Proton pump inhibitors and peptic ulcer management: Antioxidant mechanisms

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Abstract

Peptic ulcer (P.U.) is the gastrointestinal tract’s most frequent disorder affecting mainly the stomach and duodenum. Surgical intervention, ingested materials and microbial infections may trigger inflammation that further predispose to oxidative stress. Proton pump inhibitors (PPIs) are group of compounds established for suppressions of gastric acid secretions profoundly and permanently over a reasonably long period of time. Oxidative stress has been shown to be involved in the pathophysiology of various diseases and disorders, including P.U. Particularly when H. pylori infection accompanies it. In addition to the colonization of this microorganism, gastric mucosa may be subjected to extreme oxidative stress with large levels of inflammatory cell aggregation, which may eventually predispose to the disorder. PPIs exert several effects other than gastric acid suppression that can be used to treat Helicobacter pylori infections, disorders of the respiratory tract, viral infections, and other conditions related to dysfunction of endothelium by activating endogenous antioxidant protection and reducing the release of cytokine. Recent therapeutic protocols have recommended PPIs as gastro-protective compounds not only because of their acid suppression properties, but also because of their potent antioxidant and anti-inflammatory properties.

Keywords: Proton Pump Inhibitors, Peptic Ulcer, Oxidative Stress, H. pylori

Introduction:

Peptic ulcer (P.U.) is the gastrointestinal tract’s most frequent disorder affecting mainly the stomach and duodenum. As a disease, it is characterized by an upper digestive tract mucosal lesion; including the stomach, first portion of the small intestine or even may affect the lower part of the oesophagus. A stomach lesion is referred to as a gastric ulcer whereas that lesion in the lining of the first part of intestinal mucosa is known as a duodenal ulcer. The approximate estimated occurrence of P.U. in overall population is 5–10%, with an annual incidence of 0.1–0.3%2. Ulceration of the stomach and duodenum is often caused by acid-peptic damage to these parts of gastrointestinal tract, leading to erosion and loss mucosal lining, with eventual exposure of the gastric-duodenal underlying tissues to the digestive potential of acid and enzymes.3 The condition happens as a result of imbalance between mucosal protective and aggressive factors4, and it is now agreed that the majority of peptic ulcer cases are associated with H. pylori infection or the history of using non-steroidal anti-inflammatory medications or both.5 Aggressive conditions that could predispose to peptic ulcer involve; pepsin, refluxed bile, hydrochloric acid (HCL), ethanol, leukotrienes (LTs), gastric cancer, and reactive oxygen species (ROS), in addition to several minor factors such as smoking, spicy food and stress. On the other hand, the defensive players include the presence of mucus-bicarbonate barrier, mucosal blood flow, prostaglandins (PGs), non-enzymatic and enzymatic antioxidants, cell renewal and migration, as well as some growth factors6,7.

The chronicity and pattern of cyclic recurrence with seasonal peaks, especially during autumn and winter, have always been specific clinical features of the disease and as indicators for serious complications. The mortality rate of peptic ulcer complications, bleeding and perforation, despite the overall decline in PUD and complications, have not
significantly improved and is still of major concern. Recent advances in understanding the pathogenesis of the disease, mainly after the reported crucial role of antioxidants as protective mediators may suggest better options for the treatment of ulcer. Proton pump inhibitors as first line medication for the treatment of P.U. have recently shown a potential antioxidant effect at variable degree which could add a beneficial dual acid suppressant and antioxidant effect to suppress two main aggravating factors; acid secretion and oxidative stress. Therefore, our main goal is to review the impact of antioxidant potential of proton pump inhibitors on the management of P.U. and how these drugs could modulate the course of underlying pathology of ulcer to offer better care for patients.

**Peptic ulcer and oxidative stress**

The gastric mucosa plays an important role in regulating the physiological processes of the stomach. This mucous lining serves as a gastric shield, protecting the underlying tissue from the harmful activities of the components of the gastric juice and the consumed mucosal irritants. Despite the protective layer offered by the epithelial lining surgical intervention, ingested materials (such as NSAIDs) and microbial infections, such as *H. pylori* may trigger inflammation by stimulating the epithelium, macrophages and polymorphonuclear neutrophils (PMNs), to generate some mediators including inflammatory cytokines that further predispose to oxidative stress. Numerous pathological conditions of the gastrointestinal tract including gastric or duodenal ulcers, inflammatory bowel disease and malignancies arise as a result of oxidative stress. Oxidative stress is a condition of high ROS levels that stimulates either additional development of ROS or a decrease in antioxidant capacities. Under normal physiological conditions, the ROS are formed at low levels as a result of partial reduction of molecular oxygen. Reactive oxygen species, hydroxyl radical (OH·), superoxide anion (O2−), singlet oxygen (¹O2) and hydrogen peroxide (H2O2), display increased reactivity due to the presence of unpaired electron in the outer shell. However, when cells overproduce ROS more than the intrinsic antioxidant capacity, oxidative stress occurs and afterwards damage occurs in normal biomolecules of cells and tissue and essential cell components such as nucleic acids, proteins, polyunsaturated fatty acids and to a lesser extent, carbohydrates can be attacked by reactive oxygen species.

These reactions may significantly change the intrinsic structural characteristics of the membrane such as fluidity, cell signalling, enzymatic activity, ion transport, protein crosslinking and synthesis, and eventually chromatin condensation, DNA fragmentation and cell death. In general, tissue damage is mainly enhanced by peroxidation of lipids; lipid peroxides are basically metabolized to 4-hydroxynonenal (4-HNE) and malondialdehyde (MDA). Reactive oxygen species-depended mucosal damage occurs when there is a boost in the level of 4-HNE and MDA. Superoxide dismutase (SOD) is regarded as the key enzyme that neutralizes ROS to result in less harmful hydrogen peroxide. Significantly reduced SOD activity is a marker of decreased antioxidant effect at variable degree and continues significantly to further cellular damage. In the presence of reduced glutathione (GSH), hydrogen peroxide is further metabolized to water. Reactive oxygen species can also be neutralized by synergistic action of GSH and SOD.

Glutathione free radical (GS) are produced as a result of interaction ROS and GSH, these radicals can further react with GSH producing glutathione disulphide (GSSG). The latter is free radical which can then result in formation of O2·− by donating an electron to the oxygen that is eventually eliminated by SOD. Any reduction in the GSH activity may result in negative implications for the cellular processes of antioxidative defense. When exposed to stress factors, gastrointestinal mucosa shows an increase in lipid peroxidation (increase in 4-HNE and MDA and), and a reduction in GSH concentration and SOD activity. This stress-induced ROS signalling events seems to be a main determinant for interpreting the pathophysiology of stress-induced defects in the gastrointestinal mucosa that proceed to ulcerogenesis, with an effort to develop novel strategies for management of P.U.

**Proton pump inhibitors and antioxidant potential**

Proton pump inhibitors (PPIs) are group of compounds established in the late of the last century. Omeprazole (1) was the first of PPIs released to the markets in late 80s. Most of PPIs are benzimidazole (2) derivatives, esomeprazole (3), lansoprazole (4), pantoprazole (5) and rabeprazole (6) are all examples of PPIs and have the benzimidazole ring in their core structures (figure 1). Esomeprazole is a stereoisomer of omeprazole. The main action of PPIs is suppressions of gastric acid secretions profoundly and permanently over a reasonably long period of time compared to other medications that inhibit acid release from the stomach.

PPIs mechanism of action characterized mainly by irreversible inhibition of the enzyme system called Hydrogen/Potassium adenosine triphosphate (H+/K+ ATPase), this enzyme system which is located in the gastric parietal cells act by promoting continuous proton release into the gastric lumen, this action of H+/K+ ATPase system is the reason behind its popular name as the proton pump, the proton pumping is regarded as the final stage of the stomach acid production and inhibition of this process will provide a powerful reduction in the gastric acid content.

The PPIs are administered as prodrugs, which means in their inactive form, that need to be activated before exerting their full action. The activation process of PPIs requires a protonation step of the tertiary amines in the drug structure prior to the rearrangement step which provides the active form of the compound. The active drug then binds covalently and irreversibly to H+/K+ ATPase system causing its failure to pump the protons (figure 2).

The covalent interaction between the active form of the PPI and the H+/K+ ATPase enzyme will provide nearly a full day inhibition of gastric acid secretion. Termination of the inhibitory action of PPIs is thought to occur by reactivation of the H+/K+ ATPase enzyme by release of the sulfide linkage between the drug and the enzyme due to the antioxidant effect of the indigenous glutathione. The inactive form of the PPIs is more lipophilic because it’s neutral in charge and provides better ability for the drug to cross the lipid bilayer membrane of the cells. The plasma half-life of the PPIs is relatively short ranging between 1 and 2 hours.
Figure 1: Structure of proton pump inhibitors

Figure 2: Schematic mechanism of action of proton pump inhibitors
Proton pump inhibitors exert several effects that are unrelated to gastric acid suppression. They can be used to treat *Helicobacter pylori* infections, disorders of the respiratory tract, viral infections, tumours and also have therapeutic potential for pre-eclampsia, myocardial infarction and other conditions involving dysfunction of endothelium, by activating endogenous antioxidant protection and reducing the release of cytokine 18-20. Based on this potential, and their ability to modify the expression of adhesion molecules, numerous reports have demonstrated that PPIs also have anti-inflammatory effects with the ability to modify the expression of adhesion molecules through direct action on inflammatory cells such as endothelial cells, neutrophils and monocytes 21,22. This potential has been agreed by Chanchal et al. who reported the potential of omeprazole (which is the prototype of PPIs) in inhibiting nuclear factor-B activation (NF-B), the release of inflammatory cytokines, and neutrophil chemotaxis. Overall, these findings indicate that omeprazole’s cellular protective role is achieved by blocking the release of pro-inflammatory cytokines, increasing the endogenous anti-oxidant defence mechanism and maintaining the integrity of the internal structure of damaged tissue 23. The severity of lesions has been shown to associate well with the elevated amount of intrinsic hydroxyl radicals that cause about 90% reduction of lesions when scavenged by dimethyl sulfoxide, suggesting that hydroxyl radicals play a significant role in gastric injury. By suppressing stress-induced elevated production of hydroxyl radicals and related protein oxidation and lipid peroxidation, omeprazole significantly blocks gastric lesions in stress and indomethacin-induced ulcers at lower doses, without inhibiting acid secretion, suggesting an independent role for its anti-ulcer activity and that its function may be specific in gastro-protection. Omeprazole also stops the stress-induced DNA fragmentation, reflecting its antiapoptotic role in preventing cell damage during ulceration 24.

The antioxidant potential of other proton pump inhibitors has been extensively studied and revealed variable results. The possible anti-fibrotic and antioxidant effect of esomeprazole with the management of liver fibrosis has been evaluated by comparing it to silymarin, a well-known hepatoprotective substance. Esomeprazole improved liver integrity, reversed hepatocellular damage, decreased fibrosis scoring, corrected major histopathological abnormalities, attenuating lipid peroxidation and augmented antioxidant potential. Additionally, treatment with esomeprazole resulted in inhibition of inflammatory mediators such as TGFβ, IL-6 and TNF-α and retrieval of the epithelial marker e-cadherin with up-regulation of Bcl2 protein and down-regulation of hepatic Bax, which indicates its role in inhibition of tissue damage 25. Esomeprazole has also shown to have a gastro-protective role via its antioxidant activity through inhibiting the signaling pathway of NF-B and p38 MAPK. Treatment with esomeprazole also led to increased antioxidant factors expressions such as GSH and SOD and decreased MDA levels and other invasive triggers such as pepsin, gastric acid and ROS-related inflammatory damage 26.

The protective effect of lansoprazole on gastric ulcer and liver damage induced by oxidative stress has been studied, where pre-treatment with lansoprazole protected the stomach mucosa and liver from the oxidative damage via reduction in the level of oxidizing drivers like MDA and augmentation in antioxidant parameters such as GSH, SOD, catalase, GST and glutathione 27. Likewise, Blandizzi in 2005 has explored the possible pathways of protection offered by lansoprazole against gastrointestinal damage induced by various NSAIDs in rats. The findings indicate that in addition to inhibiting gastric acid secretion, lansoprazole defense against gastric damage induced by NSAIDs depends on a decline in mucosal oxidative damage 28. Gastrointestinal blood loss occur as a result of stress-related mucosal injury, which confers the major cause of death in critically ill patients. A recent protocol with pantoprazole has shown promising results in reducing clinically significant gastrointestinal bleedings due to its anti-inflammatory effects and antioxidant effects 29. All of the previous studies have revealed an important role for different drugs that belong to PPIs in combating oxidative which exacerbates mucosal damage in P.U. patients. However, it is still questionable whether different PPIs have similar antioxidant properties. For that, Swamy and colleagues have investigated the possible antioxidant potential of omeprazole, rabeprazole and lansoprazole and found that omeprazole has the most powerful antioxidant potential in comparison to others and was able to significantly reduce MDA level with augmentation in the activity of SOD in comparison to rabeprazole and lansoprazole 30. Similarly, the possible antioxidant potential of omeprazole, esomeprazole, lansoprazole, pantoprazole has been explored and compared to help the health practitioners in suggesting a PPI that has effective antioxidant potential in addition to its acid-suppression capability. The study revealed that in comparison to drugs of the same class, omeprazole and esomeprazole may confer significant antioxidant beside their acid-suppression effect and this could add a dual protection for the gastrointestinal tract. The difference in the antioxidant potential of different PPIs was attributed to the chemical structure of these drugs, where omeprazole and esomeprazole have the strongest electron-donating groups attached to benzimidazole and pyridine moieties in comparison to others, and as such, these two agents can spare one of the unshared electrons attached to their nitrogens to react with and stabilize the free radicals 31. In addition to this, the difference in antioxidant effect of various brands of esomeprazole available in community pharmacies has been investigated and revealed that different brands of the same agent may differ in their antioxidant potential and further studies are needed to address such difference 32.

In summary, Oxidative stress has been shown to be involved in the pathophysiology of various diseases and disorders, including P.U. Particularly when *H. pylori* infection accompanies it. In addition to the colonization of this microorganism, gastric mucosa may be subjected to extreme oxidative stress with large levels of inflammatory cell aggregation, which may eventually predispose to the disorder. Recent therapeutic protocols have recommended PPIs as gastro-protective compounds not only because of their acid suppression properties, but also because of their potent antioxidant and anti-inflammatory properties. These drugs can downregulate the production of ROS to enhance anti-inflammatory or anti-oxidant performance. However, these agents may show difference in their antioxidant potential and the present studies showed that omeprazole and lansoprazole may be superior to their counterparts. In our opinion, clinical trials are needed, especially with regard to ulcer-prone populations with a high oxidative level, to investigate the potential long-term gastro-protective use of these agents.

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