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Short review

Proton Pump Inhibitors

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Abstract

Acid-related disorders, including gastro esophageal reflux disease (GERD), duodenal ulcers, and gastric ulcers, are managed by H_2 receptor antagonists and proton pump inhibitors (PPIs). PPIs represent first choice for treating acid-peptic ulcers inhibits the gastric- H^+/ K^+-ATPase through covalent binding to cysteine residues of the proton pump. Achlorhydria and acute renal failure are the most common drawbacks. A reversible acid pump antagonist (APAs), currently in clinical trial removes these problems. The APAs are the conceivable future drugs for the treatment of acid-peptic disorders.

Keywords: Proton Pump Inhibitors, Acid pump antagonist, Gastro esophageal reflux disease

Introduction

Acid-peptic ulcers encompass gastro esophageal reflux disease (GERD), duodenal and gastric ulcers, stress related mucosal disease and upper gastro intestinal bleeding are due to the imbalance between aggressive factors (gastric acid, pepsin and *Helicobacter pylori* infection) and local mucosal defenses (bicarbonate, mucus and prostaglandins). The management of acid-peptic ulcer[1] is achieved by reducing aggressive factors (strengthens mucosal defenses) and by inhibiting gastric acid secretion. The later one is the key therapeutic target for the ulcer diseases (peptic / duodenal ulcers or *Helicobacter pylori* infection), Zollinger-Ellison syndrome and gastritis.

Peptic / duodenal ulcers

Peptic ulcers are the main cause of upper gastrointestinal bleeding[2]. *Helicobacter pylori* and non-steroidal anti-inflammatory drugs (NSAIDs) are major cause for peptic ulcer induction. NSAIDs inhibit the synthesis of mucoprotective prostaglandins PGE_2 and causes disturbance in the mucoprotection. Imbalance between the mucosal defense factors and aggressive factors is responsible for this clinical manifestation. Increase in basal acid secretion is seen in duodenal ulcer. The gastric ulcer weakens mucosal defense mechanism that leads to ulcer even in low acid secretion.

Helicobacter pylori infection

Helicobacter pylori are a rod shaped gram-negative bacteria associated with gastritis, peptic ulcers, gastric adenocarcinoma and gastric b cell lymphoma[3]. This infection leads to impairment of somatostatin synthesis, and results in increased gastric acid secretion and impaired bicarbonate production in duodenum. *Helicobacter pylori* are major risk factor for gastric cancer and also cause antral gastric mucosal inflammation[4,5]. The pronounced *H. Pylori* induced inflammation of the antral mucosa in the presence of an intact oxyntic mucosa will result in acid hypersecretion.

Zollinger-Ellison syndrome

Non- b cell tumor of the pancreatic islets produces gastrin and gastrin secrets gastric acid in life-threatening levels. This hyper secretion of gastric acid is responsible for the gastro-duodenal ulcers and hyperch- lorhydria[6,7].

Gastro esophageal reflux syndrome (GERD)

Oseophageal defense disorder causes regurgitation of the gastric contents[2]. GERD is associated with decreased gastric emptying and increased incidence of transient lower esophageal relaxation (T-LESR). The cardinal symptoms of GERD include acid regurgitation and heartburn. GERD is not a life threatening disorder but causes significant gastric discomfort and increased risk of Barret's esophagus[8,9]. Stress-related ulcers and non-ulcer dyspepsia are the other common types of ulcers.

Regulation of acid secretion

Acid secretion is a physiologically important process in stomach, induces digestion by activating pepsinogen[10]. It kills microbes and ensures stable intragastric environment.

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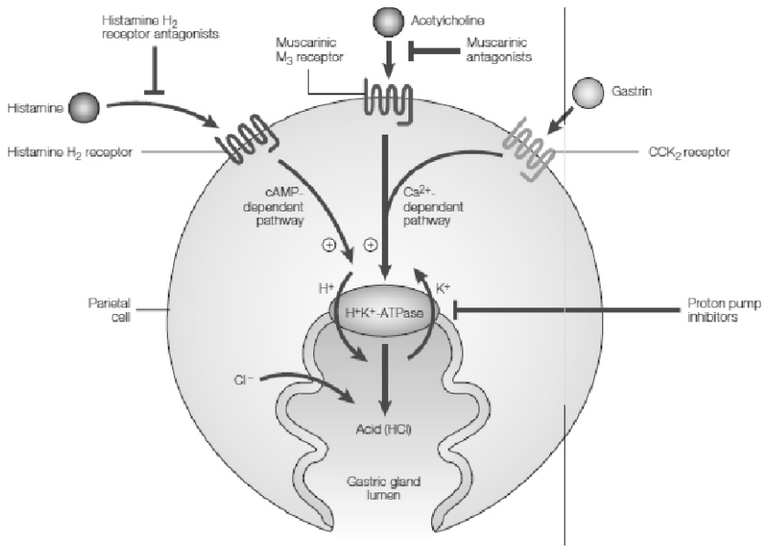


Figure 1: Normal Physiology of Acid Release[5]

The chemo and mechanosensitive receptors present in stomach are triggered by presence of food to produce specific responses. The acid secreting parietal cells present in it regulates the acid secretion, producing 2-3 L of gastric juice per day[11]. Three major pathways activating parietal acid secretion include[1,5,6]

1. Neuronal stimulation via the vagus nerve
2. Paracrine stimulation by local release of histamine from enterochromaffin like cells (ECL)
3. Endocrine stimulation via gastrin released from antral G cells.

Binding to G-protein coupled receptors by acetylcholine, gastrin and histamine results in activation of second-messenger systems and increases intracellular Ca^{2+} and finally causes increase in gastric acid secretion via activating gastric proton pump, H^+/K^+-ATPase.

Inhibiting acid secretion

The inhibition of gastric acid secretion is a key therapeutic target for the ulcer diseases[1]. Gastric acid secretion by the parietal cell is controlled through food-stimulated and neuroendocrine pathways. There are several potential ways by which gastric acid secretion might be modified [12,13,14,]

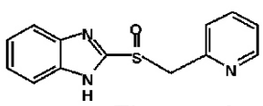
- Antacids (aluminium and magnesium hydroxide preparations) neutralize gastric acid.
- Targeting the muscarinic receptors with muscarinic antagonists (atropine) is the one approach to control acid secretion.
- Targeting H_2 receptors with H_2 receptor antagonists (cimetidine, ranitidine) is the second approach.
- Targeting the gastric proton pump, H^+/K^+-ATPase is another and most effective pharmacological approach.
- Eradication of *Helicobacter pylori* with double or triple anti-microbial therapy in combination with anti-secretory drugs is most successful in peptic ulcer treatment.
- The potassium competitive acid pump antagonists are a promising new class of agents, are in clinical trials.
- Mucosal protective agents such as sucraflate are also used for ulcer therapy.

In this present review various aspects of proton pump inhibitors are discussed, highlighting the advantages of K^+ dependent acid pump antagonists over irreversible proton pump inhibitors.

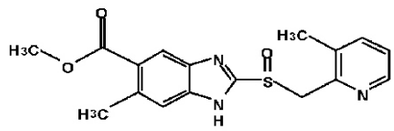
Proton pump inhibitors

The gastric proton pump, H^+/K^+ -ATPase present in cytoplasmic membranes constitutes p2 type phosphoenzyme[15] concentrated in resting parietal cells from where it secretes H^+ into the lumen of the gastric glands in electroneutral exchange for extracellular K^+. Conformations of the enzyme that bind to H^+ ions for outward transport are termed as E1 and enzyme that bind to K^+ ions for inward transport are termed as E2. Modification of the proton pump, as a result of mutations of Glu^{857} reduces the sensitivity of the pump 3 fold. Gastric proton pump inhibitors (PPIs) are important as well as valuable pharmaceuticals in the treatment of peptic ulcer disease. Inhibition of the acidic pump to control the acid secretion attracted considerable attention in recent years. PPIs inhibit both basal and stimulated secretion of gastric acid[16], independent of the nature of parietal cell stimulation. PPIs undergo extension hepatic metabolism by the cytochrome P_{450} enzyme system[17]. Gastric proton pump inhibitors are of two types

1. Irreversible gastric proton pump inhibitors



Timoprazole



Picoprazole

2. Reversible gastric proton pump inhibitors

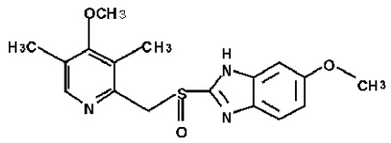
PPIs are of first choice for peptic ulcer and their complications[2,5], Gastric Oesopahgeal Reflux Syndrome (GERD), NSAIDs induced gastro intestinal lesion, Zolinger Ellison syndrome, dyspepsia and eradication of H. pylori with two antibiotics (triple drug therapy). The PPIs are more effective in the short term than the H_2-blockers in healing duodenal ulcers and erosive esophagitis.

Mechanism of action of PPIs

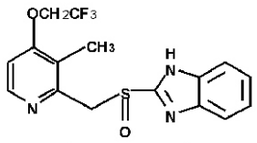
PPIs bind to cysteine 813, resulting in covalent inhibition of the enzyme via formation of disulphide that stabilizes the enzyme in the E2 conformation[17]. Several salient features required for the activity are

a) The weak basicity of the compounds (p*ka* » 4), allowing them to accumulate in the acid space adjacent to their site of action,
b) The sulphoxides undergoes Smile's rearrangement to form spiro intermediate,
c) The active thiophillic group binds to thiol group of enzymes and generates disulphide bridges to cause enzyme inactivation.

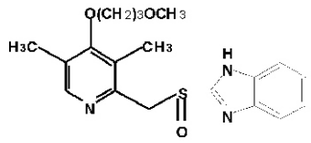
The protonation in the pyridine nitrogen initiates the formation of spiro intermediate and then sulfenamide. This sulphenamide binds covalently to sulfhydryl groups of cysteines of proton pump[18, 19, 20]. The introduction of methyl group in the 6th position of the pyridine ring of the sulfinyl benzimidazole makes the compound more stable in acid medium, prevents the formation of spiro intermediate and supports the suggested mechanism. The anti-oxidant defence protein heme oxygenase (HO-1) is a target of PPIs in both endothelial and gastric epithelial cells[6]. HO-1 induction might account for the gastroprotective effects of PPIs independently of acid inhibition.



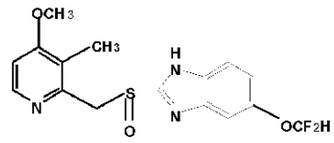
Omeprazole



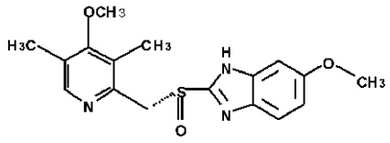
Lansoprazole



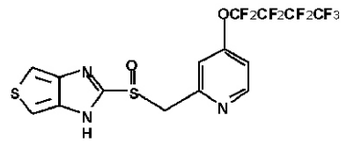
Rabeprazole



Pantaprazole



Esomeprazole



Saviprazole

Leminiprazole

Figure 2: Irreversible proton pump inhibitors

Drawbacks of irreversible proton pump inhibitors

Irreversible inhibition of acidic pump by covalent binding of the sulphenamide group with thiol group of cysteine residues produces consequences of hyper gastrinaemia[2]. Extreme acid suppression some times leads to achlorhydria and produces typhoid, cholera and dysentery. Because gastric juice plays major role in the killing of the microbes present in gastric juice. Significant drug interactions can lead to decreased absorption of some drugs griseofulvin, ketoconazole, vitamin $B_{12,}$ iron salts, etc. It is also responsible for astrinemia, gastric polips and carcinoma[6]. Acute interstitial nephritis progressing to acute renal failure has been reported to be associated with the use of PPIs.

Reversible gastric proton pump inhibitors (PPIs)

Prolonged suppression of gastric acid secretion produced by both H_2 receptor antagonists and PPIs produces extended periods of hypergastrinemia. Reversible H^+/ K^+ - ATPase inhibitors (K^+ dependent proton pump inhibitors) have aroused particular interest as potential drugs because their pharmacological activity is modulated by the attendant reduction in gastric acidity after binding to the target protein[7]. The K^+ dependent proton pump inhibitors inhibit acid secretion in a reversible manner. Their activity is independent of the intragastric acidity as they do not, unlike irreversible proton pump inhibitors, requires acid for their activation. The gastric acid inhibitory profile of reversible proton pump inhibitors may closely resemble those of the more potent and longer-acting H_2-receptor antagonists and irreversible proton pump inhibitors thereby obviating the advantages of proton pump inhibitors in healing lesions and relieving symptoms. K^+ competitive inhibitors also bind to E2 form of the ATPase both in the N and the C terminal regions[6,15].

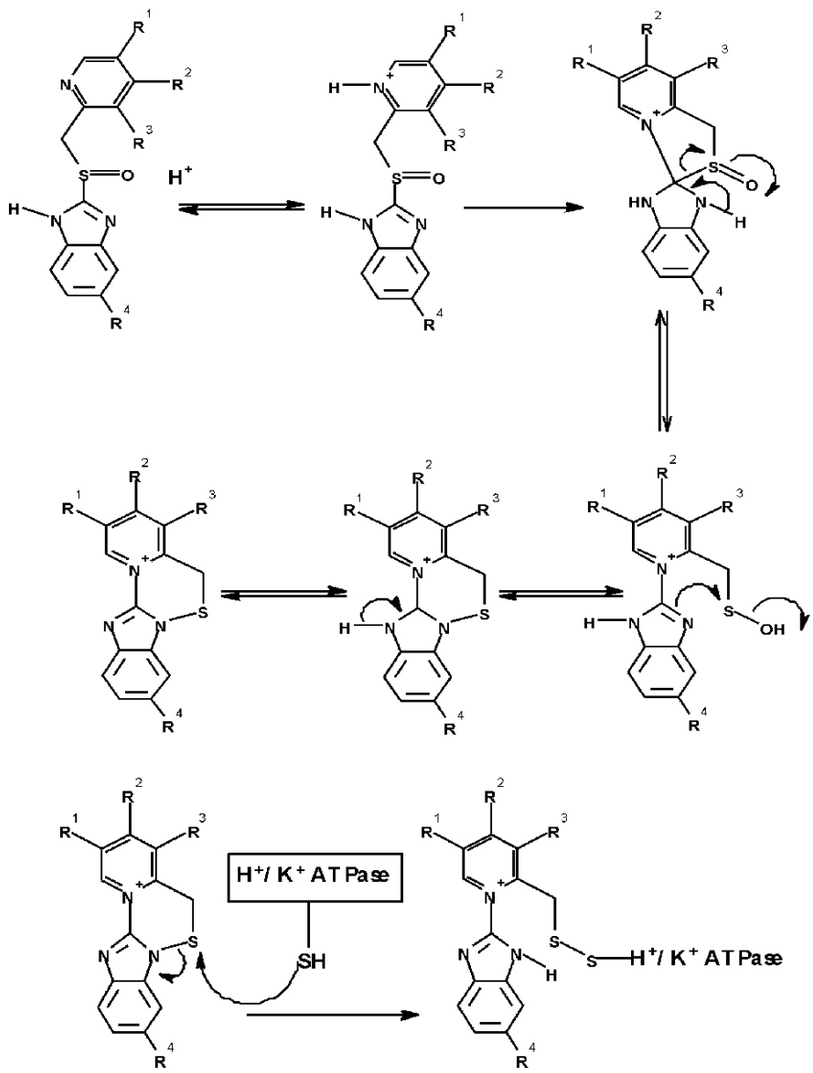
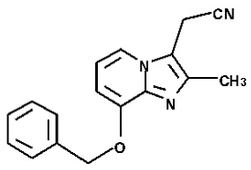
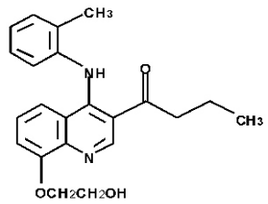


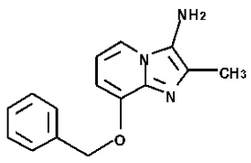
Figure 3: Acid transformation of benzimidazoles to sulphenamides[18, 19, 20].



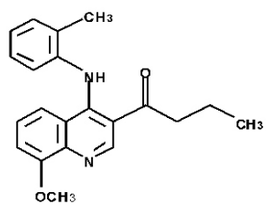
SCH 28080



SK & F 97574



SCH 32651



SK & F 96067

Reversible proton pump inhibitors[7]

In contrast to irreversible inhibitors, these compounds are competitive inhibitors of high affinity luminal K^+ site of the gastric proton pump. SCH 28080 is a protonable weak base and accumulated in the acidic compartments of the parietal cells in its protonable form. SCH 28080 is chemically stable and after protonation, is itself active and does not need an acid-induced transformation.

Conclusion

The proton pump inhibitors generally are superior to the H_2-receptor antagonists in healing lesions quickly and improving symptoms, particularly in patients with oseophagitis. The PPIs are theoretically advantageous in managing upper gastrointestinal bleeding from acid peptic lesions due to their profound inhibition of acid secretion. The theoretical advantages of K^+ dependent, reversible proton pump inhibitors depend ultimately on their acid inhibition profile relative to that H_2-receptor antagonist.

References

1. Robert S, McDonald IM, *Burger's Medicinal Chemistry and Drug Discovery*, 6th edn, John Wiley: New Jersey, 2007, 4, 86-121.
2. Klotz U, Proton pump inhibitors: an update of their clinical use and pharmacokinetics, *Eur. J. Clin. Pharmacol.,* 2008; 64: 935-952.
3. Thong-Ngam D, Tangkijvanich P, Sampatanukul P, Prichakas P, Mahachai V, Thong-Ngam PTD, Direct measurement of gastric H^+/K^+-ATPase activities in patients with or without Helicobacter pylori-associated chronic gastritis, *World. J. Gastroenterol.,* 2005, 11(23), 3514-3517.
4. Olbe L, Lars F ndriks, Hamlet A, Ann-Mari Svennerholm, Ann-Catrin Thoreson, Mechanisms involved in Helicobacter pylori induced duodenal ulcer disease: an Overview., *World. J. Gastroentero.,* 2000, 6(5), 619-623
5. Kate V, Ananthakrishnan N, Treatment of helicobacter pylori infection-a review, *Ind. J. Pharmacol*., 2001, 33, 410-416.
6. KS Jain et al., Recent advances in proton pump inhibitors and management of acid- peptic disorders, *Bioorg. Med. Chem*., 2007, 15, 1181-1205.
7. Freston JW. Future prospectus for proton pump inhibitors: Ailment Pharmacol. Ther., 1993, 7, 68-75.
8. McCarthy DM, Proton pump inhibitors in the management of patients with acid-peptic disorders: a managed care perspective., P&T., 2005; 30 (5): 282-291.
9. Ronnie Fass, MD., Advances in the Management of Gastroesophageal Reflux Disease., *Hospital. Physician*., 1999, 59-67.
10. Suchitzky JL, Comprehensive Medicinal Chemistry, Hansch, C., Pergamon press: Oxford, 2005, 2, 197-202.
11. Nelson WL. In *Foye's Principle's of Medicinal Chemistry*; Williams DA, Lemke TL, Lippincott Williams and Wilkins, 6th edn, 2008; 807- 817.
12. Wallace JL, Recent advances gastric ulcer therapeutics, *Curr. Opi. Pharmacol*., 2005, 5, 573-577.
13. Debas HT, Mulholl, Michael W. Drug therapy in peptic ulcer disease. *Curr. Prob. Surg*., 1989, 26(1), 9-54.
14. Baron JH, Treatments of Peptic Ulcer., *The. Mou. J. Med*., 2000, 67 (1): 63-67.
15. Watts JA, Watts A, Middleton DA, A model of reversible inhibitors in the gastric H^+/K^+- ATPase binding site determined by rational echo double resonance, The Journal of Biol. Chem., 2001, 276, 43197- 43204.
16. John H Block, John M Beale., Wilson and Giswold's text book of Medicinal and Pharmaceutical Chemistry, 11th edn, Lippincott William's and Wilkins, 2004, 722.
17. G. Sachs, J. M. Shin and C. W. Howden, Review article: The clinical pharmacology of proton pump inhibitors: *Ailment. Pharmacol. Ther.,* 2006; 23: 2-8.
18. Hardman, J. G., Limbard, L.E, Molinnoff, P.B, Ruddon R R W, Bruton L L. Goodmann,s *The Pharmacological Basis of Therapeutics*, Goodman AG, 10th edn; McGraw-Hill; Newyork, 2001;1006-1019.
19. Silverman RB, The Organic Chemistry of Drug Design and Discovery, 2nd edn., *Academic Press*., 2004; 528.
20. Olbe L, Carlsson E, Lindberg P, A proton pump inhibitor expedition: the case histories of omeparazole and esomeparazole., *Nat. Rev. Drug. Discov*., 2003; 2: 132-139.