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EDITORIAL

Safety of the long-term use of proton pump inhibitors

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Abstract

The proton pump inhibitors (PPIs) as a class are remarkably safe and effective for persons with peptic ulcer disorders. Serious adverse events are extremely rare for PPIs, with case reports of interstitial nephritis with omeprazole, hepatitis with omeprazole and lansoprazole, and disputed visual disturbances with pantoprazole and omeprazole. PPI use is associated with the development of fundic gland polyps (FGP); stopping PPIs is associated with regression of FGP. In the absence of *Helicobacter pylori* infection, the long-term use of PPIs has not been convincingly proven to cause or be associated with the progression of pre-existing chronic gastritis or gastric atrophy or intestinal metaplasia. Mild/modest hypergastrinemia is a physiological response to the reduction in gastric acid secretion due to any cause. The long-term use of PPIs has not been convincingly proven to cause enterochromaffin-like cell hyperplasia or carcinoid tumors. PPIs increase the risk of community acquired pneumonia, but not of hospital acquired (nosocomial) pneumonia. There is no data to support particular care in prescribing PPI therapy due to concerns about risk of hip fracture with the long-term use of PPIs. Long-term use of PPIs does not lead to vitamin B12 deficiencies, except possibly in the elderly, or in persons with Zollinger-Ellison Syndrome who are on high doses of PPI for prolonged periods of time. There is no convincingly proven data that PPIs increase the risk of *Clostridium difficile*-associated diarrhea in persons in the community. The discontinuation of PPIs may result in rebound symptoms requiring further and even continuous PPI use for suppression of symptoms. As with all medications, the key is to use PPIs only when clearly indicated, and to reassess continued use so that long-term therapy is used judiciously. Thus, in summary, the PPIs are a safe class of medications to use long-term in persons in whom there is a clear need for the maintenance of extensive acid inhibition.

Key words: Acid inhibition; Drug safety; Osteoporosis; Pneumonia; Enteric infections

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INTRODUCTION

The risk of minor adverse effects from proton pump inhibitors (PPIs) is low, approximately 1%-3%, with rates of withdrawal from clinical research studies being 1%-2%, with no significant differences noted between the PPIs[1-6]. The risk of symptomatic adverse effects with the PPIs is low as well. In pooled data from published trials involving 2812 patients, omeprazole was

reported as causing headache (2.4%), diarrhea (1.9%), nausea (0.9%), and rash (1.1%), a profile similar to that of cimetidine and ranitidine[7]. In a prospective follow-up study of 5669 patients on lansoprazole, the most common reported adverse effects were diarrhea (4.1%), headache (2.9%), and nausea (2.6%). A similar profile has been reported for pantoprazole: diarrhea, 1.5%; headache, 1.3%; dizziness, 0.7%; pruritus, 0.5%[8]; rash, 0.4%[9]; and nausea, 0.015%. Compiled data from 3556 patients taking rabeprazole for up to one year demonstrated that the most common adverse effect was headache with an incidence (2.4%) similar to placebo (3.1%).

Serious adverse events are rare, with case reports of interstitial nephritis with omeprazole, hepatitis with omeprazole and lansoprazole[10-12], and disputed visual disturbances with pantoprazole and omeprazole[13,14]. An anticipated physiological effect of acid suppression with PPIs is an elevated serum gastrin concentration, which occurs with all PPIs. Gastrin elevation may be higher with omeprazole than with pantoprazole, and higher with lansoprazole than with omeprazole[15-17], and higher with rabeprazole than with omeprazole[18]. This variation in PPI-associated elevation of gastrin concentration is not clinically relevant.

Some persons with dyspeptic conditions such as gastroesophageal reflux disease (GERD) may need to be maintained long-term on PPIs. For this reason, we have reviewed the literature on possible long-term adverse effects of PPIs. Narrative or qualitative reviews, when compared to their systematic review cousins, trade off depth in favor of breadth. After all, reviews can be comprehensive and primary, or narrow in scope and heavily guarded against various biases. Narrative reviews remain, despite a heavy battering by hordes of high quality randomized controlled trials and mathematically endowed structured reviews, on their pedestal as a premier venue for medical educators and historians. This review fits in that important tradition, and purports to fill a need for a comprehensive review on the safety of long-term use PPIs. Mulrow published criteria for minimizing bias in narrative reviews[19]. Deeks summed up these as being rigorous, informative, comprehensive, and explicit[20]. Collins and Fauser, in their editorial, enforced the view of the importance of "balancing the strengths of systemic and narrative reviews"[21]. To achieve this balance and complement a primarily journalistic approach, a search of PubMed, Google Scholar and UpToDate for articles published since 1999 on the topic of "PPI" and "safety" (and related MESH terms) was conducted to identify English language meta-analysis, publications in one of the top biomedical journals in this field (NEJM, Annals, Lancet, JAMA, American Journal of Gastroenterology, Gastroenterology, American Journal of Gastroenterology, Alimentary Pharmacology and therapeutics, Drugs, BMJ) as well as major North American and European guidelines. Checklists have been proposed for systematic and qualitative research[22,23], aiding in the review. We present this information on the long-term safety of PPIs with a series of questions, a summary of the literature, and our proposed answer.

THE USE OF PPIS IS NOT ASSOCIATED WITH AN ALTERATION OF GASTRIC HISTOLOGY

In *Helicobacter pylori* (*H. pylori*) negative persons PPIs do not worsen pre-existing gastritis[24,25], and may even improve pre-existing gastritis[26]. PPIs do not cause atrophic gastritis[27,28].

In contrast, in *H. pylori* positive persons, *H. pylori* is associated with antral or body acute or chronic gastritis, atrophy and metaplasia[29]. *H. pylori*-associated chronic gastritis may progress to gastric atrophy, intestinal metaplasia, and gastric cancer[25,27,30,31], or may not[32]. *H. pylori* and PPIs may cause progression or acceleration from gastric antrum-predominant chronic gastritis to body-predominant chronic gastritis, and it is controversial whether gastric body-predominant atrophic gastritis (gastric atrophy) is a risk factor for gastric cancer[33]. *H. pylori* eradication may cause regression of gastric atrophy or intestinal metaplasia[26,27,29,34-37] or may not[33,38-44].

Thus, the long-term use of PPIs has not been convincingly proven to cause or accelerate the progression of pre-existing chronic gastritis, corpus gastric atrophy or intestinal metaplasia.

PHYSIOLOGICAL HYPERGASTRINEMIA DOES NOT CAUSE GASTRIC CARCINOIDS OR CANCER

H. pylori infection (without use of PPIs) itself increases serum gastrin concentration[29,45].

PPIs modestly increase serum gastrin concentration in persons who are *H. pylori*-negative or positive[46,47]. While PPI's may increase apoptosis[48], PPIs do not increase risk of gastric or esophageal cancer[49-51].

It is controversial whether the hypergastrinemia associated with the use of PPIs increase enterochromaffin-like (ECL) cell numbers, as well as linear or micronodular hyperplasia - Yes[52-54] in *H. pylori* positive persons[55], and No[43,56,57]. Hypergastrinemia associated with Zollinger-Ellison Syndrome (ZES), rarely is associated with an increase in ECL cell growth or ECL carcinoid[58]. Furthermore, there is only one published report in world literature of a ZES patient treated with PPIs for associated gastric hypersecretion, who developed gastric cancer[59]. This is probably a chance association.

Thus, mild/modest hypergastrinemia is a physiological response to a reduction in acid secretion due to any cause. The long-term use of PPIs has not been convincingly proven to cause ECL cell hyperplasia or carcinoid tumors. Even when hypergastrinemia is marked and prolonged (such as with ZES or MEN-1), gastric carcinoids are rare.

THE USE OF PPIS IS ASSOCIATED WITH THE DEVELOPMENT OF FUNDIC GLAND POLYPS

PPI use is associated with parietal cell hyperplasia, and an

up to fourfold increased incidence of fundic gland polyps (FGP)[60-62]. FGP also occur in the presence of *H. pylori* infection, likely incidentally[63,64]. Eradication of *H. pylori* or stopping long-term use of PPIs is associated with regression of FGP[62,65,66]. FGP in sporadic cases is rarely associated with dysplasia, but never gastric adenocarcinoma[67]. Dysplasia may occur in 25%-44% of gastric polyps in persons with familial adenomatous polyposis[63,68].

In summary, PPI use is associated with the development of FGP. FGP occur in the presence or absence of *H. pylori* infection. The eradication of *H. pylori* or stopping PPI is associated with regression of FGP. FGP may rarely become dysplastic, but almost exclusively this rare event is seen in persons with familial adenomatous polyposis.

PPIs may mask the symptoms of gastric cancer (GC), heal malignant gastric ulcers, or shorten survival in the patient with GC.

PPIs may mask the symptoms or heal early GC, but there is no data on the effect of PPIs on rates of survival[69]. H2RA's may[70] or may not[71] actually produce longer survival in patients with GC.

BIOAVAILABILITY OR METABOLISM OF A FEW OTHER DRUGS

PPIs reduce gastric acid, and thereby reduce the bioavailability of drugs requiring intragastric acidity to maximize their absorption and bioavailability[51]. Examples of such drugs would include ketoconazole, itraconazole and indinipur[72], and may reduce the effects of locally acting drugs such as sucralfate.

PPIs may alter the intestinal first pass metabolism or the hepatic clearance of some drugs, and thereby modify their pharmacodynamics[72]. They have no effect on n-acetyltransfer or xanthine oxidase activities[73], and may show a rare class action effect on vitamin K antagonists[74]. PPIs have a low drug interaction through phase I / II effects[5,75], and may differ in their possibility of causing drug interactions. Omeprazole and lansoprazole have a high affinity for CYP2C19 and CYP3A4 but these cytochromes contribute little to rabeprazole metabolism. Pantoprazole is completely metabolized by these cytochrome enzymes, but it uniquely has no drug interactions with a wide range of drugs[72,76-78].

PPIs, with the exception of pantoprazole, have been associated with reduced effectiveness of clopidogrel and a resulting 40% increased risk of coronary stent occlusions[79]. There is no consensus yet on how to manage this[80].

Thus, PPIs have an effect in common with all acid lowering therapy to reduce the absorption of acid-dependent medications. The metabolism of PPIs by hepatic cytochrome enzymes varies significantly between drugs.

THE USE OF PPIS AND DEFICIENCIES IN IRON AND VITAMIN B12

Iron

PPIs reduce gastric acidity, and in patients treated long-term with high dose PPIs duodenal absorption of organic and non-organic iron may be reduced[81]. This effect however is small, and PPIs are not associated with an increased risk of latent iron deficiency or iron deficiency[82].

Vitamin B12

PPIs reduce gastric acidity, which is necessary to activate pepsinogen to pepsin to release vitamin B12 from B12-containing foods. PPIs used short-term may minimally reduce the absorption of protein-bound B12 in food[83-85]. In elderly patients who may already have gastric atrophy (possibly from *H. pylori* infection), PPIs used long-term may reduce serum vitamin B12 concentrations[85-87]. Five out of six studies have shown that PPIs used long-term in non-elderly patients do not reduce serum vitamin B12 concentrations, and therefore body B12 stores[81,88-93].

In ZES patients treated long-term with high dose PPIs, the serum concentration of vitamin B12 may be reduced[94]. And yet, in cystic fibrosis (CF) children with reduced secretion of pancreatic bicarbonate and increased duodenal acidity, there is no reduction in the intestinal absorption of B12[76].

Thus, long-term use of PPIs does not lead to vitamin B12 deficiencies, except possibly in the elderly or in persons with ZES who are on high doses of PPI for prolonged periods of time[95,96].

RISK OF OSTOPENIA, OSTEOPOROSIS AND WITH BONE METABOLISM

PPIs alter osteoclastic vacuolar mechanisms which may reduce bone absorption[97], and thereby actually reduce the risk of OP. PPIs have no known adverse effect on vitamin D absorption or metabolism.

What is the link between PPI use and metabolic bone disease? There is a highly variable effect of acid suppression on calcium absorption[98,99]. In persons with achlorhydria due to pernicious anemia, Ca^{2+} absorption is normal or reduced[100,101].

The real question is whether PPI use is associated with an increased risk of osteoporosis/osteopenia, and more importantly with bone fractures. In case controlled studies, PPI use long-term is associated with an increased risk of bone fractures, and this increased risk depends on the duration and dose of chronic use of the PPI[102] (e.g. Manitoba Population Health Research Data Repository[103]). Use of PPI $\geqslant$ 5 years can increase the risk of osteoporotic fractures by 1.62-fold (95% CI: 1.02-2.58). Other studies confirm that use of PPI $\geqslant$ 7 years increases the risk of osteoporotic hip fractures by 4.55-fold (95% CI: 1.68-12.29) and PPI use for 6-12 mo has been reported to be associated with an increased risk of osteoporotic hip and spine fractures[103-105]. Osteoporotic fractures of the hip and spine may be associated with many factors, which must be carefully taken into account in any case-controlled study which suggests a new association, such as the use of PPIs. However, case control studies on the risk of OP may be criticized on a methodological basis, such as the lack of appropriate stratification of the risk of other

factors known to be associated with an increased risk of OP[106]. The Canadian Association of Gastroenterology (CAG) position paper suggests that "current data would not support particular care in prescribing PPI therapy due to concern about risk of hip fracture"[107].

COMMUNITY ACQUIRED NOSOCOMIAL PNEUMONIA

What is the physiological background to speculating that PPIs might result in pulmonary complications? PPI use is associated with increased intragastric aerobic bacteria, and with the production of acetaldehyde from alcohol[108]. The increased bacterial colonization of the stomach observed with PPI users may be associated with pulmonary micro-aspiration and lung colonization[109,110]. In addition, it is postulated that secretions from the oropharynx may pass by micro-aspiration into the lower lung airways[111]. Furthermore, lung colonization may occur as a result of mechanisms other than micro-aspiration of gastric contents, because different organisms may grow from cultures of gastric juice and from bronchoalveolar lavage[112].

From the clinical perspective, the risk of community acquired pneumonia (CAP) is 0.6 per 100 person years. In persons on PPIs, the odds ratio (OR) is 1.89 (95% CI: 1.36-2.62) for current PPI use and 1.5 (95% CI: 1.3-1.7) for past PPI use (95% CI: 0.9-1.6, and 0.8-1.3, respectively)[113].

In the short-term, PPI use increases the risk of CAP: use of PPI for 2 d, OR = 6.53 (95% CI: 3.95-10.80); for 7 d, OR = 3.79 (95% CI: 2.65-5.42); for 14 d, OR = 3.21 (95% CI: 2.46-4.18); but long-term use of PPIs does not increase the risk of CAP[114], and furthermore meta-analyses have shown that there is no significant association between PPIs and CAP[115].

In contrast, PPIs do not increase the risk of hospital acquired (nosocomial) pneumonia (NP). In fact, there is a reduced risk of NP in patients with nasogastric tubes on a PPI[116]. For ventilated pediatric patients in ICU, there is no increased risk of NP[117-119].

Thus, short-term PPI use increases the risk of CAP, but PPI use does not increase the risk of hospital acquired pneumonia.

CLOSTRIDIUM DIFFICILE-ASSOCIATED PNEUMONIA

There are numerous risk factors for CDAD (use of antibiotics, age, contact with an infected patient or healthcare worker, crowding, lack of cleanliness, post-pyloric tube feeding, patient immunosuppression)[120]. These factors must be taken into account for the attribution of risk, e.g. before assigning a possible role to a new factor, such as PPIs. Some observational studies show an association between PPI use and risk of CDAD[121-132]. For example, for PPI use and CDAD in chronic renal failure patients, the AOR is 5.7 (95% CI: 1.3-39.1) (P = 0.02)[133]. In meta-analyses of studies of CDAD and PPIs, the AOR is 1.96 (95% CI: 1.28-3.00). Some of these reports involve a hypervirulent strain of *C. difficile*, and after correcting for other factors such as antibiotic use, there is no association with PPIs[134]. The bottom line is that there is no convincingly proven data that PPIs increase the risk of CDAD[134,135].

SMALL BOWEL CONTAMINATION SYNDROME AND ENTERIC INFECTIONS

It is thought that PPIs have a minor effect on altering the intestinal bacterial microbiota[136]. Observational studies have suggested that PPIs may[137] or may not[138] increase risk of enteric infections.

Thus, PPIs do not have a convincingly proven adverse effect on the enteric microbiota, and if such an effect does exist, there is no proven clinically important adverse effect[139,140].

The use and subsequent withdrawal of PPIs may be associated with an exaggeration of, or new onset of, acid-related symptoms. PPIs are a medication that is generously prescribed for a variety of symptoms that are thought, and not necessarily confirmed, to be acid-induced. One reason for this is the relatively low number of adverse effects that have been shown in the short- or long-term. One study suggests that symptoms that commence following the discontinuation of PPIs due to rebound acid hypersecretion may be as troublesome as the symptoms that the PPIs were being used to treat in the first place[141]. Because of these rebound symptoms, there may be a need for further and continuous PPI use. As with all medications, the key is to use PPIs only when clearly indicated, and to reassess continued use so that long-term therapy is used judiciously.

The risk of false-negative urea breath tests (UBT) for the diagnosis of an *H. pylori* infection is lower for pantoprazole[142,143]. While it is recommended that acid suppression therapy should be discontinued prior to a UBT, the false-negative effect is lower for pantoprazole.

The biological plausibility is poor for the possibility that PPI use is associated with an increased risk of colorectal cancer or adenomatous polyps, and there is no clinical data to suggest this possibility.

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