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A Review on Use of Proton Pump Inhibitor in NSAIDs and Ulcers

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ABSTRACT

Non-steroidal anti-inflammatory drugs (NSAIDs) are used commonly but can cause foregut symptoms, peptic ulcer disease and small bowel enteropathy. Such iatrogenic injury can be complicated by gastrointestinal bleeding and perforation.Proton pump inhibitors (PPIs) provide potent and long-lasting inhibition of gastric acid secretion and have proven efficacy in healing NSAID-associated ulcers, including those with continued exposure to NSAIDs. PPIs have also shown efficacy in reducing the risk of ulcerations due to NSAID use compared with NSAIDs alone in randomized controlled trials (RCTs) where endoscopic ulcers are used as the primary endpoint, albeit a surrogate marker for clinical ulcers and complications. Large RCT outcome trials comparing patients exposed to NSAIDs with and without PPI co-therapy have not been performed, but adequately powered RCTs in high-risk patients demonstrate that PPI nonselective NSAID provides similar rates of symptomatic ulcer recurrence rates as the use of a cyclooxygenase (COX)- 2 selective inhibitor. A RCT in high-risk patients with previous ulcer complications supports the additive benefit of two risk-reducing strategies, as ulcer complication recurrence was eliminated in high-risk patients who were given a COX-2 selective agent with a PPI. Helicobacter pylori, an independent risk factor for ulcers, should be sought out and eradicated in patients at increased gastrointestinal risk, typically those with an ulcer history. Following H. pylori eradication, however, patients remain at risk and co-therapy with a PPI is recommended. NSAID medication selection should consider both the individual patients' gastrointestinal and cardiovascular risks.

KEYWORDS: Proton pump inhibitors, NSAIDs, Ulcer

INTRODUCTION

Other articles in this supplement have reviewed the benefits of NSAID therapy. Their efficacy leads to a vast exposure of these medications in diverse patient populations. Damage to the upper gastrointestinal (GI) tract was the first of several potentially serious NSAID adverse events to be identified and remains a predominant concern. Cardiovascular and related renal toxicity, however, has further complicated strategies to reduce the overall risk of this class of drugs. The recognition of GI toxicity drove pharmaceutical research in two parallel directions in pursuit of effective anti-inflammatory therapy with reduced ulceration and bleeding.

Non-steroidal anti-inflammatory drugs (NSAIDs), beneficial for their anti-inflammatory and analgesic effects, account for 8% of prescriptions worldwide and are used most in those over the age of 65 years. Furthermore, there has been an increase in over-the-counter use with 26% using more than the recommended dose, and many undisclosed to medical professionals.1,2 Symptomatic upper gastrointestinal (GI) peptic ulcer disease and bleeding are the most recognised adverse events related to NSAIDs. However, complications related to NSAIDs can occur with or without symptoms, in the presence or absence of mucosal injury, and in the upper (to second part of the duodenum (D2)), mid- and lower gastrointestinal (GI) tract. In this article, we discuss the GI complications of NSAIDs, their presentation, risk factors and strategies to limit their occurrence.

Gastrointestinal (GI) bleeding is the most common GI diagnosis necessitating hospitalization in the United States, accounting for over half a million admissions annually Upper GI bleeding (UGIB) refers to bleeding originating from sites in the esophagus, stomach, or duodenum. Nearly 80% of patients visiting emergency departments for UGIB are admitted to the hospital with that principal diagnosis.

Proton pump inhibitors (PPIs) were clinically introduced more than 25 years ago and have since proven to be invaluable, safe, and effective agents for the management of a variety of acid-related disorders. Although all members in this class act in a similar fashion, inhibiting active parietal cell acid secretion, there are slight differences among PPIs relating to their pharmacokinetic properties, metabolism, and Food and Drug Administration (FDA)-approved clinical indications. Nevertheless, each is effective in managing

gastroesophageal reflux disease and uncomplicated or complicated peptic ulcer disease. Despite their overall efficacy, PPIs do have some limitations related to their short plasma half-lives and requirement for meal-associated dosing, which can lead to breakthrough symptoms in some individuals, especially at night. Longer-acting PPIs and technology to prolong conventional PPI activity have been developed to specifically address these limitations and may improve clinical outcomes.

Since the introduction of omeprazole in 1989, proton pump inhibitors (PPIs) have steadily become the mainstay in treatment of acid-related disorders. When compared with earlier agents such as histamine$_2$-receptor antagonists (H_2RAs), synthetic prostaglandin analogs, and anticholinergics, PPIs have demonstrated consistent patient tolerance, excellent safety, and generally superior acid suppressing capability than prior agents.

As of 2015, there are six PPIs approved by the United States Food and Drug Administration (FDA) (Table 1). Adoption of PPI use has been widespread among primary care providers, and their presence is ubiquitous within the armamentarium of the modern gastroenterologist. For most, this class of drugs represents the first choice for treatment of esophagitis, nonerosive reflux disease (NERD), peptic ulcer disease (PUD), prevention of nonsteroidal anti-inflammatory drugs (NSAID) associated ulcers, Zollinger-Ellison syndrome (ZES), and functional dyspepsia. In combination with antibiotics, PPIs are also an integral part of eradication therapy for *Helicobacter pylori*. Despite an excellent safety profile throughout their first two decades of use, the nearly universal popularity of PPIs has prompted several concerns about both their short- and long-term effects.

Table 1: Commercially Available Proton Pump Inhibitors in the United States

Drug	Dosages, mg	IV	Liquid or suspension	Generic	Over-the-counter
Omeprazole	10, 20, 40	Yes	No	Yes	Yes
Esomeprazole	20, 40	Yes	Yes	Yes	Yes
Lansoprazole	15, 30	Yes	Yes	Yes	Yes
Dexlansoprazole	30, 60	No	No	No	No
Pantoprazole	20, 40	Yes	Yes	Yes	No
Rabeprazole	20	No	No	Yes	No

WHAT ARE PPISAND HOW DO THEY WORK?

All currently approved PPIs are benzimidazole derivatives: heterocyclic organic molecules that include both a pyridine and benzimidazole moiety linked by a methylsulfinyl group. The prototypical example of this structure, omeprazole, was the first clinically useful PPI. Subsequently introduced drugs include lansoprazole, pantoprazole, rabeprazole and the stereo-isomeric compounds esomeprazole and dexlansoprazole. Although each of these drugs has different substitutions on their pyridine and/or benzimidazole rings, in general they are remarkably similar in their pharmacological properties.

More recently, the novel imidazopyridine PPI, tenatoprazole has undergone preliminary preclinical and clinical evaluation. Though not yet approved for clinical use, this new subset of PPI with a prolonged half-life may ultimately offer advantages over its benzimidazole cousins.

PPIs are membrane permeable, acid-labile weak bases. In order to prevent premature activation and degradation by luminal gastric acid, these drugs are packaged in a variety of delivery systems. These include enteric-coated tablets, gelatin capsules, or coated granules supplied as a powder for suspension. They also may be packaged in combination with bicarbonate to confer temporary luminal pH neutralization. Once clear of the stomach, PPIs are absorbed in the proximal small bowel. There are also intravenous (IV) formulations available for lansoprazole, pantoprazole, and esomeprazole, which provide immediate acid suppression and are well suited for hospitalized patients in whom the oral route of administration is not appropriate. The serum half-life of single release PPIs is extremely short (1 to 2 hours), though considerable effort has been made to develop dual release/or delayed release formulations to counteract this short-coming. Imidazopyridines such as tenatoprazole, which have a serum half-life of 7 hours, may also overcome this weakness and potentially demonstrate added clinical benefit in the future.

Once absorbed, circulation transits the PPIs to activated gastric parietal cells where they concentrate within the acidic secretory canaliculi. Here, the PPI undergoes acid-catalyzed cleavage of a chiral sulfoxide bond (except esomeprazole and dexlansoprazole which are nonchiral) into active sulfenic acid and/or sulfonamide. These compounds then bind covalently to cysteine residues on the H+/K+ ATPase and act to inhibit acid secretion until replacement pumps can be synthesized (up to 36 hours). Although

frequently considered equivalently effective with respect to clinical parameters, the specific pharmacologic properties among individual PPIs are somewhat different PPIs require the active canaliculi expression of H+/K+ ATPases for binding which occurs in response to a meal. During a single meal, neither all parietal cells nor all of its proton pumps are active. Only about two-thirds of proton pumps are inhibited by a single PPI dose, which leaves up to one-third of pumps uninhibited. With future meals, as previously inactive enzymes are recruited into the secretory canaliculi, proton exchange will again increase (though attenuated). This physiology is the rationale both for preprandial dosing (important due to short serum half-life) and the observation of escalating pharmacologic efficacy of PPIs after multiday treatment.

PPIs are highly protein bound and subject to degradation by hepatic P450 cytochromes. Although the CYP2C19 pathway is dominant overall, individual agents have variations which have led to concerns over efficacy and drug-drug interaction.Omeprazole and its stereo-isomer esomeprazole are metabolized almost entirely by CYP2C19, thereby offering the greatest potential for interaction with other drugs. Rabeprazole and lansoprazole/dexlansoprazole are also metabolized by CYP2C19, but they possess significant affinity for CYP3A4. Interactions appear less significant with these agents, perhaps owing to this difference. Pantoprazole, on the other hand, is primarily degraded by CYP2C19 O-demethylation and sulfate conjugation which results in the lowest potential for cytochrome induction or inhibition among the benzimidoles. It is our practice to favor pantoprazole or lansoprazole/dexlansoprazole in patients where this interplay of drug metabolism is a primary concern (i.e., patients with high risk for cardiovascular events who are on clopidogrel). Following hepatic metabolism, the ultimate excretion of most benzimidoles is renal, though lansoprazole/dexlansoprazole are also excreted via the biliary tree.While controversial, there are data to suggest that patients who are genetically rapid drug metabolizers, a situation more commonly encountered in Europe and North American, may be less likely to fully respond to their PPI treatment, especially *H. pylori* eradication than slower metabolizers of the drugs.

CLINICAL ADVANTAGES OF PPIs

Gastric acid secretion is a multifactorial and complex process regulated by at least three different stimuli upon the parietal cell. These pathways include the paracrine elaboration of gastrin and histamine, as well as the actions of postganglionic muscarinic acetylcholine. Unlike anticholinergics and histamine2-receptor blockers, PPIs inhibit the final common pathway of acid secretion (the H/K ATPase) in response to any and all stimulation of the parietal cell.

The PPIs represent the most potent inhibitors of gastric acid secretion available since, as noted above, they directly block the acid pump itself. Their superior biochemical effect compared with H_2RAs is based upon their ability to reliably maintain intragastric pH >4 for between 15 and 21 hours daily, as compared to only 8 hours for H_2RAs. In addition to being more long lasting, the effectiveness of PPIs is also superior with respect to postprandial and nocturnal intragastric pH control, which is of clinical importance in some patients. This effect of PPIs is also maintained over the long-term without the need for dose escalation. In contrast, tachyphylaxis may occur with H_2RAs as rapidly as within 3 to 5 days of regular use. While the short-term implications of this difference may not be relevant, consistent use of H_2RAs over a period of weeks to months may reduce their acid-suppressing effect nearly in half.

GENERAL CLINICAL USES OF PPIs

Helicobacter pylori eradication

Much debate has centered on the impact of H. pylori regarding ulcer risk in NSAID users, and the weight of the evidence supports the conclusion that it is an independent ulcer risk factor. In a comparative study of H. pylori eradication and PPI co-therapy for patients with a recent history of upper GI bleeding healed by PPI, both treatments were equally effective in preventing rebleeding among patients taking low-dose aspirin, but PPI was superior to H. pylori eradication for those taking NSAIDs. In summary, while there is limited evidence that H. pylori eradication alone may reduce ulceration in NSAID users, and while the European Helicobacter Pylori Group has recommended that H. pylori eradication be at least considered in patients in whom long-term NSAID treatment is contemplated, this recommendation has not been enthusiastically taken up in practice. H. pylori infection remains a risk factor for ulcer complications, and H. pylori eradication should be employed as an additional precaution for patients using NSAIDs with a history of ulcer disease.

Prevention of NSAID induced gastroduodenal ulcers

Gastrointestinal (GI) toxicity from NSAIDs, including aspirin, is estimated to account for at least 2,600 deaths in the United States each year. In addition, the use or misuse of these drugs cause significant morbidity in the form of UGI symptoms, GI bleeding, and increased health care utilization. A 2008 multi-society guideline and an American College of Gastroenterology guideline issued in 2009 identified patients perceived to be at risk for NSAID induced GI toxicity who should be considered for prophylaxis. Present

options for reducing the risk of NSAID associated GI toxicity in patients with obligate use of these agents include: the addition of misoprostol or acid antisecretory therapy, the use of a COX-2 selective NSAID, or any combination of these strategies.

While individual short-term studies of H_2RAs for prevention of NSAID induced ulcers have been published these results have not been consistent or observable over long-term patient follow-up. A meta-analysis of 112 individual RCTs by Koch *et al*. suggested that H2RAs demonstrated no evidence supporting the use of conventional dose H2RAs in a prophylactic role although high dose H_2RAs may be beneficial. Once daily PPIs, on the other hand, were protective against the development of gastroduodenal ulcers (OR=0.35) in asymptomatic patients taking low-dose aspirin who underwent endoscopy.

The best data in favor of PPI use come from two multicenter trials of higher-risk patients (n=1,429) taking daily NSAIDs. In these studies, the cumulative percentage of patients who developed ulcers at 6 months was substantially smaller in the group receiving esomeprazole (20 mg daily) (5.2%) versus placebo (17%). In addition, the use of a selective or nonselective COX inhibitor did not seem to impact whether patients were likely to develop an ulcer in the placebo group (17.1% vs 16.5%) while PPI co-therapy significantly reduced ulcer formation in both nonselective and selective NSAID users (6.8% vs 0.9%).

Peptic ulcer related gastrointestinal bleeding

Upper gastrointestinal (UGI) bleeding due to PUD is an important emergency medical condition which results in very high patient morbidity, health care costs, and mortality. While rapid assessment, best supportive care, and prompt endoscopic diagnosis and hemostasis are the mainstays of modern societal recommendations, the method and dose of antisecretory PPI therapy remains an important consideration. A Cochrane systematic review of six high-quality RCTs (n=2,223) demonstrated that there was no improvement in overall mortality (6.1% vs 5.5%; odds ratio [OR]=1.12, 0.72–1.73), rebleeding (13.9% vs 16.6%; OR=0.81, 0.61–1.09), or surgery (9.9% vs 10.2%; OR=0.96, 0.68–1.35) in patients who received pre-endoscopic PPI therapy. Despite this lack of improvement in hard outcomes, preadministration of PPI was noted to reduce the proportion of patients who had high-risk stigmata of hemorrhage by Forrest classification at the time of initial endoscopic exam (37.2% vs 46.5%; OR=0.67, 0.54–0.84). Furthermore, an analysis of patients in trials where endoscopic hemostatic therapy was inconsistently used, early PPI therapy was associated with reduced rebleeding (OR=0.38, 0.18–0.81) and the need for surgery (OR=0.62, 0.44–0.88). Given these data, along with the favorable risk profile of early PPI use, it is our practice to initiate a high dose IV bolus (pantoprazole or esomeprazole) and continuous infusion until endoscopic diagnosis can be ascertained. After endoscopy, the continuation of treatment and dose can be tailored to the identified source of bleeding.

Despite controversy over pre-endoscopic antisecretory therapy, there is solid agreement regarding the importance of PPI administration following endoscopy in patients with confirmed peptic ulcer related bleeding. A meta-analysis of intravenous PPI therapy (80 mg bolus followed by 8 mg/hr) versus placebo for 72 hours after endoscopic hemostasis demonstrated a significant reduction in rebleeding (number needed to treat [NNT]=12), surgery (NNT=28), and mortality (NNT=45) in patients who had high-risk endoscopic stigmata (active bleeding, visible vessel, or adherent clot) at the time of their exam. Other endoscopic stigmata, such as a clean based or flat pigmented spot, have suitably low risk for rebleeding in themselves, and standard oral antisecretory therapy is sufficient for healing.

RISK FACTORS FOR NSAID-RELATED BLEEDING AND PERFORATION

The risk factors for bleeding secondary to NSAID-induced peptic ulceration are illustrated in Box 1. The relative risk (RR) of upper GI bleeding or perforation depends on the type of NSAID. Selective COX-2 inhibitors are less toxic to the GI tract (RR 1.9) than nonselective NSAIDs, with ibuprofen generally safer (RR 2.7) and more harmful are diclofenac (RR 4.0) or naproxen (RR 5.6).5 Patients with previous peptic ulcer bleeding or perforation are at the highest risk of bleeding. Infection with H pylori has a synergistic effect on risk of peptic ulcer bleeding among NSAID users, increasing risk of bleeding by 1.2-fold.6 Other drugs also have a synergistic effect on bleeding risk. In particular, patients on dual antiplatelet therapy post-myocardial infarction (MI) and an NSAID have a two-fold increased risk of GI bleeding, and a 1.4-fold concomitant increased risk of adverse cardiovascular events (death, MI and stroke) compared with those not on an NSAID.7 In this group of patients, NSAIDs should therefore be avoided.

Table 2: Risk factors for non-steroidal anti-inflammatory drug gastrointestinal complications

Age ≥65 years.
History of peptic ulcer (complicated[a]>uncomplicated).
Concomitant therapy with antiplatelet agent, anticoagulants, corticosteroids and SSRIs.
Severe illness.
Helicobacter pylori infection.
Class of NSAID:
ns-NSAID > COX-2 inhibitor
naproxen>indomethacin>diclofenac>ibuprofen>rofecoxib[b] >celecoxib.
High dose of NSAIDs.
Chronic use of NSAIDs.

[a] = complicated (bleeding or perforated) peptic ulcer disease are at highest risk of rebleeding; [b] = withdrawn from market; COX = cyclo-oxygenase; ns = non-selective; NSAID = non-steroidal anti-inflammatory drug; SSRIs = selective serotonin reuptake inhibitors

CONCLUSIONS

NSAIDs are a common cause of peptic ulcer disease in the stomach and duodenum, and dyspeptic symptoms occur. commonly in the absence of peptic ulcer disease. Both are effectively treated by stopping NSAIDs, if possible, or using PPI therapy. Risk factors for bleeding include class, duration and dose of NSAID, concomitant drug therapies like antiplatelet agents and presence of H pylori infection. Selective COX-2 inhibitor monotherapy is an alternative to concomitant non-selective NSAIDs and PPI in protecting the upper GI tract from peptic ulcers and bleeding. It is recommended in patients who are at high risk of cardiovascular events and in combination with PPIs in patients who have previously had complicated gastroduodenal peptic ulcer disease. COX-2 inhibitor monotherapy may be more appropriate in unexplained iron deficiency anaemia given the risk of small bowel mucosal injury with NSAIDs and PPIs.

Concomitant innovations in pharmacotherapy for ulcer disease, particularly the development of potent acid suppression with proton pump inhibitors (PPIs), as well as recognition of the role of Helicobacter pylori, expanded research dramatically in ulcer-reducing approaches. Cotherapy options with NSAIDs currently include H2 - receptor antagonists (H2RAs), PPIs, and prostaglandin analogs, each of which possess varying efficacy as a gastroprotective agent and some of which cause further problems with their own side effects. Other articles in this supplement have comprehensively reviewed the epidemiology of NSAID-related ulcers as well as the mechanisms underlying the initiation and perpetuation of injury. NSAIDs inhibit prostaglandin production in the upper GI tract mucosa, and since defense and repair is prostaglandin dependent, the stomach and duodenum are rendered vulnerable in the face of continuous acid production. Th is pathophysiology provides the scientific rationale for gastroprotection options to include supplementation with synthetic prostaglandin analogs, agents that induce gastric acid suppression, or the selective use of those NSAIDs least likely to inhibit upper GI prostaglandin synthesis, such as COX-2 selective inhibitors.

PPIs represent an essential part of the modern gastroenterologist's armament for combating everyday clinical problems. In general, they are highly efficacious in the treatment of acid-related disorders Despite this, the ubiquitous presence and indiscriminant use of PPIs has led to increased oversight among insurers and appropriate concern about the risk of indefinite hypochlorhydria and drug interaction. Careful consideration by the prescriber of appropriate indication, patient cofactors, and the expected dose and duration of treatment is a necessary part of responsible use of any drug, including PPIs.

FUTURE SCOPE

• PPIs provide potent and long-lasting inhibition of gastric acid secretion.

• PPIs can heal NSAID-associated ulcers, even if NSAIDs are continued.

• PPIs reduce the risk of ulcerations due to NSAIDs in RCTs where endoscopic ulcers are used as the primary endpoint.

• Large RCT outcome trials of PPI co-therapy have not been performed.

• RCTs in high-risk patients demonstrate that PPI non-selective NSAID provides similar rates of symptomatic ulcer recurrence rates as a COX-2 selective inhibitor.

• Since COX-2 selective agents have demonstrated superiority of nonselective NSAIDS in GI outcome studies, the two strategies are considered therapeutically equivalent.

• There is an additive benefit of PPI co-therapy to use of a COX-2 selective agent to further reduce GI risk.

• NSAID medication selection should consider both the individual patient's GI and CV risk profile.

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