Proton Pump Inhibitors
Pharmacology And Rationale For Use In Gastrointestinal Disorders

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Contents

Abstract ................................................................. 307
1. Pharmacology of the Proton Pump Inhibitors (PPIs) ................................................................. 308
   1.1 Overview of Pharmacology of the H+/K⁺ ATPase Pump ............................................................ 308
   1.2 Comparative Pharmacology of the PPIs ................................................................. 308
   1.3 Pharmacokinetic Profiles ................................................................. 310
   1.4 Effects of PPIs on Gastric Acid Secretion ................................................................. 311
   1.5 Effects on Gastrin Production ................................................................. 311
   1.6 Drug Interactions ................................................................. 312
2. Therapeutic Indications ................................................................. 312
   2.1 Duodenal Ulcer ................................................................. 312
   2.2 Gastric Ulcer Healing ................................................................. 316
   2.3 Helicobacter pylori ................................................................. 318
   2.4 Prevention of Nonsteroidal Anti-Inflammatory Drug (NSAID) Induced Ulceration .................. 320
   2.5 Reflux Oesophagitis ................................................................. 322
3. Other Indications ................................................................. 326
   3.1 Zollinger-Ellison Syndrome ................................................................. 326
   3.2 Crohn’s Disease ................................................................. 326
   3.3 Prevention of Stress Ulceration ................................................................. 327
   3.4 PPIs and Upper Gastrointestinal Bleeding ................................................................. 327
4. Tolerability and Adverse Events ................................................................. 327
5. Role of PPIs in the Management of Acid-Related Disorders ................................................................. 328

Abstract

Proton pump inhibitors (PPIs) are drugs which irreversibly inhibit proton pump (H⁺/K⁺ ATPase) function and are the most potent gastric acid–suppressing agents in clinical use. There is now a substantial body of evidence showing improved efficacy of PPIs over the histamine H₂ receptor antagonists and other drugs in acid-related disorders.

Omeprazole 20 mg/day, lansoprazole 30 mg/day, pantoprazole 40 mg/day or rabeprazole 20 mg/day for 2 to 4 weeks are more effective than standard doses of H₂-receptor antagonists in healing duodenal and gastric ulcers. Patients with gastric ulcers should receive standard doses of PPIs as for duodenal ulcers but for a longer time period (4 to 8 weeks). There is no conclusive evidence to support the use of a particular PPI over another for either duodenal or gastric ulcer healing.

For Helicobacter pylori–positive duodenal ulceration, a combination of a PPI and 2 antibacterialswill eradicate H. pylori in over 90% of cases and significantly
reduce ulcer recurrence. Patients with *H. pylori*-positive gastric ulcers should be managed similarly. PPIs also have efficacy advantages over ranitidine and misoprostol and are better tolerated than misoprostol in patients taking nonsteroidal anti-inflammatory drugs (NSAIDs).

In endoscopically proven gastro-oesophageal reflux disease, standard daily doses of the PPIs are more effective than H2-receptor antagonists for healing, and patients should receive a 4 to 8 week course of treatment. For severe reflux, with ulceration and/or stricture formation, a higher dose regimen (omeprazole 40mg, lansoprazole 60mg, pantoprazole 80mg or rabeprazole 40mg daily) appears to yield better healing rates. There is little evidence that PPIs lead to resolution of Barrett’s oesophagus or a reduction of subsequent adenocarcinoma development, but PPIs are indicated in healing of any associated ulceration. In Zollinger-Ellison syndrome, PPIs have become the treatment of choice for the management of gastric acid hypersecretion.

Proton pump inhibitors (PPIs) have been one of the most important advances in the field of gastroenterology in the past 15 years. Many studies have now demonstrated their greater efficacy in acid-related conditions over other acid reducing drugs. Currently 3 PPIs, omeprazole, lansoprazole and pantoprazole are commercially available worldwide, with rabeprazole (which has been recently licensed in Japan) expected soon in other countries (fig. 1).

1. Pharmacology of the Proton Pump Inhibitors (PPIs)

1.1 Overview of Pharmacology of the H\(^+\), K\(^+\) ATPase Pump

The gastric acid pump (H\(^+\)/K\(^+\) ATPase) is the primary target for a group of drugs known as the PPIs. This H\(^+\)/K\(^+\) ATPase pump is the final common pathway for acid secretion in the stomach, and inhibitors of this pump are the most effective anti-secretory in current use.[1] This enzymatic pump is present in the canalicular membrane of gastric parietal cells where it secretes HCl and H\(^+\) is exchanged for K\(^+\) with ATP breakdown,[1,2] and contains transmembrane alpha and beta sub-units of 1034 and 291 amino acids, respectively. The alpha sub-unit consists of 10 trans-membrane spanning segments and is responsible for the transport and catalytic functions of the pump. It is also present in an inactive form in the cytoplasm and has to be transported to the luminal cell membrane surface of the acid secreting cell for it to become active (fig. 2). PPIs have a pKa of approximately 4, and are concentrated up to 1000-fold on the luminal side of the secretory canaliculus[1,2] where they are activated in the acid environment (fig. 2).

1.2 Comparative Pharmacology of the PPIs

The PPIs are pyridyl methylsulfinyl benzamides which bind to the H\(^+\)/K\(^+\) ATPase pump.[1,2] After accumulating in the acid canaliculus, they become active by undergoing acid stimulated conversion to sulphenamides, which enables them to bind to exposed cysteine residues in the luminal alpha domain of the H\(^+\)/K\(^+\) ATPase pump. The precise site of binding of individual drugs to the proton pump varies.[3] In their active form, PPIs are membrane impermeable and form disulfide covalent bonds with cysteine residues in the alpha sub-unit which inhibit the activity of the acid secreting pump.[2] The alpha sub-unit to which they bind contains a total of 28 cysteine residues and there are 9 in the beta sub-unit. In a recent study, using SDS gel separation of digested hog gastric vesicles incubated with PPIs under acid secreting conditions, Besancon et al.[3] have shown that 3 cysteine residues are accessible but that binding by different drugs varies. Thus omeprazole has been shown to bind to cysteine 813 in the fifth to sixth trans-membrane segment (and this correlates with acid inhibiting activity) and to cysteine 892 in the seventh to eighth transmembrane segment.