Practical Management of Stress-Related Gastric Ulcers

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Stress ulcers develop in patients who have been subjected to abnormally elevated levels of stress, especially stress caused by conditions associated with reduced gastric blood flow, such as major burns, hypovolemia, and sepsis. Since a significant, often fatal, upper gastrointestinal hemorrhage is a common sequela of stress ulcers, prevention of progression of the lesions is a sensible goal. In numerous clinical trials, antacids, H_2-antagonists, and sucralfate have demonstrated comparable effectiveness in preventing bleeding and the associated life-threatening sequelae. The choice of the ideal agent depends on individual patient factors, concomitant disease states and drug therapy, administration requirements, nursing availability, potential adverse effects, and expense.

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Critically ill patients are at risk for acute bleeding from stress-related gastric mucosal lesions. Depending on the severity of the illness, the frequency of occurrence of these acute inflammatory lesions ranges from a rare event to nearly 100% of patients examined.[1,2] Frequently, the first clinical manifestation of stress ulcers is severe upper gastrointestinal bleeding for which treatment is often inadequate and associated with a high mortality rate. Consequently, the use of appropriate prophylactic therapy in patients recognized to be at increased risk for the development of stress ulcers may prevent severe morbidity and mortality. In this article the rationale for aggressive prophylactic therapy in all patients at risk is discussed, and current therapeutic strategies employed to prevent the significant morbidity and mortality associated with stress ulcers are reviewed.

Normal Gastric Physiology

Under normal physiological conditions, several complex mechanisms provide resistance to hydrogen back-diffusion and the resultant mucosal injury within the gastrointestinal tract. An adherent mucus layer, mucosal bicarbonate secretion, the physical integrity of the epithelial lining, adequate mucosal blood flow, and prostaglandins afford protection from the potentially injurious luminal milieu.[1]

Pathogenesis

A variety of lesions, including acute gastric and duodenal ulcers, hemorrhagic gastritis, and multiple superficial gastric erosions, are collectively termed *stress ulcers*. The gross appearance of stress ulcers differs from peptic ulcers in several ways. Lesions associated with stress ulcers are numerous, are located in the acid/pepsin secretory mucosa of the proximal gastric area, and lack evidence of chronic inflammation.

Mucosal injury results from back-diffusion of hydrogen, histamine release from mast cells, acid and pepsin secretion, and localized hypoxia. Since gastric ulceration does not occur with a gastric pH above 7.0, and since the incidence of hemorrhage from stress ulcers can be reduced by maintaining the pH above 3.5, acid appears to be necessary for the development of mucosal injury.[1,3–5] In fact, intramural acidosis is highly correlated with the development of massive bleeding from stress ulcers; however, hypersecretion of acid is unusual in patients susceptible to stress ulcers.

The precipitating events that may lead to the development of stress ulcers frequently cause significant redistribution of blood flow to preserve function of vital organs. Since gastric mucosal blood flow is necessary to dispose of back-diffused hydrogen, supply bicarbonate, and provide oxygen and nutrients, ischemia is the primary factor leading to stress ulcers.[1] In addition, local-

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Table 1. Risk Factors Associated with the Development of Stress Ulcers*

Burns >35% of total body surface	Major trauma
Coagulopathy	Peritonitis
Sepsis	Renal failure
Head injury	Respiratory failure
Hepatic failure	Shock
Hypotension	Surgery
Jaundice	Underlying malignancy
Multiple organ failure	

**Risk increases with increasing number of individual factors listed above, eg, sepsis and coagulopathy.*

ized hypoxia results in the accumulation of lactic acid, potentiating intramural acidosis, which is highly correlated with the development of massive bleeding from stress ulcers. Although the pathogenesis of stress ulcers remains incompletely understood, it appears to be a multifactorial process, with the principal factors being local ischemia and elevated local hydrogen ion concentration.[1,6] The role of local hypoxia is illustrated by the fact that most critically ill medical patients have gastric mucosal abnormalities shortly after the acute event; however, the lesions often do not become clinically significant.

Risk Factors

Numerous risk factors for the development of stress ulcers have been identified (Table 1). The likelihood of developing stress lesions and subsequent bleeding directly correlates with the severity of the underlying injury or illness. The most powerful predictors of bleeding appear to be the need for mechanical ventilation and the presence of a coagulopathy.[7] In addition, conditions such as major burns, hypotension, and sepsis, which greatly reduce gastric blood flow, increase the risk of developing stress ulcers.[4,5,7]

Diagnosis

Since many stress ulcers do not bleed, testing for the presence of blood in the nasogastric (NG) aspirate is an inadequate diagnostic method. The presence of visible or occult blood in the NG aspirate underestimates the true prevalence of mucosal injury, does not detect nonbleeding stress ulcers, and may inappropriately attribute all bleeding to stress ulcers. In fact, occult blood in the gastric juice of patients in intensive care units (ICUs) is frequently detected and does not indicate impending hemorrhage.[5]

The specificity and sensitivity of the detection of occult blood in the NG aspirate is not optimal. For example, guaiac testing may be less sensitive in detecting blood in gastric juice neutralized by antacid than in gastric juice from patients given intravenous cimetidine, which is a potential problem when interpreting some clinical studies.[8] Furthermore, an interesting phenomenon that has been documented only with cimetidine is the ability of this chemical entity to produce false-positive "hemoccult" reactions when gastric juice is tested. Once thought to be related to the dye present in the tablets, it has been demonstrated that all dosage forms can produce this concentration-dependent reaction.[9]

Intragastric pH monitoring correlates with the underlying mucosal damage. Maintenance of a pH value >3.5 may be sufficient to prevent major gastrointestinal (GI) bleeding, but an intragastric pH level >5.0 is the point at which 99.9% of gastric acid is buffered and the activity of the proteolytic enzyme pepsin is essentially negated.[10] Nevertheless, while a persistently low intragastric pH value may permit stress-related mucosal injury, low pH values do not necessarily indicate the presence of injury, nor do high pH values indicate the absence of injury.[2]

Endoscopic examination is necessary to accurately diagnose stress ulcers. Remarkably, up to 50% of early stress ulcers have endoscopic evidence of recent or ongoing bleeding, resulting in guaiac positivity. The incidence of clinically significant hemorrhage is much smaller, however, occurring in only 5% to 20% of patients in ICUs.[11] Consequently, even with an endoscopic examination, it is difficult to predict which patients will have GI bleeding that is clinically significant.

Pharmacotherapeutic Management

Macroscopic damage to the mucosa occurs early, often within hours of the onset of stress. Consequently, prevention of lesions is an impractical therapeutic goal. Early and appropriate prophylactic therapy can, however, prevent rapid progression of the lesions to a state in which significant bleeding occurs.[2] The multifactorial etiology of stress ulcers suggests the possibility that a variety of pharmacological agents are potentially useful in their prophylaxis. Antacids, H_2-antagonists, and sucralfate have demonstrated the ability to protect critically ill patients from the bleeding associated with stress-related mucosal damage.

Antacids

Antacids neutralize gastric acidity and inactivate the proteolytic activity of pepsin by buffering the hydrogen ions secreted by parietal cells. For optimal results, the dosage must be titrated against the gastric pH. Thirty milliliters of a magnesium hydroxide and aluminum hydroxide antacid combination is administered every 1 to 2 hours through an NG tube, which is then clamped for 15 to 30 minutes. If the pH of the NG aspirate is below the goal, the next dose is doubled. The dose is not reduced until three consecutive pH measurements are above the goal pH. Some patients may require as much as 100 to 120 mL of antacid per hour because of hypersecretion of acid and pepsin secondary to elevation of the pH in the gastric antrum.[12] Acid neutralizing capacity (ANC) is a primary consideration in selecting an antacid. The ANC is defined as the number of milliequivalents of 1 N HCl that can be brought to a pH of 3.5 in 15 minutes.[12] It is expressed as mEq/5 mL and varies among commercially available antacid preparations. The relative in vitro neutralizing capacity of antacids used for stress ulcer prophylaxis is as follows: magnesium hydroxide > magnesium aluminum combinations > aluminum hydroxide. Antacids with high ANC values are usually more effective in vivo.

High doses of antacids often produce minor adverse effects. As many as 16% to 29% of patients develop metabolic alkalosis, electrolyte shifts, or diarrhea.[3,13] In addition, aspiration of gastric contents is a potential problem among patients receiving large quantities of antacids, particularly in elderly or obtunded patients.[3] If persistent diarrhea or hypermagnesemia develops, an aluminum-dominant antacid can be administered, alternating it with a magnesium-aluminum combination.[13] Continued use of a magnesium-aluminum combination is important because the ANC of aluminum is not as great as that of magnesium. Serum magnesium concentrations should be monitored in all patients receiving large quantities of magnesium-containing antacids and in patients with acute or chronic renal failure. If hypermagnesemia develops, large quantities of an aluminum-dominant antacid may be preferred to an aluminum-magnesium combination product.

Drug interactions are common with antacids. Antacids can impair the absorption of other agents by increasing the gastric pH or adsorbing drugs to their surface. The need for hourly administration of antacids to critically ill patients results in the frequent occurrence of drug interactions with orally administered agents. Alternate routes of administration may be indicated for certain medications, such as digoxin and ferrous sulfate.

H_2-Antagonists

In addition to reducing gastric-acid volume and concentration and inactivating the proteolytic activity of pepsin, H_2-antagonists may exert a gastroprotective effect.[2,14] Development of stress ulcers is not completely prevented, but H_2-antagonists may decrease the severity, prevent the progression, and expedite the healing of the ulcers.

Intermittent intravenous infusions of H_2-antagonists result in erratic control of gastric acid secretions. Frequently, the gastric pH is not maintained above 3.5 for the duration of the dosing interval. In fact, often the pH will be less than 5.0 within 3 hours into the dosing interval of cimetidine or ranitidine and within 8 to 9 hours of famotidine.[15] On the other hand, owing to sustained drug serum concentrations, continuous intravenous infusions are capable of maintaining the gastric pH above 4.0.[15] Theoretically, maintenance of an elevated pH would produce a better clinical outcome; however, direct comparisons between continuous and intermittent dosage regimens are needed to determine the actual clinical benefits of each regimen.

Consistent elevation in intragastric pH has been observed when the available H_2-antagonists have been administered in equipotent doses.[15] To rapidly achieve adequate serum drug concentrations, a bolus intravenous dose should be administered before the continuous infusion.[4,5] Common dosing regimens to prevent GI bleeding from stress ulcers are: cimetidine 300-mg bolus followed by 37.5 to 50 mg/h; famotidine 20-mg bolus followed by 1.7 mg/h; and ranitidine 50-mg bolus followed by 6 to 8 mg/h.[4,15] In addition, some authors advocate regular monitoring of the gastric pH to assess potential refractoriness to the neutralizing effects of H_2-antagonists and to optimize therapy.[4,5]

The incidence of adverse effects associated with intravenous H_2-antagonists is low (less than 1%). In addition, there is insufficient evidence to conclude that one agent results in fewer side effects than another. Potential adverse events include headache, neutropenia, thrombocytopenia, and reversible confusion. It is important to note that 70% to 75% of an intravenous H_2-antagonist dose is excreted unchanged in the urine. Consequently, to prevent accumulation of the drug and potentiation of dose-dependent adverse effects, dosage reduction is recommended in patients with decreased renal function. In general, if the creatinine clearance is between 10 and 50 mL per minute, 75% of the recommended daily dose should be administered. If the creatinine clearance is less than 10 mL per minute, the dose should be reduced by 50%. Alternatively, for intermittent bolus infusions, the dosing interval can be extended by 1.5 to 3 times.

Drug interactions are more commonly reported

with cimetidine than with the other H_2-antagonists. Since cimetidine reduces the hepatic metabolism of agents metabolized by the cytochrome P-450 pathway, elimination of drugs metabolized by this pathway is delayed and serum drug concentrations may increase. However, the incidence of clinically significant drug interactions appears to be similar among the H_2-antagonists. Patients receiving theophylline, phenytoin, or warfarin concomitantly with an H_2-antagonist should be monitored closely for adverse effects.

Sucralfate

Sucralfate is a sulfated disaccharide of aluminum. Without affecting gastric acid secretion or increasing the gastric pH, sucralfate protects critically ill patients from upper GI bleeding.[16] The mechanism of action of sucralfate is multifactorial. It binds to exposed proteins for several hours, adsorbs pepsin and bile salts, and stimulates mucosal prostaglandin synthesis, which enhances mucosal defensive factors.[17,18]

Sucralfate is administered 1 g every 4 or 6 hours to prevent GI bleeding. To facilitate administration by an NG tube, sucralfate easily dissolves in small amounts (15 mL) of water. Only 3% to 5% of sucralfate is absorbed. Adverse effects are rare; however, since it is an aluminum salt, constipation and hypophosphatemia may develop. Since pH monitoring is not required, the administration of sucralfate requires minimal nursing time. Also, since dosage adjustments are not required, the cost of sucralfate is fixed and predictable.

Other Means of Prophylaxis

In a retrospective study, continuous enteral feedings were shown to be more effective in reducing stress ulcer formation and clinically significant GI bleeding than a fixed-dose antacid or H_2-antagonist regimen.[19] However, although enteral feedings may buffer gastric acid, they do so poorly and may even result in a further reduction of the gastric pH. Nevertheless, enteral feedings have a cytoprotective effect and may improve global nutrition, which reduces the susceptibility to stress ulcers. Further clinical investigation into the role of enteral feedings in the prophylaxis of stress ulcers is needed.

In addition, newer agents may have a role in the prevention of GI bleeding from stress ulcers. Misoprostol, a prostaglandin E_1 analogue, increases the defenses of the mucosal cells and inhibits gastric acid secretion.[20] Omeprazole inhibits the H^+/K^+ ATPase enzyme system, resulting in decreased gastric acid secretion.[21] It is a gastric acid pump inhibitor that blocks the final step of acid production. Clinical studies are needed to determine the usefulness and the potential role of these agents in stress ulcer prophylaxis.

Comparative Studies

Great variation in the designs of clinical studies comparing regimens to prevent GI bleeding from stress ulcers makes interpretation difficult. In fact, the results of clinical trials are available to support nearly every opinion regarding prophylactic therapy of stress ulcers. Studies are often unblinded and nonrandomized, and involve both surgical and medical patients. In addition, studies differ in patient population, therapeutic regimens, acid-neutralizing capacity of antacids, gastric pH goals and titration quantities, assessment criteria, methods to detect bleeding, and definitions of bleeding (overt vs occult).

An endoscopic study to determine the incidence of stress erosions and ulcers and to assess the efficacy of acid-reducing prophylactic treatment was conducted in critically ill neurosurgical patients.[22] Of the 97 eligible patients, only 40 (41%) completed the trial because of various factors. Patients were randomized to receive either ranitidine plus antacids if necessary to maintain gastric pH $\geq$ 4.0 (19 patients) or no drug prophylaxis (21 patients). There were no statistically significant differences in endoscopic findings between treatment and control groups at admission or at repeat endoscopy on day 5. Nine patients in each group developed more than five gastroduodenal erosions, and one patient in each group developed ulcers. None of the patients showed endoscopic or clinical evidence of GI bleeding. The authors concluded that while the treatment regimen effectively increased the gastric pH, the extent of gastroduodenal mucosal lesions was not affected, and therefore, routine stress lesion prophylaxis may not be necessary in critically ill patients with comparable risk factors. The large number of patients not completing the trial, the small sample size, the short study period ($\leq$7 days), and the lack of any patient developing clinically significant GI bleeding make interpretation of these data difficult. However, this endoscopic study does demonstrate the need for further large scale studies comparing acid-reducing prophylaxis and placebo for the prevention of clinically significant GI bleeding in those patients at risk.

The combined results from 16 prospective trials involving 2133 patients appear to suggest that antacids prevent stress ulcer bleeding more effectively than does cimetidine.[11] When the data from these trials were categorized according to the criteria used for the diagnoses of bleeding, however, there was no significant difference

between antacids and cimetidine in the prevention of overt bleeding (hematemesis, melena, or bleeding requiring transfusions). In the 11 studies that used these criteria, 15 of 458 (3.3%) patients receiving antacids bled compared with 11 of 402 (2.7%) patients receiving cimetidine ($P = .69$). In addition, both agents were more effective than the placebo in preventing overt bleeding, ie, 108 of 720 (15%) patients receiving placebo bled ($P < .001$ vs either antacids or cimetidine). This analysis demonstrated that both cimetidine and antacids are statistically better than no prophylactic therapy, and cimetidine and antacids are equally effective in preventing overt stress ulcer bleeding. The authors conclude that therapy should be tailored to the individual patient and that the choice of treatment depends on factors such as cost, ease of administration, and side effects.

The administration of sucralfate every 6 hours was compared to hourly antacid administration titrated to a pH > 3.5 in 155 critically ill patients for the prevention of upper GI bleeding.[23] Occult bleeding occurred in 2 of 75 (2.6%) patients receiving antacid and in 3 of 80 (3.8%) patients receiving sucralfate (not statistically significant). None of the patients required blood transfusions. No adverse effects occurred in the sucralfate group, but 13 (17%) of the patients receiving antacids developed diarrhea, and 1 (1%) patient developed reversible hypermagnesemia. Although the mortality rate in each group was high (28% in antacid group and 17.5% in sucralfate group), bleeding did not contribute to any fatal event. In a similar study involving 74 critically ill patients, sucralfate every 4 hours was compared with antacids administered to maintain a pH > 4.0.[24] Significant upper GI bleeding occurred in one patient receiving sucralfate. Insignificant overt bleeding occurred in an additional 4 of 38 (10.5%) patients receiving sucralfate and in 7 of 36 (19.4%) patients receiving antacids (not statistically significant). No patients in the sucralfate group developed side effects, while 8 patients in the antacid group did (4 had severe diarrhea and 4 had elevated magnesium levels). The authors of each of these studies state that since comparable efficacy was demonstrated with sucralfate and antacids, sucralfate may be preferred since it produces few side effects, is easy to administer, and can reduce the time and costs associated with stress ulcer prophylaxis.

Finally, in a prospective, controlled, randomized study, 100 critically ill patients received sucralfate every 4 hours, antacids every 2 hours, or continuous infusion of cimetidine (2 g per day).[17] In addition, each patient received a European anticholinergic agent that decreases gastric secretions (pirenzepine 50 mg infusion per day). Mild bleeding occurred in 2 of 33 (6%) patients receiving cimetidine and in 2 of 33 (6%) patients receiving antacids; bleeding did not occur in any of the 34 patients receiving sucralfate. Gastrointestinal hemorrhage contributed to the death of one patient receiving cimetidine. The efficacy of antacid and H_2-antagonist prophylaxis was found to be inversely related to the frequency of pH levels below 4.0. Interestingly, the efficacy of sucralfate was independent of intragastric pH, evidenced by the fact that one half or more of the measured pH values were less than 4.0, but hemorrhage did not occur in any of these patients.

In a multicenter, prospective, double-blind, double-placebo study, misoprostol 200 μg every 4 hours (187 patients) was compared with antacids titrated to maintain the gastric pH $\geq$ 4.0 (181 patients) for the prevention of stress gastritis and bleeding in postoperative surgical patients.[25] During the study period, the average pH remained $\geq$4.0 in both groups. Prophylaxis was considered successful (no endoscopic evidence of erosions or ulcer craters) in 69.2% of patients in the antacid group and 70.5% of patients in the misoprostol group ($P = .82$). No clinically evident upper GI bleeding occurred in either group. The most common adverse effect was diarrhea, which occurred in 22.8% of the antacid group and in 25.3% of the misoprostol group ($P = .58$). The authors concluded that fixed-dose misoprostol and antacid titration are similarly effective in preventing clinically evident upper GI hemorrhage and in the development of endoscopically proven stress lesions. They also stated that misoprostol is easier to administer and can significantly reduce the amount of nursing time required for stress ulcer prophylaxis.

In summary, determination of the most effective and safest method of stress ulcer prophylaxis has been attempted in numerous studies. Endpoints vary among the studies; however, it is important to remember that the need for blood transfusions or death as a result of hemorrhage is the most clinically relevant indicator of the effectiveness of stress ulcer prophylaxis. As discussed above, the effectiveness of antacids, H_2-antagonists, and sucralfate in preventing a significant gastrointestinal hemorrhage is comparable. It appears that regardless of the method of prophylaxis, the greatest predictor of a significant risk of upper GI hemorrhage in an individual is the number of risk factors and the severity of the underlying medical problems.

Nosocomial Pneumonia

Endotracheal intubation, lung disease, diabetes, antibiotic therapy, and elevation of the gastric pH predispose an individual to colonization of gram-negative bacteria in the upper respiratory tract.[26] Gram-negative nosocomial pneumonia is a common sequela of this colonization. It

has been suggested that maintenance of the normal acidity of the stomach may result in a lower incidence of pulmonary nosocomial infections than has been experienced with an elevation of the gastric pH.

The incidence of nosocomial pneumonia in 130 mechanically ventilated patients receiving prophylactic sucralfate, antacids, H_2-antagonists (cimetidine or ranitidine), or both antacids and H_2-antagonists was examined.[27] The authors concluded that sucralfate resulted in a lower incidence of pneumonia, as 7 of 61 (11.5%) patients receiving sucralfate developed pneumonia, compared with 16 of 69 (23.2%) patients receiving the other combinations. No statistical significance was achieved. The authors state that in mechanically ventilated patients, an agent that preserves the natural gastric acid barrier against bacterial overgrowth may be preferred to antacids and H_2-antagonists in stress ulcer prophylaxis. Further examination of the data reveals, however, that pneumonia developed in 9 of 39 (23.1%) patients receiving antacids alone, 1 of 17 (5.9%) patients receiving H_2-antagonists alone, and 6 of 13 (46.2%) patients treated with both antacids and H_2-antagonists. It appears that the use of antacids, whether alone or with H_2-antagonists, increased the incidence of pneumonia. In other words, the additional risk of aspiration associated with antacids may increase the risk of nosocomial pneumonia to a greater extent than elevating the gastric pH alone. However, the large number of patients who crossed over into different groups has made analysis of this study difficult. Interestingly, only 2 patients in the sucralfate group and 1 patient in the antacid–H_2-antagonist group developed bright-red blood in the NG tubes.

In another study, sucralfate was compared with antacids for the risk of developing nosocomial pneumonia in ventilated ICU patients.[28] One hundred ventilated high-risk patients in a surgical ICU were randomized to receive either sucralfate or antacids. The rate of bleeding was similar in both groups. Because of thoracic trauma or pneumonia at the time of admission, 39 patients had to be withdrawn from the analysis. Nosocomial pneumonia developed in 3 of 19 (10.3%) patients receiving sucralfate and in 11 of 32 (34.4%) patients receiving antacids ($P < .05$). For four cases in the antacid group, the pneumonia influenced the lethal outcome of the patients. Owing to the large number of patients not completing the study, interpretation of these data is difficult; however, the authors concluded that sucralfate provides adequate protection against stress bleeding while minimizing the possibility of pneumonia.

A meta-analysis was conducted to examine the differential effect of drugs used for stress ulcer prophylaxis on nosocomial pneumonia in critically ill patients.[26] Of the 48 randomized controlled trials of prophylaxis, only 8 studies (involving 535 patients) recorded or reported the outcome of nosocomial pneumonia and were included in this study. The conclusion of the analysis was that elevation of the gastric pH does not increase the incidence of pneumonia in comparison with placebo. In addition, the use of sucralfate is associated with a lower incidence of nosocomial pneumonia in comparison with agents that raise the gastric pH. However, because of small sample sizes, methodologic deficiencies, and the fact that only 8 of 48 studies of stress ulcer prophylaxis were relevant, the inferences that can be made from these data are limited.

Until further data become available, it remains unclear if the increased incidence of nosocomial pneumonia is due to elevation of the pH of the gastric contents, intubation, or simply the ICU environment. In addition, it has been suggested that ischemic mucosal injury and its associated translocation of enteric bacteria and toxins may be more important in the pathogenesis of nosocomial pneumonia in the critically ill than the aspiration of contaminated nasopharyngeal secretions.[29] It is apparent that a large, methodologically sound, prospective, randomized study that examines the different methods of stress ulcer prophylaxis while controlling for confounding risk factors for nosocomial pneumonia is needed.

Duration of Prophylaxis

The duration of stress ulcer prophylaxis is variable. Simply, prophylaxis should continue until the patient is no longer at risk for the development of bleeding from stress ulcers. Often this occurs when the patient leaves the ICU, is extubated, or receives enteral nutrition.

Following the successful prevention of bleeding from stress ulcers by any of the recommended methods, oral maintenance therapy is often initiated. There is a considerable lack of data to support or refute the practice of administering oral agents for prolonged periods following the discontinuation of prophylactic therapy. Significant cost savings, in both the inpatient and outpatient settings, could result if clinical trials were conducted that demonstrated that patients at risk for hemorrhage from stress ulcers do not require maintenance therapy after elimination of that risk.

Cost Issues

Current costs of agents used for stress ulcer prophylaxis are presented in Table 2. Depending on pH determinations and titration quantities, the cost of antacids could increase significantly. For example, during a typical day,

Table 2. Cost of Stress Ulcer Prophylaxis

Regimen	Drug Cost/Day ($)*
Antacids	
Aluminum dominant	
Amphojel (ANC = 10 mEq/5 mL)	
30 mL PO/NG every hour	8.70
Magnesium aluminum combination	
Mylanta II (ANC = 25.4 mEq/5 mL)	
30 mL PO/NG every hour	9.05
H_2 Antagonists	
Cimetidine	
37.5 mg/h (900 mg/d)	11.34
50 mg/h (1200 mg/d)	15.12
Famotidine	
1.7 mg/h (40 mg/d)	11.88
Ranitidine	
6 mg/h (150 mg/d)	11.97
8 mg/h (200 mg/d)	15.96
Sucralfate	
1 g PO/NG every 4 hours	3.83

**1991 average wholesale price.*
ANC denotes acid neutralizing capacity; PO/NG denotes by mouth or by nasogastric tube.

if just two pH determinations are less than the goal, the total daily antacid requirement would increase from 720 to 900 mL. In addition, antacid administration and titration is labor-intensive and time-consuming, functions to which it is difficult to assign a price. Side effects, such as metabolic alkalosis and diarrhea, occur with antacids and often require additional medication and treatment, which contribute to the total cost of care.

Continuous infusions of H_2-antagonists have an advantage over intermittent bolus infusions by being more cost-effective. Since the pharmacy prepares only one dose per day and nurses hang only one infusion per day, the reduced time required for preparation and administration results in decreased labor requirements and cost savings for the patient and hospital. In addition, there is evidence supporting the stability of these agents in parenteral nutrient admixtures.[30,31] Admixing the H_2-antagonists into TPN (total parenteral nutrition) solutions can spare an intravenous access line and may result in further cost savings, while avoiding confusion and mistakes at the bedside. For some patients, continuous infusions can result in additional cost reductions compared with intermittent infusions because of a decrease in the total daily dose required to achieve comparable pH control. However, like antacids, if the dose of the H_2-antagonists is titrated against pH determinations, the daily dose and cost could increase substantially.

As is evident in the table, sucralfate is significantly less expensive than other agents used for stress ulcer prophylaxis. Since pH determinations are not required when administering sucralfate, nursing time for this cumbersome task is saved for other activities. A potential, but minor, additional cost would be that associated with the administration of phosphate to replace any that might be lost as a result of sucralfate administration.

Inconsequential of the method of stress ulcer prophylaxis employed, the cost is significantly affected by the duration of prophylaxis. Unnecessary administration of any of these regimens can significantly elevate the total cost of care for the patient. It is important to remember that once enteral feedings are initiated or the patient is discharged from the ICU, stress ulcer prophylaxis is no longer required.

Conclusions

Historically, critically ill patients with endoscopically proven lesions have developed clinically significant bleeding in up to 25% of the cases.[15] The therapy of bleeding ulcers, even with surgical treatment, is associated with a discouraging mortality rate of 30% to 40%.[32] Fortunately, with meticulous attention to stress ulcer prophylaxis in intensive care patients during the past decade, the incidence of stress bleeding has been reduced from 25% to approximately 4%.[1] Numerous factors have contributed to the overall improved condition of patients in ICUs, including improved ventilatory support, maintenance of acid-base balance, early treatment of shock, adequate sedation, use of sufficient parenteral alimentation, and early enteral feedings. In addition, stress ulcer prophylaxis using appropriate pharmacological agents may also contribute to prevention of GI bleeding.

Stress ulcers increase the morbidity and mortality of critically ill patients; however, this increase is small and not as great as earlier reports have emphasized. Although prophylactic therapy decreases the incidence of stress ulcers and, therefore, bleeding, little benefit on ultimate mortality has been documented. The severity of the patient's underlying diseases is a more critical determinant of mortality than the development of stress ulcers and the occurrence of bleeding.[18]

The findings from numerous clinical trials in which the issues of stress ulcer prophylaxis were examined are available. Before making explicit recommendations, however, further studies are required. Clinical trials that involve large numbers of critically ill patients are needed to determine the incidence of major bleeding (ie, bleeding that requires blood transfusions or contributes to death) with stress ulcer prophylaxis vs placebo. Until this information is available, it appears reasonable to make use of some form of prophylaxis. In general, the data demonstrate comparable efficacy among the antacids, H_2-antagonists, and sucralfate. In addition, newer agents may

demonstrate equivalent efficacy, eliminate the need for compulsive monitoring of the gastric pH, have fewer side effects, and be less expensive and labor-intensive. Currently, there is no agent of choice for all patients. Until conclusive data are available, the decision of which agent to administer should be based on factors such as availability of trained nursing personnel, potential drug-drug or drug-disease interactions, renal function, experience of the prescribing physician, cost, and other appropriate individual patient factors.

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