Stress-related Mucosal Disease

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Opinion statement

Stress-related mucosal disease (SRMD) includes stress-related injury (superficial mucosal damage) and stress ulcers (focal deep mucosal damage). Both types are caused by mucosal ischemia, and both show a propensity for the acid-producing corpus and fundus. Prophylaxis of stress ulcers may reduce major bleeding but, so far, has not been shown to improve survival. The most widely used drugs for stress-related injury are the intravenous histamine H_2-receptor antagonists. Proton pump inhibitors (PPIs) are the most potent acid-suppressive pharmacologic agents. The available PPIs significantly increase gastric pH for up to 24 hours after one dose. Tolerance does not develop, and adverse effects are few. Preliminary studies have demonstrated a significant reduction in SRMD bleeding for patients receiving PPI prophylaxis. PPIs may become an effective tool for reducing the incidence of SRMD in critically ill patients.

Introduction

The association between severe physiologic stress and gastrointestinal (GI) ulceration is well established. The pathogenesis has not been completely clarified, but strong evidence points to hypoperfusion of the upper GI tract as the major cause. The most important intervention to prevent stress ulceration is the aggressive management of the underlying disease. Understanding the different types of stress injury and improving classification will facilitate communication and aid diagnosis, prognosis, and therapeutic management. A variety of available medications can reduce the incidence of this condition. Elucidating the mechanism of this injury will help us develop strategies so that our interventions may lead to a reduction in mortality.

TERMINOLOGY

The terminology of stress-related mucosal disease (SRMD) is confusing. Unfortunately, throughout the literature, authors use the terms stress ulcer, stress gastritis, stress erosions, and stress lesions interchangeably. Important differences exist among these entities. In an attempt to clarify the terminology, we have broken down SRMD into two major types of mucosal lesions: stress-related injury (SRI) and the stress ulcer. SRI involves superficial mucosal damage and primarily erosions, and is found in physiologically stressed patients, particularly those requiring mechanical ventilation. The discrete stress ulcer, found in the same subgroup of patients, is different in terms of the risk of bleeding. Each type of SRMD is discussed separately and compared with the other.

PATHOGENESIS

The gastric mucosa is exposed to a very low intraluminal pH. The integrity of the tissue is maintained under normal physiologic conditions by a balance between aggressive factors, such as gastric acid, enzymes, and infection, and the countervailing mucosal defense mechanisms. In animal models, mucosal defense was shown to be intricately related to adequate microcirculation through tissues of the upper GI tract, which provides nutrients and removes waste products, particularly oxygen radicals. Longer periods of ischemia lead to more lesions, and reperfusion (retransfusion) is a critical factor in lesion development.

In a study from The Netherlands [1], maintenance of patients with low-dose inotropes and vasodilators (dopamine 2 to 6 μg/kg per minute, nitroglycerin 2 to 4 mg/h, or ketanserin 2 to 6 mg/h), selective gut decontamination, and steroids virtually eliminated stress ulcer–related

bleeding in intensive care unit (ICU) patients receiving prolonged mechanical ventilation without any prophylaxis. These studies point to a multifactorial etiology for stress ulcers, particularly to the key role played by breakdown of the mucosal defenses, usually by ischemia and reperfusion, so as to allow aggressive physiologic processes to cause injury and ulceration.

LOCATION

In contrast to outpatient peptic ulcers, SRMD is typically seen in the acid-producing areas, that is, the corpus and fundus. Outpatient peptic ulcers are more common in the antrum or duodenal bulb. Leung *et al.* [2] found in a rat model that, during hemorrhagic shock, gastric lesions begin to appear when blood pressure falls to 33% of baseline. They reported that, at blood pressures of 80% below baseline, 26.8% ± 4.5% of the total corpus area developed lesions versus 5.3% ± 1.4% of the antral area. In addition, with rare exceptions, corpus mucosal lesions were significantly larger than antral mucosal lesions at all levels of hypotension. It is believed that low-grade mesenteric ischemia occurs during sepsis and multiple organ failure because of blood volume changes and blood flow redistribution. We measured blood flow by endoscopic reflectance spectrophotometry in normotensive, septic, critically ill, ventilated patients as an index of hemoglobin saturation and oxygen concentration. Control values came from patients undergoing routine endoscopy to evaluate symptoms of gastroesophageal reflux disease. We found that ICU patients with septic disease had a 50% to 60% reduction in upper GI mucosal blood flow compared with controls [3••].

MORTALITY

Stress-related mucosal disease differs considerably from the peptic disease found in outpatients in many respects, including risk factors, pathophysiology, prognosis, recurrence, management, and therapy. In one study, the mortality rate in patients with endoscopic evidence of severe SRMD at admission to a medical ICU was 57% compared with 24% in patients with normal mucosa [4]. The high mortality rate has been confirmed in several other studies [5,6,7•]. The high mortality rate associated with SRMD, as well as the condition itself, is related to hypoperfusion of the mesenteric system. Once the patient recovers, the lesions remit and, with a healthy host, do not recur.

RISK FACTORS

A large multicenter study of 2252 patients found that the two strongest risk factors for bleeding were respiratory failure (odds ratio 15.6) and coagulopathy (odds ratio 4.3) [8••]. The risk increases with increasing number of days of mechanical ventilation and length of stay in the ICU [9]. Other high-risk conditions for both subgroups of SRMD include recent major surgery, major trauma, severe burns, head trauma, hepatic or renal disease on admission, sepsis, or hypotension [5,8••,10–14].

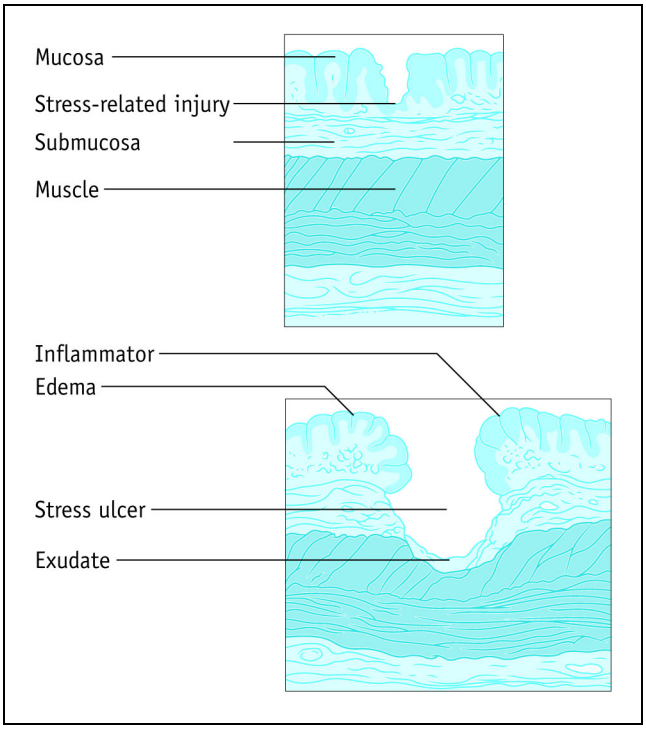

Figure 1. Illustration of tissue injury, mechanism, and depth of injury: stress-related injury (*top*) and stress ulcer (*bottom*).

STRESS-RELATED INJURY

Most studies show that 75% to 100% of patients in the ICU have abnormalities of the gastric mucosa within hours after admission [4,5,11,14,15] and that 35% to 100% of critically ill patients have gastric juice samples that test positive for blood [16,17]. However, occult blood in the gastric juice does not predict impending hemorrhage [16]. The mucosal changes are mostly small erosions that usually do not lead to hemodynamically significant GI bleeding (Fig. 1). When bleeding occurs in patients with SRI, there is usually a concomitant coagulopathy. Clinically apparent bleeding occurs in approximately 20% of patients, whereas hemodynamically significant bleeding is found in probably less than 5% [18].

Erosions associated with SRI are not caused by hyperacidity, because affected patients have normal or slightly decreased gastric acid volume. If massive bleeding occurs, it is usually from a discrete stress ulcer, as opposed to diffuse SRI. These lesions tend to be superficial, and perforation is distinctly uncommon compared with that in the 1% to 2% of patients with gastric and duodenal ulcers.

STRESS ULCERS

Stress ulcers are different from SRIs and from routine peptic ulcer disease. Peptic ulcer disease is a comparatively manageable condition that usually presents with abdominal pain and epigastric discomfort. It is easily

treated on an outpatient basis. Only 10% to 15% of outpatients with peptic ulcer disease develop complications requiring hospitalization (*eg*, bleeding, obstruction, perforation). In contrast, stress ulcers are noted with GI bleeding and are usually not associated with abdominal pain. Clinical bleeding often occurs 3 to 7 days after ICU admission. In their review from 1987, Zuckerman and Shuman [6] reported that ICU patients with stress ulcer bleeding experience a mortality rate of 50% to 77%, compared with a rate of 9% to 22% in nonbleeding ICU patients. Compared to patients with SRI, patients with stress ulcers are at increased risk of hemodynamically significant GI hemorrhage, although the cause of death is rarely GI bleeding. Death usually results from multiple organ failure and is probably related to a global hypoperfusion state of the entire gut, promoting translocation of bacteria and endotoxin. Stress-related ulcers are the most easily recognizable sign of this low-perfusion state. The prophylaxis of stress ulcers has not been shown to improve survival, even in the few trials in which major bleeding appeared to have been favorably reduced [19–21].

Prophylaxis of stress ulcers Prophylaxis against stress ulcers is the standard of care in most ICUs. Notwithstanding, the incidence of significant stress-related bleeding has decreased dramatically. The variety of definitions of bleeding in clinical studies tends to obscure the true incidence of stress-related bleeding. Reported criteria range from guaiac-positive stool and guaiac-positive nasogastric (NG) aspirate to frank hematemesis and the need for blood transfusion. Using strict criteria (coffee-ground emesis, hematemesis, or melena), the occurrence of acute stress-related GI bleeding ranges from 2% to 6%. The average risk of clinically important bleeding from all causes is 6% in patients not receiving prophylaxis [7•]. The best predictors are respiratory failure requiring prolonged mechanical ventilation and the presence of coagulopathy in ICU patients [7•,8••]. A more radical viewpoint might question whether prophylaxis is necessary at all, because bleeding from such lesions, although predictive of death, usually is not the cause, and therapy has never been demonstrated to reduce mortality. There is a lot of disagreement in this area, but there is a consensus that patients at very high risk for stress bleeding should receive prophylaxis. A list of the available agents and information pertinent to their use can be found in the treatment section of this article.

SUMMARY

Improvement in GI mucosal hemodynamics by aggressive treatment of the underlying disease is paramount in the treatment of SRMD. In addition, removal of mucosal irritants, such as gastric acid, is critical. Histamine 2 (H_2) receptor antagonists (H_2RAs) do not completely suppress acid secretion; they have a potential for development of tolerance, and they can have side effects. The most potent available agents are the PPIs. The efficacy of PPIs and the low incidence of side effects or adverse drug interactions make them attractive candidates for prophylactic therapy for SRMD. Preliminary studies show promise in this area. Further studies are needed.

Treatment

Pharmacologic treatment

Histamine 2 receptor antagonists

- A variety of H_2RAs can be used for prophylaxis in the ICU. The available H_2RAs are not equally potent at blocking histamine's actions on parietal cells. Cimetidine is the least potent, ranitidine and nizatidine are more potent, and famotidine is the most potent. However, cimetidine, is the only H_2RA approved in the United States for the prevention of upper GI bleeding in the ICU. Other differences exist among the medications and methods of administering them. Although H_2RAs can effectively protect against SRI [4,22], their efficacy in the prophylaxis of true stress ulcers is of only moderate effectiveness (Table 1).

Routes of administration

The two main methods of intravenous (IV) infusion are bolus and continuous. Continuous infusion of H_2RAs is superior in maintaining gastric pH at levels greater than 4 when compared with intermittent bolus administration [23,24]. However, no studies have demonstrated improved safety, more effective prophylaxis, faster healing of existing ulcers, or a lower rebleeding rate with either method. There is also no conclusive evidence that maintaining an intragastric pH of 7 improves prevention of SRMD. However, it seems reasonable that maintaining intragastric pH at levels above 4 will decrease the incidence of bleeding. Because some drug-related

Table 1. Stress-related mucosal disease prophylaxis: high-risk trials

Trial	Patients, *n*	Bleeding rate, %	*P* value
Antacid*	51	4	
Placebo	49	25	< 0.05
$H_2RA^{\dagger}$	65	14	
Placebo	66	33	< 0.05
$H_2RA^{\ddagger}$	100	5	
Sucralfate	100	5	
Placebo	100	6	NS

*Hastings *et al.* [21].
†Martin *et al.* [26].
‡Ben-Menachem *et al.* [50].
H_2RA—histamine 2 receptor antagonist; NS—not significant.

Table 2. Drug-to-drug interactions of cimetidine

Warfarin	Phenytoin	Propranolol	Nifedipine
Diazepam	Lidocaine	Chlordiazepoxide	Theophylline
Metronidazole	Tricyclic antidepressants		

side effects associated with H_2RAs are thought to result from high serum concentrations, maintenance of steady blood levels within the therapeutic range may reduce the potential for these side effects. Continuous infusion avoids the peaks and troughs associated with bolus administration. Oral therapy can also be used. Enteral administration of ranitidine every 12 hours leads to effective absorption of the drug from the upper GI tract. After 12 hours, serum concentrations of ranitidine for both 150-mg and 300-mg enteral doses remained within, or exceeded, the therapeutic range in nearly 80% of ICU patients with clinically important risk factors for SRMD. Irrespective of the route of administration or dosing interval, daily doses should be reduced in patients with renal insufficiency.

One major concern that requires further research is the development of tolerance. Tolerance develops with IV administration of H_2RAs within 42 hours. This occurs in the ICU with repeated and continuous infusion [25,26]. The reduction in the antisecretory effect of H_2RAs is not explained by altered pharmacokinetics.

Cimetidine

Cimetidine has been marketed in the United States for almost 25 years and has proven to be a safe drug. Drug interactions, which occur more frequently than with other H_2RAs, are the major concern with its use (Table 2). Thrombocytopenia has also been associated with the use of cimetidine. Because it can cause neurologic manifestations and drug interactions, cimetidine should be used with caution in ICU patients.

Ranitidine

Ranitidine's antisecretory effect is five to 12 times more potent than that of cimetidine. However, there is no evidence of its superiority to cimetidine in preventing SRMD. It is usually well tolerated. However, in ICU patients given the usual doses, the drug can cause adverse central nervous system reactions including agitation and restlessness. Ranitidine is known to interact with warfarin. In patients with renal function impairment, lethargy, confusion, somnolence, and disorientation may be noted.

Famotidine

Famotidine is the most potent H_2RA. It is approximately eight to 10 times more potent than ranitidine. Famotidine requires a lower volume of administration, 10 mL daily versus 60 to 80 mL for cimetidine and ranitidine. This may be particularly useful in patients with congestive heart failure or those requiring fluid restriction.

Table 3. Prophylaxis for stress-related muscosal disease: high-risk trials

Trial	Patients, *n*	Bleeding rate, %	*P* value
H_2RA*	35	31	
PPI	32	6	< 0.05
PPI† (open label)	75	0	NA
PPI‡ (open label)	60	0	NA
H_2RA§	36	10.5	
Sucralfate	36	9.3	
PPI	36	0	< 0.05

*Levy *et al*. [48].
†Phillips *et al*. [32].
‡Lasky *et al*. [31].
§Azevedo *et al*. [51].
H_2RA—histamine 2 receptor antagonist; NA—not applicable; PPI—proton pump inhibitor.

Twice-daily dosing (20 mg every 12 hours) maintains pH above 4 for most of the day; higher doses (50 mg every 24 h) can achieve 24-hour maintenance of this pH level. Drug interactions appear to be minimal with famotidine. Rare cases of thrombocytopenia have been associated with famotidine. In controlled trials of famotidine, no drug interactions were observed with agents metabolized by the P-450 enzyme system, including warfarin, theophylline, phenytoin, and diazepam.

Proton pump inhibitors

- Five PPIs are available: omeprazole, esomeprazole, lansoprazole, rabeprazole, and pantoprazole. These medications are prodrugs and are the most potent antisecretory agents. They block the final pathway for acid secretion by irreversibly inhibiting the H^+/K^+ ATP (proton pump) in the gastric parietal cells. The medications are very well tolerated. These drugs appear promising for effective prophylaxis of SRMD (Table 3).

Omeprazole

A single morning dose of omeprazole maintains an intragastric pH of at least 5 for up to 24 hours. After 15 to 24 hours, acid begins to return to the stomach and omeprazole is cleared within 72 hours. The drug is given orally; no IV form is available in the United States. Early studies demonstrated that single IV doses of an experimental formulation of 10 to 80 mg cause a dose-dependent and long-lasting inhibition of pentagastrin-stimulated gastric acid secretion [27]. A daily dose of omeprazole 40 mg IV causes a significant reduction of intragastric pH after 5 days of treatment, but it is not sufficient to keep intragastric pH above 4 in all patients during the first day of treatment [28]. Continuous infusion of omeprazole maintains pH above 4 for approximately 95% of the time during the first 72 hours of treatment, with maximal effect occurring between 3 and 5 days [29,30]. Omeprazole suspension administered through an NG tube has been shown to prevent clinically significant GI bleeding safely and to maintain gastric pH at favorable levels [31,32]. It appears that tolerance does not develop. Although efficacy and safety studies are under way, oral omeprazole has not been approved for prophylaxis of stress ulcers.

The most recent PPI is esomeprazole, the S-isomer of omeprazole. It is metabolized in the liver and may interfere with CYP2C19, the major metabolizing enzyme of the hepatic cytochrome P-450 enzyme system. Significant drug interactions between esomeprazole and phenytoin, warfarin, quinidine, clarithromycin, or amoxicillin have not been demonstrated in clinical studies. If the drug is administered with diazepam (a CYP2C19 substrate), a decrease of 45% in clearance of diazepam results. Esomeprazole is well tolerated; the most common adverse events are diarrhea (4.3%), headache (3.8%), and abdominal pain (3.8%).

Lansoprazole

Lansoprazole was the second PPI available in the United States. Lansoprazole is well tolerated, and reported adverse effects are similar to those observed in patients treated with other PPIs. The only significant side effect is occasional diarrhea.

Rabeprazole

The third PPI available is rabeprazole. Rabeprazole has a rapid onset of H^+, K^+-ATPase inhibition and is reported to have a greater effect on intragastric pH than omeprazole after the first dose. Similar to pantoprazole, rabeprazole has a minimal effect on the hepatic cytochrome P-450 enzyme system and has shown no clinically relevant drug interactions.

Pantoprazole

Pantoprazole is the fourth approved PPI in the United States. It has the lowest potential for drug interactions among PPIs. PPIs inhibit acid production by binding to specific cysteine residues within the proton transfer domain of actively secreting pumps. Whereas lansoprazole, omeprazole, and rabeprazole interact with only one of the two available residues at a time, pantoprazole appears to covalently modify both [33]. Furthermore, unlike pantoprazole, lansoprazole, omeprazole, and rabeprazole are capable of binding other cysteines on the proton pump unrelated to acid suppression, which may dilute the level of available drug for interaction with active enzymes and possibly contribute to unwanted systemic effects. Of the PPIs, pantoprazole has the lowest pH of activation and the highest stability under moderately acidic conditions. Consequently, pantoprazole is predicted to have high gastric selectivity and a low likelihood of interacting with ion pumps in cell types other than the parietal cell.

High potency and the availability of an IV form make pantoprazole well suited for prophylaxis of SRMD in the ICU. Intermittent PPI infusion is markedly superior when compared with intermittent H_2 blocker infusion [34].

Intravenous proton pump inhibitors

Most patients with SRMD are in the ICU. Many of these critically ill patients require mechanical ventilation, have acute gastroparesis or ileus, and cannot tolerate oral or NG medications. The prevalence of abnormalities is estimated to be as high as 50% in ICU patients and as high as 80% in patients with head injury. In critically ill patients, IV pantoprazole is equipotent with the oral form in suppression of acid secretion, exhibiting a dose-dependent inhibition of gastric acid secretion [35]. A dosage of 80 mg daily suppresses acid secretion by more than 90% [36].

Other treatments

Sucralfate

Sucralfate consists of a core of sucrose molecules surrounded by aluminum hydroxide sulfate salts. Sucralfate does not inhibit secretion or neutralize gastric acid. It coats the gastric mucosa and forms a thin, protective layer between the mucosa and the gastric acid in the lumen. Another mechanism of action may be the stimulation of mucosal defenses, triggering the release of cytoprotective agents, specifically prostaglandin E_2. Sucralfate is comparable to antacids in healing ulcers. The medication is not a systemic drug, which offers advantages over some other agents. Its major drawback is that it may decrease absorption of other concomitant oral medications (Table 4). Aluminum toxicity has occurred in patients with chronic renal failure. A liquid form of sucralfate is now available and can be easily administered through an NG tube.

Prostaglandins

The only prostaglandin commercially available is misoprostol, a synthetic prostaglandin E_1 analog. The medication has mucosal protective properties and diminishes gastric acid secretion. Very few studies have evaluated prostaglandin analogs

Table 4. Drug interactions with sucralfate

Simultaneous omeprazole administration reduces the elimination of:
Diazepam
Warfarin
Cyclosporine
Phenytoin
Simultaneous sucralfate administration reduces absorption of:
Cimetidine
Digoxin
Fluoroquinolone antibiotics
Ketoconazole
Phenytoin
Ranitidine
Tetracycline
Theophylline
1-Thyroxine
Quinidine

for prophylaxis of stress-related bleeding in the ICU patient. One study, which compared misoprostol to antacid titration [37], found no difference between the two treatment groups in upper GI tract lesions or serious side effects. Both groups had a diarrhea rate greater than 22%, which is considerably higher than is noted with other stress prophylaxis agents.

Somatostatin analogs

Somatostatin is a powerful inhibitor of acid secretion, exerting a tonic inhibitory restraint on acid secretion. A local feedback mechanism exists whereby intraluminal acid stimulates somatostatin, which, in turn, attenuates acid secretion. Somatostatin is the main inhibitor of gastrin in vivo. There are no clinical data evaluating somatostatin for the prophylaxis of SRMD; therefore, it cannot be recommended for stress ulcer prophylaxis.

Antacids

Antacids work by neutralizing gastric acid and by inactivating the proteolytic activity of pepsin. At a pH of 5, both are achieved. With frequent dosing and pH monitoring, antacid administration can maintain a luminal pH of 3.5 or higher [20]. A randomized study of 100 patients demonstrated that two of 51 patients (4%) receiving antacid prophylaxis and 12 of 49 ICU patients (25%) not receiving antacid prophylaxis had stress-related bleeding [21]. Patients with renal failure or hypotension were at particular risk of bleeding. More deaths (11 patients) occurred in ICU patients receiving antacid prophylaxis than in those who were not (seven patients) [21]. Care should be taken when increasing the pH of the stomach and concomitantly increasing gastric volume through frequent NG tube dosing. The combination may increase the number of pathogenic flora, with the large volumes increasing the risk of aspiration.

Antibiotics

There is no available evidence that *Helicobacter pylori* plays a role in SRMD. In a recent prospective study [37], serologic analysis was performed on all consecutive patients over a 1-year period who showed significant upper GI bleeding (defined as hematemesis, melena, or grossly bloody NG aspirate) after cardiac surgery. Patients with no evidence of GI hemorrhage after cardiac surgery were chosen as controls. *H. pylori* was not a risk factor for upper GI bleeding; patients who required prolonged mechanical ventilation were at high risk [38]. Treatment with antibiotics for *H. pylori* in the ICU setting can be associated with severe consequences,

including selecting for resistant organisms, acquiring methicillin-resistant *Staphylococcus aureus,* promoting ventilator-associated pneumonia [39], and inducing *Clostridium difficile* colitis. Therefore, we strongly discourage the use of antibiotics for the eradication of *H. pylori* in the acute setting until there is further evidence demonstrating that the benefit of early treatment outweighs the risks.

Continuous nasogastric feeds

Continuous NG feeds to prevent stress-related bleeding in critically ill patients have not been well studied. The mechanism proposed is a constant neutralization of gastric acidity because most enteral feeding solutions have a high pH. Studies on volunteers demonstrated that continuous enteral nutrition produces gastric pH values similar to those seen with fasting or standard nutrition. This suggests that, under most healthy physiologic conditions, gastric acidity is subject to strict feedback control. Enteral feeding effects in critically ill patients have not been well studied. Only one paper found that enteral nutrition conferred a lower bleeding rate [40]. It is recommended that another form of therapy should be added for high-risk patients.

Nosocomial pneumonia and prophylaxis for stress-related mucosal disease

- One concern associated with stress ulcer prophylaxis is the risk of nosocomial pneumonia, which is the most frequent infection in mechanically ventilated patients. The etiology may be related to increasing the gastric pH, followed by aspiration. Alternatively, it may be related to incomplete acid volume suppression. Antacids and H_2RAs have been associated with increased gastric colonization, primarily with gram-negative organisms, at gastric pH levels greater than 4. When the pH is less than 3.5, gram-negative bacteria do not grow well in the stomach. Several early studies had suggested that gastric colonization may be less frequent and of lesser magnitude in ventilated patients given sucralfate than in those given antacids or H_2RAs [41–44]. It was thought that not raising gastric pH may confer an advantage, conceivably reducing the incidence of nosocomial pneumonia because it is known that organisms from the stomach may be aspirated into the pulmonary tree. Earlier studies suggested an increase in nosocomial pneumonia with H_2RA acid suppression, but later and more definitive studies have clearly refuted this premise.

Evolution of nosocomial pneumonia studies

- In one of the earliest studies [45], in 130 ventilated patients, nosocomial pneumonia was reported in significantly fewer patients given only sucralfate than in those given antacids or an H_2RA. However, on stratification, antacids were associated with a 23% incidence of pneumonia, whereas the H_2RA group had an incidence of only 5.9% (less than those receiving sucralfate). It is unclear whether this increase in pneumonia is caused by acid suppression or increased gastric volumes from the frequent antacid administration. The mortality was higher in the antacid/H_2RA–treated group. A meta-analysis of the efficacy of sucralfate compared with H_2RAs (nine studies) and with antacids (10 studies) showed sucralfate to be at least as effective as the other prophylactic methods. Another meta-analysis showed that pneumonia occurred significantly less frequently in patients given sucralfate than in those given H_2RAs (five studies) or antacids (four studies) [46]. A more recent randomized controlled trial of 244 patients found that sucralfate reduced the risk for developing late-onset pneumonia by maintaining a low gastric pH and reduced bacterial colonization in many patients [47].

- In a study comparing omeprazole and ranitidine for stress ulcer prophylaxis, 14% of patients receiving ranitidine developed nosocomial pneumonia versus 3% of patients receiving omeprazole; this difference was not statistically significant ($P > 0.05$) [48]. The largest trial to date is a 4-year, multicenter, prospective, randomized trial from 16 Canadian ICUs ($n = 1200$) [49•]. The authors found clinically important bleeding in 1.7% of IV ranitidine–treated patients versus 3.8% in NG or oral sucralfate–treated patients. There was no statistically significant difference in ventilator-associated pneumonia rates (19.1% vs 16.2%, respectively). More study is needed to clarify pneumonia rates and effectiveness of prophylaxis, particularly compared with PPIs in mechanically ventilated patients.

Side-effect profiles

- All medications used for the prophylaxis of stress ulcers are associated with some side effects.

Histamine 2 receptor antagonists

All H_2RAs are capable of crossing the blood-brain barrier and can be associated with neuropsychiatric symptoms, including agitation, confusion, lethargy, and disorientation. Most side effects with H_2RAs are dose dependent. As previously mentioned, drug interactions are associated with H_2RAs. Up to 30% of patients treated with very high-dose ranitidine intravenously have increases in their serum aminotransferase levels, with only 10% affected at lower doses. The side effects are more pronounced in patients with renal insufficiency.

Proton pump inhibitors

The drug interactions of omeprazole are comparable to those of cimetidine, with particular reference to clearance of several drugs (Table 4). All five PPIs significantly increase the pH of the gastric fluid, which can alter the chemistry, absorption, or release of oral medications. There is no evidence that this leads to clinically significant consequences. The interaction of PPIs with the hepatic cytochrome P-450 enzyme family is a potential source of adverse drug interactions. Lansoprazole and omeprazole have been shown to induce the activity of these enzymes, which might affect the metabolism of other compounds such as caffeine, theophylline, carbamazepine, warfarin, phenytoin, diazepam, mephenytoin, cyclosporine, bismuth, methotrexate, and ketoconazole. Studies to investigate this possibility have shown an increase in the metabolism of these agents when used in conjunction with lansoprazole and omeprazole. Of the five PPIs, pantoprazole and rabeprazole have the lowest induction potential for the hepatic cytochrome P-450 enzymes, reducing the potential for interactions. Despite that PPIs can alter metabolism or absorption of other medications, the possibility for adverse reactions with these medications is minimal.

Sucralfate and misoprostol

Sucralfate can decrease the absorption of some medications when administered concomitantly. Misoprostol is associated with diarrhea even at moderate doses and can induce a flare of colitis in patients with inflammatory bowel disease. Prostaglandins are associated with a diarrhea rate in nearly one third of patients treated, thus limiting their clinical usefulness.

Antacids

Antacids are associated with electrolyte abnormalities and changes in bowel motility. Magnesium-containing preparations predispose the patient to diarrhea and cannot be given to patients with renal insufficiency, whereas preparations containing aluminum and calcium lead to constipation. Prolonged use may cause alkalosis.

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