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Research Article

Pleiotropic Benefits of Proton Pump Inhibitors Beyond Gastric Acid Control

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ABSTRACT

Proton pump inhibitors are recommended for the treatment of peptic acid disorders like duodenal ulcer, gastric ulcer, oesophageal reflux disorders. They are also used for NSAID induced and for ischemia reperfusion related gastrointestinal injuries. In addition to the anti secretary effect, PPIs have been found to have antioxidant, anti inflammatory and antidiabetic properties They are also used as an adjunct in the treatment and prevention of chemoresistant tumors. Their anti inflammatory property is attributed to the inhibition of expression of adhesion molecules on the neutrophils, monocytes and the endothelial cells. In addition, decreased release of pro inflammatory mediators and up regulation of heme oxygenase –l also contribute to this action. Keap-1/Nrf-2 and MAP kinases have role to play in the upregulation of enzyme heme oxygenase-1 by PPIs. Inhibition of oxidative burst by neutrophils and impaired neutrophil migration also help in anti inflammatory actions of PPIs. Antioxidant effect of PPIs is attributed to the scavenging of reactive oxygen species, replenishment of protective sulfhydryl molecule in the gastric mucosa and the induction of heme oxygenase-1. Recently anti diabetic properties of PPIs have been highlighted. PPIs mediate glucose lowering effect by increased gastrin levels, increased beta cell neogenesis and mass, increased insulin secretion. Inhibition of ghrelin, activation of central CCK-B receptors and GLP-1 activation from intestinal L cells also contribute to this effect. The PPIs are used as an adjunct treatment for malignancy and also to prevent chemoresistance. The mechanism responsible for this effect of PPIs on the malignant cells is through inhibition of V-ATPases and change in physiological pH which makes them succeptible for apoptosis and self digestion. This also results in to the increased drug retention in the alkaline pH of malignant cells.

Keywords:

INTRODUCTION

Proton pump inhibitors [PPIs] are the substituted benzimidazoles, which inhibit gastric parietal cell P type H^+K^+ATPase proton pumps and block the gastric acid secretion[1]. PPIs are the weak bases which after absorption, accumulate in the parietal cell acidic environment. They are the pro drugs which get activated after protonation of their pyridine and benzimidine nitrogen in to active tetracyclic sulfenamide which bind to proton pumps and inhibit them[2]. PPIs are the most effective anti secretory agents recommended for the treatment of acid peptic disorders like duodenal ulcer, gastric ulcer, gastro esophageal reflux disorders[GERDs], NSAID induced gastric mucosal injury and Helicobacter pylori infection[2-10]. PPI protect the bowel mucosa against indomethacin and ischemia induced injury. This effect is unrelated to the acid suppressive effect of PPI and is attributed to the anti inflammatory property of PPI[9,10]. In addition to anti inflammatory property , PPIs have been proved to have anti diabetic[11], antioxidant[12] , anti malignancy[13] and antimicrobial actions[14].

Effect of PPI on the glycemic control in diabetes mellitus [DM]

PPIs bind to proton pumps irreversibly and block the gastric acid secretion. They indirectly elevate serum gastrin levels via a negative feedback mechanism[15-20]. Gastrin is a linear peptide hormone secreted by gastric pyloric antrum G cells, in which biologically active gastrin 17 and gastrin 34 are formed[15,21]. Gastrin acts as a growth factor and stimulates parietal cell proliferation[22,23]. It is also known to stimulate beta cell neogenesis in pancreatic ductal complex[24], replicate pancreatic beta cells and improves glucose homeostasis[23]. Increased gastrin levels arising out of negative feedback mechanism improve glycemic control in diabetics probably by augmenting beta cell mass and insulin release[25]. Most of the clinical studies have shown significant control of hyperglycemia in type 2 DM[11,26-31]. But there are few studies which observed, negative results regarding the effect of PPIs on glycemic control[32,33]. In some of the clinical studies where glycemic control was improved by PPIs[26-31]. it appeared that higher the levels of blood sugar and HbA1c, better was the

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control[27]. The observed negative effect of PPI on blood sugar control was correlated to the already good controlled blood sugar and of HbA1c[32,33]. It was observed that the elevated gastrin level by PPI is not always needed for good glycemic control[30]. This suggests the possibility of some other mechanisms other than increased gastrin levels and increased beta cell mass for glycemic control. Other suggested possible mechanism is the interrelation of gastrin with ghrelin which has an important role to play in appetite regulation and energy homeostasis. Gastrin and ghrelin have negative correlation in human beings, thereby increased gastrin and decreased ghrelin result in to reduced appetite and good glucose control[34]. Cholecystokinin B [CCK-B] receptors are present in the brain mainly in the hypothalamic region[35,36]. Cholecystokinin[CCK] is secreted from the duodenum in response to food. CCK acts on CCK-B receptors in the brain and suppresses satiety centre and is anorexigenic. Diffusion of gastrin in the brain is limited by blood brain barrier[37]. But either peptide or peptide fragments might enter in to the brain through circum ventricular organs[38]. Circulating gastrin can stimulate CCK-B receptors in the area postrema neurons which project to the nucleus tractus solitaries [NTS] and suppresses the appetite[39]. Thus it is possible that increase in serum gastrin by PPIs directly inhibits appetite through central nervous system and also by acting indirectly on the brain stem via vagal nerve[39]. Now it is revealed that gastrin stimulates Glucagon like peptide-1[GLP-1] secretion from the L cells in the small intestine[40]. GLP-1 induces both beta cell replication with mitogens and neogenesis of beta cells from the ductal cells. GLP-1 stimulates insulin release, inhibits glucagon secretion, suppresses the appetite by central effect and decreases gastro intestinal motility[41,42]. This all help to control hyperglycemia. Clinical studies have proved the synergestic effect of PPI like lansoprazole either with dipeptidyl peptidase-4 [DPP-4] inhibitors like sitagliptin which blocks the degradation of GLP-1 and increases its levels or with GLP-1 analogue like liraglutide[43-45]. Thus, the various mechanisms for the effect of PPI on glycemic control are- increased gastrin release, enhanced beta cell mass and insulin release, inhibition of ghrelin, action on CCK-B receptors centrally and on vagus nerve and stimulation of GLP-l. The combination of GLP-1 and gastrin may protect from the onset or the progression of type I DM by an immune regulatory effect. It may be possible that PPI might be having other unknown mechanisms also for glycemic control which needs to be explored by further studies.

Antioxidant property of PPI

Antioxidant property of PPI is mediated by direct scavenging of reactive oxygen species [ROS] and by up regulation of stress inducible cytoprotective enzyme heme oxygenase-1[HO-1] in endothelial and epithelial cells. In addition PPI increase mucosal levels of glutathione and other antioxidants[12]. HO-1 induction is related to the anti-inflammatory, antioxidant and cytoprotective action. This enzyme catalyses heme degradation and generate antioxidant bilirubin and cytoprotective carbon monoxide [CO][12]. HO-1 is inducible by stimuli like oxidative stress, ischemia reperfusion injury, bacterial liposaccharides, cytokines, nitric oxide, heat shock, ultraviolet radiation and also by its substrate heme. Enzyme HO-1 while catalyzing heme degradation generate ferrous iron [Fe++]. Release of Fe++ triggers the synthesis of ferritin which sequestrates free iron, slows down iron dependent redox [Fenton] reaction and acts as an antioxidant[46,47]. CO has been shown to have antioxidant, anti apoptotic, anti-inflammatory, antiproliferative and bronchodilator properties[48,49]. Omeprazole and other PPI get converted in to tetracyclic sulfenamide in gastric parietal cell acidic PH which provide sulfhydryl compounds to gastric mucosa and function as antioxidant. In rats, indomethacin induced gastric mucosal injury and glutathione depletion was prevented by pre treatment with esomeprazole[50,51]. PPIs like lansoprazole and omeprazole have been proved to have direct scavenging action against ROS which were generated during reaction with transition metals or by copper induced oxidation of low density lipoproteins[LDL][52-54]. In inflammatory conditions like peptic ulcer disease, oxidative stress causes tissue damage. Oxidant injuries are mediated by the production of toxic agents like hypochlorus acid by phagocytes and by transition metals like iron and copper present in various tissues[55,56]. In vitro studies omeprazole was found to prevent the hypochlorus acid induced oxidation of beta carotene and was also observed to inhibit oxidation of deoxyribose sugar, mediated by iron and copper[56]. Several signaling molecules like mitogen activated protein kinases [MAPK] and transcriptional regulators like activator protein-1, NF-E2 related factor- 2 [Nrf-2], hypoxia-inducible factor-1 and Bach-1 regulate the ho-1 gene[57-60]. Lansoprazole was observed to upregulate HO-1 expression by activation, phosphorylation, nuclear translocation of Nrf-2 along with dissection of oxidized Kelch like ECH dissociating protein- 1[Keap- l][61]. By production of proinflammatory cytokines like TNF alpha and interleukin 1-B [IL-1B], neutrophils, macrophages and mononuclear cells play an important role in gastrointestinal inflammation[62]. In addition to acid suppression, PPI like lansoprazole has been observed to reduce the inflammation and oxidative stress resulting in to amelioration of mucosal injuries in the esophagus[63-65], stomach[66], intestines[9,10,67] and lungs[68]. PPI were also found to block NADPH dependent ROS formation[69].

Anti inflammatory property of PPI

This property of PPI is attributed to Prevention of expression of adhesion molecules on polymorphonuclear leucocytes and on endothelial cells. Down regulation of proinflammatory cytokines like TNF alpha and interleukin [IL].1-B and IL-6. Upregulation of stress inducible protein HO-1. Helicobacter pylori and NSAIDs are known to induce gastric mucosal injury by activating polymorphonuclear leucocytes which initially adhere to the venules and then migrate in to the interstitium and induce inflammation[70-74]. Certain adhesion molecules expressed on the surface of leucocytes facilitate their adhesion to endothelial cells[75,76]. These are CD 11/CD 18 integrin family composed of alpha subunit [CD 11 a-c] and beta-2 subunit of CD 18[75,77,78]. Adhesion and trans

endothelial migration of leucocytes is facilitated by these molecules. Similarly, adhesion molecules are also expressed on activated endothelial cells which help for the adhesion of leucocytes and mononuclear cells to the endothelial cells. These are intercellular adhesion molecule-1 [ICAM-1] and vascular adhesion molecule -1[VCAM-1]. ICAM-1 acts as ligand for CD 11/CD 18 on leucocytes[77] and VCAM -1 for very late activation antigen-4 [VLA-4] on mononuclear cells[79]. In experimental studies surface expression of CD 11 and CD 18 on leucocytes and their adhesion to endothelial cells was reduced by lansoprazole and omeprazole. It is possible that PPI act either on signal transduction pathway or translocation and conformational changes of CD 11/CD 18 complex[80]. Activation of transcription factor, nuclear factor kappa B and synthesis of mRNA is required for the expression of ICAM-1 and VCAM-1 on the endothelial cells. Possibly PPI act on signal transduction of protein synthesis of these adhesion molecules- ICAM -1 and VCAM-1[81,82]. PPI reduced the migration of neutrophils[83]. Neutrophils treated with omeprazole showed inhibited oxidative burst and also had impaired ability of phagocytosis[84]. Inhibition of vacuolar type[V type] H+ ATPase located on the leucocytes by PPI may be responsible for reduced superoxide production, inhibition of chemotaxis and degranulation[81]. PPI are proved to block V-ATPases on the leucocytes and on the endothelial cells[85-87]. Inhibition of these V-ATPases on the leucocytes and endothelial cells prevent the expression of their adhesion molecules like CD 11/CD 18 on leucocytes and ICAM-1 and VCAM –1 on endothelial cells[80,88-91]. This prevents ROS release and the adhesion of leucocytes to the endothelial cells resulting in to the prevention and progression of inflammation. In human studies PPIs like omeprazole and lansoprazole were found to decrease the number of peripheral mononuclear cells that express ICAM-1[92]. PPI may exert anti-inflammatory activity by inhibiting the production of pro-inflammatory cytokines which recruit the inflammatory cells at the site of inflammation[88,93]. PPIs have been shown to decrease the levels of IL-6, IL-8 and TNF alpha[89]. Mammalian enzyme heme oxygenase [HO] has three isoenzymes. HO-1 is one of them, which is a stress responsive protein. HO-1 plays an important role in the anti inflammatory and antioxidant effect of PPI[12]. HO-1 catalyses heme degradation, generates bilirubin having antioxidant property and CO with cytoprotective property. It was found that lansoprazole and omeprazole both induce the expression of HO-1 mRNA and protein in human endothelial cells and gastric cell lines. Thus PPI regulate HO-1 expression and its up-regulation[12]. Keap-1 and Nrf-2 have a role to play in the lansoprazole induced upregulation of HO-1. Nrf-2 is a key regulator of adaptive response to oxidative stress[94-97] and of the transcriptional activation of ho-1 gene[98]. Common mechanism involve for the stress response element [StRE]/Nrf-2 transcription pathway for the gene regulation in response to various HO-1 inducers. Lansoprazole mediated upregulation of HO-1 was Nrf-2 dependent and was also due to increased binding of Nrf-2 to StREs[99]. MAP kinases have important role in upregulation of HO-1 induced by lansoprazole. HO-1 induction can take place by multiple protein kinase pathways such as MAP kinase, protein kinase C and p38 MAP kinase. Experimental studies indicated that HO-1 upregulation by lansoprazole was partly mediated by ERK pathway[100,101]. Thus lansoprazole exerts anti-inflammatory effect through HO-1 upregulation. Phosphorylation of ERK, Nrf-2 activation, nuclear translocation of Nrf-2 and oxidation of Keap-1 are involved in the lansoprazole induced HO-1 upregulation. Nuclear translocation of Nrf-2 and StRE binding of Nrf-2 upregulate HO-1 mRNA leading to upregulation of HO-1 protein reuptake resulting in to anti inflammatory effect[99]. The potential benefits of anti inflammatory action of PPI may be considered in treating inflammatory diseases, intestinal or extra intestinal, unrelated to acid–pepsin etiology. Eosinophilic esophagitis was successfully treated by PPIs[102] and now PPIs are recommended for the treatment of eosinophilic esophagitis[103-105]. Effect of esomeprazole was studied in lung inflammation and fibrosis. It was observed that along with anti inflammatory and antioxidant effect as described earlier, it was also suggested to have anti fibrotic, anti proliferative and anti apoptotic effect. Anti fibrotic effect was thought to be mediated by upregulation of HO-1[12,106], down regulation of DDAH activity and down regulation of inducible NOS[iNOS][107,108]. The other contributing factors for this effect are down regulation of TGF –beta machinery [TGF betaR1 and TGF beta R2]and also down regulation of MMPs and fibronectin[109]. Upregulation of HO-1 and increased CO levels were also responsible for anti proliferative and anti apoptotic actions of PPI[12,106]. Anti apoptotic effect was also attributed to the down regulation of p53 and up regulation of chitinase-3 like -1[CHI 3L1][109].

Role of PPI in the treatment of malignancy

Modification of cellular pH by the action of PPI on vacuolar H+ATPases [V-ATPases] of the malignant cells has been proposed modality to treat malignancy and to prevent the chemoresistance. V-ATPases are the large multi unit proton pumps distributed within the plasma membrane and membranes of some organelles such as lysosomes, endosomes and secretary vescicles of many cells including tumor cells[110]. Their function includes acidification of lysosome, endosome and phagosome compartments and also extracellular environment of the cell and to keep cytosolic pH around 7[111,112]. This pH regulation is essential for regulation of physiological functions of the cells[111-113]. It is now confirmed that V-ATPase is responsible for carcinogenesis, growth, progression, invasion and metastasis of cancer. Hence inhibition of V-ATPase becomes an important target for cancer chemotherapy[114]. Agents altering tumor pH homeostasis exert antitumor activity by inhibiting tumor growth, its metastasis and by reverting chemoresistance[115-118]. Mammalian V-ATPase is composed of V1 and Vo domain.[113, 119] V1 governs ATP hydrolysis and Vo by trans membrane transport of protons, keeps extracellular milieu and lysosomal pH acidic and intracellular cytosolic pH alkaline around 7[111-113]. In the tumor cells the energy generation shifts from oxidative phosphorylation to aerobic glycolysis known as Warburg effect, creating

intracellular acidosis which is not conducive for the cell survival and can result in to self digestion of the cell[120,121]. Hence for their survival and for protection from self digestion and apoptosis, protons need to get extruded to maintain cytosolic pH between neutral to alkaline[121-123]. V-ATPase plays a major role to maintain this pH.[124] Suppression of this proton extrusion by inhibition of V-ATPase makes tumor cell more susceptible to cell death and apoptosis, as was found in various human cancer cell lines like liver cancer,[125] breast cancer[126], gastric cancer[127] and B cell hybridoma cells[128,129]. Inhibition of V-ATPase will decrease cytosolic pH and increase lysosomal pH affecting lysosomal function and resulting in to apoptosis through lysosomal mediation. This can be also due to increased lysosomal pH and permeability, triggering the release of cathepsin D and activation of caspase[127]. Inhibition of V-ATPase suppresses anti apoptotic Bcl-2 and Bcx-L and facilitate caspase dependent apoptotic pathway[130]. Inhibition of V-ATPase initiates apoptosis due to accumulation of reactive oxygen species[ROS][131,129]. V-ATPase are known to regulate tumor associated m-TOR [mammalian target of rapamycin][132], Notch[133,134] or Wnt[135,136]. V-ATPase is required for the activation of Notch which is common hallmark of increasing numbers of cancers[137,138]. The invasive nature of malignancy is correlated with highly active V-ATPase causing activation of proteases and breaking down of the extracellular matrix. Tumors like melanoma[139] pancreatic cancer[140] and breast cancer[141,142] are correlated with this phenomenon. Extracellular acidic pH of malignant cells along with activated proteases also activate cathepsin, metalloproteases and gelatinase, which in turn activate other proteases and matrix metalloproteases causing invasion[143-145]. The plasma membrane V-ATPase gets recruited at the proceeding edge of the cancer cells which interacts with F-actin to produce acidic microenvironment at the edge. Intracellular V-ATPase also helps in invasion and metastasis by shifting the proteases containing secretory vescicles to the cell surface to be exocytosed. Acquired multi drug resistance [MDR] limits the therapeutic potential resulting in to relapse.MDR is correlated with the family of ATP binding cassette [ABC] proteins –P glycoprotein and V-ATPase. Inhibition of V-ATPase directly suppresses the tumor cells and sensitize them to chemotherapy and reverses the chemoresistance[146]. It is documented that pretreatment with PPI like omeprazole sensitize the tumor cells for cisplatin, 5-flurouracil and vinblastin along with enhanced cytosolic retention of these drugs[147]. The drugs which are known to change tumor pH are prone to be having antitumor effect by reverting drug resistance and inhibiting tumor growth and metastatic progression. Hence these have become suitable therapeutic adjuncts. Several studies have shown that PPI like omeprazole, esomeprazole and pantoprazole have anti neoplastic activity against human haemopoetic and solid tumors.PPI being pro drugs get activated in tumor cell acidic pH. Treatment with PPI changes tumor pH gradient leading to drug retention and traffick of acidic vescicles in human melanoma and gastric carcinoma.PPI have shown to decrease chemoresistance in the drug resistant tumors and can induce direct tumor cell killing[13,129]. Hence PPI have been proposed as valid and feasible approach with relatively low toxicity and potential selectivity for tumor cells. Chemically modified omeprazole containing NAC molecule [NACO] to increase its bioavailability has been shown to induce apoptosis in human melanoma[148,149]. Thus inhibition of V-ATPases of malignant cells by PPI inhibited tumor growth and proved to revert the chemoresistance.

Effects of PPI on gut microflora

Normally gastric acid kills the ingested microbials and limits their transmission to the intestines. By blocking gastric acid secretion, PPI increase the concentration of organisms in the stomach, oral cavity and upper small intestine and in the lungs through acid reflux[150,151]. But PPIs are also known to act on bacterial cell membrane H+ATPase and block them. They inhibit their growth and even can kill some of the organisms like Helicobacter pylori, streptococci, lactobacilli, candida albicans and s cerevisiae[14,151,152]. Thus, effect of PPI on organisms could be pro inflammatory in some parts of the gut and anti inflammatory in others. Lansoprazole when tried on rhinovirus infected human tracheal epithelial cell culture, was found to inhibit this infection by reducing ICAM-1 and by reducing the endogenous production of IL-1 beta and also by blocking the entry of rhinovirus RNA in to endosomes[89]. Lansoprazole was found to have intracellular activity against m. tuberculosis. Lansoprazole kills the tubercular bacilli by targeting their cytochrome bc1 complex by intracellular sulfoxide reduction of lansoprazole to lansoprazole sulfide. This novel class of cytochrome bc1 inhibitor is highly active against drug resistant clinical isolates and spares the human H+K+ATPase. This provides an excellent opportunity for targeting the major pathogen M. tuberculosis.

CONCLUSION

PPIs along with being gastric acid anti secretary drug have got pleiotropic benefits beyond acid control. These include anti inflammatory, antioxidant, and antidiabetic. They also have role to play as an adjunct in the treatment of neoplastic disorders and in the prevention of chemoresistance. PPIs have been used to treat tumors of breast, liver, stomach and melanomas. Recently their role as an antidiabetic is very much highlighted by many studies conducted on type 2 DM patients, which showed positive results, where pretreatment levels of blood sugar and of HbA1c were high and uncontrolled. For this anti diabetic effect various mechanisms have been put forth. Although PPIs promise to be potential anti diabetics, a prospective, long term, randomized, double blind and placebo controlled studies are required to confirm this effect in a large number of patients with type 2 DM.

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