REVIEWS IN BASIC AND CLINICAL GASTROENTEROLOGY AND HEPATOLOGY

John P. Lynch and David C. Metz, Section Editors

Safety of Proton Pump Inhibitor Exposure

YU–XIAO YANG[*,‡] and DAVID C. METZ[‡]

[*]Center for Clinical Epidemiology and Biostatistics and [‡]Division of Gastroenterology, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania

Podcast interview: www.gastro.org/gastropodcast.

Proton pump (H^+/K^+–adenosine triphosphatase) inhibitors (PPIs) are widely used to treat patients with acid-related disorders because they are generally perceived to be safe and effective. However, as with any pharmacologic agent, they have the potential for side effects. Many studies have examined the side effects of long-term or short-term PPI exposure. We review the mechanism of action of PPIs, focusing on recently released products that might have greater risks of adverse effects than older products because of increased potency and/or duration of action. We summarize the data available on the putative adverse effects of PPI therapy and propose guidelines for clinicians who prescribe these agents to limit the potential for adverse outcomes in users of these effective therapeutic agents.

Keywords: Drug Safety; Side Effects; Acid Suppressive Therapy.

Proton pump (H^+/K^+–adenosine triphosphatase [ATPase]) inhibitors (PPIs) have been available in the United States as acid-suppressing agents since the mid-1980s.[1,2] They are widely used (sales of PPIs are in excess of $10 billion per year[1,3]) because they are generally safe and effective; they have essentially replaced histamine H_2-receptor antagonists (H2RAs) for most chronic indications because of these perceived advantages.[2,4] However, as for other pharmacologic agents, they have the potential for side effects.[1,5,6] In general, when selecting any therapeutic strategy, physicians need to determine if the risks outweigh the gain.[1,2,4,5] Much research has evaluated the potential side effects of PPIs (Figure 1). Most of these putative effects are a direct consequence of inhibition of acid production by parietal cells (hypochlorhydria or reflex hypergastrinemia), but idiosyncratic effects, metabolic issues from interactions with hepatic cytochrome P450, immunosuppression, and other effects have been proposed.[1,2,4,7] The potential for side effects from use of PPIs is an important issue not only because these drugs are used so frequently but also because newer agents, with longer serum half-lives and potentially greater inhibition of acid output, are now available.[8–16]

We review the mechanism of action of PPIs, with specific attention to potential differences in recently released products (stereotypic isomers and drugs with longer serum half-lives) and recent data on side effects. We also summarize a risk-benefit approach that can be used to determine which patients should receive PPIs; we recommend ways to minimize the potential for adverse effects among users of these effective therapeutic agents.

Mechanism of Action of Proton Pump Inhibitor Therapy

PPIs are prodrugs; they require activation by parietal cells in the presence of gastric acid, which leads to formation of an active sulfenamide moiety. This moiety binds irreversibly to the hydrogen potassium ATPase on the secretory canaliculus of actively secreting parietal cells, which inhibits the ability of cells to produce hydrochloric acid.[2,4,16–18] The prodrug is systemically absorbed or delivered directly into the bloodstream, resulting in a relatively short half-life in serum; during this time, it is distributed to the stomach and other organs.[19–23] In the stomach, the prodrug is activated by a 2-step process; it is first converted to its sulfenamide derivative and then protonated to form a benzimidazole, which binds irreversibly with the canalicular H^+/K^+-ATPase. Binding blocks the exchange of hydrogen (out) for potassium (in), which prevents the cell from producing acid.[2,16,17] Be-

Abbreviations used in this paper: BMD, bone mineral density; CI, confidence interval; FDA, Food and Drug Administration; GPRD, General Practice Research Database; H2RA, H_2-receptor antagonist; OR, odds ratio; PPI, proton pump inhibitor.

0016-5085/$36.00
doi:10.1053/j.gastro.2010.08.023

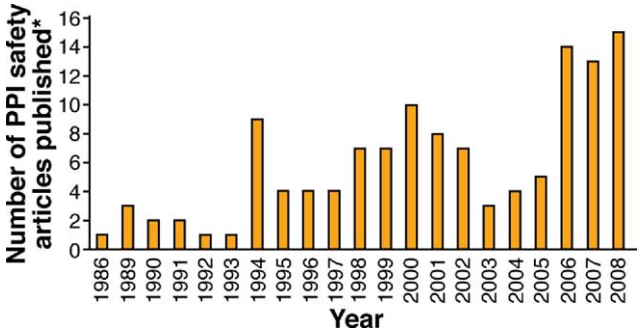

Figure 1. Publications that have examined the side effects of PPIs since the release of omeprazole. *Number of articles was calculated based on a PubMed search and then individually selected based on relevance. The PubMed Search terms were "proton pump inhibitor" OR "pantoprazole" OR "lansoprazole" OR "omeprazole" OR "esomeprazole" OR "rabeprazole" AND safety OR adverse events OR risk AND Humans (MeSH) AND English (lang).

cause all PPIs are weak bases with first-step dissociation constants that are within the acidic range (pKa1s range from 3.8 to 4.9, with rabeprazole having the highest pKa1), they concentrate in the parietal cell secretory canaliculus, where the pH is approximately 1.0.[1,16–18] The second step in activation has a low pKa2 for all PPIs (approximately 1.0), which permits the formation of the benzimidazole moiety that binds to all available actively secreting pumps and inactivates them.[2,16–18] Other low pH spaces, such as the renal medulla or the resorptive surfaces of bone (with high densities of osteoclasts), do not seem to have a low enough pH to permit the second step of PPI activation.[1,24,25] Elsewhere in the body PPIs follow first-order kinetics; blood levels of PPIs decrease as the drugs are metabolized in the liver (primarily by cytochrome P450 enzymes) and then excreted in the urine (primarily) or stool.[1,2,4]

The proton pump consists of 2 transmembrane subunits: an α subunit with 10 transmembrane domains and a β subunit with a single transmembrane domain.[4,16–18] All PPIs bind to a cysteine located in transmembrane region 6 (cysteine [C] 813) of the α subunit, forming a covalent disulfide bond that keeps the pump in an open position, prevents the reuptake of potassium, and blocks the exchange of hydrogen for potassium.[17,18] PPIs also bind to other cysteines (eg, dexlansoprazole/lansoprazole and rabeprazole to C321, pantoprazole to C822, and esomeprazole/omeprazole, dexlansoprazole/lansoprazole, and rabeprazole to C892), but these interactions do not appear to provide any additional inhibition beyond the activity at C813 alone.[16]

Even high, once-daily doses of PPIs are believed to only inhibit about 75% of the proton pumps of each parietal cell, because even a maximally stimulated secretory canalicular surface cannot expand sufficiently to accommodate and activate all intracellular pumps.[16–18] Therefore, once blood levels have decreased below the threshold required to permit delivery of additional prodrug to the secretory canalicular space, activation of residual intracellular pumps by subsequent meals could restore acid secretion.[13,16] Pharmacodynamic crossover studies have shown that acid inhibition (after appropriate administration in fasting patients 30–60 minutes before breakfast) ranges from 10.1 hours for pantoprazole 40 mg to 14.1 hours for esomeprazole 40 mg (the durations of action of lansoprazole 30 mg, rabeprazole 20 mg, and omeprazole 20 mg are within this range).[16,26] Equivalent dose ranges of esomeprazole and omeprazole were not compared in these studies, although other studies indicated that the purified enantiomer esomeprazole has a slightly longer serum half-life than an equivalent dose of its racemic cousin omeprazole.[2,16]

As a consequence of reduced acid output from long-term PPI therapy, the increased basal gastric pH inhibits somatostatin release from D cells in the gastric antrum, leading to unimpeded gastrin release from G cells and increased serum levels of gastrin at rest.[1,13] Studies with all the marketed PPIs revealed increased serum levels of gastrin with therapy, although they might not reach the abnormal range in all individuals (patients with *Helicobacter pylori*–associated gastritis tend to have greater gastrin responses following therapy with PPIs than uninfected individuals).[5,6,8,10,11,14,27–30]

As many as 30% of patients who take PPIs find their symptoms are inadequately controlled at certain times of the 24-hour cycle (primarily at night).[31] This might result, in part, from poor timing of therapy in relation to meals, but other possibilities are that the patients do not really have acid-peptic disease or they metabolize a once-daily standard dose of PPI therapy too rapidly, which permits recovery of acid secretion.[9,12,15] A number of approaches have been proposed to improve intragastric pH control with PPIs for patients who rapidly metabolize the drug: (1) increasing the once-daily dose, (2) increasing the dose frequency, (3) administering the PPI with ligands, such as gastrin derivatives that directly activate proton pumps and allow for better acid secretory inhibition, or (4) administering the drug with alkaline products to indirectly activate existing proton pumps (by stimulating the feedback inhibition arc).[9,12,13,15] The first 2 approaches have not been shown to be effective and the third approach has not made it beyond preclinical trials, but the fourth approach has resulted in an product that was approved by the US Food and Drug Administration (FDA): immediate-release omeprazole.[32]

Immediate-release omeprazole is believed to inhibit gastric acid production to a greater extent than standard omeprazole because it raises the gastric pH, which activates the pumps without the need for a meal to be administered after dosing.[33,34] Critics of this approach have suggested that any symptomatic benefit encountered with this agent arises because the drug is coadministered with an antacid that allows for initial control of symptoms before the drug is absorbed.[35] No studies have