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EDITORIAL

Protons pump inhibitor treatment and lower gastrointestinal bleeding: Balancing risks and benefits

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Abstract

Proton pump inhibitors (PPIs) represent a milestone in the treatment of acid-related diseases, and are the mainstay in preventing upper gastrointestinal bleeding in high-risk patients treated with nonsteroidal anti-inflammatory drugs (NSAIDs) or low-dose aspirin. However, this beneficial effect does not extend to the lower gastrointestinal tract. PPIs do not prevent NSAID or aspirin-associated lower gastrointestinal bleeding (LGB). PPIs may increase both small bowel injury related to NSAIDs and low-dose aspirin treatment and the risk of LGB. Recent studies suggested that altering intestinal microbiota by PPIs may be involved in the pathogenesis of NSAID-enteropathy. An increase in LGB hospitalization rates may occur more frequently in older patients with more comorbidities and are associated with high hospital resource utilization, longer hospitalization, and increased mortality. Preventive strategies for NSAID and aspirin-associated gastrointestinal bleeding should be directed toward preventing both upper and lower gastrointestinal damage. Future research should be directed toward identifying patients at low-risk for gastrointestinal events associated with the use of NSAIDs or aspirin to avoid inappropriate PPI prescribing. Alternatively, the efficacy of new pharmacologic strategies should be evaluated in high-risk groups, with the aim of reducing the risk of both upper and lower gastrointestinal bleeding in these patients.

Key words: Proton pump inhibitor; Small bowel; Small bowel; Lower gastrointestinal bleeding; Nonsteroidal anti-inflammatory drugs

Core tip: Proton pump inhibitors (PPIs) reduce the risk of upper, but not lower gastrointestinal bleeding (LGB) in patients receiving nonsteroidal anti-inflammatory drugs (NSAIDs) or low-dose aspirin. PPIs could

exacerbate small bowel damage related to NSAIDs and low-dose aspirin, which contributes to an increased risk of LGB possibly related to pathological modifications of small bowel microbiota. LGB is a life-threatening condition, especially in older patients with comorbidities treated with NSAIDs, aspirin, or anticoagulants. No accepted treatments exist for decreasing the risk of LGB in these patients. Future research is needed on reducing inappropriate PPI use and evaluating possible pharmacologic interventions to decrease the risk of gastrointestinal bleeding.

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INTRODUCTION

Proton pump inhibitors (PPIs) are one of the most prescribed drugs worldwide. PPIs are used to treat acid-related disorders like gastro-esophageal reflux disease peptic ulcer, peptic ulcer bleeding, and *Helicobacter pylori* infection when combined with antibiotics. PPIs should also be considered in any patient with risk factors for gastrointestinal bleeding who receives treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) or prophylaxis for cardiovascular events with aspirin or other antiplatelet agents[1].

Treatment with NSAIDs, low-dose aspirin, other antiplatelet drugs, and anticoagulation are associated with an increased risk of both upper and lower gastrointestinal bleeding (LGB). Concomitant treatment with these compounds and PPIs has been associated with a decreased risk of upper gastrointestinal bleeding (UGB) but, obviously, not with an increased risk of LGB. The beneficial effect of PPIs is not expected to occur beyond the duodenum because NSAID-gastropathy, but not NSAID-enteropathy, is a pH-dependent phenomenon and gastroduodenal mucosal protection by PPIs is due mainly to their antisecretory effects[2].

PROTON PUMP INHIBITOR TREATMENT AND RISK OF LOWER GASTROINTESTINAL BLEEDING

In a recent case-control study that included 1008 patients hospitalized for gastrointestinal bleeding, treatment with NSAIDs, low-dose aspirin, other antiplatelet agents, and anticoagulants increased the risk of both UGB and LGB. In this work, concomitant use of PPI was associated with a reduced risk of UGB but not LGB[3]. In fact, there was a significant increase in the risk of LGB with PPI use, which has also been detected by other authors[3-8]. Due to the intrinsic nature of observational studies, the finding was explained as probably due to a "confounding by indication" bias. PPI use could be a marker of a group of patients that have an increased risk of LGB because of their clinical characteristics rather than the PPI use itself[3]. In a previous study, we observed that among patients on dual antiplatelet treatment who received concomitant PPI treatment, gastrointestinal bleeding events were more frequent in the lower gastrointestinal tract (74% *vs* 26%)[9]. There are several potential reasons explaining this change in the pattern of gastrointestinal events, which include (1) a very high protective effect of PPIs on the gastroduodenal mucosa associated with a profound decrease in the rate of UGB and a relative (but not absolute) increase in the proportion of LGB in low-dose ascorbic acid users; (2) an absence of the mucosal protective effect of PPIs beyond the duodenum; (3) a direct harmful effect of low-dose aspirin on the small bowel; (4) promotion of bleeding of pre-existing lesions by these compounds; and (5) exacerbation of NSAID- and aspirin-enteropathy by PPI treatment[10-14].

Lately, a hypothesis proposed that PPIs exacerbate NSAID and low-dose aspirin-associated small bowel injury by inducing changes in the intestinal microbiota[15-17]. A multicenter, cross-sectional study including data collected from endoscopic capsule explorations from 205 patients treated with low-dose aspirin for 3 mo showed that 57.6% of patients had at least one mucosal lesion. In the multivariate analysis, concomitant PPI use (OR = 2.04; 95%CI: 1.05-3.97) and use of enteric-coated aspirin (OR = 4.05; 95%CI: 1.49-11.0) were independent risk factors for the presence of mucosal injury[8]. Similar results were observed in patients receiving NSAIDs. In a recent randomized clinical trial, 57 healthy volunteers were allocated to receive celecoxib plus placebo or rabeprazole for 2 wk. The patients were evaluated by capsule endoscopy at the start and end of treatment. In the PPI group, the authors observed an increased rate of small bowel injury (44.7% *vs* 16.7%, $P = 0.04$)[6].

Some authors suggest that acid gastric suppression induced by PPI treatment is related to changes in small bowel microbiota and explain, at least in part, NSAID-induced enteropathy. It is well known that in addition to bile acids[18] and inhibition of cyclooxygenase activity[19], bacterial mucosal translocation and the consequent activation of the innate inflammatory cascade are important factors in the pathogenesis of NSAID-enteropathy[20,21]. In an animal model, Wallace *et al*[17] demonstrated that concomitant treatment with PPIs and NSAIDs resulted in a higher rate of small bowel mucosal ulceration and bleeding. The authors observed that PPI treatment was related to a modification in the small bowel microbiota, consisting of a decrease in jejunal Actinobacteria and Bifidobacteria spp. In this study, the restoration of physiologic microbiota with probiotic treatment prevented intestinal injury[17].

Similar findings have been observed in human subjects. A small randomized clinical trial, including 25

patients treated with low-dose enteric-coated aspirin and omeprazole randomized to either placebo or probiotic treatment with *Lactobacillus casei* for 3 mo, observed that patients in the probiotic group had a significant decrease in the number of mucosal breaks when evaluated by capsule endoscopy ($P = 0.039$)[15].

All these data suggest that PPI treatment not only does not protect the lower gastrointestinal tract from NSAID- and aspirin-related injury, but that they may increase the intestinal mucosal damage and the risk of LGB. We observed that the LGB hospitalization rate has increased significantly in the past years[9,12,13]. These LGB events occur more frequently in older patients, who usually have a higher number of comorbidities, and are associated with a longer hospital stay and higher mortality rates[12]. These events are associated with greater use of hospital resources and also complicate the management of patients at discharge[12]. A considerable percentage of patients did not resume prophylactic treatment with low-dose aspirin or anticoagulants after an acute episode of LGB, increasing the risk of serious cardiovascular events[22]. A recent retrospective analysis including 295 patients with a previous diagnosis of LGB and low-dose aspirin observed that discontinuing low-dose aspirin is related to a decreased risk in LGB recurrence (6.9% *vs* 18.9%; $P = 0.007$), but increased the rates of mortality (26.7% *vs* 8.2%, $P = 0.001$) and cardiovascular events (36.5% *vs* 22.8%, $P = 0.017$)[23]. This study is a clear example of how difficult it is to find the right balance between risks and benefits in these patients. On one side, there is a need to reduce or prevent cardiovascular events and on the other side there is an increased risk of LGB.

BALANCING RISK AND BENEFITS OF PROTON PUMP INHIBITOR TREATMENT

Current clinical practice faces several dilemmas in patients who need NSAIDs or aspirin, since damage to the upper gastrointestinal tract must be prevented without injuring the lower gastrointestinal tract. This clinical dilemma is especially important in patients who need, for example, preventive treatments against cardiovascular disease and who have had a previous LGB episode. Alternative therapeutic approaches with non-aspirin antiplatelet agents poses a similar risk of LGB as aspirin and many not be a valid option[3]. The same is true for patients who need NSAIDs, although COX-2 selective NSAIDs have been shown to be less damaging to the lower gastrointestinal tract than traditional NSAIDs[2,11,24]. The addition of a PPI to celecoxib increases intestinal mucosal damage[6,10,17]. Therefore, future efforts must concentrate on finding strategies that help clinicians in the decision making process. The first relevant issue is to improve overall PPI prescribing and avoid use of PPIs in patients at low risk of gastrointestinal complications who take NSAIDs, aspirin, other antiplatelet agents, or anticoagulants. PPIs are prescribed too often in routine clinical practice, where at least 50% of prescriptions are for non-approved indications[25]. Therefore, the first step should be to promote the proper use of these drugs. Identifying patients at low risk of gastrointestinal events who may not benefit from treatment with PPIs is essential. Tools that could help physicians in the decision making process are now available[26]. On the other hand, we have to reconsider whether current guidelines are valid or respond to problems in daily clinical practice. For example, the PPI treatment indication in patients receiving NSAIDs is based on data from clinical trials of chronic NSAID users. However, observational studies suggest that the risk of gastrointestinal bleeding may be higher when the drug use is recent, and most patients take these drugs for short periods of time[11]. We also need more evidence to evaluate the risks of upper and lower gastrointestinal bleeding with new antiplatelet drugs, new oral direct anticoagulants, and the multiple combinations available in order to better assess the risks and benefits.

On the other hand, in patients at high risk for LGB, preventive strategies are needed. This group includes older patients, with a great number of comorbidities who need more complex management[9,12,23]. As mentioned above, in these patients LGB represents a serious and life threatening complication. Currently, there is no clear effective pharmacological treatment to prevent LGB in NSAID, aspirin, or anticoagulant users. Some studies have evaluated the effect of the prostaglandin analogue misoprostol on small bowel injury induced by NSAIDs[7,27]. Other mucosal protectants such as rebamipide[28-31], irsogladine[32,33], or geranylgeranylacetone[34,35] have been tested and are only available in the Asia-Pacific region. Their potential beneficial effects in these patients still need to be evaluated in new studies.

In the same way, some studies have evaluated the efficacy of probiotics in preventing lower gastrointestinal tract injury among patients treated with NSAIDs or low-dose aspirin[15,16]. The probiotic administered in these two trials was *Lactobacillus casei* in patient treated with low-dose aspirin, while patient treated with NSAIDs received the probiotic mixture VSL#3®, that includes *Streptococcus thermophilus*, *Bifidobacterium breve*, *Bifidobacterium longum*, *Bifidobacterium infantis*, *Lactobacillus paracasei*, *Lactobacillus delbrueckii subsp. Bulgaricus*, *Lactobacillus acidophilus* and *Lactobacillus plantarum*[15,16]. The results are promising and suggest that pharmacological prophylaxis could be provided by this strategy. However, more studies with a larger number of patients are also needed. At present, there is not sufficient evidence to recommend a specific probiotic strain to prevent lower gastrointestinal injury. However some bacteria have demonstrated antiinflammatory activity and a protective effect on intestinal mucosa. For example: (1) *Lactobacillus GG* protect mucosal cells from apoptosis and increase mucosal integrity; (2) *Lactobacillus plantarum*

promotes mucine from epithelial cells; (3) *Lactobacillus reuterii* and *Lactobacillus casei* have demonstrated to suppress tumor necrosis factor production *in vivo*; and (4) *Streptococcus thermophillus* and *Lactobacillus acidophilus* could prevent bacterial translocation[36].

CONCLUSION

In conclusion, PPIs represent a milestone in the treatment of acid-related disease. Moreover, PPIs significantly reduce the risk of UGB in patients treated with NSAIDs, low-dose aspirin, other antiplatelet agents, or anticoagulants. This beneficial effect is not observed in the lower gastrointestinal tract. Furthermore, recent studies suggest that PPIs may in fact increase small bowel injury and contribute to the observed increase of LGB in the past years; however, results are controversial. Clinicians very often face clinical dilemmas and need to balance the risks and benefits of treatment. The use of aspirin in preventing cardiovascular disease and the risk of gastrointestinal bleeding is one of these situations. The dilemma is even more difficult to resolve when one of the drugs (PPI) can have a dual and opposite effect (beneficial to the upper GI tract but damaging to the lower GI tract). Clinicians have to evaluate carefully the risk of upper gastrointestinal bleeding in patients that have a previous episode of LGB in order to discontinue inappropriate administration of PPI. Future research should be focused on identifying patients at low risk for upper gastrointestinal bleeding to avoid inappropriate PPI treatment and to evaluate the efficacy of new pharmacologic strategies in high-risk groups. The aim of this strategy is to reduce the risk of LGB in these patients while at the same time providing the maximal beneficial effect to the upper gastrointestinal tract.

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