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 H2 receptor antagonists (H_2RAs). The H_2RAs are currently the most widely used agents in prophylactic acid suppression; however, proton pump inhibitors (PPIs) have recently replaced H_2RAs 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_2RAs. 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 H2 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_2RAs = histamine H2 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 H2 receptor antagonists (H_2RAs) [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_2RAs have each been shown to be effective in reducing the risk of overt and clinically significant bleeding compared with placebo [5,14]. H_2RAs 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 H2 receptor antagonists

Although placebo-controlled clinical studies demonstrate that the H_2RAs 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_2RAs 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_2RAs include headaches, dizziness, diarrhoea, nausea and constipation [1]. More rarely, H_2RAs can also cause serious adverse effects such as thrombocytopenia [33], changes in liver function, and interstitial nephritis [34]. All H_2RAs 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_2RAs 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_2RAs, 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_2RA 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_2RAs [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_2RAs 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_2RAs 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 lanzoprazole 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_2RAs	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_2RAs, 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_2RAs 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 pharmacoeconomic data to confirm these potential benefits are not currently available, and given the cost differential between intravenous formulations of PPIs and H2RAs, 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.

References

1. Metz DC: **Potential uses of intravenous proton pump inhibitors to control gastric acid secretion.** *Digestion* 2000, **62:** 73-81.
2. Fennerty MB: **Pathophysiology of the upper gastrointestinal tract in the critically ill patient: rationale for the therapeutic benefits of acid suppression.** *Crit Care Med* 2002, **30:**S351-S355.
3. Cook DJ, Griffith LE, Walter SD, Guyatt GH, Meade MO, Heyland DK, Kirby A, Tryba M: **The attributable mortality and length of intensive care unit stay of clinically important gastrointestinal bleeding in critically ill patients.** *Crit Care* 2001, **5:**368-375.
4. **ASHP Therapeutic Guidelines on Stress Ulcer Prophylaxis. ASHP Commission on Therapeutics and approved by the ASHP Board of Directors on November 14, 1998.** *Am J Health Syst Pharm* 1999, **56:**347-379.
5. Tryba M, Cook D: **Current guidelines on stress ulcer prophylaxis.** *Drugs* 1997, **54:**581-596.
6. **Institute for Healthcare Improvement: resources** [http://www.ihi.org/resources/]
7. Dellinger RP, Carlet JM, Masur H, Gerlach H, Calandra T, Cohen J, Gea-Banacloche J, Keh D, Marshall JC, Parker MM, *et al.*. **Surviving Sepsis Campaign guidelines for the management of severe sepsis and septic shock.** *Intensive Care Med* 2004, **4:** 536-555. [www.survivingsepsis.com/treatments.html]
8. Cook D, Guyatt G, Marshall J, Leasa D, Fuller H, Hall R, Peters S, Rutledge F, Griffith L, McLellan A, *et al.*: **A comparison of sucralfate and ranitidine for the prevention of upper gastrointestinal bleeding in patients requiring mechanical ventilation. Canadian Critical Care Trials Group.** *N Engl J Med* 1998, **338:**791-797.
9. Vincent JL, de Mendonca A, Cantraine F, Moreno R, Takala J, Suter PM, Sprung CL, Colardyn F, Blecher S: **Use of the SOFA score to assess the incidence of organ dysfunction/failure in**

intensive care units: results of a multicenter, prospective study. Working group on 'sepsis-related problems' of the European Society of Intensive Care Medicine. *Crit Care Med* 1998, **26:**1793-1800.
10. Vincent JL, Moreno R, Takala J, Willatts S, de Mendonca A, Bruining H, Reinhart CK, Suter PM, Thijs LG: **The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine.** *Intensive Care Med* 1996, **22:**707-710.
11. MacLaren R, Jarvis CL, Fish DN: **Use of enteral nutrition for stress ulcer prophylaxis.** *Ann Pharmacother* 2001, **35:**1614-1623.
12. Hastings PR, Skillman JJ, Bushnell LS, Silen W: **Antacid titration in the prevention of acute gastrointestinal bleeding: a controlled, randomized trial in 100 critically ill patients.** *N Engl J Med* 1978, **298:**1041-1045.
13. Aris R, Karlstadt R, Paoletti V, Blatcher B, McDevitt J: **Intermittent intravenous pantoprazole achieves a similar onset time to pH > 4.0 in ICU patients as continuous infusion H2-receptor antagonist, without tolerance [abstract].** *Am J Gastroenterol* 2001, **96 Suppl:**147.
14. Geus WP: **Are there indications for intravenous acid-inhibition in the prevention and treatment of upper GI bleeding?** *Scand J Gastroenterol* 2000, **232 Suppl:**10-20.
15. Lam NP, Le PT, Crawford SY, Patel S: **National survey of stress ulcer prophylaxis.** *Crit Care Med* 1999, **27:**98-103.
16. Smythe MA, Zarowitz BJ: **Changing perspectives of stress gastritis prophylaxis.** *Ann Pharmacother* 1994, **28:**1073-1085.
17. Miller SJ, Simpson J: **Medication–nutrient interactions: hypophosphatemia associated with sucralfate in the intensive care unit.** *Nutr Clin Pract* 1991, **6:**199-201.
18. Krupp KB, Johns P, Troncoso V: **Esophageal bezoar formation in a tube-fed patient receiving sucralfate and antacid therapy: a case report.** *Gastroenterol Nurs* 1995, **18:**46-48.
19. Hemstreet BA: **Use of sucralfate in renal failure.** *Ann Pharmacother* 2001, **35:**360-364.
20. Pai S, Melethil S, Cuddy P, Hall T: **Elevation of serum aluminum in humans on a two-day sucralfate regimen.** *J Clin Pharmacol* 1987, **27:**213-215.
21. Leung AC, Henderson IS, Halls DJ, Dobbie JW: **Aluminium hydroxide versus sucralfate as a phosphate binder in uraemia.** *Br Med J (Clin Res Ed)* 1983, **286:**1379-1381.
22. Robertson JA, Salusky IB, Goodman WG, Norris KC, Coburn JW: **Sucralfate, intestinal aluminum absorption, and aluminum toxicity in a patient on dialysis.** *Ann Intern Med* 1989, **111:**179-181.
23. Rey AM, Gums JG: **Altered absorption of digoxin, sustained-release quinidine, and warfarin with sucralfate administration.** *DICP* 1991, **25:**745-746.
24. Smart HL, Somerville KW, Williams J, Richens A, Langman MJ: **The effects of sucralfate upon phenytoin absorption in man.** *Br J Clin Pharmacol* 1985, **20:**238-240.
25. **Summary of product characteristics – sucralfate.** http://emc.medicines.org.uk/ (last accessed 6th October 2004).
26. Bresalier RS, Grendell JH, Cello JP, Meyer AA: **Sucralfate suspension versus titrated antacid for the prevention of acute stress-related gastrointestinal hemorrhage in critically ill patients.** *Am J Med* 1987, **83:**110-116.
27. Borrero E, Margolis IB, Bank S, Shulman N, Chardavoyne R: **Antacid versus sucralfate in preventing acute gastrointestinal bleeding. A randomized trial in 100 critically ill patients.** *Am J Surg* 1984, **148:**809-812.
28. Somberg L, Karlstadt R, Gallagher K, McDevitt J, Graepel J, Paoletti V: **Intravenous pantoprazole rapidly achieves pH greater than 4.0 in ICU patients without development of tolerance [abstract].** *Gastroenterology* 2001, **120:**A157.
29. Huggins RM, Scates AC, Latour JK: **Intravenous proton-pump inhibitors versus H2-antagonists for treatment of GI bleeding.** *Ann Pharmacother* 2003, **37:**433-437.
30. Mathot RA, Geus WP: **Pharmacodynamic modeling of the acid inhibitory effect of ranitidine in patients in an intensive care unit during prolonged dosing: characterization of tolerance.** *Clin Pharmacol Ther* 1999, **66:**140-151.
31. Sandvik AK, Brenna E, Waldum HL: **Review article: the pharmacological inhibition of gastric acid secretion – tolerance and rebound.** *Aliment Pharmacol Ther* 1997, **11:**1013-1018.
32. Merki HS, Wilder-Smith CH: **Do continuous infusions of omeprazole and ranitidine retain their effect with prolonged dosing?** *Gastroenterology* 1994, **106:**60-64.
33. Wade EE, Rebuck JA, Healey MA, Rogers FB: **H_2 antagonist-induced thrombocytopenia: is this a real phenomenon?** *Intensive Care Med* 2002, **28:**459-465.
34. Fisher AA, Le Couteur DG: **Nephrotoxicity and hepatotoxicity of histamine H2 receptor antagonists.** *Drug Saf* 2001, **24:**39-57.
35. Garg DC, Baltodano N, Jallad NS, Perez G, Oster JR, Eshelman FN, Weidler DJ: **Pharmacokinetics of ranitidine in patients with renal failure.** *J Clin Pharmacol* 1986, **26:**286-291.
36. Shinn AF: **Clinical relevance of cimetidine drug interactions.** *Drug Saf* 1992, **7:**245-267.
37. Somogyi A, Muirhead M: **Pharmacokinetic interactions of cimetidine.** *Clin Pharmacokinet* 1987, **12:**321-366.
38. Hendeles L, Jenkins J, Temple R: **Revised FDA labeling guideline for theophylline oral dosage forms.** *Pharmacotherapy* 1995, **15:**409-427.
39. Hamilton FA: **Incidence and cost of hospital admissions secondary to drug interactions involving theophylline.** *Ann Pharmacother* 1992, **26:**1507-1511.
40. Britton ML, Waller ES: **Central nervous system toxicity associated with concurrent use of triazolam and cimetidine.** *Drug Intell Clin Pharm* 1985, **19:**666-668.
41. Bauer LA, Black D, Gensler A: **Procainamide–cimetidine drug interaction in elderly male patients.** *J Am Geriatr Soc* 1990, **38:** 467-469.
42. Feely J, Wilkinson GR, McAllister CB, Wood AJ: **Increased toxicity and reduced clearance of lidocaine by cimetidine.** *Ann Intern Med* 1982, **96:**592-594.
43. Baciewicz AM, Baciewicz FA Jr: **Effect of cimetidine and ranitidine on cardiovascular drugs.** *Am Heart J* 1989, **118:**144-154.
44. Richards DA: **Comparative pharmacodynamics and pharmacokinetics of cimetidine and ranitidine.** *J Clin Gastroenterol* 1983, **5 Suppl 1:**81-90.
45. Kirch W, Hoensch H, Janisch HD: **Interactions and non-interactions with ranitidine.** *Clin Pharmacokinet* 1984, **9:**493-510.
46. Murialdo G, Piovano PL, Costelli P, Fonzi S, Barberis A, Ghia M: **Seizures during concomitant treatment with theophylline and ranitidine: a case report.** *Ann Ital Med Int* 1990, **5:**413.
47. Tse CST: **Phenytoin concentration elevation subsequent to ranitidine administration.** *Ann Pharmacother* 1993, **27:**1448-1451.
48. Klotz U: **Lack of effect of nizatidine on drug metabolism.** *Scand J Gastroenterol* 1987, **136 Suppl:**18-23.
49. Cournot A, Berlin I, Sallord JC, Singlas E: **Lack of interaction between nizatidine and warfarin during chronic administration.** *J Clin Pharmacol* 1988, **28:**1120-1122.
50. Humphries TJ: **Famotidine: a notable lack of drug interactions.** *Scand J Gastroenterol* 1987, **134 Suppl:**55-60.
51. Richter JE, Campbell DR, Kahrilas PJ, Huang B, Fludas C: **Lansoprazole compared with ranitidine for the treatment of nonerosive gastroesophageal reflux disease.** *Arch Intern Med* 2000, **160:**1803-1809.
52. Agrawal NM, Campbell DR, Safdi MA, Lukasik NL, Huang B, Haber MM: **Superiority of lansoprazole vs ranitidine in healing nonsteroidal anti-inflammatory drug-associated gastric ulcers: results of a double-blind, randomized, multicenter study. NSAID-Associated Gastric Ulcer Study Group.** *Arch Intern Med* 2000, **160:**1455-1461.
53. Jansen JB, Van-Oene JC: **Standard-dose lansoprazole is more effective than high-dose ranitidine in achieving endoscopic healing and symptom relief in patients with moderately severe reflux oesophagitis. The Dutch Lansoprazole Study Group.** *Aliment Pharmacol Ther* 1999, **13:**1611-1620.
54. Kovacs TO, Wilcox CM, Devault K, Miska D, Bochenek W: **Comparison of the efficacy of pantoprazole vs. nizatidine in the treatment of erosive oesophagitis: a randomized, active-controlled, double-blind study.** *Aliment Pharmacol Ther* 2002, **16:** 2043-2052.
55. Meneghelli UG, Boaventura S, Moraes-Filho JP, Leitao O, Ferrari AP, Almeida JR, Magalhaes AF, Castro LP, Haddad MT, Tolentino M *et al.*: **Efficacy and tolerability of pantoprazole versus ranitidine in the treatment of reflux esophagitis and the influence of *Helicobacter pylori* infection on healing rate.** *Dis Esophagus* 2002, **15:**50-56.

56. Kaspari S, Biedermann A, Mey J: **Comparison of pantoprazole 20 mg to ranitidine 150 mg b.i.d. in the treatment of mild gastroesophageal reflux disease.** *Digestion* 2001, **63:**163-170.
57. van Zyl JH, de KG, van Rensburg CJ, Retief FJ, O'Keefe SJ, Theron I, Fischer R, Bethke T: **Efficacy and tolerability of 20 mg pantoprazole versus 300 mg ranitidine in patients with mild reflux-oesophagitis: a randomized, double-blind, parallel, and multicentre study.** *Eur J Gastroenterol Hepatol* 2000, **12:**197-202.
58. Meneghelli UG, Zaterka S, de Paula C, Malafaia O, Lyra LG: **Pantoprazole versus ranitidine in the treatment of duodenal ulcer: a multicenter study in Brazil.** *Am J Gastroenterol* 2000, **95:**62-66.
59. Mears JM, Kaplan B: **Proton pump inhibitors: new drugs and indications.** *Am Fam Physician* 1996, **53:**285-292.
60. Garnett WR: **Considerations for long-term use of proton-pump inhibitors.** *Am J Health Syst Pharm* 1998, **55:**2268-2279.
61. Freston JW: **Long-term acid control and proton pump inhibitors: interactions and safety issues in perspective.** *Am J Gastroenterol* 1997, **92:**51S-55S.
62. Phillips JO, Olsen KM, Rebuck JA, Rangneker NJ, Miedema BW, Metzler MH: **A randomized, pharmacokinetic, and pharmacodynamic, cross-over study of duodenal or jejunal administration of omeprazole suspension in patients at risk for stress ulcers.** *Am J Gastroenterol* 2001, **96:**367-372.
63. Balaban DH, Duckworth CW, Peura DA: **Nasogastric omeprazole: effects on gastric pH in critically ill patients.** *Am J Gastroenterol* 1997, **92:**79-83.
64. Levy MJ, Seelig CB, Robinson NJ, Ranney JE: **Comparison of omeprazole and ranitidine for stress ulcer prophylaxis.** *Dig Dis Sci* 1997, **42:**1255-1259.
65. Roberts KW, Pitcher WD, Cryer B: **Effects of lansoprazole suspension versus continuous intravenous ranitidine on gastric pH of mechanically ventilated intensive care unit patients [abstract].** *Crit Care Med* 2000, **28:**A185.
66. Morris J, Karlstadt R, Blatcher D, Field D: **Intermittent intravenous pantoprazole rapidly achieves and maintains gastric pH > 4.0 compared with continuous infusion H2-receptor antagonist in intensive care unit patients [abstract].** *Crit Care Med* 2001, **29:**A147.
67. Phillips JO, Metzler MH, Palmieri TL, Huckfeldt RE, Dahl NG: **A prospective study of simplified omeprazole suspension for the prophylaxis of stress-related mucosal damage.** *Crit Care Med* 1996, **24:**1793-1800.
68. Lasky MR, Metzler MH, Phillips JO: **A prospective study of omeprazole suspension to prevent clinically significant gastrointestinal bleeding from stress ulcers in mechanically ventilated trauma patients.** *J Trauma* 1998, **44:**527-533.
69. Phillips JO, Metzler MH, Huckfeldt RE, Olsen K: **A multicenter, prospective, randomized clinical trial of continuous infusion I.V. ranitidine vs omeprazole suspection in the prophylaxis of stress ulcers [abstract].** *Crit Care Med* 1998, **26:**101A.
70. Cohen H, Baldwin SN, Mukherji R, Ramos L, Dasgupta S, DiGregorio RV, Popadopoulos J, Reilly J, Hayat L: **A comparison of lansoprazole and sucralfate for the prophylaxis of stress-related mucosal damage in critically ill patients [abstract].** *Crit Care Med* 2000, **28:**A185.
71. Laterre PF, Horsmans Y: **Intravenous omeprazole in critically ill patients: a randomized, crossover study comparing 40 with 80 mg plus 8 mg/hour on intragastric pH.** *Crit Care Med* 2001, **29:**1931-1935.
72. Otani Y, Kitajima M, Sugiyama M, Watanabe Y, Aoki T: **Inhibitory effects of intravenous lansoprazole on gastric acid hypersecretion in patients with postoperative stress.** *J Clin Gastroenterol* 1995, **20 Suppl 2:**S22-S26.
73. Huber R, Hartmann M, Bliesath H, Lühmann R, Steinijans VW, Zech K: **Pharmacokinetics of pantoprazole in man.** *Int J Clin Pharmacol Ther* 1996, **34:**S7-S16.
74. Lins RL, De Clercq I, Hartmann M, Huber R, Bliesath H, Lühmann R, Wurst W: **Pharmacokinetics of the proton pump inhibitor Pantoprazole in patients with severe renal impairment [abstract].** *Gastroenterology* 1994, **106 Suppl 4:**A126.
75. Kliem V: **Pharmacokinetics of pantoprazole in hemodialysis patients [abstract].** *Kidney Int* 1995, **47:**984.
76. Cheer SM, Prakash A, Faulds D, Lamb HM: **Pantoprazole: an update of its pharmacological properties and therapeutic use in the management of acid-related disorders.** *Drugs* 2003, **63:**101-133.
77. Zech K, Steinijans VW, Huber R, Kolassa N, Radtke HW: **Pharmacokinetics and drug interactions—relevant factors for the choice of a drug.** *Int J Clin Pharmacol Ther* 1996, **34 Suppl:**S3-S6.
78. Meyer UA: **Metabolic interactions of the proton-pump inhibitors lansoprazole, omeprazole and pantoprazole with other drugs.** *Eur J Gastroenterol Hepatol* 1996, **8 Suppl 1:**S21-S25.
79. Tucker GT: **The interaction of proton pump inhibitors with cytochromes P450.** *Aliment Pharmacol Ther* 1994, **8 Suppl 1:** 33-38.
80. Kokufu T, Ihara N, Sugioka N, Koyama H, Ohta T, Mori S, Nakajima K: **Effects of lansoprazole on pharmacokinetics and metabolism of theophylline.** *Eur J Clin Pharmacol* 1995, **48:** 391-395.
81. Granneman GR, Karol MD, Locke CS, Cavanaugh JH: **Pharmacokinetic interaction between lansoprazole and theophylline.** *Ther Drug Monit* 1995, **17:**460-464.