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A Pharmacological Approach to Gastric Acid Inhibition

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Abstract

Proton pump inhibitors have changed our approach to gastric acid-related diseases. They are much more potent acid inhibitors than H_2-antagonists and exhibit a sophisticated mechanism of action. The present review analyses the general pharmacology of proton pump inhibitors and differentiates the specific characteristics of the various compounds that belong to this family. Special emphasis has been placed in describing the clinical implications of such differences and the potential importance for adverse effects.

1. Parietal Cell Activity

The human stomach contains more than 1 billion (10^9) parietal cells that produce hydrochloric acid in quantities sufficient to attain an intragastric pH of 0.8 for substantial periods of time. This production of acid is controlled by a host of endogenous mediators. The most significant of the inhibitory stimuli are somatostatin and prostaglandins, which are normally produced as a response to a decrease in the gastric pH. The most noteworthy of the mediators that induce acid production are: (i) acetylcholine, released by intramural vagal terminations; (ii) gastrin, produced by antral cells and released into the circulation; and (iii) histamine, stored by the mast cells and the enterochromaffin-like cells (a variety of Amine precursor uptake and decarboxylation cells) and released into the interstitial fluid. Each one of these secretagogues acts upon specific receptors associated with G-proteins located in the basolateral membrane of the parietal cells. The final function of the cholinergic (M_3) and gastrin (CCK_B) receptors is to activate phospholipase, thereby increasing the concentrations of inositol-1,4,5-triphosphate and cytosolic calcium. The stimulation of histamine$_2$ (H_2) receptors activates adenylate cyclase and increases cAMP concentrations. There is a potentiating synergism between the actions of histamine and those induced by acetylcholine or gastrin, which seems to be caused by an interaction between the two systems of intracellular signalling (calcium and cAMP), or by a histamine-releasing effect exerted on the mucosal enterochromaffin-like cells.

In all cases, the final stage in the acid secretion process implies activation of H^+/K^+-ATPase (the 'proton pump'), which is located in the apical membrane of the parietal cell. This enzyme is a heterodimer composed of two subunits: a larger α-subunit with catalytic activity, and a smaller β-subunit, the function of which remains unclear but which is essential for enzymatic activity. In baseline conditions, the H^+/K^+-ATPase is located in the membranes of the tubulovesicles within the cellular cytoplasm, where it is inactive because these vesicles do not contain K^+ and their membrane is not permeable to that ion (figure 1). When the parietal cell is stimulated, the membrane of the tubulovesicles is integrated into that of the secretory canaliculus. The H^+/K^+-ATPase is thus exposed to K^+ ions in the extracellular environment

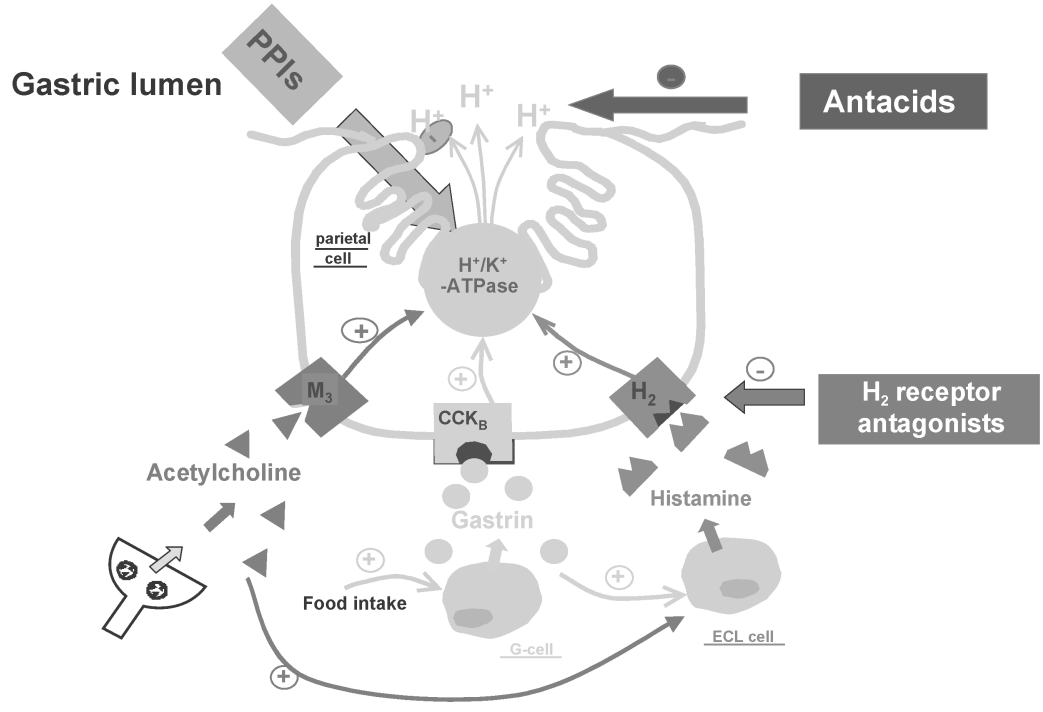


Fig. 1. Mechanisms of secretion of hydrochloric acid in the gastric parietal cell and strategies for their control. **CCK_B**, **H_2**, **M_3** = gastrin, histamine$_2$ and cholinergic receptors; **ECL** = enterochromaffin-like; **PPI** = proton pump inhibitor.

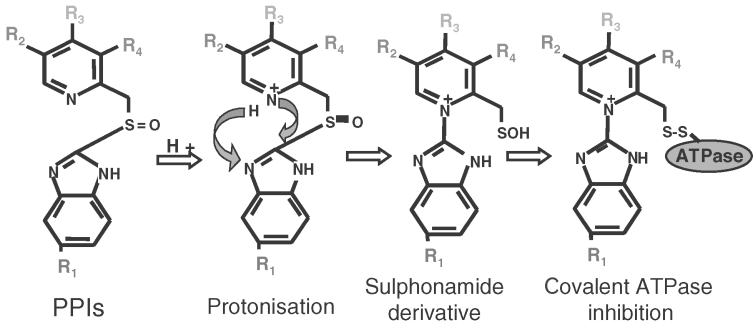
and begins to secrete protons. This active transport process occurs even when there exists a gradient 1-million-fold greater (pH 1) than the H^+ concentrations prevailing within the cell (pH 7.4).[1,2]

2. Proton Pump Inhibitors

Proton pump inhibitors (PPIs) share a mechanism of action and a common structural nucleus (2-pyridyl-methyl-sulphilnyl-benzimidazole) and, therefore, exhibit similar pharmacokinetic and pharmacodynamic properties (figure 2). *Omeprazole*[3] was the first to enter the market, followed by *lansoprazole*[4] and *pantoprazole*.[5,6] The most recent additions to the group are *rabeprazole*[7,8] and *esomeprazole*[9] (an optical isomer of omeprazole), comprising a series of second-generation PPIs that are both more potent and more rapid in their onset of effect.

2.1 Mechanism of Action

PPIs are weak bases ($pK_a \approx 4$) that reach the parietal cell after being absorbed in the duodenum. At physiological values of pH, the molecule(s) cross biological membranes and move with relative ease, first into the cytoplasm, and then into the secretory canaliculus of the parietal cells. However, the latter environment is highly acidic, which protonises the molecular structure of the PPIs and cancels out their lipolytic capacity. As they are rendered incapable of crossing the cell membrane, these molecules cannot re-enter the parietal cell and remain 'trapped' in the canalicular lumen. PPIs are thus pro-drugs, as they themselves do not interact with the proton pump, but require conversion from their protonised form into that of an active tetracyclic compound (the sulphonamide derivative). That compound gives rise to



PPIs	R_1	R_2	R_3	R_4
Omeprazol [(R)-Isomer]	$-OCH_3$	$-CH_3$	$-CH_3$	$-CH_3$
Lansoprazole	--	--	$-OCH_2CF_3$	$-CH_3$
Pantoprazole	$-OCF_2H$	--	$-OCH_3$	$-OCH_3$
Rabeprazole	--	--	$-O(CH_2)_3-OCH_3$	$-CH_3$
Esomeprazole [(S)-Isomer]	$-OCH_3$	$-CH_3$	$-OCH_3$	$-CH_3$

Fig. 2. Chemical structure of proton pump inhibitors (PPIs) and structural modifications induced by acid in these drugs.

disulphide bridges with certain cysteine residues in the α-chain of the luminal segment of H^+/K^+-ATPase, producing the so-called 'inhibitory complex' (figure 3). Although their life in the plasma is short, PPIs exert a long-lasting pharmacological action as a result of the irreversible nature of their effect on these enzymes and the fact that synthesis of new proton pumps is required for the full restoration of acid production. In addition to pharmacokinetic considerations, a more rapid onset of action depends largely on the speed at which the sulphonamide derivative is formed from the PPI molecule. This speed varies according to pH, and is greater the more acid is present. Among the various PPIs, rabeprazole and esomeprazole seem to act most rapidly in this respect.[7]

When dormant, most of the H^+/K^+-ATPase of the parietal cell is located within intracytoplasmic vesicles and, is thus beyond the reach of the activated PPI. Even at maximal acid production, not all the parietal cells are functional, and not all of the proton pumps in each activated cell are exposed to the acid of the secretory canaliculus. Consequently, as the plasma half-life of the PPI is relatively short, the enzymes that have not been blocked initially may be recruited later on, and are responsible for the acid secretion that persists after conventional dosing with a PPI. This also explains why simultaneous use of other antisecretory agents undermines the effectiveness of the PPIs, as they diminish the activity of the parietal cell and reduce the number of pumps available for pharmacological activity. In order to achieve anything near 100% inhibition, either considerably high oral doses at short intervals or continuous intravenous infusion are required.

2.2 Pharmacological Actions

PPIs inhibit, in a dose-dependent manner, both resting acid secretion and that induced

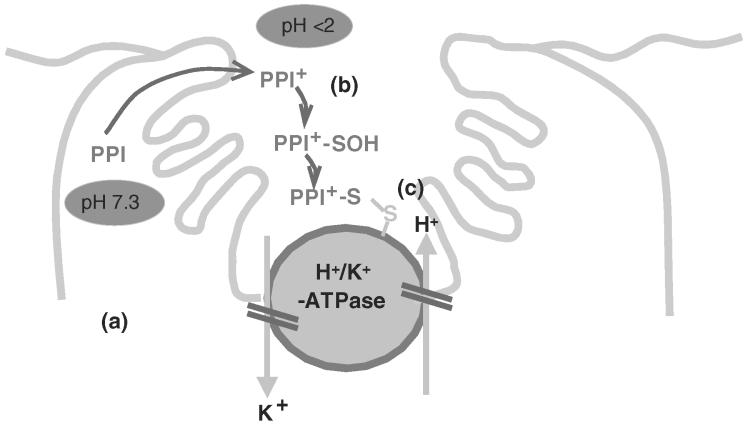


Fig. 3. Mechanism of action of the proton pump inhibitors (PPIs) on H^+/K^+-ATPase. The PPI, transported by the bloodstream, reaches the parietal cell and diffuses into the cytoplasm (**a**). In the acidic environment of the secretory canaliculus, the PPI molecule is protonised (**b**), thereby losing its ability to cross biological membranes and becoming trapped and bound. Next, as a result of the action of the same acidic environment, its chemical structure is modified into the sulphonamide derivative (**c**). This compound reacts through covalent bindings with the sulfhydryl groups of the luminal sector of H^+/K^+-ATPase.

by any stimulus, including food intake.[1,10–12] They also moderately reduce the volume of pepsinogen secreted and, as a result of the increase in intragastric pH that they produce, inhibit the proteolytic activity of pepsin. Furthermore, PPIs inhibit the enzyme urease, which protects *Helicobacter pylori* from acid, and are effective against this microorganism *in vitro*, although *in-vivo* eradication is a very rare event. In addition, they significantly boost the bactericidal action of some antibiotics, particularly clarithromycin, as the increased pH delays their degradation in the gastric lumen.

The antisecretory effect of PPIs peaks during the first 4–6 h, and their efficacy is far greater than that achieved with standard doses of H_2 receptor antagonists. Continued administration of PPIs does not induce tachyphylaxis, but actually improves their clinical efficacy by blocking previously respected pumps. Low doses of conventional PPIs show a considerable between-individual variation in effectiveness, but greater doses or the use of newer PPIs such as esomeprazole result in greater degrees of acid inhibition and more homogeneous responses. When therapy is interrupted, acid production requires several days to return to normal, and rebound increased acid secretion has been observed in *H. pylori*-negative, but not *H. pylori*-positive, individuals.[13]

2.3 Pharmacokinetic Features

Because of their pK_a, PPIs would be rapidly inactivated in the acidic environment of the stomach, and therefore require an enteric-coated formulation for oral administration. They are swiftly absorbed in the duodenum, although intake of food delays this absorption, and their bioavailability generally increases after repeated doses. PPIs undergo significant first-pass hepatic metabolism, which generates a number of inactive metabolites that are excreted in the urine or bile.

With the partial exception of rabeprazole, the metabolism of which has an important non-enzymic component, the metabolism of PPIs involves the cytochrome P450 system, mainly the cytochrome P 2C19 (CYP2C19) and 3A4 (CYP3A4) isoenzymes (figure 4). The CYP2C19 pathway is utilised more extensively than the CYP3A4 pathway – its kinetic velocity allowing the PPIs to function more rapidly – and it has a different kinetic velocity. Small changes in the ratio of utilisation of these pathways result in important variations in their effects. Esomeprazole,

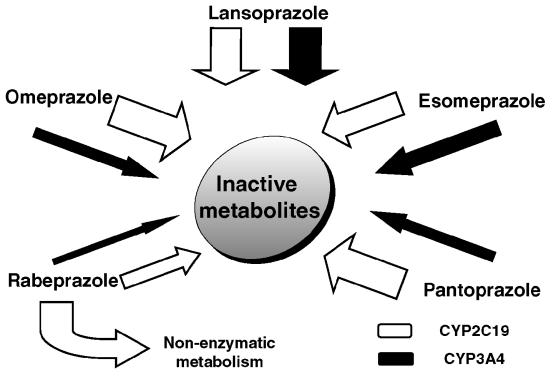


Fig. 4. Role of the cytochrome P 2C19 (CYP2C19) and 3A4 (CYP3A4) isoenzymes of the cytochrome P450 system in the hepatic metabolism of various proton pump inhibitors. The importance of the relative contribution of each isoenzyme is represented approximately by the thickness of the arrow.

for instance, is one of the two optical isomers comprising omeprazole, and is unique in its superior affinity for the CYP3A4 isoenzyme, which also metabolises esomeprazole at a slower rate. This leads to a diminished first-pass hepatic metabolism and to greater plasma concentrations than those achieved with an equivalent dose of omeprazole. All PPIs are eliminated rapidly, and toxic plasma concentrations are unlikely to occur, even when the clearance of the PPI is reduced, such as in older patients and those with hepatic or renal insufficiency. In fact, it is normally deemed necessary to modify the dosage of a PPI only in the most severe cases of inefficient clearance.[12] There is a small percentage of persons (1% among Black populations, 3–6% among White populations and 15–25% in the Sino-Japanese population) in whom the hepatic metabolism of PPIs is prolonged because of an inherited disturbance of the CYP2C19 isoenzyme. In these individuals the plasma half-life may increase by as much as 3-fold, and the area under the curve of plasma concentrations over time may increase 10-fold. This metabolic singularity affects all PPIs, with only small variations; it is not specific to these molecules, as it appears in other drugs such as diazepam or phenytoin. The residual capacity of standard doses for PPI metabolism prevents excessive accumulation and their low toxicity rules out any significant iatrogenic phenomena and, thus, the need for a reduction in the dose.

2.4 Adverse Reactions and Drug Interactions

The PPIs have a good safety profile, and there is no evidence that they cause direct toxic effects that are of clinical relevance. Enzymes similar to gastric H^+/K^+-ATPase exist in the kidney and in the colon but, as the environment is not sufficiently acidic, the PPI is neither bound nor activated, and therefore remains unaffected. PPIs do not inhibit the secretion of intrinsic factor or affect the absorption of vitamin B12 in healthy volunteers. They exert no action on lower oesophageal sphincter pressure, and do not modify the rate of gastric emptying of either solids or liquids.

The most frequent adverse reactions to these drugs are episodes of diarrhoea, nausea, abdominal pain, dizziness, headache and skin rashes. These

Table I. Interaction of proton pump inhibitors (PPI) with vitamin K antagonists: adverse effects reported to the FDA of the USA (marketing date, September 2001). (Modified from Labenz J, Petersen KU, Rösch W, et al. A summary of Food and Drug Administration-reported adverse events and drug interactions occurring during therapy with omeprazole, lansoprazole and pantoprazole. Aliment Pharmacol Ther 2003; 17: 1015–19.)

PPI (date of launch in USA)	Packs sold world-wide (millions)	PPI as main or secondary suspect (n)	Frequency of interactions (per million packs)	PPI as main suspect or single co-medication (n)	Frequency of interactions (per million packs)
Omeprazole (October 1989)	950.1	81	0.09	20	0.02
Lansoprazole (June 1995)	195.4	21	0.11	5	0.03
Pantoprazole (February 2000)	79.6	9	0.11	6	0.08

manifestations are almost invariably transient and moderate, and require no reduction in the dose of the compound. The spectrum and incidence of adverse side effects are independent of patient age. The use of PPIs induces an increase in serum concentrations of gastrin, which subside once treatment is suspended. A similar finding has been described for H_2 receptor antagonists, and the extensive clinical evidence obtained over the past decades confirms that sustained and profound acid inhibition causes no permanent modifications in clinical or biochemical parameters or in gastric cytology. This accumulated evidence effectively overrides reservations regarding the use of PPIs for long periods of time.

There are many drugs that are metabolised equally by the CYP2C19 and CYP3A4 isoenzymes of the cytochrome P450 system, which raises the possibility of multiple and potentially relevant interactions.[14] In current practice, such interactions are restricted to the CYP2C19 isoenzyme, as the low affinity of PPIs for the CYP3A4 pathway mean that the concentrations required to achieve an effect are so high that they are considered clinically irrelevant. Even in the case of the CYP2C19 pathway, which is the primary route in PPI metabolism, a possible interference need be monitored only in the case of phenytoin, carbamazepine, diazepam and warfarin. In the case of warfarin, as confirmed by a recent analysis of cases recorded by the FDA of the USA, the clinical impact of such interactions is limited, with a frequency of 0.1–0.2 per million prescriptions, and in this context there is no difference between the various PPIs (table I).[15] Furthermore, when the intragastric pH is increased, all PPIs diminish the absorption of a number of drugs – ketoconazole being the most relevant – and increase that of acid-labile drugs such as digoxin, furosemide and acetylsalicylic acid. As clarithromycin is noted and often used for its effectiveness in the eradication of *H. pylori*, it should be emphasised that its concomitant administration with esomeprazole and omeprazole causes an increase in the areas under the curve of those drugs, although this does not induce clinically relevant changes in the interaction profile.[12]

References

1. Esplugues JV, Flórez J. Farmacología de la secreción digestiva y de la ulceración mucosa. In: Flórez J, editor. Farmacología humana, 4th ed. Barcelona: Masson SA, 2003: 44:785-783.
2. Sachs G, Shin JM, Briving C, et al. The pharmacology of the gastric acid pump: the H,K-ATPase. Ann Rev Pharmacol Toxicol 1995; 35: 277-305
3. Wilde MI, McTavish D. Omeprazole: an update of its pharmacology and therapeutic use in acid-related disorders. Drugs 1994; 48: 91-132
4. Barradell LB, Faulds D, McTavish D. Lansoprazole: a review of its pharmacodynamic and pharmacokinetic properties and its therapeutic efficacy in acid-related disorders. Drugs 1993; 44: 225-50
5. Cheer SM, Prakash A, Faulds D, et al. Pantoprazole: an update of its pharmacological properties and therapeutic use in the management of acid-related disorders. Drugs 2003; 63: 101-32
6. Shin JM, Besancon M, Prinz C, et al. Continuing development of acid pump inhibitors: site of action of pantoprazole. Aliment Pharmacol Ther 1994; 8 Suppl 1: 11-23
7. Langtry HD, Marham A. Rabeprazole: a review of its use in acid-related gastrointestinal disorders. Drugs 1999; 58: 725-42
8. Carswell CI, Goa KL. Rabeprazole: an update of its use in acid-related disorders. Drugs 2001; 61: 2327-56
9. Andersson T, Röhss K, Bredberg E, et al. Pharmacokinetics and pharmacodynamics of esomeprazole, the (S)-isomer of omeprazole. Aliment Pharmacol Ther 2001; 15: 1563-9
10. Armstrong D, Bair D, James C, et al. Oral esomeprazole vs intravenous pantoprazole: a comparison of the effect on intragastric pH in healthy subjects. Aliment Pharmacol Ther 2003; 18: 705-11
11. Miner P, Katz PO, Chen Y, et al. Gastric acid control with esomeprazole, lansoprazole, omeprazole, pantoprazole, and rabeprazole: a five-way crossover study. Am J Gastroenterol 2003; 98: 2616-20
12. Robinson M, Horn J. Clinical pharmacology of proton pump inhibitors: what the practising physician needs to know. Drugs 2003; 63: 2739-54
13. Gillen D, Wirz AA, McColl KE. H. pylori eradication releases prolonged increased acid secretion following omeprazole treatment. Gastroenterology 2004; 126: 980-8
14. Andersson T, Hassan-Alin M, Hasselgren G, et al. Drug interaction studies with esomeprazole, the (S)-isomer of omeprazole. Clin Pharmacokinet 2001; 40: 523-37
15. Labenz J, Petersen KU, Rösch W, et al. A summary of Food and Drug Administration-reported adverse events and drug interactions occurring during therapy with omeprazole, lansoprazole and pantoprazole. Aliment Pharmacol Ther 2003; 17: 1015-9

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