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Potential Anti-inflammatory Effects of Proton Pump Inhibitors: A Review and Discussion of the Clinical Implications

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Abstract

Proton pump inhibitors (PPIs) are potent blockers of gastric acid secretion, and are widely regarded as the agents of choice for the treatment of acid-peptic disorders. For patients with upper gastrointestinal symptoms of uncertain etiology, improvement with PPI therapy is considered prima facie evidence of a pathogenetic role for acid-peptic disease. In addition to anti-secretory effects, however, PPIs have been found to have anti-oxidant properties and direct effects on neutrophils, monocytes, endothelial, and epithelial cells that might prevent inflammation. Those anti-inflammatory effects of the PPIs might influence a variety of inflammatory disorders, both peptic and non-peptic, within and outside of the gastrointestinal tract. The purpose of this report is to review the mechanisms whereby PPIs might exert anti-inflammatory effects exclusive of gastric acid inhibition, to discuss the clinical implications of those effects, and to emphasize that a clinical response to PPIs should not be construed as proof for an underlying acid-peptic disorder.

Keywords

Proton pump inhibitors; Inflammation; Anti-inflammatory agents; Anti-oxidants; Oxidative stress; Eosinophilic esophagitis

Introduction

Proton pump inhibitors (PPIs) are substituted benzimidazoles that block gastric acid secretion by inhibiting H^+, K^+ ATPase, the proton pump of the gastric parietal cell [1]. PPIs are the most effective anti-secretory agents available, and they are among the most commonly used medications in the world [2,3]. PPIs are widely regarded as the agents of

choice for the treatment of acid-peptic disorders including gastric ulcer, duodenal ulcer, and gastroesophageal reflux disease (GERD). For patients with upper gastrointestinal symptoms of uncertain etiology, such as non-ulcer dyspepsia, improvement with PPI therapy is considered *prima facie* evidence of a pathogenetic role for acid-peptic disease. In animal studies on certain non-peptic disorders, however, PPIs have been found to have beneficial effects that cannot be explained by a reduction in gastric acid secretion. In rats, for example, lansoprazole has been found to protect against ischemia-reperfusion injury of the bowel and against indomethacin-induced injury of the distal small intestine [4,5]. A beneficial effect of PPIs has even been described for the colon of a patient with ulcerative colitis [6].

Recent studies have elucidated a number of mechanisms whereby PPIs can exert anti-inflammatory effects unrelated to the inhibition of gastric acid production [7]. Those anti-inflammatory properties of the PPIs, which have nothing to do with their effects on parietal cells, may contribute to the beneficial clinical actions of the PPIs, even in acid-peptic disorders. The purpose of this report is to review the mechanisms whereby PPIs might exert anti-inflammatory effects exclusive of gastric acid inhibition, to discuss the clinical implications of those effects and to emphasize that a clinical response to PPIs should not be construed as proof for an underlying acid-peptic disorder.

Anti-oxidant Effects

In inflammatory conditions like peptic ulcer disease, tissue damage results from oxidative injuries mediated by agents like hypochlorous acid, the most toxic and abundant oxidant produced by phagocytes, and by transition metals like iron and copper, which are present in tissues in various forms [8,9]. In studies performed *in vitro*, omeprazole (in a concentration of 10 μM at acidic pH levels) was found to prevent the oxidation of β -carotene by hypochlorous acid, and to inhibit the oxidation of deoxyribose sugar mediated by iron and copper [9]. Peak mean plasma concentrations of 3.2 μM have been documented for omeprazole with conventional oral dosing [10], whereas levels as high as 10 μM have been reported with intravenous administration [11]. In another *in vitro* study, lansoprazole (in concentrations as low as 3 μM) was found to inhibit the copper-induced oxidation of low density lipoproteins (LDLs) [12]. Peak mean plasma concentrations for lansoprazole as high as 4.8 μM have been documented with conventional oral dosing [10]. Both pantoprazole and lansoprazole were shown to be potent scavengers of hydroxyl radicals generated during chemical reactions involving transition metals, but at concentrations substantially higher than can be achieved in plasma with conventional dosing [13,14]. In DNA isolated from rat gastric mucosal cells, furthermore, omeprazole (in concentrations $\geq 100 \mu\text{M}$) was found to prevent copper-induced oxidative DNA damage in a dose-dependent fashion [14]. These studies show that PPIs have substantial anti-oxidant effects *in vitro*. Although some of these effects have been seen only using PPIs in concentrations considerably higher than can be achieved in plasma with conventional dosing, it is not clear how plasma levels correlate with tissue levels of these drugs. PPIs accumulate in acidic tissue environments, where it has been proposed that their concentrations might reach even millimolar levels [9].

Studies involving animals have demonstrated that PPIs also exhibit anti-oxidant effects *in vivo*. Rats subjected to restraint and cold stress develop gastric ulcers that are caused largely by the gastric mucosal production of hydroxyl radicals [14]. Biswas observed that the stomachs of rats that were treated with omeprazole prior to cold stress exhibited lower levels of hydroxyl radicals as well as lower levels of lipid peroxidation and protein oxidation [14]. Importantly, those stress-induced gastric ulcers were prevented by omeprazole given in doses too low to inhibit gastric acid secretion.

Rats treated with indomethacin develop gastric ulcerations associated with the mucosal depletion of glutathione, a potent, endogenous anti-oxidant that contains cysteine, a sulfhydryl amino acid [15]. In rats given indomethacin, Pastoris et al. [15] noted that gastric mucosal injury and glutathione depletion were prevented by pretreatment with esomeprazole. The mechanisms whereby esomeprazole prevented gastric glutathione depletion in that study are not clear, but the authors suggested that in the presence of gastric acid, esomeprazole is converted into a tetracyclic sulfenamide, which might provide the mucosa with sulfhydryl compounds to function as anti-oxidants.

The potential importance of PPI effects on gastric sulfhydryl compounds was highlighted in another study in rats, which found that lansoprazole protected against gastric mucosal injury induced by ethanol and HCl, but the PPI afforded no such protection when the rats were treated with *N*-ethylmaleimide, which renders sulfhydryl compounds unavailable [16]. In the stomachs of mice treated with indomethacin, Koch found that esomeprazole increased levels of superoxide dismutase as well as total anti-oxidant capacity [17]. It is not clear that those increases in superoxide dismutase and total anti-oxidant capacity were caused by any direct anti-oxidant properties of esomeprazole, however.

In addition to scavenging certain reactive oxygen species (ROS) and increasing mucosal levels of glutathione and other anti-oxidants, in vitro studies suggest that PPIs might protect against oxidative damage in the gastrointestinal tract by inducing the enzyme heme-oxygenase-1 in endothelial and epithelial cells [18]. This enzyme catalyzes heme degradation, thereby generating bilirubin, which has anti-oxidant effects, and carbon monoxide, which has cytoprotective properties. Becker found that both omeprazole and lansoprazole induced the expression of heme oxygenase-1 mRNA and protein in human endothelial and gastric cancer cell lines [18]. The PPIs also blocked NADPH-dependent ROS formation in the cell lines, an effect that was abolished by treatment with zinc deuteroporphyrin 2,4-bis glycol, which inhibits heme oxygenase-1. The importance of heme oxygenase-1 induction in the ulcer-healing effects of PPIs is not clear, however.

Effects on Inflammatory Cells

The PPIs are weak bases that accumulate in an acidic environment, where protonation of their pyridine and benzimidazole nitrogens converts the PPI pro-drugs into the active, tetracyclic sulfenamides that bind to and inhibit proton pumps [1]. In the stomach, the PPIs accumulate in the acid-secreting mucosa, where they block the p-type H^+, K^+ ATPases of parietal cells that secrete acid into the gastric lumen. Non-gastric cells also have proton pumps that, conceivably, might be inhibited by PPIs. For example, Ritter found immunoreactivity for a monoclonal antibody to the β -subunit of gastric (p-type) H^+, K^+ ATPase in human neutrophils [19]. In addition, some non-gastric cells, like neutrophils and endothelial cells, have vacuolar (v-type) H^+ ATPases that may pump acid into the extracellular space and into intracellular organelles like lysosomes [20,21]. Some of these v-type H^+ ATPases appear to be susceptible to inhibition by PPIs [22].

Vacuolar proton pumps are especially prominent in the membranes of the phagolysosomes of neutrophils. When neutrophils are activated by chemotactic factors, those vacuolar H^+ ATPases pump H^+ into the phagolysosome [23]. This lysosomal acidification appears to play a role in mediating the neutrophil's oxidative burst, the rapid release of toxic ROS that results from activation of NADPH oxidase. In the stimulated neutrophil, lysosomal acidification also appears to be involved in elevating cytosolic Ca^{++} levels and in affecting the expression of activated adhesion molecules, like those of the CD11/CD18 integrin family [24]. The adhesion molecules on neutrophils recognize adhesion molecules expressed by endothelial cells in certain disease states, thereby enabling the neutrophil to home into

diseased tissues. If PPIs inhibit neutrophil proton pumps, then it is conceivable that PPI treatment might interfere with neutrophil functions, like ROS release and adhesion molecule expression, that contribute to the development and progression of inflammation.

Human neutrophils can be activated by exposure to bacterial substances like formyl-methionyl-leucyl-phenylalanine (fMLP) and *Helicobacter pylori* water extract (HPE). In 1992, Wandall reported that omeprazole, in concentrations that could be achieved in plasma with intravenous dosing, inhibited neutrophil superoxide generation and chemotaxis stimulated by fMLP in vitro [23]. Suzuki found that lansoprazole also inhibited the oxidative burst of human neutrophils stimulated by HPE in vitro [25]. In gastric biopsy specimens from patients with *H. pylori* gastritis, autoradiographic examination showed that there was a binding site for radiolabeled lansoprazole in the cytoplasmic granules of the neutrophils infiltrating the gastric mucosa [25]. When those infected patients were treated with lansoprazole, furthermore, their gastric mucosal levels of myeloperoxidase (an index of neutrophil infiltration) decreased significantly. These data suggest that PPIs can bind to neutrophils, and can inhibit neutrophil accumulation and release of ROS.

In studies that predated the widespread availability of PPIs, Styrt and Klempner [26] showed that the maintenance of lysosomal acidification was important for certain key neutrophil functions. When neutrophils were treated with weak bases that accumulated in lysosomes, like ammonium chloride, the resulting increase in intralysosomal pH was found to be associated with inhibition of the oxidative burst. In studies on human neutrophils performed in the 1990s, Suzuki estimated intralysosomal pH by measuring the fluorescence intensity ratio of FITC-tagged dextran, which accumulates in the phagolysosomes, and studied the oxidative burst stimulated by fMLP using a luminol-dependent chemiluminescence (ChL) assay [27]. In a dose-dependent fashion, omeprazole treatment of the neutrophils was found to result both in elevated intralysosomal pH and in inhibition of the oxidative burst. Agastya also found that acid-activated omeprazole inhibited the acidification of phagolysosomes in human neutrophils, and that this phenomenon was associated with impaired ability of the neutrophil to phagocytose yeast [28]. In healthy volunteers, furthermore, both Suzuki et al. [27] and Zedtwitz-Liebenstein et al. [29] found that orally administered omeprazole caused a significant decrease in neutrophil production of ROS.

Yoshida found that omeprazole and lansoprazole, in clinically relevant concentrations in vitro, inhibited the HPE-induced expression of CD11b and CD18 by human neutrophils as well as neutrophil-dependant adhesion to endothelial cells [30]. In human umbilical vein endothelial cells stimulated with interleukin-1b, furthermore, those PPIs inhibited the expression of intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) as well as endothelial-dependent neutrophil adhesion. Lansoprazole also has been found to inhibit the expression of ICAM-1 by human tracheal epithelial cells in culture [31], and to decrease the number of peripheral blood mononuclear cells that express ICAM-1 in human volunteers [32].

It is not clear that the PPI effects on neutrophil function are mediated by the inhibition of v-type H⁺ATPases. In one study in which omeprazole and pantoprazole were found to block the migration of human neutrophils stimulated by fMLP and by interleukin-8, bafilomycin (a specific inhibitor of v-type H⁺ATPases) was found to have no significant effects on neutrophil migration [33]. Furthermore, the PPI-induced inhibition of neutrophil migration was reversed by treatment with nigericin, a K⁺ ionophore. The authors suggested that the observed PPI effects on neutrophil function might have been mediated by inhibition of neutrophil H⁺,K⁺ATPases. Nevertheless, the precise mechanisms underlying PPI effects on neutrophil function remain to be elucidated.

Effect on the Production of Pro-inflammatory Cytokines by Epithelial and Endothelial Cells

Proton pump inhibitors may exert anti-inflammatory effects by inhibiting the production of pro-inflammatory cytokines that recruit inflammatory cells to diseased tissues. Gastric mucosal production of interleukin-8 (IL-8), a potent neutrophil chemoattractant, appears to play an important role in mediating gastric inflammation mediated by infection with *H. pylori* [34]. Handa et al. [24] observed that omeprazole and lansoprazole significantly blocked IL-8 production stimulated by HPE in a human gastric cancer cell line and in human umbilical vein endothelial cells, possibly by interfering with the nuclear factor- κ B (NF- κ B) pathway. In rats treated with indomethacin, Kuroda found that lansoprazole significantly decreased the production of cytokine-induced neutrophil chemoattractant-1 (CINC-1, a rat homologue of IL-8) by the small intestine [5]. In cultured human tracheal epithelial cells, furthermore, lansoprazole was shown to decrease levels of a number of pro-inflammatory cytokines including IL-6, IL-8, and tumor necrosis factor- α [31]. The mechanisms underlying the PPI-induced decrease in pro-inflammatory cytokine production by epithelial and endothelial cells are not clear.

Effects on Gut Microflora

Although it is known that the vast microflora of the gut has myriad effects on human physiology, the mechanisms underlying those effects and the physiological consequences of normal microbe-host interactions are not well understood [35]. Under normal conditions, gastric acid kills numerous ingested microbial pathogens and limits the number of commensal microorganisms that live in the upper gastrointestinal tract. By blocking gastric acid secretion, PPI therapy can result in a significant increase in the concentration of bacteria in the stomach, the oral cavity, and the proximal small intestine [36,37]. However, the membranes of a number of bacteria and fungi have H⁺ATPases that might be blocked by PPIs (e.g., *Helicobacter pylori*, *Streptococci*, *Lactobacilli*, *C. albicans*, *S. cerevisiae*), and PPIs have been shown to inhibit growth and even kill some of those microorganisms [37–39]. Those anti-microbial effects of PPIs could be beneficial if they destroy harmful microorganisms, or detrimental if they eliminate advantageous ones. The overall PPI effects on the gut microflora (i.e., the combination of microbial growth-promotion in the upper gastrointestinal tract due to gastric acid inhibition, and growth-interference from the direct anti-microbial actions of the PPIs throughout the gut) are not known. Conceivably, PPI effects on microorganisms could be pro-inflammatory in some parts of the gut and anti-inflammatory in others.

Clinical Implications of Anti-inflammatory Effects of PPIs

There remain many unanswered questions regarding the anti-inflammatory effects of the PPIs. The underlying mechanisms are not well established, and it is not clear that oral PPI dosing can achieve the high drug concentrations in plasma and tissue that would be needed to reproduce some of the anti-inflammatory actions that have been observed in vitro. It is also not clear whether the anti-inflammatory properties of the PPIs contribute substantially to their beneficial effects in treating the acid-peptic diseases. Nevertheless, the studies discussed above raise the possibility that the PPIs might have considerable anti-inflammatory effects that are unrelated to the inhibition of gastric acid secretion, and that possibility has some profound clinical implications.

The data presented above raise a serious challenge to the common clinical practice of assuming that a symptomatic response to PPI treatment is proof of an underlying acid-peptic disorder. It is conceivable that the PPIs might have beneficial effects in any number of

inflammatory diseases, gastrointestinal or extra-intestinal, in which acid and pepsin have no role. Eosinophilic esophagitis is a case in point.

Eosinophilic esophagitis appears to be a manifestation of food allergy in which eosinophils infiltrate the esophageal epithelium, where they cause symptoms and tissue injuries that are mediated by the release of cytokines [40]. Whereas GERD also can be associated with eosinophilic infiltration of the esophagus, and both GERD and eosinophilic esophagitis may cause symptoms like heartburn and dysphagia, it can occasionally be difficult to distinguish between the two disorders [41]. Furthermore, there may be a complex interaction between GERD and eosinophilic esophagitis. GERD may play a pathogenetic role in some patients with eosinophilic esophagitis and vice versa.

In 2006, researchers at Boston Children's Hospital published a report describing three pediatric patients who had profound esophageal eosinophilia and symptoms that resolved completely when they were treated with PPIs [42]. Although none of the three had a history typical of GERD, the authors concluded that the response to PPI therapy was proof for the underlying reflux disease, and that the profound esophageal eosinophilia was a manifestation of peptic esophagitis. On the basis of this and many similar reports, a trial of PPI therapy now is recommended as initial treatment for patients with eosinophilic esophagitis, even if the diagnosis seems clear-cut [41,43,44]. The rationale for this recommendation is that PPIs are treating the peptic esophagitis that underlies the esophageal eosinophilia. Based on the data reviewed above, however, a reasonable alternative rationale is that eosinophilic esophagitis might respond to the anti-inflammatory effects of PPIs.

One mechanism that has been proposed for how acid reflux might attract eosinophils to the esophagus involves VCAM-1 [41]. In human esophageal microvascular endothelial cells, acid exposure has been shown to induce the expression of VCAM-1 [45], an adhesion molecule that is recognized by ligands on the eosinophil cell surface [46]. As discussed above, PPIs have been found to inhibit the expression of VCAM-1 by endothelial cells [30]. Thus, it is conceivable that PPIs may reduce esophageal eosinophilia, at least in part, by inhibiting VCAM-1 production by esophageal endothelial cells. When assessing a patient's response to PPI therapy, physicians should consider the potential contribution of the anti-inflammatory effects of those medications, and a clinical response to PPIs should not be construed as proof for an underlying acid-peptic disorder.

In addition to beneficial therapeutic effects, it is also conceivable that the anti-inflammatory effects of PPIs could have adverse consequences in certain clinical situations. For example, such effects might predispose to the development of infectious diseases. Perhaps such actions might underlie the predisposition to both community- and hospital-acquired pneumonia that has been described for patients who take PPIs [47,48]. Anti-inflammatory effects may also contribute to the association between PPI therapy and spontaneous bacterial peritonitis that has been described in patients with cirrhosis and ascites [49]. Clearly, the role of PPIs as anti-inflammatory agents is an area that warrants further investigation (Table 1).

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Table 1

Proposed mechanisms underlying anti-inflammatory effects of proton pump inhibitors

<i>Anti-oxidant effects</i>
Direct scavenging of reactive oxygen species [9,12–14]
Replenishment of protective sulfhydryl molecules in the gastric mucosa [15,16]
Induction of heme oxygenase-1 [18]
<i>Effects on inflammatory cells</i>
Inhibition of oxidative burst in neutrophils [23,25,27,29]
Impaired phagocytosis of micro-organisms by neutrophils [28]
Decreased expression of adhesion molecules by neutrophils and monocytes [24,30,32]
Impaired neutrophil migration [33]
<i>Effects on endothelial cells</i>
Decreased expression of adhesion molecules [30]
Decreased production of pro-inflammatory cytokines [24,34]
<i>Effects on epithelial cells</i>
Decreased production of pro-inflammatory cytokines [5,24,31]
<i>Effects on gut microflora</i>
Growth inhibitory and killing effects on a number of bacteria and fungi [37–39]