

## Review

# Science review: The use of proton pump inhibitors for gastric acid suppression in critical illness

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## Abstract

Prophylaxis is routinely provided for critically ill patients admitted to intensive care units (ICUs) who are at high risk for stress-related mucosal damage (SRMD), an erosive process of the gastroduodenum associated with abnormally high physiological demands. Traditionally, treatment options have included sucralfate, antacids and histamine H<sub>2</sub> receptor antagonists (H<sub>2</sub>RAs). The H<sub>2</sub>RAs are currently the most widely used agents in prophylactic acid suppression; however, proton pump inhibitors (PPIs) have recently replaced H<sub>2</sub>RAs in the treatment of many acid-related conditions. PPIs achieve a more rapid and sustained increase in gastric pH and are not associated with the rapid tachyphylaxis seen with H<sub>2</sub>RAs. As a result, and after the introduction of intravenous formulations, PPIs are beginning to be used for the prophylaxis of SRMD in critically ill adults. The high prevalence of renal and hepatic impairment among the ICU population, as well as the need for multiple drug therapy in many patients, means that pharmacokinetic characteristics and the potential for drug interactions may be important considerations in the choice of prophylactic agent. This review seeks to present the pharmacological evidence that may inform decision-making about the prescription of drugs for prophylaxis of SRMD.

**Keywords** histamine H<sub>2</sub> receptor antagonists, intensive care units, omeprazole, pantoprazole, proton pump inhibitors

## Stress ulcer prophylaxis in critically ill patients

Stress-related mucosal damage (SRMD) is an erosive gastritis of unclear pathophysiology, which can occur rapidly after a severe insult such as trauma, surgery, sepsis or burns. SRMD is apparent in 75–100% of critically ill patients within 24 hours of admission to an intensive care unit (ICU) [1,2]. Clinically important bleeding, defined as macroscopic bleeding resulting in hemodynamic instability or the need for red blood cell transfusion, occurs as a result of SRMD in about 3.5% of ICU patients who are mechanically ventilated for 48 hours or more [3]. Along with mechanical ventilation, risk factors for clinically important bleeding from SRMD include coagulopathy, shock, severe burns, a history of gastrointestinal (GI) ulceration, and multiple organ failure [4,5]. Bleeding is associated with a 20–30% increase in absolute risk of mortality, and with an increase of 1–4 in

relative risk [3]. In addition, it increases the demand on limited blood stocks and extends the length of ICU stay by about 4–8 days [3], thereby adding to overall management costs.

To avert these consequences, prophylaxis has been recommended for all ICU patients at high risk of SRMD [4,5]. Stress ulcer prophylaxis is included in the care bundle for critically ill patients on mechanical ventilation recommended by the Institute for Healthcare Improvement and adopted by the National Health Service Modernization agency in the UK [6]. The Surviving Sepsis Campaign, an international initiative founded by the European Society of Intensive Care Medicine, the Society of Critical Care Medicine and the International Sepsis Forum, has also recommended that prophylaxis be a part of critical care [7]. Specific risk factors for SRMD include: mechanical ventilation (more than 48 hours), coagulopathy, neurosurgery, any kind of shock, respiratory

GI = gastrointestinal; H<sub>2</sub>RAs = histamine H<sub>2</sub> receptor antagonists; ICU = intensive care unit; IV = intravenous; PPIs = proton pump inhibitors; SRMD = stress-related mucosal damage.

failure, sepsis, polytrauma, tetraplegia, severe burns (more than 30%) and multiple organ failure [4,5]. Patients in the ICU with a history of gastric or duodenal ulceration, or with liver cirrhosis or acute renal failure, may also benefit from prophylactic measures [4,5].

Although there was once concern that prophylaxis for SRMD by means of gastric alkalinisation might independently increase the risk of nosocomial pneumonia, this seems to have been unfounded. No significant difference in the rate of pneumonia was seen among 1200 patients randomised to treatment with intravenous (IV) ranitidine (19.1%) or intragastric sucralfate (16.2%), the latter having little effect on gastric pH [8]. In practice, the risk of ventilator-associated pneumonia can be reduced in any event through the adoption of the fundamental measures included in the recommended care bundle, such as elevating the head of the patient's bed to 30° or higher [6].

## Method

Few clinical trials have investigated the use of a proton pump inhibitor (PPI) in the prophylaxis of stress ulcer in critically ill patients. In the absence of robust data allowing a systematic review, the points made in this paper are based on a narrative review of the literature concerning the pharmacology of the PPIs and their use in other indications. Literature searches were undertaken on PubMed Medline, using broad terms such as 'stress ulcer' 'critically ill', 'intensive care', 'gastric acid', 'proton pump inhibitor' and 'histamine antagonist', as well as specific drug names, to identify relevant, peer-reviewed papers. Manual searching was conducted within the reference lists of the primary papers identified, and among relevant conference abstracts.

## Pharmacokinetic considerations

The pharmacokinetic characteristics of a drug are particularly important in prescribing in critical care, because of the prevalence of organ dysfunction. In a prospective study to assess the incidence of organ dysfunction or failure among 1449 patients admitted to 40 ICUs, it was found that 40% had at least some degree of renal impairment, and 19% had some degree of hepatic impairment [9]. Among ICU patients with sepsis (one of the patient groups most at risk for SRMD), these proportions were even higher, with 60% of 1643 patients found to have renal impairment and 73% hepatic impairment [10]. However, it is possible that even these figures might not accurately reflect the high prevalence of renal and hepatic dysfunction among the ICU population. Thus, a pharmacokinetic profile that obviates the need for dose adjustment in patients with renal or hepatic dysfunction is an important characteristic for a drug used routinely in critical care. Also important is the potential for drug interactions, and this is dealt with below.

## Current treatment options

Prophylaxis for SRMD essentially involves either protecting the gastric mucosa or increasing the intragastric pH. The

principal means of directly protecting the gastric mucosa is the use of sucralfate. Although the potential protective effect of enteral nutrition on the gastric mucosa means that it should be considered as an adjunct to pharmacological prophylaxis in appropriate cases, there is currently no evidence that enteral nutrition alone is sufficient to reduce the risk of stress-related bleeding [11].

Traditionally, the options for elevating intragastric pH have been antacids and histamine H<sub>2</sub> receptor antagonists (H<sub>2</sub>RAs) [5]. An early study in ICU patients demonstrated that maintaining the gastric pH above 3.5 significantly reduced the risk of upper gastrointestinal (GI) bleeding [12]. It is now generally accepted that the aim of acid suppression in the prophylaxis of SRMD is to maintain gastric pH above 4, a value at which there is a significant decrease in back-diffusible hydrogen ions and inactivation of pepsin [5]. The time taken to elevate pH is also important, because increasing the percentage of time at which pH is greater than 4 is associated with a lower incidence of lesions and subsequent haemorrhagic complications [13].

Sucralfate, the antacids, and the H<sub>2</sub>RAs have each been shown to be effective in reducing the risk of overt and clinically significant bleeding compared with placebo [5,14]. H<sub>2</sub>RAs are currently the most widely used agents [15].

## The limitations of current therapies

### Sucralfate

Sucralfate must be administered intragastrically and is therefore unsuitable for patients in whom a gastric tube cannot be placed. Administration of sucralfate has been associated with acid aspiration and subsequent aspiration pneumonia [16]. Sucralfate is a basic aluminium salt of sucrose octasulphate and there is doubt over its effectiveness in conditions of elevated pH [16], for example after enteral feeding or the administration of an acid-suppressing agent. Adverse events associated with sucralfate include constipation, feeding-tube occlusion, bezoars, aluminium accumulation and hypophosphataemia [4,5,17,18]. Additionally, caution is required in patients with renal impairment because of the risk of aluminium toxicity [4,19–22]. Furthermore, drug binding with sucralfate can reduce the effects of warfarin, phenytoin, digoxin, quinidine [23,24] and the fluoroquinolones ciprofloxacin and norfloxacin [25].

### Antacids

Antacids are not widely administered routinely nowadays, with an exception being before Caesarean section. Like sucralfate, antacids need to be administered intragastrically. They must be administered at intervals of 1–2 hours and the dose depends on intragastric pH, requiring frequent pH monitoring and dose titration. The potential adverse effects associated with antacids include aluminium toxicity if an aluminium-containing antacid is used, electrolyte disturbances and diarrhoea [26,27]; feeding-tube occlusions are also a potential drawback.

## Histamine H<sub>2</sub> receptor antagonists

Although placebo-controlled clinical studies demonstrate that the H<sub>2</sub>RAs significantly reduce the risk of overt and clinically significant GI bleeding in critically ill patients [5,8], these agents have a number of limitations concerning efficacy. Perhaps the most significant is the potential for tachyphylaxis to develop during prolonged IV dosing, which means that gastric pH is not reliably maintained above 4 [13,28–30]. This is believed to result from an increase in the release of endogenous histamine, which competes for the receptor sites with the antagonist [31]. Tolerance can occur within 42 hours [30] and pH control can deteriorate quickly despite the use of a high-dose regimen [32]. In addition, H<sub>2</sub>RAs do not inhibit vagally induced acid secretion, making them less efficacious in neurosurgical or head trauma patients with hyperacidity.

The most common adverse effects associated with H<sub>2</sub>RAs include headaches, dizziness, diarrhoea, nausea and constipation [1]. More rarely, H<sub>2</sub>RAs can also cause serious adverse effects such as thrombocytopenia [33], changes in liver function, and interstitial nephritis [34]. All H<sub>2</sub>RAs are eliminated renally to some extent, and their clearance is therefore appreciably reduced in patients with renal failure, mandating dose adjustment in such patients [35].

With respect to drug interactions, the H<sub>2</sub>RAs cimetidine and ranitidine have the drawback of a potent inhibitory effect on the cytochrome oxidase enzyme system [16]. Cimetidine increases the plasma levels of theophylline, warfarin, metronidazole, imipramine, triazolam, diazepam, phenytoin, lidocaine, quinidine, nifedipine and propranolol [36–42]. Cimetidine must therefore be used with caution in patients treated concomitantly with other medications [43,44]. Ranitidine has a lower potential for clinically significant drug interactions but has been shown to potentiate the sedative effect of midazolam and increase plasma levels of theophylline and phenytoin [45–47]. The newer H<sub>2</sub>RAs, nizatidine and famotidine, seem not to be associated with significant drug interactions [48–50].

## The use of PPIs for acid suppression in critical illness

PPIs, such as esomeprazole, lansoprazole, omeprazole, pantoprazole and rabeprazole, are the most effective agents for suppressing gastric acidity; the superior efficacy of a PPI over an H<sub>2</sub>RA has been demonstrated in patients with peptic ulcer disease, gastroesophageal reflux disease, GI damage caused by non-steroidal anti-inflammatory drugs, and Zollinger–Ellison syndrome [51–58]. In general GI practice, PPIs are now considered the drug of choice in the management of most acid-related GI disorders [1]. No tachyphylactic phenomena have been reported in patients taking PPIs [13,28], resulting in more predictable and sustained pH control than with H<sub>2</sub>RAs [14,29]. Adverse effects from PPIs are uncommon, but can include headaches, diarrhoea, nausea, constipation and pruritis [59–61].

The possibility of achieving a more profound and sustained acid suppression provides a rationale for the use of the PPIs in preference to H<sub>2</sub>RAs in prophylaxis for SRMD, although few studies have evaluated PPIs specifically for stress ulcer prophylaxis. However, most such studies have demonstrated clearly that enteral or IV administration of a PPI elevates intragastric pH and maintains a pH of at least 4 [62–72]. Furthermore, comparative studies have shown PPIs to be more effective than H<sub>2</sub>RAs for elevating intragastric pH [13,28,65,66], and two have shown enteral omeprazole to be more effective than ranitidine in reducing the risk of SRMD-associated bleeding [64,69].

## Which PPI for stress ulcer prophylaxis?

The ideal agent for stress ulcer prophylaxis should be effective in reducing the risk of ulceration, with a low potential for adverse effects and drug interactions, should have pharmacokinetic characteristics that facilitate its use in patients with organ dysfunction, and should be cost effective, taking into account not only the cost of acquisition but the costs of administration and monitoring. How the available agents compare with regard to this ideal is outlined in Table 1.

### Use in organ dysfunction

Given the prevalence of organ dysfunction or failure among ICU patients, ease of drug handling is an important factor in the choice of prophylaxis for SRMD. Because it exhibits dose linearity [73] and does not accumulate in the body after repeat administration, pantoprazole can be used without dose adjustment in elderly patients and in those with renal impairment or failure, or moderate hepatic impairment [73–76]. Because of their nonlinearity of dose [77], omeprazole and lansoprazole do not afford this same independence of dose.

### Drug interactions

The metabolism of all PPIs initially involves the hepatic cytochrome P450 and isoenzymes 2C19 and CYP3A4 [76,78]. However, individual PPIs differ considerably in their potential for clinically significant drug interactions [78]. Omeprazole, for example, reduces the clearance of carbamazepine and diazepam, and also that of phenytoin, which has a narrow therapeutic index [79]. Interaction studies with lansoprazole have demonstrated a significant decrease in the elimination half-life [80] and the area under curve [81] of concomitant theophylline.

After the initial CYP450-dependent phase of its metabolism, pantoprazole is further metabolised by non-saturable phase II reactions [73]. This results in a much lower potential for pantoprazole to interact with the cytochrome P450 system [77]. Pantoprazole has shown no clinically significant drug interactions in formal studies investigating a wide variety of concomitant drugs, including carbamazepine, cisapride, diazepam, diclofenac, digoxin, glibenclamide, naproxen, nifedipine, theophylline and warfarin [76,77].

**Table 1**

**Comparison of options for stress ulcer prophylaxis**

Characteristic	Sucralfate	Antacids	H <sub>2</sub> RAs	Esomeprazole	Lansoprazole	Omeprazole	Pantoprazole	Rabeprazole
Efficacy in elevating gastric pH		+	+	+++	+++	+++	+++	+++
Tolerability	+	+	+	+++	+++	+++	+++	+++
Use in organ failure							+	
Low potential for drug interactions							+	
Administration options								
Oral				+	+	+	+	+
Intravenous			+	+		+	+	
Nasogastric	+	+		+	+	+		

H<sub>2</sub>RAs, histamine H2 receptor antagonists.

**Administration options**

The availability of an IV formulation is important for credible stress ulcer prophylaxis, because enteral administration might not always be possible in critically ill patients. An IV formulation of pantoprazole is available worldwide, and IV preparations of omeprazole and esomeprazole are available in many countries. There is currently no IV formulation of lansoprazole, but it is available as a syrup suspension, which can be administered nasogastrically. Omeprazole can be prepared for nasogastric administration by mixing crushed tablets with a vehicle such as apple juice.

**Summary**

As the most effective antisecretory agents, PPIs undoubtedly have the potential to benefit ICU patients at risk for SRMD. However, further clinical studies in the ICU setting are required to confirm this expectation. The link between the superior acid-suppressive efficacy of the PPIs and a reduced risk of SRMD versus H<sub>2</sub>RAs has been demonstrated in only a limited number of clinical trials, and this evidence base needs to be extended. As far as their cost effectiveness is concerned, PPIs might be expected to offer potential cost savings compared with no treatment or treatment with traditional agents, through reducing the incidence of stress-related bleeding, costs associated with red cell transfusions and avoiding the consequent extension of ICU stay. In addition, both the option of continuous infusion of IV formulations and the lack of any need for pH monitoring with the PPIs have the potential to save costs associated with nursing time. However, it must be emphasised that the pharmaco-economic data to confirm these potential benefits are not currently available, and given the cost differential between intravenous formulations of PPIs and H<sub>2</sub>RAs, studies to define the overall cost effectiveness of PPIs in critical care should be a further avenue of future research.

In a clinical situation in which most patients may have renal and/or hepatic dysfunction and require multiple drug

treatment, differences between PPIs in terms of pharmacokinetics and the potential for drug interactions may be of significant importance. Pantoprazole can be used without dose adjustment in patients with organ dysfunction and has a low potential for drug interactions, and therefore among the currently available agents it may have advantages in stress ulcer prophylaxis for certain patient groups in the ICU setting.

**Competing interests:**

The author has received consultancy payments from Altana and GlaxoSmithKline, which both have products mentioned in the review.

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