Stress-related Mucosal Disease: Considerations of Current Medication Prophylaxis

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Stress ulcer prophylaxis is recommended in orthopedic patients with well-defined risk factors such as coagulopathies and mechanical ventilation.

Stress-related mucosal disease (SRMD) is a potential complication in critically ill patients. This acute insult to the gastric mucosa and the resultant gastrointestinal bleeding may create hemodynamic instability and warrant transfusions, contributing to the severity of a patient's disease. Several risk factors have been identified for stress-related mucosal disease. One large study by Cook et al[1] determined that coagulopathies and mechanical ventilation are two main risk factors. Although this is the landmark trial, others have proposed additional patient factors including recent major surgery, hepatic or renal failure, and sepsis.[1,2]

Use of measures to prevent bleeding related to stress-related mucosal disease has been debated. A recent survey of internal medicine physicians, anesthesiologists, and surgeons revealed that 28.6% prescribed stress ulcer prophylaxis (SUP) regardless of any risk factors present, and despite only a 2% incidence of clinically important bleeding reported by a majority of respondents.[3] A similar survey of intensive care unit physicians from 86% of the institutions polled revealed that >90% of their patients received stress ulcer prophylaxis.[4]

Stress ulcer prophylaxis has not been directly studied in the orthopedic population. However, patients exhibiting risk factors such as traumatic injury, major surgery, or other critical illnesses, should be considered for therapy to prevent stress-related mucosal disease. This article provides an overview of the current definitions, risk factors, and pharmacologic options for the prevention of stress-related ulcers.

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Definitions

Stress-related mucosal disease is an acute condition in which erosion of the gastric mucosa occurs secondary to a physiologic stress.[5] The manifestations of stress-related mucosal disease, such as bleeding, have not been consistently defined and therefore results from early controlled trials are difficult to interpret. For the purpose of this article, clinically important bleeding will be considered equivalent to overt gastroduodenal bleeding that results in hemodynamic instability (measured through a drop in blood pressure or an increase in heart rate) and subsequent need for red blood cell transfusions or surgical intervention of the gastric ulcers.[1,6]

Pathophysiology

Many processes contribute to the formation of stress ulcers in critically-ill patients. Splanchnic hypoperfusion results in decreased mucosal blood flow and breakdown of mucosal defenses.[5] Critical illness such as trauma, sepsis, or burns can stimulate the release of catecholamines and proinflammatory cytokines leading

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Table

Dosage And Considerations of Common Medications Used to Prevent SRMD*

Medication Class	Medication	Usual Adult Dosage Range	Medication Considerations
Histamine Type 2 Receptor Antagonists	Cimetidine (Tagamet)	50 mg/h continuous infusion 300 mg every 6 h (IV) (Nasogastric tube, PO, IV)	
	Famoditine (Pepcid)	1.7 mg/h continuous infusion (IV) 20 mg every 12 h (Nasogastric tube, PO, IV)	Available in many dosage forms allowing ease of administration Considered by many as first line treatment in SRMD
	Ranitidine (Zantac)	6.25 mg/h continuous infusion (IV) 150 mg every 12 h (Nasogastric tube, PO) 50 mg every 12 h (IV)	Adjust doses for renal insufficiency
Proton Pump Inhibitors	Esomeprazole (Nexium)	40 mg daily (IV, nasogastric tube, PO)	Available in many dosage forms allowing for ease of administration
	Lansoprazole (Prevacid)	15-30 mg daily (PO), nasogastric tube, IV	Considered the most potent antisecretory agents available
	Omeprazole (Prilosec)	20-40 mg daily (PO, nasogastric/jejunal, duodenal tube)	Oral lansoprazole may be administered as a capsule or as a disintegrating tablet
	Pantoprazole (Protonix)	40 mg daily (IV, nasogastric tube, PO)	Less efficacious than H2 antagonists
Other	Sucralfate (Carafate)	1 g every 6 hours (PO, nasogastric tube) Only oral forms available	Complications of esophageal obstruction have been reported Must be administered into the site of action (stomach) Should not be placed in jejunum or duodenum

Abbreviations: IV=intravenous, PO=oral, and SRMD=stress-related mucosal disease.
**Includes medications commonly used in practice.*

to splanchnic hypoperfusion. Hypovolemia and subsequent decreased cardiac output also can contribute to this process. As the body attempts to shunt blood flow to vital organs, visceral blood flow is compromised. As this continues over time, reduced bicarbonate secretion, decreased gastrointestinal motility, and decreased gastrointestinal integrity can lead to ulcer formation. Increased gastric acid secretion also is believed to be a major factor for stress-related mucosal disease. Its direct insult to the gastric mucosa, in addition to the breakdown of mucosal defenses, leads to acute stress ulcer formation.[2]

Risk Factors

Several risk factors have been implicated in the development of stress ulcers. Most studies, however, only include critically-ill patients. A large, prospective, multicenter cohort study of 2252 patients revealed two strong independent risk factors for clinically important bleeding in critically-ill patients: coagulopathy and respiratory failure.[1] Similar findings resulted from a prospective evaluation of the upper gastrointestinal bleeding in 174 patients in the medical intensive care unit.[7]

An additional analysis of 1077 ventilated patients demonstrated that increased serum creatinine was a significant risk factor; however these results should only be extrapolated to this specific patient population.[8] Other proposed risk factors include recent major surgery (organ transplantation), hepatic failure, renal failure, use of anticoagulant therapy, sepsis, burns, use of high dose corticosteroids, and hypotension.[1,2,9]

Prophylaxis of Stress-Related Mucosal Disease

Many agents are available for use in patients at risk for stress-related mucosal disease. These agents include histamine type 2 receptor antagonists

(H2RAs), proton pump inhibitors (PPIs), sucralfate, antacids, and prostaglandin analogs. Common products, usual dosage ranges, and considerations are shown in the Table.

Current studies reveal that histamine type 2 receptor antagonists are the most widely used first-line agents; however proton pump inhibitors are widely used and their diverse routes of administration and favorable side effect profile are desirable features.[3]

Much of the data regarding H2 antagonists is variable and their comparison to sucralfate, antacids, and placebo have shown mixed results.

H2 Receptor Antagonists

Histamine type 2 receptor antagonists are the most studied and used agents for stress ulcer prophylaxis. Many clinicians consider these agents to be first-line therapy for this indication; a recent survey identified that 63.9% of intensive care unit physicians use this class of medications as their primary treatment.[3] The agents available in this class include cimetidine (Tagamet; GlaxoSmithKline, Reasearch Triangle Park, North Carolina), famotidine (Pepcid; Merck and Co, Whitehouse Station, New Jersey), nizatidine (Axid [oral]; Reliant Pharmaceuticals, Liberty Corner, New Jersey, [capsules]; Eli Lilly and Co, Indianapolis, Indiana), and ranitidine (Zantac; GlaxoSmithKline). Of these agents only continuous infusion cimetidine has been approved by the Food and Drug Administration (FDA) for stress ulcer bleeding in critically-ill patients, but it has fallen out of favor secondary to its drug interaction profile.[6,10] The other agents in the class are considered to be as equally effective as cimetidine.[6]

Histamine type 2 receptor antagonists exert their effect through inhibition of H2-receptors located on the acid-secreting parietal cells. Histamine type 2 receptor antagonists are therefore antisecretory agents. This effect seems to be selective for this histamine receptor, and does not significantly contribute to other histamine receptor sites.[2]

Many studies have been conducted to prove the efficacy of histamine type 2 receptor antagonists for stress-related mucosal disease. Martin et al[11] revealed that continuous infusion cimetidine was superior to placebo in prevention of stress-ulcer related upper gastrointestinal bleeding. The meta-analysis performed by Cook et al[12] revealed that histamine type 2 receptor antagonists significantly reduced clinically important bleeding versus placebo. However, as mentioned by the most recent practice guidelines, much of the data regarding H2 antagonists is variable and their comparison to sucralfate, antacids, and placebo have shown mixed results.[6]

Adverse reactions to histamine type 2 receptor antagonists are relatively uncommon, although central nervous system toxicity, including confusion and hallucinations, cardiovascular effects through possible coronary vasoconstriction and inotropic effects, cytopenia, and hepatitis may occur limiting their use in certain patients.[6,13] In addition, histamine type 2 receptor antagonists may lose their antisecretory effect over prolonged administration, with tolerance shown to occur within the first 2 to 3 days of therapy.[14] Drug interactions through the CYP450 system are possible with cimetidine and ranitidine, however nizatidine and famotidine avoid this complication.[13] Most histamine type 2 receptor antagonists can be administered through both oral and intravenous routes, allowing for convenient medication use, contributing to their role as first-line treatment for stress ulcer prophylaxis by many physicians.[3]

Proton Pump Inhibitors

Proton pump inhibitors have not been FDA-approved for stress ulcer prophylaxis and the existing guidelines do not recommend the use of these agents for this purpose.[6] However, the guidelines do not incorporate more recent studies indicating that proton pump inhibitors are noninferior to histamine type 2 receptor antagonists. Nevertheless, use of proton pump inhibitors has significantly increased in recent years.

Many available agents include omeprazole (Prilosec; AstraZenecaLP, Wilmington, Delaware), esomeprazole (Nexium; AstraZenecaLP), lansoprazole (Prevacid; TAP Pharmaceutical Products, Lake Forest, Illinois), rabeprazole (Aciphex; Eisai Inc, Teaneck, New Jersey, [delayed release capsules]; Janssen Pharmaceutica, Titusville, New Jersey), and pantoprazole (Protonix; Wyeth Pharmaceuticals Inc, Philadelphia, Pennsylvania). Collectively they are considered the most potent acid antisecretory agents available.[5] Proton pump inhibitors exert their effect through inhibition of the H+, K+−ATPase pump at the surface of the parietal cell. It is through the regulation of this final step in acid secretion that proton pump inhibitors can be efficacious in decreasing acid secretion.[2]

Reports on the use of proton pump inhibitors for stress ulcer prophylaxis are limited. One recent trial comparing omeprazole suspension to intravenous cimetidine in 359 intensive care unit patients revealed that omeprazole was not inferior to the intravenous histamine type 2 receptor antagonists.[15] A smaller study revealed that omeprazole significantly reduced the risk of clinically significant bleeding compared to ranitidine. However, this trial was small and patients in the ranitidine group had more risk factors for bleeding making the comparison difficult.[16]

Proton pump inhibitors are well tolerated with few adverse effects. Headaches, abdominal pain, nausea, and some other gastrointestinal side effects have been reported, although the incidence of these effects is low.[6,17] Potential drug interactions are possible with these agents through cytochrome P450 enzymes, with omeprazole having the greatest potential for these drug interactions.[5,10] Proton pump inhibitors are administered orally (tablets, capsules, and suspensions) and intravenously. Lansoprazole and esomeprazole also are available as oral powder packets allowing convenient administration via gastric or duodenal tubes, and lansoprazole alone is available as an oral disintegrating tablet (Table).

Sucralfate

Sucralfate is a basic aluminum salt that provides protection of the gastrointestinal tract through multiple mechanisms: formation of a protective layer via interaction with the mucosal epithelium, preservation of mucosal blood flow, and increased bicarbonate and prostaglandin production.[18] Additionally, sucralfate may enhance mucosal cell proliferation through its interaction with epidermal growth factor. It does not seem to significantly decrease intraluminal acid secretion or have effects on acid neutralization.[19]

Randomized, controlled trials have revealed mixed results regarding the use of sucralfate compared to other therapies. In a meta-analysis of critically-ill patients, results suggest that antacids may be slightly more favorable than sucralfate for the prevention of clinically important bleeding; however these results did not reach statistical significance. This trial was unable to compare histamine type 2 receptor antagonists and sucralfate secondary to insufficient data.[12] A follow-up meta-analysis revealed that histamine type 2 receptor antagonists were comparable to sucralfate in regards to clinically important bleeding, though the same analysis concluded that sucralfate reduced mortality compared with both antacids and histamine type 2 receptor antagonists.[20]

Sucralfate therapy has been implicated in the formation of esophageal bezoars and obstruction with concomitant enteral feedings.

A randomized, placebo-controlled, blinded trial of 1200 mechanically ventilated patients assessed ranitidine and sucralfate for the prevention of clinically significant upper gastrointestinal bleeding.[21] Results revealed that ranitidine reduced clinically significant bleeding compared to sucralfate. No difference in the risk of ventilator-associated pneumonia, duration of stay in the intensive care unit, or mortality in the intensive care unit was observed between the two groups. Due to the clear superiority of ranitidine compared to sucralfate in this trial, use of sucralfate is no longer favorable.

Adverse drug reactions and administration issues with sucralfate also have limited its use. Common drug interactions with ranitidine, digoxin, fluoroquinolone antibiotics, phenytoin, ketoconazole, tetracyclines, and levothyroxine have been identified. As a result, these medications should be administered at least 2 hours prior to sucralfate.[22] In addition, sucralfate therapy has been implicated in the formation of esophageal bezoars and obstruction with concomitant enteral feedings, a common practice in the intensive care unit.[23,24] Other adverse effects include constipation, indigestion, vomiting, dizziness, and possible hypersensitivity reactions.[22]

Antacids and Prostaglandin Analogs

Antacids and prostaglandin analogs are other options for stress ulcer prophylaxis, however use of these medications is limited. Antacids are orally administered medications that directly neutralize acid within the stomach.[2] They do not have the ability to decrease acid secretion or production. Currently available antacids include calcium carbonate, sodium bicarbonate, aluminum hydroxide, and magnesium hydroxide. Antacids have been shown to significantly reduce overt bleeding (defined as hematemesis, bloody gastric aspirate, melena, or hematochezia) compared to placebo, but not clinically important bleeding.[12] Antacids are not commonly used for stress ulcer prophylaxis due to their need for frequent administration (every 1-2 hours), and gastrointestinal adverse reactions, including both constipation and diarrhea.[2,10]

Prostaglandin analogs have not been extensively studied for use in stress ulcer prophylaxis. The available prostaglandin analog used for this indication is misoprostol, a prostaglandin E1 analog that exhibits both antisecretory and gastric mucosal protective properties. Misoprostol is administered orally and is available in tablet form. It should be used with caution in women of childbearing age as it is an abortifacient.[25] Common side effects of misoprostol include diarrhea and abdominal pain, which can be exacerbated by concomitant use of magnesium-containing antacids. Diarrhea can be dose-related and may result in discontinuation of therapy.[25,26] Prostaglandin analogs are currently indicated for prevention of nonsteroidal anti-inflammatory drug induced-gastric ulcers, but not for stress ulcer prophylaxis.[25]

Recommendations/ Conclusion

The most current guidelines for stress ulcer prophylaxis were set forth by the

American Society of Health-System Pharmacists in 1999.[6] However, because these guidelines do not include recent data regarding proton pump inhibitors, they are obsolete. The advent of proton pump inhibitors has contributed greatly to the prevention of stress-related mucosal disease, with trials revealing that they are noninferior to histamine type 2 receptor antagonists.[15] Although proton pump inhibitors are not FDA-approved for use in this population, their ease of administration and favorable side effect profile make them a viable option in addition to histamine type 2 receptor antagonists for the prevention of stress-related mucosal disease.

It is important to consider availability, ease of administration, and adverse events when choosing agents for the prevention of stress ulcers. In addition, risk factors should be assessed.

Stress ulcer prophylaxis is recommended in patients with well-defined risk factors such as coagulopathies and mechanical ventilation. It should be considered in patients with other risk factors such as recent major surgery (organ transplantation), hepatic failure, renal failure, use of anticoagulant therapy, sepsis, burns, use of high dose corticosteroids, and hypotension. However, stress ulcer prophylaxis has not been proven to affect mortality rates in those with stress-related mucosal disease.[6] Therefore, such use is still debated and both the risks and benefits of therapy must be considered. If stress ulcer prophylaxis is initiated in high-risk patients, therapy should be ceased when the risk is no longer present. This assures that patients are not continued or discharged on these therapies when they are not required.

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