REVIEW

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Indications for the Use of Proton Pump Inhibitors for Stress Ulcer Prophylaxis and Peptic Ulcer Bleeding in Hospitalized Patients

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ABSTRACT

Proton pump inhibitors are widely used throughout the world for the treatment of gastrointestinal disorders that are related to acid secretion, such as peptic ulcer disease and dyspepsia. Another common indication for proton pump inhibitors is stress ulcer prophylaxis. Proton pump inhibitors have proven efficacy for the treatment of acid-related gastrointestinal disorders, but there is concern that their use may be associated with the development of significant complications, such as fractures, *Clostridium difficile* infection, acute kidney injury, chronic kidney disease, and hypomagnesemia. Proton pump inhibitors are overused in the hospital setting, both for stress ulcer prophylaxis and gastrointestinal bleeding, and then they are often inappropriately continued after discharge from the hospital. This narrative review article outlines the evidence surrounding appropriate proton pump inhibitor use for stress ulcer prophylaxis and peptic ulcer bleeding.

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KEYWORDS: Gastrointestinal bleed; Indications; Peptic ulcer; Proton pump inhibitor; Stress ulcer prophylaxis

INTRODUCTION

Proton pump inhibitors are one of the most commonly prescribed medications in the world because they are effective for the treatment of acid-related gastrointestinal orders, including gastroesophageal disease and peptic ulcer disease.[1] Use of acid-suppressive therapy is common among hospitalized patients; that is, approximately 40%-70% of them receive either proton pump inhibitors or histamine 2 receptor antagonists during their hospitalization.[2,3] Unfortunately, about half of the patients who are newly started on acid suppressive therapy during their hospitalization are discharged to home on this medication, even though its ongoing use is usually not warranted.[2,3]

Although proton pump inhibitors were previously thought to be relatively safe medications with few side effects, over time their association with significant complications has been demonstrated, including acute kidney injury,[4] chronic kidney disease,[4] *Clostridium difficile* infection,[5] hypomagnesemia,[6] and fractures.[7] Because there is concern about the ubiquitous use of proton pump inhibitors and the complications associated with these medications, their appropriate use in the hospital setting should be a priority. With the intention of promoting value-based quality improvement, in this narrative review article we discuss the evidence behind the

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use of proton pump inhibitors for stress ulcer prophylaxis and peptic ulcer bleeding.

EVIDENCE AND GUIDELINES FOR PROTON PUMP INHIBITOR USE FOR SPECIFIC INDICATIONS

In this narrative review we address 2 indications for proton pump inhibitor use, that is, stress ulcer prophylaxis and peptic ulcer bleeding, and provide our evidence-based recommendations on appropriate use.

CLINICAL SIGNIFICANCE

- Proton pump inhibitors are widely used for treatment of gastrointestinal bleeding related to acid secretion and also for stress ulcer prophylaxis.
- Overuse of proton pump inhibitors may be associated with complications.
- Proton pump inhibitors are often inappropriately initiated in the hospital setting and then are often inappropriately continued after hospital discharge.
- Clinicians require guidance in regard to appropriate proton pump inhibitor use to improve patient outcomes.

Stress Ulcer Prophylaxis

Stress ulcers usually start to develop within hours following the onset of serious illness or major trauma. They are most commonly noted in the body and fundus of the stomach and are typically shallow. Stress ulcers are thought to develop most often because of deficient mucosal protection (which is commonly noted in patients with critical illness). Hypersecretion of acid is a less common factor in the development of stress ulcers. Stress ulcers in the upper gastrointestinal tract can lead to gastrointestinal bleeding, the severity of which can range from being minimal (ie, no overt bleeding) to clinically important stress-related gastrointestinal bleeding (ie, overt gastrointestinal bleeding: hematemesis or melena). Medications such as proton pump inhibitors and histamine 2 receptor antagonists are often administered prophylactically to decrease the risk of stress ulcer development. However, recent studies have questioned the efficacy of stress ulcer prophylaxis.

A pilot randomized controlled trial and meta-analysis in 2017 evaluating the safety of withholding pantoprazole for stress ulcer prophylaxis in critically ill patients found no significant increase in risk for upper gastrointestinal tract bleeding, mortality, or infections when pantoprazole was held for stress ulcer prophylaxis.[8]

A 2018 European study enrolled 3298 patients in 33 intensive care units in Denmark, Finland, Netherlands, Norway, Switzerland, and the United Kingdom.[9] This multicenter, parallel-group, blinded, randomized controlled trial evaluated patients who were admitted to an intensive care unit and were at risk for clinically important stress-related gastrointestinal bleeding. The trial compared pantoprazole with placebo, and it did not show a difference in 90-day mortality or composite outcome of clinically important event, which was a composite of clinically important stress-related gastrointestinal bleeding, pneumonia, *C. difficile* infection, or myocardial ischemia.[9] For patients receiving pantoprazole, 2.5% had clinically important stress-related gastrointestinal bleeding, in comparison with 4.2% of those who received a placebo. Although the relative risk was 0.58, no *P* value was presented because the study did not make adjustments for multiple comparisons.

Multiple national and international clinical guidelines outline the role of stress ulcer prophylaxis in intensive care unit settings, including the American Society of Health System Pharmacists in 1999, Surviving Sepsis Campaign in 2016 and the Danish Society of Intensive Care Medicine and the Danish Society of Anesthesiology and Intensive Care Medicine in 2014.[10-12] No national or society guidelines recommend routine stress ulcer prophylaxis in noncritical care settings. All guidelines recommend stress ulcer prophylaxis to be administered to patients with critical illness with additional risk factors for clinically important stress-related gastrointestinal bleeding. The most important additional risk factors are coagulopathy and the need for mechanical ventilation for more than 48 hours. Other risk factors for clinically important stress-related gastrointestinal bleeding include the requirement for renal replacement therapy, established liver disease, and elevated scores of organ failure.

Prior studies on the utility of stress ulcer prophylaxis had been inconclusive and suggested the need for a large randomized controlled trial. With the recent data discussed previously it appears that stress ulcer prophylaxis is not beneficial overall in hospitalized patients, although it may decrease the rate of clinically important stress-related gastrointestinal bleeding in the critically ill at high risk.[12] However, patients with a valid indication for proton pump inhibitors for other medical reasons, who take these medications in the outpatient setting, should continue to take them during their hospitalization.

Peptic Ulcer Bleeding

In vitro studies have shown that a pH > 4 (some studies suggest pH > 6) helps in platelet aggregation and clot stabilization and, thus, reduces risk of rebleeding.[13,14] This provides the rationale for prescribing proton pump inhibitors to patients who have high-risk stigmata of bleeding on endoscopy (ie, active bleeding, overlying clot on an ulcer, or a visible vessel).

Before endoscopy, it is not known which patients have high-risk stigmata. Hence, the conservative and practical approach has been to assume all patients are at high risk when they present with upper gastrointestinal tract bleeding. However, it is important to note that there is no strong evidence to support the widespread (and now considered

Table PPI Dose, Frequency, Route, and Type

PPI	Standard dose	High dose
Esomeprazole	20 mg once a day	40 mg once a day
Lansoprazole	30 mg once a day	30 mg twice a day
Omeprazole	20 mg once a day	40 mg once a day
Pantoprazole	40 mg once a day	40 mg twice a day
Rabeprazole	20 mg once a day	20 mg twice a day

standard of care) practice of administering proton pump inhibitors to patients before endoscopy. There have been 2 randomized trials of intravenous omeprazole versus placebo administered to patients with hematemesis or melena before endoscopy. In both studies, omeprazole failed to reduce transfusion requirements, rebleeding, or mortality, but patients were less likely to have high-risk stigmata of bleeding on endoscopy and, thus, had a reduced need for endoscopic therapy.[15,16] This, in turn, may also help to reduce length of hospital stay because patients with high-risk stigmata on endoscopy are often monitored in the hospital for 72 hours.[16]

There are 4 factors to consider when prescribing proton pump inhibitors: dose, frequency, route, and type. High-dose proton pump inhibitor (Table) is often thought to be necessary to consistently achieve pH > 4 (or pH > 6) across different populations. Given the pharmacokinetics of proton pump inhibitors and diurnal variation in acid secretion, at least twice-a-day dosing may be necessary. Proton pump inhibitors have a half-life of about 60-90 minutes, and they covalently bind to active H^+-K^+ pumps. Hence, their inhibitory effects last much longer (up to 48 hours). However, newly activated H^+-K^+ pumps may continue to produce some acid.[17] A theoretical explanation notwithstanding, a meta-analysis of 9 randomized controlled trials comparing rebleeding rates with high-dose proton pump inhibitor versus low-dose proton pump inhibitor following endoscopic treatment showed that the 2 dosages had similar efficacy.[18] Moreover, the initial studies on proton pump inhibitors and upper gastrointestinal tract bleeding used the intravenous route and given the favorable clinical results, this was adopted in clinical practice. However, oral proton pump inhibitors have excellent bioavailability ranging from 70%-90% and should be as efficacious as those administered intravenously.[18] Studies comparing oral proton pump inhibitors versus placebo achieved clinical outcomes similar to those that used intravenous proton pump inhibitors.[19-21] Three studies directly comparing intravenous and oral proton pump inhibitors in preventing rebleeding after endoscopic treatment found the 2 routes to have similar outcomes.[22-24] However, giving a loading dose intravenously may achieve higher pH up to an hour earlier.[24] After review of the evidence, there was no consistent clinical difference between different formulations of proton pump inhibitors, but it is worth noting that the dosages vary among the studies. Practice patterns do not consistently follow this evidence, in turn leading to lower value care.[25]

The American College of Gastroenterology Guidelines for Management of Patients with Ulcer Bleeding makes a conditional recommendation for pre-endoscopic medical therapy, such as proton pump inhibitor 80 mg bolus followed by 8 mg/h infusion, which may reduce the frequency of higher risk stigmata of hemorrhage at the time of endoscopy.[26,27] Following endoscopy, the American College of Gastroenterology has a strong recommendation for the administration of intravenous proton pump inhibitor 80 mg bolus followed by 8 mg/h infusion for 72 hours for patients who have any of the following: ulcer with active bleeding, adherent clot, or a nonbleeding visible vessel.[27]

For generalizability, ease in formulating recommendations, and a value-based approach, while remaining cognizant that it may be difficult to change practices (pending more data), we recommend a bolus dose of intravenous proton pump inhibitor when patients present with active upper gastrointestinal bleeding (hematemesis or melena) followed by oral or intravenous proton pump inhibitor twice a day (high-dose proton pump inhibitor). After endoscopy, patients with high-risk stigmata (especially those with significant comorbidities) remain at rebleeding risk for up to 72 hours. Hence, high-dose proton pump inhibitor (twice-a-day dosing) should be continued for 72 hours. This can be given orally if the patient is having per oral intake. It should be noted that the data on high-dose proton pump inhibitor (twice-a-day dosing) is geared to lower rebleeding risk and not for ulcer healing, so patients need not be discharged home on high-dose proton pump inhibitors. Further, if patients are given oral proton pump inhibitor, they need not stay in the hospital for 72 hours provided they are otherwise stable to be discharged and understand there may be a risk of rebleeding (due to lack of studies). Duration of treatment with proton pump inhibitors for gastric ulcer is generally 2 months except when the risk of bleeding is not mitigated (ongoing use of nonsteroidal anti-inflammatory drugs, anticoagulation, or antiplatelets, unresectable malignant ulcer). At the time of discharge, the frequency and duration of proton pump inhibitors should be specified.

REDUCING INAPPROPRIATE USE OF PROTON PUMP INHIBITORS AFTER HOSPITAL DISCHARGE

Proton pump inhibitors are often initiated in the hospital setting, and up to half of these new prescriptions are continued at discharge.[28-30]

The inappropriate continuation of proton pump inhibitors at the time of discharge exposes patients to an excess risk of long-term adverse events.[31] Therefore, it is desirable to implement interventions that lead to the discontinuation of inappropriate proton pump inhibitor use both during hospitalization and at the time of discharge from the hospital. Such interventions focus on appropriate indications for proton pump inhibitor use and include education for providers,

development of clinical guidelines, and pharmacist-led interventions.[32-37]

COMPLICATIONS OF LONG-TERM PROTON PUMP INHIBITOR USE

Complications of proton pump inhibitor use include bone fractures, hypomagnesemia, *C. difficile* infection, acute kidney injury, and chronic kidney disease. An increased risk of bone fractures may be noted within the first year of proton pump inhibitor use.[38] In a meta-analysis that included 18 observational studies (with 244,109 fracture cases), Zhou et al[38] concluded that the use of proton pump inhibitors modestly increased the risk of fractures. The relative risk of fractures occurring in the hip was 1.26 in proton pump inhibitor users compared with nonusers. For fractures in the spine, the relative risk in proton pump inhibitor users versus nonusers was 1.58, and for fractures at any site, the relative risk was 1.33 in proton pump inhibitor users versus nonusers.[38]

Proton pump inhibitor use can lead to hypomagnesemia, which when severe can precipitate cardiac arrhythmias, seizures, muscle weakness, tetany, and hypotension. Also, the risk of developing acute kidney injury is increased in patients with hypomagnesemia, and this electrolyte abnormality decreases the likelihood of resolution of acute kidney injury. For proton pump inhibitor users who develop hypomagnesemia, the initiation of magnesium supplementation may not be sufficient to replete low magnesium levels, unless the proton pump inhibitor is discontinued. The pooled risk ratio of hypomagnesemia was 1.43 in proton pump inhibitor users compared with nonusers, according to a meta-analysis of 9 observational studies (which included 109,798 patients).[6]

An increased risk of *C. difficile* infection has been noted in proton pump inhibitor users. In their meta-analysis of 39 observational studies, Kwok et al[5] found that the risk of developing a *C. difficile* infection was increased in proton pump inhibitor users, who had an odds ratio of 1.74 compared with nonusers. Similarly, the risk of recurrent *C. difficile* infection was higher in proton pump inhibitor users, who had an odds ratio of 2.51 compared with nonusers.

Adverse effects of proton pump inhibitor use on kidney function have been documented; that is, this may lead to the development of both acute kidney injury and chronic kidney disease. Acute interstitial nephritis may be the mechanism by which proton pump inhibitors cause acute kidney injury. In a population-based study that included 290,592 patients, Antoniou et al[39] found that in comparison with nonusers, proton pump inhibitor users had a hazard ratio of 2.52 for the development of acute kidney injury. The study also showed a hazard ratio of 3.00 in proton pump inhibitor users versus nonusers for the development of acute interstitial nephritis. The nested case control study involving 184,480 patients that was done by Klepser et al[40] showed that proton pump inhibitor use was associated with an increased risk of acute kidney injury in proton pump inhibitor users, who had an odds ratio of 1.72 compared with nonusers.

In a population-based cohort study by Lazarus et al[41] that involved 10,482 patients who were followed for 13.9 years, the hazard ratio for incident chronic kidney disease was 1.45 for proton pump inhibitor users compared with nonusers. A dose response was noted in this study because the risk of developing chronic kidney disease was higher in patients who used a proton pump inhibitor twice daily, in comparison with those who used a proton pump inhibitor once daily. These findings were reproduced in another large cohort study.[41] The mechanism by which proton pump inhibitor use leads to chronic kidney disease may be either hypomagnesemia or recurrent episodes of acute kidney injury.

CONCLUSION

The use of proton pump inhibitors for stress ulcer prophylaxis should be limited to high-risk patients in the intensive care unit. Patients who receive proton pump inhibitor for treatment for gastrointestinal bleeding during their hospitalization do not need to be discharged home on high-dose (twice daily) proton pump inhibitors. Overuse of proton pump inhibitors during hospitalization is prevalent and often leads to the inappropriate continuation of these medications at the time of hospital discharge. Because the long-term use of proton pump inhibitors is often inappropriate and may be associated with significant adverse effects, it is important to limit their use to only appropriate indications.

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