation for nosocomial pneumonia observed during stress ulcer prophylaxis. However, there are important differences between these agents that are not often emphasized [46]. When antacids are used exclusively to control pH in the prophylaxis of stress-related upper gastrointestinal bleeding, large volumes are needed. Volume, with or without subsequent reflux, may be the underlying mechanism(s) promoting the development of pneumonia in susceptible patient populations, rather than the increased gastric pH. The rate of pneumonia in our study (12%) was not unexpected in this critical care population and compares with sucralfate, which does not significantly increase gastric pH [44,45].

Because stress ulcer prophylaxis is frequently employed in the ICU, it is essential from both a clinical and economic standpoint to optimize the pharmacotherapeutic approach. In an attempt to identify optimal therapy, cost of care becomes an issue. All treatment costs should be considered, including the costs of treatment failures and drug-related adverse events. While the actual number of failures resulting in mortality is low, morbidity (e.g., bleeding that requires blood transfusion) can be high, even though its association with the failure of a specific drug is often unrecognized. The cost of care using simplified omeprazole suspension for the prevention of stress-related mucosal damage in our study was $11.12/day, less than the daily costs for acquisition, preparation, and administration of intravenous H_2-antagonists or sucralfate. The

majority of omeprazole cost was related to preparation, administration, and monitoring time.

A recent cost-effectiveness analysis [47] concluded that the cost of prophylaxis in patients at low risk of stress-related hemorrhage may be prohibitive, but that cost savings could be recognized for very high-risk patients. As was noted earlier, patients enrolled in this study had a very high risk of upper gastrointestinal hemorrhage. Another factor increasing cost which was identified by Ben-Menachem et al. [47] was prophylaxis-induced nosocomial pneumonia. The incidence of pneumonia in our study was similar to that reported for patients receiving non-acid suppressing prophylaxis. We performed a cost-effectiveness analysis utilizing the data provided by Ben-Menachem et al [47]. This analysis demonstrated a cost savings of approximately $170 per patient when omeprazole suspension was employed for stress-ulcer prophylaxis in our group of patients. Our analysis assumed a 90% risk reduction with omeprazole suspension prophylaxis, a 12% risk of stress-related hemorrhage and calculated the cost of omeprazole suspension as per the method of Ben-Menachem et al. [47] at $39.06 per 7 days.

The methodological accuracy of pH paper has been called into question [48,49]. There are potential inaccuracies related to visual color comparison. However, Dobkin et al. [49] found the ability of nurses to read the pH of standard solutions with pH paper to be excellent (100% sensitive and specific). Other reports [50,51] found little discrepancy between pH paper and meter when parenteral H sub 2-antagonists are used. In the study by Eisenberg et al. [50], a poor correlation was found when antacids were evaluated, and a correlation coefficient of 1 was found when H_2-antagonists were employed. We have reviewed the literature and considered omeprazole's central mechanism of action (unlike antacids), the high pH values previously achieved with omeprazole suspension in this setting, and the actual measurement accuracy required to make sound clinical decisions. We think the measurement accuracy of pH paper is sufficient to achieve our study objectives.

In this prospective investigation, simplified omeprazole suspension proved to be a safe and effective therapy for the prevention of clinically significant stress-related mucosal bleeding in critical care patients. The contribution of many risk factors to stress-related mucosal damage has recently been challenged [6]. All of the patients in this study had at least one risk factor that has clearly been associated with stress-related mucosal damage--mechanical ventilation. We believe that previous trials and data from a recently published study [7] show that stress ulcer prophylaxis is of proven benefit in patients at risk. Therefore, we felt it was unethical to include a placebo group in this study. No clinically significant upper gastrointestinal bleeding occurred during simplified omeprazole suspension therapy. Gastric pH was maintained >4 on omeprazole 20 mg/day in 73 of 75 patients. No adverse events or drug interactions associated with omeprazole were encountered. The entericcoated pellets of omeprazole must be allowed to completely break down in the suspension vehicle before administration.

This study did not directly evaluate the comparable costs of care for other agents commonly used for the prophylaxis of stress-related upper gastrointestinal bleeding. As mentioned previously, total cost of care for prophylaxis of stress-related upper gastrointestinal bleeding involves not only drug, supplies, and labor costs, but also the actual costs of failure and adverse effects. Such data can only come from a comparative trial. The costs of drug acquisition, preparation, and administration for some of the traditional agents used in the prophylaxis of stress-related upper gastrointestinal bleeding are listed in Table 3.

Table 3:

		Per Day
Ranitidine (days 1 to 9)[a]		
Product	150 mg/24 hrs	4.99
Ancillary product (1)	Piggyback	0.59
Ancillary product (2)	Microtubing	2.00
Miscellaneous	Syringe, needle, waste disposal	.20
R.N. time ($20/hr)	20 mins/day (includes pH monitoring)	6.67
Pharmacy time	Pick-up order, prepare, check, label, deliver	2.00
Total for 9 days		148.05
Ranitidine cost/day ($)[b]		16.45
Cimetidine (days 1 to 9)[a]		
Product	900 mg/24 hrs	2.97
Ancillary product (1)	Piggyback	.59
Ancillary product (2)	Microtubing (etc.)	2.00
Miscellaneous	Syringe, needle, waste disposal	.20
R.N. time ($20/hr)	20 mins/day (includes pH monitoring)	6.67
Pharmacy time	Pick-up order, prepare, check, label, deliver	2.00
Total for 9 days		129.87
Cimetidine cost/day ($)[b]		14.43
Sucralfate (days 1 to 9)		
Product	1 g × 4	2.56
Miscellaneous	Syringe, waste disposal	.16
R.N. time ($20/hr)	30 mins/day (includes pH monitoring)	10.00
Total for 9 days		114.48
Sucralfate cost/day($)[b]		12.72

(1) piggyback intravenous solution bag; (2) microtubing for intravenous pump. A piggyback is a small volume intravenous solution bag, usually used for delivery drugs intravenously.

[a]Does not include the cost of the infusion pump; [b]does *not* include the cost of failure and/or adverse effect.

Acquisition, preparation, and administration costs of traditional agents

In this prospective, open-labeled study of simplified omeprazole suspension, we demonstrated desirable outcomes with regard to efficacy, safety, cost, and

convenience. A randomized clinical trial comparing simplified omeprazole suspension with continuous-infusion H_2-antagonist therapy in the prophylaxis of stress-related bleeding is in progress.

ACKNOWLEDGMENTS

The authors would like to thank Christy Khojasteh, MA, MEd, for her editorial assistance, Shane Bradley for his dedication to data collection, Jim Bramich for his dedication and support, Richard Moore, PharmD, for his help with the pharmacoeconomic evaluation, and the nursing staffs of the surgical, burn, and neurosurgery intensive care units for their invaluable assistance in this study.

REFERENCES

1. Marrone GC, Silen W: Pathogenesis, diagnosis and treatment of acute gastric mucosa lesions. Clin Gastroenterol 1984; 13:635-650
2. Zinner MJ, Zuiderman GD, Smith PL, et al: The prevention of gastrointestinal tract bleeding in patients in an intensive care unit. Surg Gynecol Obstet 1981; 153:214-220
3. Larson GM, Koch S, O'Dorisio TM, et al: Gastric response to severe head injury. Am J Surg 1984; 147:97-105
4. Czaja AJ, Mcalhany JC, Pruitt BA: Acute gastroduodenal disease after thermal injury: An endoscopic evaluation of incidence and natural history. N Engl J Med 1974; 291:925-929
5. Skillman JJ, Bushnell LS, Goldman H, et al: Respiratory failure, hypotension, sepsis and jaundice: A clinical syndrome associated with lethal hemorrhage from acute stress ulceration. Am J Surg 1969; 117:523-530
6. Cook DJ, Fuller HD, Guyatt GH, et al: Risk factors for gastrointestinal bleeding in critically ill patients. N Engl J Med 1994; 330:377-381
7. Martin LF, Booth FV, Karlstadt RG, et al: Continuous intravenous cimetidine decreases stress-related upper gastrointestinal hemorrhage without promoting pneumonia. Crit Care Med 1993; 21:19-30
8. Peura DA, Johnson LF: Cimetidine for prevention and treatment of gastroduodenal mucosal lesions in patients in an intensive care unit. Ann Intern Med 1985; 103:173-177
9. Bennett DR, Dickinson BD (Eds). Gastrointestinal Drugs. Volume II. In: The American Medical Association Drug Evaluations. Vol 1. Chicago, The American Medical Association, 1994, pp 7-8
10. Gafter U, Zevin D, Komlos L, et al: Thrombocytopenia associated with hypersensitivity to ranitidine: Possible cross-reactivity with cimetidine. Am J Gastroenterol 1989; 64:560-562
11. Martin LF, Booth FV, Reines D, et al: Stress ulcers and organ failure in intubated patients in surgical intensive care units. Ann Surg 1992; 215:332-337

12. Cook DJ, Witt LG, Cook RJ, et al: Stress ulcer prophylaxis in the critically ill: A meta-analysis. Am J Med 1991; 91:519-527
13. Tryba M: Stress ulcer prophylaxis--Quo vadis? Intensive Care Med 1994; 20:311-313
14. Ostro MJ, Russell JA, Soldin SJ, et al: Control of gastric pH with cimetidine boluses versus primed infusions. Gastroenterology 1985; 89:532-537
15. Siepler JK: A dosage alternative for H-2 receptor antagonists--constant infusion. Clin Ther 1986; 8(Suppl A):24-33
16. Ballesteros MA, Hogan DL, Koss MA, et al: Bolus or intravenous infusion of ranitidine: Effects on gastric pH and acid secretion: A comparison of relative cost and efficacy. Ann Intern Med 1990; 112:334-339
17. Sax MJ: Clinically important adverse effects and drug interactions with H2-receptor antagonists: An update. Pharmacotherapy 1987; 7(6 pt 2): 110S-115S
18. Vial T, Goubier C, Bergeret A, et al: Side effects of ranitidine. Drug Saf 1991; 6:94-117
19. Cantu TG, Korek JS: Central nervous system reactions to histamine-2 receptor blockers. Ann Intern Med 1991; 114:1027-1034
20. Spychal RT, Wickham NW: Thrombocytopenia associated with ranitidine. BMJ 1985; 291:1687
21. Smythe MA, Zarowitz BJ: Changing perspectives of stress gastritis prophylaxis. Ann Pharmacother 1994; 28:1073-1084
22. Fellenius E, Berglindh T, Sachs G, et al: Substituted benzimidazoles inhibit gastric acid secretion by blocking H+/K+-ATPase. Nature 1981; 290:159-161
23. Wallmark B, Larsson H, Humble L: The relationship between gastric acid secretion and gastric H+/K+-ATPase activity. J Biol Chem 1985; 260:13681-13684
24. Fryklund J, Helander HF, Elander B, et al: Function and structure of parietal cells after H+/K+-ATPase blockade. Am J Physiol 1988; 254 (3 pt 1):G399-G407
25. Barie PS, Hariri RJ: Therapeutic use of omeprazole for refractory stress-induced gastric mucosal hemorrhage. Crit Care Med 1992; 20:899-901
26. Phillips J, Metzler M: Simplified omeprazole solution for the prophylaxis of stress-related mucosal damage in critically ill patients. Abstr. Crit Care Med 1994; 22:A53
27. Bone RC: Let's agree on terminology: Definitions of sepsis. Crit Care Med 1991; 19:973-976
28. Garner JS, Jarvis WR, Hughes JM, et al: CDC definitions for nosocomial infections, 1988. Am J Infect Control 1988; 16:128-140
29. Fabian TC, Boucher BA, Croce MA, et al: Pneumonia and stress ulceration in severely injured patients. Arch Surg 1993; 128:185-191
30. Cook DJ, Laine LA, Guyatt GH, et al: Nosocomial pneumonia and the role of gastric pH: A meta-analysis. Chest 1991; 100:7-13
31. Schuster DP: Stress ulcer prophylaxis: In whom? With what? Crit Care Med 1993; 21:4-6
32. Schepp W: Stress ulcer prophylaxis: Still a valid option in the 1990s? Digestion 1993; 54:189-199
33. Borrero E, Ciervo J, Chang JB, et al: Antacids vs. sucralfate in preventing acute gastrointestinal tract bleeding in abdominal aortic surgery. Arch Surg 1986; 121:810-812

34. Tryba M: Risk of acute stress bleeding and nosocomial pneumonia in ventilated intensive care patients. Sucralfate vs. antacids. Am J Med 1987; 87(3B):117-124
35. Cioffi WG, McManus AT, Rue LW, et al: Comparison of acid neutralizing and non-acid neutralizing stress ulcer prophylaxis in thermally injured patients. J Trauma 1994; 36:541-547
36. Driks MR, Craven DE, Celli BR, et al: Nosocomial pneumonia in intubated patients given sucralfate as compared with antacids or histamine type 2 blockers. N Engl J Med 1987; 317:1376-1382
37. Schuman RB, Schuster DP, Zuckerman GR: Prophylactic therapy for acute ulcer bleeding: A reappraisal. Ann Intern Med 1987; 106:562-567
38. Fiddian-Green RG, McGough E, Pittenger G, et al: Predictive value of intramural pH and other risk factors for massive bleeding from stress ulceration. Gastroenterology 1983; 8:613-620
39. Skillman JJ, Gould IA, Chung RSK, et al: The gastric mucosal barrier: Clinical and experimental studies in critically ill and normal man and in the rabbit. Ann Surg 1970; 172:564-584
40. Priebe HJ, Skillman JJ: Methods of prophylaxis in stress ulcer disease. World J Surg 1981; 5:223-233
41. Wilder-Smith CH, Merki HS: Tolerance during dosing with H sub 2-receptor antagonists. An overview. Scand J Gastroenterol 1992; 27(Suppl 193):14-19
42. Kiilerich S, Rannem T, Elsborg L: Effect of intravenous infusion of omeprazole and ranitidine on twenty-four-hour intragastric pH in patients with a history of duodenal ulcer. Digestion 1995; 56:25-30
43. Simms HH, DeMaria E, McDonald L, et al: Role of gastric colonization in the development of pneumonia in critically ill trauma patients: Results of a prospective randomized trial. J Trauma 1991; 31:531-536
44. Pickworth KK, Falcone RE, Hoogeboom JE, et al: Occurrence of nosocomial pneumonia in mechanically ventilated trauma patients: A comparison of sucralfate and ranitidine. Crit Care Med 1993; 12:1856-1862
45. Ryan P, Dawson J, Teres D, et al: Nosocomial pneumonia during stress ulcer prophylaxis with cimetidine and sucralfate. Arch Surg 1993; 128:1353-1357
46. Laggner AN, Lenz K, Base W, et al: Prevention of upper gastrointestinal bleeding in long-term ventilated patients. Am J Med 1989; 86(Suppl 6A):81-84
47. Ben-Menachem T, McCarthy BD, Fogel R, et al: Prophylaxis for stress-related gastrointestinal hemorrhage: A cost effectiveness analysis. Crit Care Med 1996; 24:338-345
48. Heath MJ, Owen JD, Sanders SW, et al: Intragastric pH measurement using a novel disposable sensor. Intensive Care Med 1988; 14:232-235
49. Dobkin ED, Valcour A, Roher-McCloskey C, et al: Does pH paper accurately reflect gastric pH? Crit Care Med 1990; 18:985-988
50. Eisenberg PG, Cort D, Zuckerman GR: Prospective trial comparing a combination pH probe-nasogastric tube with aspirated gastric pH in intensive care unit patients. Crit Care Med 1990; 18:1092-1095

51. Meiners D, Clift S, Kaminski D: Evaluation of various techniques to monitor intragastric pH. Arch Surg 1982; 117:288-291