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THE ROLE OF PROTON PUMP INHIBITORS IN THE MANAGEMENT OF UPPER GASTROINTESTINAL DISORDERS

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Abstract
Drug-related problems (DRPs) are common among surgical patients, especially older patients with polypharmacy and underlying diseases. DRPs can potentially lead to morbidity, mortality, and increased treatment costs. The enhanced recovery after surgery (ERAS) system has shown great advantages in managing surgical patients. Medication therapy management for surgical patients (established as "surgical pharmacy" by Guangdong Province Pharmaceutical Association (GDPA)) is an important part of the ERAS system. Improper medication therapy management can lead to serious consequences and even death. In order to reduce DRPs further, and promote the rapid recovery of surgical patients, the need for pharmacists in the ERAS program is even more pressing. However, the medication therapy management services of surgical pharmacy and how surgical pharmacists should participate in ERAS programs are still unclear worldwide. Therefore, this article reviews the main perioperative medical management strategies and precautions from several aspects, including antimicrobial agents, antithrombotic agents, pain medication, nutritional therapy, blood glucose monitoring, blood pressure treatment, fluid management, treatment of nausea and vomiting, and management of postoperative delirium. Additionally, the way surgical pharmacists participate in perioperative medication management, and the relevant medication pathways are explored for optimizing medication therapy management services within the ERAS programs. This study will greatly assist surgical pharmacists' work, contributing to surgeons accepting that pharmacists have an important role in the multidisciplinary team, benefitting medical workers in treating, counseling, and advocating for their patients, and further improving the effectiveness, safety and economy of medication therapy for patients and promoting patient recovery.

Keywords: surgical pharmacy, ERAS, pharmacist, perioperative medication therapy, work path

Introduction

Gastroesophageal reflux disease (GERD) was defined by the Montreal Consensus Group as a condition that develops when the reflux of stomach contents causes troublesome symptoms and/or complications.[1] The American College of Gastroenterology (ACG) defines GERD as symptoms or complications resulting from the reflux of gastric contents into the esophagus or the oral cavity, larynx, or even lungs.[2] GERD can be further classified according to the presence or absence of erosions (erosive esophagitis vs nonerosive reflux disease, respectively). Pharmacologic options for the management of GERD include antacids, histamine-2 receptor antagonists (H_2RAs), and PPIs. PPI therapy has consistently demonstrated higher healing rates and lower relapse rates in erosive esophagitis than H2RAs or placebo.[3] Chiba and colleagues[4] also reported faster healing rates in erosive esophagitis with PPIs than with H_2RAs or placebo (12% per week vs 6% per week and 3% per week, respectively). Additionally, the cumulative healing rate irrespective of treatment duration was highest with PPIs (84%) as compared to H_2RAs (52%) and placebo (28%).[4] PPIs alleviate

symptoms in 80% of patients with erosive esophagitis and in approximately 60% of patients with nonerosive reflux disease.[5,6]
The ACG treatment guidelines[2] gave a strong recommendation for an 8-week course of PPI therapy for the initial management of erosive esophagitis in terms of healing and symptom control. The guidelines also reported no difference in symptom relief and erosive esophagitis healing among various PPIs. A meta-analysis of 10 studies including more than 15,000 patients had reported an 8% relative increase in GERD symptom relief at 4 weeks and a 5% relative increase in the probability of erosive esophagitis healing after 8 weeks with esomeprazole over other PPIs[7]; however, the clinical relevance of this finding is unclear. Except for dexlansoprazole (Dexilant, Takeda Pharmaceuticals) and immediate-release omeprazole with sodium bicarbonate, PPIs should be administered approximately 1 hour before meals to ensure maximal efficacy. Immediate-release omeprazole with sodium bicarbonate can be taken at bedtime and is highly effective in controlling nocturnal acidity.[8] Dexlansoprazole is a dual delayed-release formulation of R-lansoprazole and can be taken at any time regardless of food intake.[9]
A Cochrane systematic review[10] comparing the use of PPIs, H_2RAs, and prokinetics in patients with nonerosive reflux disease reported that PPIs were more effective than H_2RAs (relative risk, 0.66; 95% CI, 0.60-0.73) and prokinetics (relative risk, 0.53; 95% CI, 0.32-0.87).

Helicobacter pylori is a major cause of peptic ulcer disease and gastric cancer. The updated ACG clinical guidelines for the management of *H pylori* infection[22] recommend that all patients who test positive for the infection should receive treatment. The guidelines list several treatment regimens for the management of *H pylori* infection, all of which include a PPI; these treatments are listed in the Table. Monotherapy with a PPI is ineffective in eradicating *H pylori* infection. However, the addition of a PPI to a combination of antibiotics improves eradication rates compared to those achieved with antibiotics alone.[23] PPIs elevate intragastric pH levels and optimize the antibacterial action of concomitantly administered antibiotics. Furthermore, because PPIs decrease gastric secretory volume, they increase the concentration of antibiotics within the stomach.

medication therapy involves all aspects of the preoperative and postoperative periods and includes special management of certain drugs, such as anesthetics, psychotics, radiopharmaceuticals, off-label medication, and proton pump inhibitors . Surgical pharmacists are indispensable as ERAS team members; they can focus on patients to formulate clinical drug treatment strategies, prescribe rational drug use based on medication treatment management, pharmaceutical evaluation and monitoring of patients with underlying diseases, manage patients throughout the perioperative period, and coordinate multidisciplinary comprehensive diagnosis to promote recovery from surgery. There is evolving literature that proves the collaborative contributions of pharmacists in selecting pharmacotherapy or alternative drugs, minimizing misuse or overuse of medications, contributing to improved outcomes, reducing complications and decreasing costs and thus shortening LOS . The detailed entry points for surgical pharmacists to participate in perioperative ERAS medication therapy management are as follows [17]:
GI bleeding was the most common hospital admission diagnosis in 2012 among all GI-related disorders.[24] Peptic ulcer disease remains the most common cause of upper GI bleeding. For upper GI bleeding, it is now common practice to initiate intravenous PPI therapy once the hemodynamic status has been assessed and any necessary resuscitative measures have been implemented. Lau and colleagues[25] reported in a randomized trial the benefit of a high-dose bolus followed by continuous infusion of omeprazole before patients underwent endoscopy. Endoscopic treatment was required in 19.1% of patients who received omeprazole compared to 28.4% of patients who received placebo (*P*=.007). Likewise, among patients with peptic ulcer disease, active bleeding was significantly less common in patients who received omeprazole (6.4% vs 14.7%; *P*=.01), and clean-based ulcers were found more often (64.2% vs 47.4%; *P*=.001). A systematic review of 6 randomized trials with 2223 patients[26] evaluating the use of a PPI before endoscopic evaluation found that PPI therapy prior to endoscopy did not significantly reduce mortality (odds ratio [OR], 1.12; 95% CI, 0.72-1.73),

rebleeding (OR, 0.81; 95% CI, 0.61-1.09), or the requirement for surgery (OR, 0.96; 95% CI, 0.68-1.35). However, there was a significantly lower proportion of peptic ulcers with high-risk stigmata at endoscopy (OR, 0.67; 95% CI, 0.54-0.84) and significantly lower rates of endoscopic treatment (OR, 0.68; 95% CI, 0.50-0.93). The ACG guidelines for peptic ulcer bleeding[27] recommend the use of a bolus PPI and continuous infusion to decrease the proportion of patients with ulcers with high-risk stigmata and the requirement for endoscopic treatment. PPI therapy can be discontinued after endoscopy if the patient is found to have an etiology for bleeding other than peptic ulcer. However, if endoscopic evaluation has to be delayed or cannot be performed, intravenous PPI therapy should be continued to reduce the risk of further bleeding.

The ACG guidelines for the management of eosinophilic esophagitis (EoE)[54] define the condition as a distinct clinicopathologic disorder that fulfills the following criteria: (1) symptoms related to esophageal dysfunction, (2) eosinophil-predominant inflammation on esophageal biopsy characterized by a peak value of at least 15 eosinophils per high-power field, (3) mucosal eosinophilia that is isolated to the esophagus and persists after a PPI trial, (4) exclusion of secondary causes of esophageal eosinophilia, and (5) response to treatment (eg, dietary elimination, topical corticosteroids). PPI–responsive esophageal eosinophilia (PPI-REE) may represent a different clinical entity. Patients with PPI-REE have symptoms suggestive of EoE and may have endoscopic features of EoE, but have resolution of symptoms and esophageal eosinophilia after a course of PPI therapy. Therefore, the ACG guidelines[55] recommend that all patients who have symptoms of EoE and are found to have isolated esophageal eosinophilia should be given an 8-week trial of a PPI and should then undergo repeat endoscopy with biopsies. Resolution of esophageal eosinophilia is classified as PPI-REE rather than EoE. More than one-third of patients diagnosed with esophageal eosinophilia will respond to PPI treatment. The mechanisms of action of PPIs in this regard are incompletely understood. One hypothesis is that acid exposure in patients with GERD damages esophageal epithelial tight junctions, allowing allergen penetration and eosinophil recruitment.[57] Alternatively, PPIs may have a direct anti-inflammatory effect on the esophageal epithelium by blocking the secretion of eotaxin, which recruits eosinophils.

Conclusion

Based on several reported associations, there has been recent widespread media attention given to the safety of PPIs. This has resulted in considerable patient anxiety and, in some cases, the inappropriate discontinuation of treatment for conditions for which it is strongly recommended. Vaezi and colleagues[59] have comprehensively reviewed the evidence for the various proposed complications of PPI therapy using the Hill criteria.[60] The authors found moderate strength of evidence to suggest that PPI use may be associated with bacterial enteric infections, including *Clostridium difficile*. However, the remaining associations, including fracture, hypomagnesemia, renal failure, dementia, myocardial infarction, hepatic encephalopathy, and spontaneous bacterial peritonitis, were weak and were most likely explained by residual confounding due to study design issues. The overextrapolation of quantitatively small effect sizes has led to disproportionate safety concerns. As with all other drugs, PPIs should be prescribed in the lowest effective doses and only continued for as long as necessary. However, for some indications (eg, erosive esophagitis, the prevention of NSAID-related ulcers or bleeding), treatment may be needed indefinitely.

Although PPIs were initially approved only for the treatment of erosive esophagitis, they have subsequently been used in the treatment of a number of other conditions of the upper GI tract. PPIs contribute to the management of diverse states, including *H pylori* infection, Barrett esophagus, and the prevention of NSAID-related ulcers. However, PPIs have only limited value for the management of uninvestigated and functional dyspepsia, and they should not be continued if they are not providing symptom relief. Conversely, PPIs play an important role in the prevention of upper GI bleeding in high-risk patients taking NSAIDs, aspirin, or DAPT. Such patients are often elderly and with comorbidity; however, PPI treatment should be continued for as long as is appropriate even though patients may not experience any upper GI symptoms. Despite the multiple recent reports

alleging a range of harms associated with PPI use, these drugs are generally safe for continuous use assuming they are being given for an appropriate indication.

References

1. Vakil N, van Zanten SV, Kahrilas P, Dent J, Jones R. Global Consensus Group. The Montreal definition and classification of gastroesophageal reflux disease: a global evidence-based consensus. Am J Gastroenterol. 2006;101(8):1900–1920. quiz 1943. [PubMed] [Google Scholar]
2. Katz PO, Gerson LB, Vela MF. Guidelines for the diagnosis and management of gastroesophageal reflux disease. Am J Gastroenterol. 2013;108(3):308–328. quiz 329. [PubMed] [Google Scholar]
3. Labenz J, Malfertheiner P. Treatment of uncomplicated reflux disease. World J Gastroenterol. 2005;11(28):4291–4299. [PMC free article] [PubMed] [Google Scholar]
4. Chiba N, De Gara CJ, Wilkinson JM, Hunt RH. Speed of healing and symptom relief in grade II to IV gastroesophageal reflux disease: a meta-analysis. Gastroenterology. 1997;112(6):1798–1810. [PubMed] [Google Scholar]
5. Robinson M, Sahba B, Avner D, Jhala N, Greski-Rose PA, Jennings DE. Multicentre Investigational Group. A comparison of lansoprazole and ranitidine in the treatment of erosive oesophagitis. Aliment Pharmacol Ther. 1995;9(1):25–31. [PubMed] [Google Scholar]
6. Vantrappen G, Rutgeerts L, Schurmans P, Coenegrachts JL. Omeprazole (40 mg) is superior to ranitidine in short-term treatment of ulcerative reflux esophagitis. Dig Dis Sci. 1988;33(5):523–529. [PubMed] [Google Scholar]
7. Gralnek IM, Dulai GS, Fennerty MB, Spiegel BM. Esomeprazole versus other proton pump inhibitors in erosive esophagitis: a meta-analysis of randomized clinical trials. Clin Gastroenterol Hepatol. 2006;4(12):1452–1458. [PubMed] [Google Scholar]
8. Gerson LB, Mitra S, Bleker WF, Yeung P. Control of intra-oesophageal pH in patients with Barrett's oesophagus on omeprazole-sodium bicarbonate therapy. Aliment Pharmacol Ther. 2012;35(7):803–809. [PubMed] [Google Scholar]
9. Metz DC, Vakily M, Dixit T, Mulford D. Review article: dual delayed release formulation of dexlansoprazole MR, a novel approach to overcome the limitations of conventional single release proton pump inhibitor therapy. Aliment Pharmacol Ther. 2009;29(9):928–937. [PubMed] [Google Scholar]
10. van Pinxteren B, Sigterman KE, Bonis P, Lau J, Numans ME. Short-term treatment with proton pump inhibitors, H2-receptor antagonists and prokinetics for gastro-oesophageal reflux disease-like symptoms and endoscopy negative reflux disease. Cochrane Database Syst Rev. 2010;(11):CD002095. [PubMed] [Google Scholar]
11. Schindlbeck NE, Klauser AG, Berghammer G, Londong W, Müller-Lissner SA. Three year follow up of patients with gastrooesophageal reflux disease. Gut. 1992;33(8):1016–1019. [PMC free article] [PubMed] [Google Scholar]
12. Pace F, Tonini M, Pallotta S, Molteni P, Porro GB. Systematic review: maintenance treatment of gastro-oesophageal reflux disease with proton pump inhibitors taken 'on-demand' Aliment Pharmacol Ther. 2007;26(2):195–204. [PubMed] [Google Scholar]
13. Dickman R, Boaz M, Aizic S, Beniashvili Z, Fass R, Niv Y. Comparison of clinical characteristics of patients with gastroesophageal reflux disease who failed proton pump inhibitor therapy versus those who fully responded. J Neurogastroenterol Motil. 2011;17(4):387–394. [PMC free article] [PubMed] [Google Scholar]
14. Singh S, Sharma AN, Murad MH, et al. Central adiposity is associated with increased risk of esophageal inflammation, metaplasia, and adenocarcinoma: a systematic review and meta-analysis. Clin Gastroenterol Hepatol. 2013;11(11):1399–1412.e7. [PMC free article] [PubMed] [Google Scholar]
15. Rubenstein JH, Mattek N, Eisen G. Age- and sex-specific yield of Barrett's esophagus by endoscopy indication. Gastrointest Endosc. 2010;71(1):21–27. [PMC free article] [PubMed] [Google Scholar]

16. Rubenstein JH, Morgenstern H, Appelman H, et al. Prediction of Barrett's esophagus among men. Am J Gastroenterol. 2013;108(3):353–362. [PMC free article] [PubMed] [Google Scholar]
17. Singh S, Garg SK, Singh PP, Iyer PG, El-Serag HB. Acid-suppressive medications and risk of oesophageal adenocarcinoma in patients with Barrett's oesophagus: a systematic review and meta-analysis. Gut. 2014;63(8):1229–1237. [PMC free article] [PubMed] [Google Scholar]
18. Kastelein F, Spaander MC, Steyerberg EW, et al. ProBar Study Group. Proton pump inhibitors reduce the risk of neoplastic progression in patients with Barrett's esophagus. Clin Gastroenterol Hepatol. 2013;11(4):382–388. [PubMed] [Google Scholar]
19. Hillman LC, Chiragakis L, Shadbolt B, Kaye GL, Clarke AC. Proton-pump inhibitor therapy and the development of dysplasia in patients with Barrett's oesophagus. Med J Aust. 2004;180(8):387–391. [PubMed] [Google Scholar]
20. Nguyen DM, El-Serag HB, Henderson L, Stein D, Bhattacharyya A, Sampliner RE. Medication usage and the risk of neoplasia in patients with Barrett's esophagus. Clin Gastroenterol Hepatol. 2009;7(12):1299–1304. [PMC free article] [PubMed] [Google Scholar]
21. Shaheen NJ, Falk GW, Iyer PG, Gerson LB. American College of Gastroenterology. ACG Clinical Guideline: diagnosis and management of Barrett's esophagus. Am J Gastroenterol. 2016;111(1):30–50. [PMC free article] [PubMed] [Google Scholar]
22. Chey WD, Leontiadis GI, Howden CW, Moss SF. ACG Clinical Guideline: treatment of Helicobacter pylori infection. Am J Gastroenterol. 2017;112(2):212–239. [PubMed] [Google Scholar]
23. Malfertheiner P, Bayerdörffer E, Diete U, et al. The GU-MACH study: the effect of 1-week omeprazole triple therapy on Helicobacter pylori infection in patients with gastric ulcer. Aliment Pharmacol Ther. 1999;13(6):703–712. [PubMed] [Google Scholar]
24. Peery AF, Crockett SD, Barritt AS, et al. Burden of gastrointestinal, liver, and pancreatic diseases in the United States. Gastroenterology. 2015;149(7):1731–1741.e3. [PMC free article] [PubMed] [Google Scholar]
25. Lau JY, Leung WK, Wu JC, et al. Omeprazole before endoscopy in patients with gastrointestinal bleeding. N Engl J Med. 2007;356(16):1631–1640. [PubMed] [Google Scholar]
26. Sreedharan A, Martin J, Leontiadis GI, et al. Proton pump inhibitor treatment initiated prior to endoscopic diagnosis in upper gastrointestinal bleeding. Cochrane Database Syst Rev. 2010;(7):CD005415. [PMC free article] [PubMed] [Google Scholar]
27. Laine L, Jensen DM. Management of patients with ulcer bleeding. Am J Gastroenterol. 2012;107(3):345–360. [PubMed] [Google Scholar]
28. Neumann I, Letelier LM, Rada G, et al. Comparison of different regimens of proton pump inhibitors for acute peptic ulcer bleeding. Cochrane Database Syst Rev. 2013;(6):CD007999. [PMC free article] [PubMed] [Google Scholar]
29. Sachar H, Vaidya K, Laine L. Intermittent vs continuous proton pump inhibitor therapy for high-risk bleeding ulcers: a systematic review and meta-analysis. JAMA Intern Med. 2014;174(11):1755–1762. [PMC free article] [PubMed] [Google Scholar]
30. Laine L, Peterson WL. Bleeding peptic ulcer. N Engl J Med. 1994;331(11):717–727. [PubMed] [Google Scholar]