



# AMERICAN JOURNAL OF PHARMTECH RESEARCH

Journal home page: <http://www.ajptr.com/>

## Proton Pump Inhibitors in Treatment of Peptic Ulcers

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### ABSTRACT

Acid-related disorders, including gastro esophageal reflux disease (GERD), duodenal ulcers, and gastric ulcers, are managed by H<sub>2</sub> receptor antagonists and proton pump inhibitors (PPIs). PPIs represent first choice for treating acid-peptic ulcers inhibits the gastric- H<sup>+</sup>/ K<sup>+</sup> -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, Proton pump inhibitors, Acid secretion, Acid related disorders

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Received 1 March 2013, Accepted 8 March 2013

Please cite this article in press as: Gangurde PV *et al* Proton Pump Inhibitors in Treatment of Peptic Ulcers. American Journal of PharmTech Research 2013.

## INTRODUCTION

Peptic ulcer disease is a problem of the gastrointestinal tract characterized by mucosal damage secondary to pepsin and gastric acid secretion. It usually occurs in the stomach and proximal duodenum; less commonly, it occurs in the lower esophagus, the distal duodenum, or the jejunum, as in unopposed hypersecretory states such as Zollinger-Ellison syndrome, in hiatal hernias (Cameron ulcers), or in ectopic gastric mucosa (e.g., in Meckel's diverticulum). Proton pump inhibitors are the most potent medications available to reduce gastric acid secretion.

Since their introduction in the late 1980s, these efficacious acid suppressants have rapidly assumed a major role for the treatment of acid-peptic disorders. They are now among the most widely prescribed drugs worldwide because of their outstanding efficacy and safety.

### **Disorders due to Hyper secretion of Gastric Acid**

#### **Peptic / duodenal ulcers**

Peptic ulcers are the main cause of upper gastrointestinal bleeding. *Helicobacter pylori* and non-steroidal anti-inflammatory drugs are major cause for peptic ulcer induction. NSAID inhibit the synthesis of mucoprotective prostaglandins PGE and causes disturbance in the mucoprotection<sup>1</sup>. 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 (H. pylori)**

More than 50% of the world's population has a chronic *H pylori* infection of the gastric mucosa, yet only 5–10% of those infected develop ulcers. Factors determining whether the infection will produce disease are the pattern of histological gastritis induced; changes in homeostasis of gastric hormones and acid secretion; gastric metaplasia in the duodenum; interaction of *H pylori* with the mucosal barrier and immunopathogenesis; ulcerogenic strains; and genetic factors. Clinical outcomes are dependent on the pattern of chronic mucosal inflammation induced<sup>2,3</sup>.

*Helicobacter pylori* are a rod shaped gram-negative bacteria associated with gastritis, peptic ulcers, gastric adenocarcinoma and gastric B cell lymphoma<sup>4</sup>. 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 inflammations<sup>5,6</sup>. The pronounced *H. Pylori* induced inflammation of the antral mucosa in the presence of an intact oxyntic mucosa will result in acid hyper secretion.

**NSAIDS (Non-steroidal anti-inflammatory drug)**

NSAIDs are the most common cause of peptic ulcer disease in patients without *H. pylori* infection<sup>5</sup>. Topical effects of NSAIDs cause submucosal erosions. In addition, by inhibiting cyclooxygenase, NSAIDs inhibit the formation of prostaglandins and their protective cyclooxygenase-2-mediated effects (i.e., enhancing gastric mucosal protection by stimulating mucus and bicarbonate secretion and epithelial cell proliferation and increasing mucosal blood flow). Coexisting *H. pylori* infection increases the intensity of NSAID-induced damage. The annual risk of a life-threatening ulcer-related complication is 1 to 4 % in patients who use NSAIDs for long-term, with older patients at the highest risk<sup>7</sup>. NSAIDs use is responsible for approximately one half of perforated ulcers, which occur most commonly in older patients who are taking aspirin or other NSAIDs for cardiovascular disease or arthropathy<sup>8</sup>. Acid suppression has been the mainstay of management of NSAID-associated ulcer disease. Gastric acid probably exacerbates NSAID injury by converting superficial mucosal lesions to produce deeper injury<sup>9</sup>, interfering with platelet aggregation<sup>10</sup>, and impairing ulcer healing<sup>11</sup>. Patients taking NSAIDs have about a four-fold increase in risk of ulcer complications such as bleeding compared with non-users.

**Zollinger-Ellison syndrome**

Non- b cell tumor of the pancreatic islets produces gastrin and gastrin secretes gastric acid in life-threatening levels. This hyper secretion of gastric acid is responsible for the gastro-duodenal ulcers and hyperchlorhydria<sup>12, 13</sup>. The development of H<sup>+</sup> / K<sup>+</sup> ATPase inhibitors has enabled adequate inhibition of gastrin-stimulated acid secretion to be achieved for longer periods. Up to 80–90% of ulcers may be associated with *H. pylori* infection of stomach. *H. pylori* infection also causes inflammation of the antral gastric mucosa. *H. pylori* infection is now proven to be a risk factor for gastric cancer and the organism was classified as a Group 1 carcinogen by the International Agency for Research on Cancer sponsored by the World Health Organization in 1994<sup>14</sup>.

**Gastro Oesophageal reflux syndrome (GERD)**

Oesophageal defense disorder causes vomiting of the gastric content. GERD is associated with decreased gastric emptying and increased incidence of transient lower esophageal relaxation (TLESR)<sup>1</sup>. 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 columnar lined oesophagus<sup>15, 16</sup>. 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 stomachs, induces digestion by activating pepsinogen<sup>17</sup>. It kills microbes and ensures stable intragastric environment. The chemo and mechano sensitive 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 juices per day<sup>18</sup>. Three major pathways activating parietal acid secretions include<sup>12, 19, 20</sup>

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.

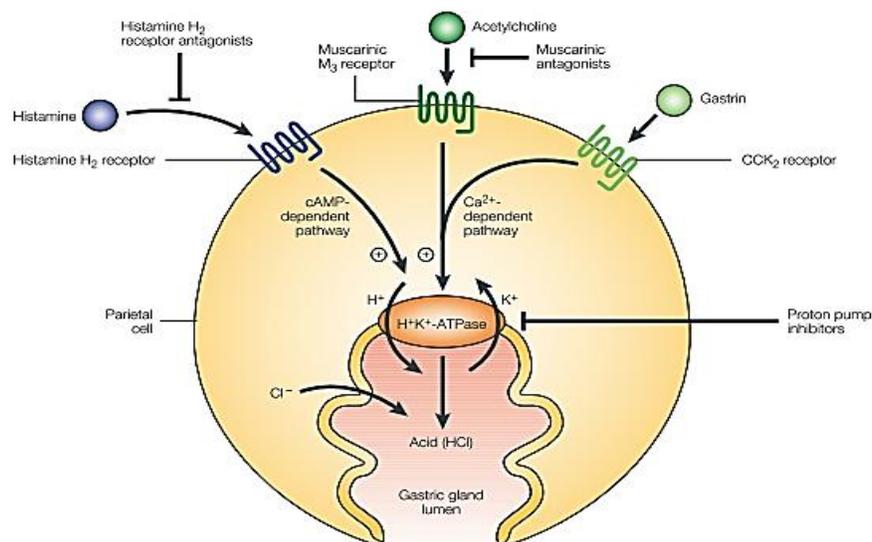
Binding to G-protein coupled receptors by acetylcholine, gastrin and histamine results in activation of second- messenger systems and increases intracellular  $Ca^{2+}$  and finally causes increase in gastric acid secretion via activating gastric proton pump,  $H^+/K^+$ -ATPase.

More data are also available on the role of GI hormones in the regulation of aggressive factors, especially gastric acid. In fact, the antral hormone gastrin was detected by its property to stimulate gastric acid secretion<sup>21</sup>. In 1971, McGuigan and Trudeau observed that patients with duodenal ulcer had an exaggerated gastrin release in response to meals and suggested that the trophic effect of gastrin might be responsible for the increase in parietal cell mass characteristic of duodenal ulcer disease<sup>22</sup>. In the late 1980s, several investigators also examined meal-stimulated gastrin release in relation to *H. pylori* infection<sup>23</sup>.

## Discovery of Proton Pump Inhibitors (PPIs)

The discovery and development of  $H_2$ -receptor antagonists was the beginning of a novel therapeutic approach to diseases associated with the hypersecretion of gastric acid. During the 1980,  $H_2$ -antagonists became first-line therapy in peptic ulcer disease. These  $H_2$ -receptor antagonists represented a dramatic improvement in control of gastric acid and, consequently, in the management of acid-mediated disorders. Not only were these drugs effective, they proved to be exceptionally safe and well-tolerated. Despite the success of the histamine<sub>2</sub>- receptor antagonists, there were patients whose acid related disorders failed to respond to or required very high doses of these drugs. It soon became apparent that  $H_2$ -receptor antagonist therapy had some drawbacks. In a small but significant number of patients, the disease was resistant<sup>24</sup>. In another small group of patients,  $H_2$ -receptor antagonists were particularly poor when it came to inhibiting the nocturnal secretion of gastric acid<sup>25</sup>. A further problem was that acid rebound occurred after cessation of  $H_2$ -antagonist therapy<sup>26</sup>. In some patients, tolerance to  $H_2$ -antagonist therapy also

appeared to develop when long-term treatment was necessary<sup>27</sup>. From the late 1960s onwards, the pharmaceutical company Astra was also pursuing a program aimed at finding a drug to inhibit acid secretion.



**Figure 1: Normal Physiology of Acid Release<sup>20</sup>**

In the 1970s, this led to the development of specific inhibitors of the proton pump in the acid-secreting parietal cells of the stomach, activation of which is now known to be the final step in acid secretion. These compounds were shown to be very potent inhibitors of gastric acid secretion, and demonstrated a surprisingly long-lasting duration of action. Proton pump inhibitors were subsequently developed, and, in most respects, have been found to be superior to H<sub>2</sub>-receptor antagonists in their acid suppressing ability.

### Inhibiting Acid Secretion

The inhibition of gastric acid secretion is a key therapeutic target for the ulcer diseases<sup>1</sup>. 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<sup>28, 29, 30</sup>

- Antacids (aluminum 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<sub>2</sub> receptors with H<sub>2</sub> receptor antagonists (cimetidine, ranitidine) is the second approach.
- Targeting the gastric proton pump, H<sup>+</sup>/ K<sup>+</sup>-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 Sucralfate 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 concentrated in resting parietal cells from where it secretes  $H^+$  into the lumen of the gastric glands in electroneutral exchange for extracellular  $K^+$  <sup>31</sup>. 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<sup>857</sup> 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, independent of the nature of parietal cell stimulation. PPIs undergo extensive hepatic metabolism by the cytochrome P<sub>450</sub> enzyme system<sup>32,33</sup>. Gastric proton pump inhibitors are of two types,

1. Irreversible gastric proton pump inhibitors
2. Reversible gastric proton pump inhibitors

PPIs are of first choice for peptic ulcer and their complications<sup>1, 20</sup> Gastric Oesophageal Reflux Syndrome, (GERD), and NSAIDs induced gastro intestinal lesion, Zollinger 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**

PPIs bind to cysteine 813, resulting in covalent inhibition of the enzyme via formation of disulphide that stabilizes the enzyme in the E2 conformation<sup>33</sup>. Several salient features required for the activity are

- a. The weak basicity of the compounds ( $pka \gg 4$ ), 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 thiophilic 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 cysteine's of proton pump<sup>34, 35, 36</sup>. The introduction of methyl group in the 6<sup>th</sup> 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<sup>6</sup>. HO-1 induction might account for the gastro protective effects of PPIs independently of acid inhibition.

#### **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<sup>1</sup>. Extreme acid suppression sometimes 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<sub>12</sub> iron salts, etc. It is also responsible for astrinemia, gastric polyps and carcinoma<sup>12</sup>. Acute interstitial nephritis progressing to acute renal failure has been reported to be associated with the use of PPIs.

#### **Drawbacks Reversible gastric proton pump inhibitors (PPIs):**

Prolonged suppression of gastric acid secretion produced by both H<sub>2</sub> receptor antagonists and PPIs produces extended periods of hypergastrinemia. Reversible H<sup>+</sup> / K<sup>+</sup> -ATPase inhibitors (K<sup>+</sup> 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<sup>13</sup>. The K<sup>+</sup> 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<sub>2</sub>-receptor antagonists and irreversible proton pump inhibitors thereby obviating the advantages of proton pump inhibitors in healing lesions and relieving symptoms. K<sup>+</sup> competitive inhibitors also bind to E2 form of the ATPase both in the N and the C terminal regions<sup>12, 31</sup>.

## Reversible proton pump inhibitors

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<sup>60</sup>.

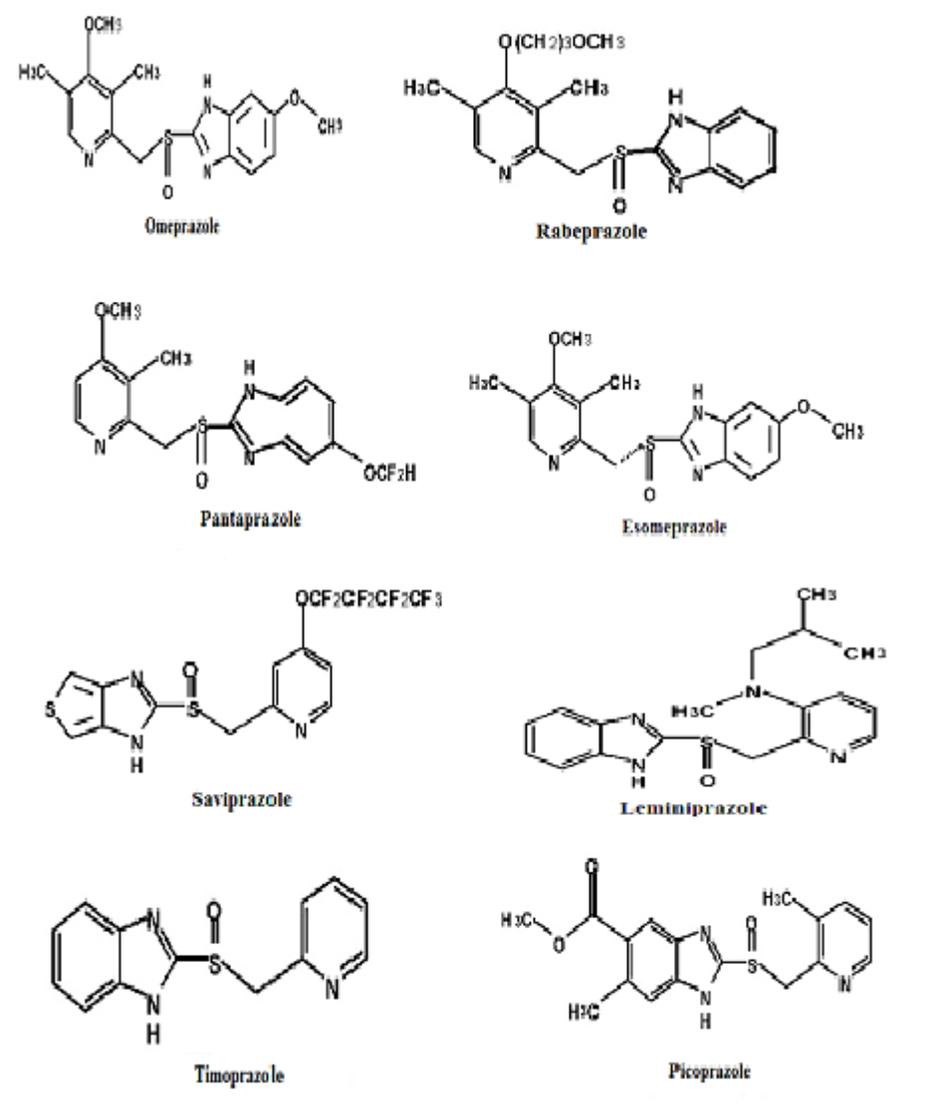
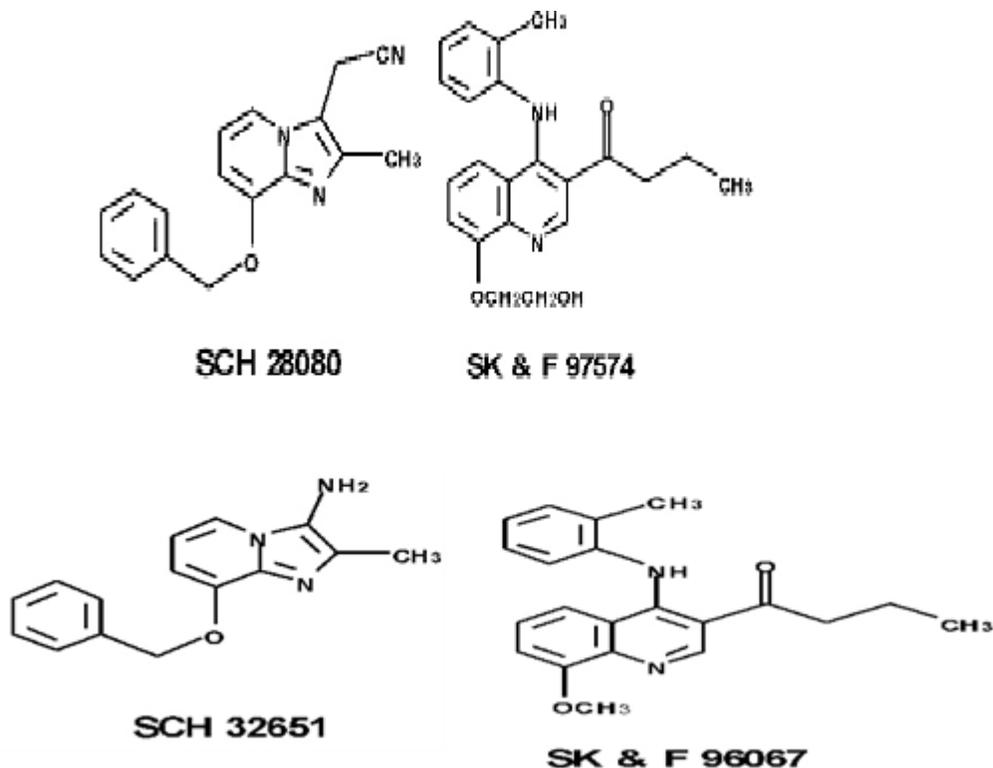


Figure 2: Irreversible gastric proton pump inhibitors

## Pharmacology of the Proton Pump Inhibitors

PPIs are substituted benzimidazole derivatives that inhibit the proton pump ( $H^+/K^+$  adenosine triphosphates) in the parietal cells of the stomach. PPIs work by accumulating in the secretory canaliculus of the acid-secreting parietal cell, where they are protonated to the active form, a cationic sulfonamide. This active form then binds to a sulfhydryl group on the proton pump and,

by irreversible inhibition, prevents secretion of acid into the gastric lumen. Acid secretion resumes only after new pump molecules are synthesized, providing a prolonged (24-48 hours) suppression of acid secretion. PPIs undergo rapid first-pass and systemic hepatic metabolism by hepatic cytochrome P, particularly cytochrome P2C19 and cytochrome P3A4, and have negligible renal clearance<sup>37</sup>.



**Figure 3: Reversible gastric proton pump inhibitors**

### Overuse of proton pump inhibitor

A major concern about PPIs is their potential overuse and abuse. Several studies have confirmed the overuse of these agents in both inpatient and outpatient settings. Approximately 50% to 60% of prescriptions of acid-suppressive medications in hospitalized patients are found to be without appropriate indications<sup>38, 39, 40</sup>.

### Clinical Significance of Proton Pump Inhibitors<sup>41</sup>

- Proton pump inhibitors are the most potent medications available to reduce gastric acid secretion.
- With the widespread use of PPIs, the long-term safety issues need to be considered.
- The collective body of information overwhelmingly suggests increased risk of infectious complications and nutritional deficiencies.

- Data on the risk of increased gastric and colon malignancy, despite a physiologic theoretic basis, is less convincing.
- The long-term need for PPIs must be reassessed frequently.

### Side Effects

PPIs generally cause few adverse effects. The most common side effects are headaches, nausea, abdominal pain, constipation, and diarrhea. These side effects are usually mild, self-limiting, and unrelated to dosage or age. However, long-term side effects of PPIs have recently gained attention, and several studies have looked at various side effects that may be associated with potential long-term use of PPI. These side effects are discussed in detail.

### Vitamin B<sub>12</sub> Deficiency

Marcuard, *et al.*<sup>42</sup> evaluated vitamin-B<sub>12</sub> absorption before and after a short term omeprazole therapy in ten healthy male volunteers (age range 22–50 years). Five patients were randomized to receive 20 or 40 mg of omeprazole daily for two weeks. At the end of the therapy in patients receiving omeprazole 20 mg, cyanocobalamin absorption decreased from 3.2% to 0.9%, and in patients receiving 40 mg, cyanocobalamin absorption decreased from 3.4% to 0.4%<sup>42</sup>. Recent reports described the cases of seven patients developing hypomagnesaemia while on long term PPI, with resolution after PPI withdrawal<sup>43, 44</sup>. The incidence and the mechanism of hypomagnesaemia development in long term PPI users have still to be determined by specific studies.

### Iron Deficiency

Dietary iron is present in food as either non-heme iron or heme iron. Dietary non-heme iron absorption is markedly improved in the presence of gastric acid<sup>45</sup>.

Several clinical studies suggest that gastric acid hyposecretion, especially over a prolonged period, might result in clinically significant malabsorption of iron. Decreased non-heme iron absorption has been reported in patients with achlorhydria<sup>46</sup> and various gastric acid-hyposecretory conditions (gastric resection, vagotomy, atrophic gastritis)<sup>47</sup>.

Stewart, *et al.*<sup>48</sup> studied 109 patients with Zollinger-Ellison syndrome. Continuous treatment with omeprazole for 6 years or continuous treatment with any gastric anti-secretory drug for 10 years did not cause decreased body iron stores or iron deficiency. These results suggest that iron deficiency secondary to decreased gastric acid secretion is theoretically possible but has not been clinically proven; thus, monitoring for iron deficiency is not necessary.

However, it must be noted that Zollinger-Ellison syndrome is a rare disorder, and the results cannot be applied to the average PPI user. In the absence of such data, the results of such studies

cannot be applied to the general population, and there is a need for long-term safety data trials in the average patient population using PPIs for more general indications, such as reflux disease.

### **Osteoporosis**

Proton pump inhibitor therapy can influence bone metabolism. Specifically, inhibition of the osteoclastic proton pumps may reduce bone resorption, while profound acid suppression could potentially hamper intestinal calcium absorption, and secondary hypergastrinemia may enhance bone resorption through the induction of parathyroid gland hyperplasia<sup>49</sup>. Several case control studies demonstrated an increased risk of osteoporosis and hip fractures with increasing duration and dosage of the PPI<sup>50,51</sup>. It may be worth considering increasing calcium intake for prevention and assessing bone mineral density in those requiring. The TGA is currently considering upgrading warnings about the increased risk of osteoporosis and further studies are awaited to confirm this association.

### **Gastric cancer**

Mowat, *et al.*<sup>52</sup> investigated the effects of a four week course of 40 mg of omeprazole on gastric juice concentration of vitamin-C in 20 healthy volunteers. They showed that omeprazole increase the levels of nitrites and reduce those of vitamin-C. The reduced ascorbate/nitrite ratio induced by PPI, may increase the risk of gastric cancer. This effect was more marked in H. Pylori positive patients, probably because the acid suppressive effect of PPIs is more pronounced in these patients<sup>52,53</sup>.

### **Enteric infection**

Loss of the normal stomach acidity has been associated with colonization of the normally sterile upper gastrointestinal tract<sup>54</sup>. Therefore it is biologically possible that raising the pH of the stomach with acid suppressive therapy may result in an increased load of pathogenic microbes. The gastrointestinal tract has many defence mechanisms, such as the integrity of the membranes and mucous layer, the gastrointestinal microflora and gastric acidity. A decrease in gastric acidity may induce changes in the normal microbial flora with bacterial overgrowth. Diarrhoea is the most frequent adverse event in the long term PPI use and the most frequent cause of PPI withdrawal, with reported incidence ranging between 3.8% and 4.0%<sup>55,56</sup>.

### **Acute interstitial nephritis**

Proton pump inhibitor induced acute interstitial nephritis is uncommon, however increasing numbers of cases are being reported<sup>57,58</sup>. The underlying mechanism is thought to involve an immune component<sup>57</sup>. Symptoms are nonspecific and include weight loss, fatigue, malaise, nausea and vomiting. A dose response relationship has not been established and onset may be

delayed up to several months<sup>59</sup>. Renal function should be checked and a nephrologist opinion should be sought if acute interstitial nephritis is suspected.

## CONCLUSION

PPIs are highly effective drugs that have revolutionized the management of acid-related disorders during the last two decades. Launch of omeprazole in 1988 introduced a conceptually new approach of inhibition of proton pump in the management of acid related disorders. The proton pump inhibitors generally are superior to the H<sub>2</sub>-receptor antagonists in healing lesions quickly and improving symptoms, particularly in patients with oesophagitis. 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<sup>+</sup> dependent, reversible proton pump inhibitors depend ultimately on their acid inhibition profile relative to that H<sub>2</sub>-receptor antagonist.

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