Preventing Stress Related Mucosal Disease in the Intensive Care Unit

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Abstract

The two clinically significant risk factors for stress related mucosal disease (SRMD) in the intensive care unit (ICU) that necessitate the need for prophylaxis are respiratory failure requiring mechanical ventilation and coagulopathy. Patients who do not have these risk factors do not routinely require a prophylactic agent. Health care providers, including advanced practice nurses, must identify those patients who are most at risk for SRMD and begin prophylactic treatment as soon as possible with the goal of raising gastric pH to a level that is > 4. In addition, aggressive treatment should begin immediately to support the patient's underlying conditions. Medical literature does not support use of antacids or sucralfate and no prospective studies compare efficacy and outcomes of H2RA and PPI. Choice of an agent must be made considering available medical literature along with health care institution and patient specific variables.

INTRODUCTION

Gastrointestinal mucosal damage as a result of physiologic stress in the intensive care unit (ICU) continues to be a problem for acutely ill patients despite many available prophylactic modalities. At least three-quarters of ICU patients will develop stress related mucosal disease (SRMD) within the first 24 hours of their ICU stay ([1,2,3]). These mucosal lesions occur as a direct consequence of stressors on other organ systems. SRMD can manifest as superficial injuries or deep mucosal lesions that have a high probability of bleeding ([4]). This article will address the problem in a general manner and refer only to SRMD.

SRMD increases patients' morbidity and mortality through complications such as ulcer development which can cause significant gastrointestinal hemorrhage, increased length of stay in the ICU, cost of care, as well as increased risk for adverse reactions related to blood transfusions ([2,3]). SRMD can be prevented; however careful consideration by the health care provider must be made to choose the correct pharmacologic treatment modality given a patient's current condition and medications as well as past medical history. The purpose of this paper is to address optimal management strategies for the prevention of SRMD. While overt or significant gastrointestinal bleeding as result of SRMD is indeed a serious complication, the management of that problem is beyond the scope of this paper.

PATHOPHYSIOLOGY AND RISK FACTORS

SRMD often first develops in the stomach, but migrates towards the small intestine over time. The depth of tissue injury also increases as time progresses. Systemic physiologic stress leads to increased secretion of gastrin by parietal cells which trigger additional acid secretion, thereby lowering gastric pH. A built-in protective mechanism exists in the form of a glycoprotein mucus layer that coats and protects the gastric mucosa which secretes bicarbonate and neutralizes potentially damaging acid. Hypoperfusion of the splanchnic bed disrupts this system, leading to decreased gastric blood flow which in turn diminishes the amount of protective mucus secreted. When the protective layer is altered, bicarbonate is not secreted to neutralize acid. The acid then diffuses back into the gastric mucosal layer causing tissue damage. Hypoperfusion eventually leads to reperfusion with additional associated cell injury and further mucosal damage ([1, 3]). The acidic environment, in conjunction with the altered protective mechanism of the mucus layer can result in SRMD.

Multiple physiologic and iatrogenic factors play a role in the development or exacerbation of SRMD (Table 1). However, only two risk factors have been shown to contribute to clinically significant gastrointestinal bleeding in ICU patients: respiratory failure requiring mechanical ventilation (MV) for at least 48 hours and coagulopathy (i.e., a platelet

count < 50,000 per cubic millimeter, an International Normalized Ratio [INR] of > 1.5 or a partial-thromboplastin time > 2 times the control value). ([8]). The etiology of MV as a risk factor is two fold. MV is felt to contribute to splanchnic hypoperfusion by lowering mean arterial blood pressure and/or increasing vascular resistance of the gastrointestinal system ([9]). Second, proinflammatory cytokine production is known to increase with MV, which in turn is felt to contribute to splanchnic hypoperfusion and alters smooth muscle function ([9]).

Table 1: Risk Factors Associated with SRMD ([3,4,5,6,7,8])

- *Respiratory failure requiring mechanical ventilation
- *Coagulopathy
- Renal failure
- Hepatic failure
- Sepsis
- Hypotension
- Trauma and neurotrauma
- History of gastrointestinal bleeding
- Burns
- Prolonged surgery
- Glucocorticoid administration
- Myocardial infarction
- Neurosurgery
- Multiple organ failure
- Ileus
- Organ transplantation
- Anticoagulant therapy

* = risk factors proven to be associated with clinically significant gastrointestinal bleeding in ICU patients

Identifying those patients who are most at risk for SRMD and beginning prophylactic treatment as soon as possible with the goal of raising gastric pH > 4 is imperative. ([1,2, 10]). Additionally, aggressive treatment must be started immediately to treat the patient's underlying conditions, promote adequate systemic and splanchnic perfusion, and correct coagulopathies ([3]).

PHARMACOLOGIC OPTIONS FOR PREVENTION OF SRMD

Several pharmacologic options exist for the prevention of SRMD. These options include antacids, sucralfate, histamine-2 receptor antagonists (H_2RA) and proton pump inhibitors (PPI) (Table 2). While these classes of medications are relatively safe, no drug is without side effects and caution must be used when prescribing these medications, particularly to patients with renal dysfunction or hematological disorders.

Figure 1

Table 2: Pharmacologic Profile of Prophylactic Medications (, , ,)

Drug class	Mechanism of action	Side effect profile	Common preparations
Antacids	Neutralize gastric acid, decrease rate of gastric emptying	fluid retention, dementia, aluminum toxicity, metabolic alkalosis, hypercalcemia, uremia, calcinosis, hypophosphatemia, hypermagnesemia, trace element deficiency, constipation, diarrhea, gastrointestinal obstruction, nephrotoxicity, aspiration pneumonia, and osteomalacia.	PO
Sucralfate	Forms a protein barrier over ulcer that protects it from acid, bile and pepsin	Constipation, aluminum toxicity, hypophsophatemia, drug interactions	PO
Histamine-2 receptor antagonists (H_2RA)	Decreases gastric secretions via competitive inhibition of histamine at H-2 receptor site	Constipation, diarrhea, dizziness, headache, thrombocytopenia, seizure, bronchospasm, drug interactions	PO, IV
Proton pump inhibitors (PPI)	Inhibits H+/K+ ATPase enzyme system in parietal cells, blocks final step of acid production	Constipation, nausea, vomiting, diarrhea, headache, dizziness, abdominal pain, rash, upper respiratory infection, pancytopenia, leukocytosis	PO, IV

PO = by mouth
IV = intravenous

SUCRALFATE AND ANTACIDS

Sucralfate and antacid use is less common than H_2RA or PPI, although these agents remain treatment options ([1,2,3]). Antacids are capable of raising gastric pH to levels > 4 and are relatively inexpensive, but require frequent administration and gastric pH monitoring, thereby increasing

nursing workload and cost of care ([4, 10]). Antacids may also not be an appropriate choice for patients with chronic kidney disease because of the electrolytes or metallic components contained. For example, hypermagnesemia can result from magnesium hydroxide-containing antacids or aluminum toxicity with aluminum hydroxide-containing antacids. Sucralfate is another cost effective choice that requires frequent administration, but a landmark trial has shown that sucrafate is less effective than H_2RA probably because this agent does not significantly alter the gastric pH but instead acts as a gastroprotective agent by forming a complex that binds to and protects the lesion ([8]). Sucralfate also is a poor choice for patients with renal impairment because of the potential for increasing serum aluminum concentrations. However, this problem has not been shown when the drug is used for short terms (less than two weeks) in critically ill patients for ([12]). One other adverse effect of using aluminum hydroxide-containing antacids or sucralfate in patients with normal renal function is the development of hypophosphatemia.

HISTAMINE 2 RECEPTOR ANTAGONISTS VERSUS PROTON PUMP INHIBITORS

Much debate remains between the superiority of H_2RA versus PPI for the use of SRMD prophylaxis because no randomized, double blind, placebo controlled trials exist comparing the two agents for this indication. Arguments in favor of using H_2RA include: approval by the Food and Drug Administration (FDA) for use in the prevention of SRMD, relatively low cost, efficacy in raising gastric pH to levels that inhibit mucosal damage, and the availability of oral and intravenous (bolus or continuous infusions) formulations. Additionally, minimal drug interactions exist, and H_2RA have been proven successful in decreasing the incidence of bleeding in patients at risk for stress related mucosal changes ([3,4]). Despite these positive attributes, H_2RA also have some negative characteristics. These agents have been shown to lose effectiveness in maintaining a gastric pH > 4 after less than 48 hours of use if bolus dosing is used. H_2RA may also have the potential to increase the risk of developing nosocomial pneumonia by increasing gastric pH. An acidic gastric environment could eradicate ingested potential pulmonary pathogens before the organisms can be transmitted in a retrograde fashion and cause pneumonia. By increasing gastric pH to prevent ulcer formation, health care providers may be decreasing the ability of the stomach to defend against bacteria that are ingested, which then may enter the lungs ([12, 13]). Mechanically ventilated patients should be placed with the head of bed elevated > 30° unless medically contraindicated to minimize the possibility of aspiration and ventilator-associated pneumonia. Other rare but serious adverse effects of H_2RA include thrombocytopenia and central nervous system disturbances; the former may be due to complement activation secondary to drug-antibody complex formation while the latter is due to decreased excretion of the drug in patients with renal failure ([1,2, 4, 14]).

Proton pump inhibitors are more costly than H_2RA but have been shown to raise and sustain a gastric pH > 4 for a longer portion of the dosing interval. These agents can increase gastric pH to > 6 for up to 99% of the dosing interval ([15]). Other advantages include the rapid onset of action and lack of metabolism through the cytochrome P450 isoenzymes, thereby eliminating the potential for many drug-drug interactions ([2, 10, 16]). Tolerance to PPIs have not been reported and dosing is required less frequently at once to twice daily ([4, 6, 16]). Disadvantages of PPIs include higher cost, lack of comparative studies showing any benefit in preventing SRMD as compared to H_2RA, drug-drug interactions with diazepam, warfarin and phenytoin causing prolonged elimination of these agents, and the potential to increase the risk of developing nosocomial pneumonia. ([13]).

CONCLUSION

Patients should be carefully assessed for risk factors for SRMD in order to make the most prudent and cost effective decision regarding use of SRMD prophylaxis. Using evidence-based medicine, only two significant risk factors for SRMD have been found in ICU patients: respiratory failure and coagulopathy ([8]). Patients in the ICU who do not have these risk factors do not routinely require a prophylactic agent.

These authors recommend that health care providers, including advanced practice nurses, choose an agent and administration route using all of the following institution and patient-specific variables: ability of the patient to receive oral medications (e.g., functioning gastrointestinal tract), potential for adverse effects, and total costs (medication, administration, nursing time). In patients with no previous history of gastric ulcers or gastrointestinal bleeding, data on the superiority of PPIs over H_2RA for SRMD prophylaxis in either the intravenous or oral formulations are lacking. FDA approval for the use of PPIs as an agent for SRMD prophylaxis has not yet been attained and its use should be reserved for patients in whom H_2RA are not appropriate.

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