Proton Pump Inhibitor

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ABSTRACT

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Acid peptic disease manifests in a variety of ways leading to significant morbidity and loss of productivity and illness. The common factor in all these conditions is the over action of acid milieu. Proton pump inhibitors are one of the most significant class of drugs to be developed in gastroenterology. They are prodrugs that act at the appropriate time. The article considers these facts.

Keywords: PPI, Acid peptic disease, Drug management

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Proton pump inhibitors or PPIs are a group of drugs whose main action is pronounced and long standing suppression of gastric acid production. Their introduction in late 1980s optimized the medical treatment of acid related disorders. They are the most potent inhibitors of acid secretion available today.[1] These drugs are among the most widely selling drugs in the world as a result of their outstanding efficacy and safety. Currently five PPIs are used-Omeprazole, Esomeprazole (S optical isomer), lansoprazole, Pantoprazole and Rabeprazole.

The normal human stomachcontains1billion parietal cells that secrete 0.16 M Hydrochloric acid (HCl). The hydrogen ions are actively secreted in exchange for potassium ions by means of H-K ATPase, the so-called Proton pump located on the apical surface of the parietal cell. The H-K-ATPase comprises the 'final pathway' by which HCl is secreted into gastric lumen. PPIs inhibit this pump irreversibly.

These compounds are prodrugs. They are substituted benzimadazoles, weak bases with a pKa of4-5. (The pKa of a PPI is the pH at which half the drug is protonated and half is unionized). These agents are lipophilic and upon entering the parietal cell they are protonated and trapped within the acidic environment of tubulovesicular and canalicular system. PPIs are most effective when the parietal cell is stimulated to secrete acid post prandially because the environment is acidic in the parietal cell at this time. Because the amount of H-K-ATPase present in the parietal cell is greatest after prolonged fasting, PPIs should be administered about 20 minutes before the first meal of the day. With this dosing, at the time the bioavailability is maximum for the drug, the parietal cells will be active and the drug can concentrate in the parietal cells. In most individuals once daily dosing is sufficient to produce the desired level of inhibition, second dose if required, should be administered before the evening meal.[1] They should not be given concomitantly with H2 antagonist, prostaglandins or other anti secretory agents because of marked reduction of acid inhibitory effects when administered simultaneously.[2]An H2 antagonist can be used with a PPI provided there is sufficient time interval between the administration. For example, during night for those who report nocturnal breakthrough symptoms.

Onset of action is rapid with maximum acid inhibitory effect between 2-6 hrs after administration and duration of inhibition lasting up to 72-96 hrs. With repeated daily dosing, more H-K-ATPase will be recruited and subsequently inhibited and progressive acid inhibitory effects are observed. Basal and secretagogue stimulated acid production are inhibited by greater than 95% after 1 week of therapy. Thus the occasional use of PPI taken on an "as needed" basis does not reliably provide adequate acid inhibition and does not produce a consistent or satisfactory clinical response. The half life of PPI is - 18 hrs. Thus it can take between 2 and 5 days for gastric acid secretion to return to normal levels once these drugs have been discontinued.

PPIs differ in their pKa, bioavailability, peak plasma levels and route of excretion, with lansoprazole and pantoprazole being the most bioavailable and achieving highest plasma levels. Rabeprazole possess a slightly faster onset of action while pantoprazole is often

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touted as being the most "Gastro-specific" because of its binding to cysteine residues 813 and 822 within alpha subunit of proton pump. Rabeprazole has an additional effect in that it enhances percentage of mucin protein in mucus, mucus content and viscosity of gastric juice.[13]However, clinically it is hard to pick and choose between the various PPIs regarding efficacy.

PPIs are effective for treatment of all acid related disorders

a. Peptic Ulcer disease- PPIs heal gastro duodenal ulcers more rapidly than H2 receptor antagonist. Recommendation for PPI doses in treatment of acid related disorders are - Omeprazole 20 mg, Lansoprazole 30 mg, Rabeprazole 20mg , Pantoprazole 40mg, Esomeprazole 40 mg
b. NSAID associated ulcer -Current evidence indicate that PPI is superior to standard dose H2 receptor antagonist therapy. In a large scale randomized comparison of omeprazole vs ranitidine, ulcer healing was found in 80% in pts with omeprazole but only in 63% with those on ranitidine.[3] PPIs are also effective for primary prevention of NSAID associated ulcers. One study showed omeprazole to be more effective than standard dose ranitidine and comparable to misoprostol in preventing gastric ulcers[3,4] and better than misoprostol in preventing Duodenal ulcers.
c. H pylori eradication- PPI based triple and quadruple therapies are the most effective regimens available till date. In vitro PPI inhibits growth of H pylori. When PPIs are employed as single agents invivo, H pylori infection is suppressed but not eliminated.[5]
d. Gastro esophageal reflux disease- Numerous studies have documented the marked efficacy of PPIs in GERD.A large meta analysis report revealed complete healing of severe ulcerative esophagitis after 8 weeks in more than 80% compared with51% with h2 receptor blockers.[6] A landmark study for maintenance therapy showed remission in 80-90% in omeprazole groups versus 49-60% in other groups.[7]
e. Zollinger Ellison syndrome-All patients with ZES require antisecretory therapy and PPIs is the drug of choice for medical treatment of ZES.

Barrett's esophagus- PPIs are frequently used in patients with Barrets metaplasia though no studies have shown unequivocal regression of Barrett's esophagus.

PPIs are an extremely safe class of drugs. The initial fears about the long-term danger of profound acid suppression are not justified because sufficient gastric acid is produced allowing for normal nutrient digestion and absorption. The main concern was reports of omeprazole producing hypergastrinemia and gastric carcinoid tumours in rats, however extensive experience has failed to demonstrate carcinoid tumor development in humans.[8] Recent studies suggested that patients on long term omeprazole who are infected with H pylori develop atrophic gastritis, a precursor to gastric adenocarcinoma, at a more rapid rate than non infective patients.[9] Nevertheless a subsequent FDA panel determined that available data was insufficient for recommending screening and treatment of H pylori infection in patients on long term PPI therapy.[10] Hepatic CP450 can be inhibited by earlier PPIs like omeprazole and lansoprazole. Rabeprazole, Pantoprazole and Esomeprazole do not appear to interact significantly with drugs metabolized by CP450 system. The overall clinical significance of this observation is not definitely established. Caution should be taken when using warfarin, diazepam, phenytoin, theophylline, digoxin, carbamazepine. None of the PPIs require dose adjustment for hepaticorenal insufficiency. Possible associations with hip fractures and community acquired pneumonia have also been suggested.[11]

New PPI prodrugs with longer biological half lives are under development and may address some of the present short comings of PPI. The substitution of benzimidazole with an imidazo-pyridine moiety (Tenatoprazole) reduces the rate of metabolism increasing both plasma and biological half lives significantly.[12]

In conclusion, it would be safe to say that PPIs were one of the landmark drug discoveries in the field of Gastroenterology over the past three decades. It has made a sea change in the management of ulcer disease and GERD, with very effective and rapid amelioration of symptoms. With the widespread use of these drugs, surgery in ulcer disease has become a thing of the past (unless for complicated ulcers).

END NOTE

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