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Research Article

Antimicrobial Properties of Proton Pump Inhibitors

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ABSTRACT
Proton pump inhibitors [PPI] are acid activated pro drugs which convert in to sulfenic acid and then in to tetracycline sulfenamide in the acidic pH of parietal cell canaliculi. They block H+K+ATPase proton pumps and reduce gastric acid secretion. They are used to treat acid peptic disorders and NSAID induced gastric mucosal injury. Activity of PPI against Helicobactor pylori [H.pylori] is proved undisputably. Lansoprazole is the most effective PPI against H.pylori due to its unique chemical structure.PPI inhibit urease activity of H. pylori. They affect respiration and energy metabolism of these organisms as result of decreased ATP synthesis. Structural similarity of benzimidazole PPI with imidazole like metronidazole and tinidazole may contribute for their antibacterial property. Omeprazole and lansoprazole have been found to have anti fungal activity by inhibition of fungal H^+K^+ATPase-vacuolar ATPase which are essential for fungal survival and to carry out essential physiological functions, the inhibition of which leads to fungicidal action. Recently anti tubercular action of lansoprazole was highlighted which is attributed to its intra mycobacterial sulfoxide reduction to lansoprazole sulfide. This acts on mycobacterial cytochrome bc1 complex and inhibits ATP synthesis and compromises energy metabolism threatening its survival. Cytochrome bc1 of plasmodium also forms a drug target for lansoprazole. Thus, lansoprazole can emerge as a potential drug to treat MDR tuberculosis and malaria. Antiviral action of lansoprazole was noted against rhinovirus. Gram positive and negative organisms other than H.pylori were found to be inhibited by omeprazole in vitro. But this is not supported by in vivo studies.

Keywords: antimicrobial, antitubercular, H pylori, proton pump inhibitors.

INTRODUCTION

Proton pump inhibitors [PPIs] are weak bases and consists of two moieties. One of it is substituted pyridine with primary pKa of about 4.0 which helps for its selective accumulation in the secretary canaliculus of parietal cells. Other being benzimidazole with second pKa of about 1.0. PPIs are acid activated pro drugs which convert in to sulfenic acid and then in to tetracyclic sulfenamide. The gastric P type parietal cell H^+K^+ATPase-proton pump- is the primary target for the PPIs. Activated sulfenamide react co-valently with one or more cysteine accecible from luminal surface of the ATPase. This co-valent binding makes their inhibitory effect to last longer than their plasma half life-Hit and run drugs[1-3].

PPIs are most commonly preferred drugs to treat acid peptic disorders like duodenal ulcer, gastric ulcer, gastro oesophageal reflux disorders and NSAID induced gastric mucosal injuries. They are used in combination with antibiotics like amoxicillin and clarithromycin in the treatment of Helicobactor pylori [H. pylori] infection eradication[4]. PPIs also have antioxidant[5], anti inflammatory[6,7] and anti diabetic actions[8]. PPI have been used to reduce chemoresistance in the treatment of malignancy[9]. Thus, PPIs have pleiotropic benefits.

Recently their antimicrobial actions are getting highlighted. They are proved to be effective in the treatment of H. pylori infection. PPIs are considered to be effective in fungal[10] and viral infections[11]. Latest evidence suggests the role of PPI like Lansoprazole in the treatment of Myocobacterium tubercolosis[MTB] infection[12].

Effect of PPIs on H. pylori infection

H. pylori is a gram negative, urease positive, curved or spiral bacterium which colonises on the human gastric mucosa and damages it by release of cytotoxins.[13] They were first isolated by Warren and Marshall in 1983 from gastric mucosae of patients of gastritis.[14] H. pylori is the principal cause of gastritis and peptic ulcer and also predisposes to gastric carcinoma[15-17]. Benzimidazole PPIs like lansoprazole and omeprazole bind to gastric parietal cell proton pumps, inhibit them and reduce gastric acid secretion[18]. Lansoprazole and its analogues inhibit H. pylori growth selectively. Other bacterial species are not affected by lansoprazole even at higher concentrations[19].

Possible mechanisms for action of lansoprazole on H. pylori are as follows

PPI induced increase in gastric pH and reduced gastric juice volume enhances the effect of co- administered antibiotics like amoxicillin and clarithromycin by

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increasing their concentration in the reduced gastric juice[20].

It is also thought that lansoprazole and omeprazole inhibit the urease activity of H. pylori. H. pylori produce large amount of urease which help the bacterium to survive in the acidic environment of the stomach[21].

H. pylori is a microaerophilic bacterium having strict respiratory form metabolism and also oxidizes organic acids as an energy source[22]. When H. pylori cells were incubated with lansoprazole, their cellular ATP levels were decreased in dose dependent manner. This reduction in ATP levels by lansoprazole was attributed to the inhibition of ATP synthesis as result of respiratory inhibition. Lansoprazole inhibited cellular respiration of endogenous substrate[23]. H. pylori does not have complete tri carboxylic acid cycle[24]. Organic acids like pyruvate, succinate, isocitrate and alpha ketoglutarate are metabolised by H.pylori which form the respiratory substrates[22]. The respiratory pathways for pyruvate or alpha ketoglutarate and succinate differ in H. pylori. In H. pylori, alpha ketoglutarate and pyruvate get dehydrogenated by different dehydrogenase system. Two step system which generate NADPH appear to be present in H. pylori. Alpha ketoglutarate and pyruvate may get oxidized with flavodoxin and this flavodoxin is responsible for reduction of NADP. The enzyme system corresponding to complex III is present in H. pylori. The main inhibitory target of lansoprazole is NADPH quinine oxidoreductase system corresponding to complex-I, though it might inhibit the ketoacid dependent NADPH reduction.[23] Pyruvate appears to be the main substrate for energy production in H. pylori[25].

Antimicrobial activity of PPI may be due their structural similarity with imidazole like metronidazole and tinidazole[26,27].

PPIs with substituted benzimidazole derivatives who have pyridine ring which show significant activity against H. pylori. But there were significant differences in their potential. This was related to their structure activity relationship. Substitution at the number 4 of pyridine ring with fluroalkoxy exhibited several times more antibacterial activity. Presence of trifluroethoxy group at C4 position of pyridine ring in lansoprazole makes it more potent antibacterial agent against H.Pylori than omeprazole. Lansoprazole was found to have no antibacterial activity against other bacteria except H. pylori[19].

Effect of PPI on fungal infection

Candida albicans is the most frequent fungal pathogen causing hospital acquired blood stream infections[28]. Usually it is a harmless commensal in the oral cavity, genital regions and digestive tract of healthy people and sometimes associated with superficial infections. Entry of pathogen in the blood stream is facilitated by tissue damage or by the formation of fungal biofilms on the medical implants or devices resulting into sepsis and organ failure. This is more common in immunocompromised patients or in those who are undergoing immunosuppressive therapy[29]. C. albicans exists either in unicellular yeast or filamentous hyphae form. Yeast form is non pathogenic and hyphael form being virulent induces host tissue damage and invasion[30]. Serine aspartyl proteinases and lipases secreted by c.albicans are involved in nutrient acquisition, immune invasion and host cell degradation[31]. Other c. albicans virulence pathways include iron acquisition from hemoglobin, protection against reactive oxygen species, expression of adhesion molecules and formation of biofilms. These pathways help in host cell invasion and provide protection against the host immune response[32].

H^+K^+ATPase located in the vacuolar organelle are vacuolar V-ATPases. V-ATPase pumps are molecular proton motors with multi subunits responsible for active transport of protons and hydrolysis of ATP. Energy arising out of ATP hydrolysis is needed for proton transport. This is required for acidification of intracellular compartment like golgi apparatus, endosomes and lysosomes[33,34]. V-ATPase redistributes protons from cytosol to the acidic organelle lumen and maintain their PH homeostasis. V-ATPase also contribute to regulation of cytosolic pH in fungi[35]. In fungi plasma memebrane proton transporter Pmalp regulates cytosolic pH by pumping protons out of the cell in to the extracellular space to maintain cytosolic pH ranging from neutral to alkaline and extracellular acidic[36]. Pmalp expression and activity gets upregulated during filamentation of fungi like c.albicans[37,38] which correlates with their virulence. Germ tube formation which is the precursor step to hyphae formation needs alkaline cytoplasm[10, 39,40]. V-ATPase is known to regulate Pmalp activity in fungi like saccharomyces cervisiae [s.cervisiae] [41,35,42].

Vacuolar pH contributes for virulence and physiological function of c.albicans. Maintaining proton gradient across vacuolar membrane is essential for cellular metabolism, receptor mediated endocytosis, intracellular membrane trafficking, protein degradation and pro-hormone processing. It is also responsible for the uptake of small molecules and storage and detoxification of metabolites and ions[43]. Activation and secretion of proteinase and lipase virulence factors depends on optimal vacuolar pH[31]. Some aspartyl proteinases and lipase secreted by c. albicans are also involved in acquisition of nutrients, immune invasion and host cell degradation[31]. V-ATPase is highly conserved across species and best characterized in fungus like s.cervisiae. But mammals differ from fungi in the isoform composition of 14 sub units and in the complex disassembly regulation[44]. These differences could be used for selectivity of V-ATPase as a target of antifungal drug which would not affect human V-ATPases. V-ATPase proton transport requires structural and functional coupling of domain V1 which is peripheral with the domain V0 which is embedded in the membrane[45,34].

Various structural changes have taken place in V-ATPase from fungi to human in the process of evolution for e.g c ring of all fungal species contain three sub units V_oc, V_oc', V_oc''. But mammal c ring lacks the V_oc' subunit which is specifically found in fungi[46]. In the process of evolution human V-ATPase have developed multiple isoforms for V1 and V0 subunits which are tissue and membrane specific[47,48, 49].

Pharmacological inactivation of V-ATPpase pumps of fungi change both extra and intracellular pH which disturbs important cellular processes like protein processing and sorting, protein secretion, zymogen activation, vesicular membrane trafficking, receptor mediated endocytosis and autophagy[33,34].

Thus acting on fungal V-ATPases PPI compromise on nutrition, vital physiological functions and development of virulent form of fungi resulting in to inhibition of fungal growth.

Thus, plasma membrane H^+K^+ATPase forms a molecular target for antifungal drug therapy and inhibition of their enzyme activity correlates with cell growth inhibition. PPI like omeprazole was found to inhibit growth of c.albicans as a result of Inhibition of H^+K^+ATPase[38,50]. In a study conducted by Sivoshi F (2012) lansoprazole showed weak fungicidal activity requiring 24 hours to reach their desired antifungal activity. Lansoprazole also had antifungal activity against c.tropicalis and c. spp[51].

Anti tubercular activity of PPI

Multi drug resistant [MDR] tuberculosis is the major concern in the field of treatment of tuberculosis. Despite therapeutic advances in the treatment of tuberculosis, it continues to be the major cause of morbidity and mortality. Overall success rate in the cure of tuberculosis is not very promising [about 48%] due to lack of effective regimens, fast development of drug resistance and the failure on patients part to complete the prescribed chemotherapy of tuberculosis. Co-existing immunocompromised conditions like HIV infection complicates the prognosis[52]. Hence the drug resistant pathogens require development of newer effective drugs to overcome the resistance.

Lansoprazole [LPZ], a gastric proton pump inhibitor, was found to have intracellular anti tubercular activity. LPZ is a pro drug which is relatively unstable gets converted in to its analogue lansoprazole sulfide [LPZS] intracellularly by sulfoxide reduction through enzymatic or non enzymatic reactions. LPZS is a highly stable metabolite. In conducted studies, it showed highly M.tuberculosis selective antimicrobial action without affecting Gram negative and Gram positive organisms. Cytochrome bc1 [complex III] is an essential respiratory chain component which is required for ATP synthesis. Ratio of ADP/ATP in LPZS treated mycobacterium was about 7 fold more than in those of LPZS untreated mycobacterium. LPZS prevents the generation of ATP from ADP by acting on bc1 cytochrome complex and thus disrupts the mycobacterial respiratory chain, challenging its viability[12]. Cytochrome b subunit of the cytochrome bc1 complex-QcrB- was identified as drug target of mycobacterium tuberculosis[53]. QcrB is a putative ubiquinol cytochrome c reductase [sub unit B] an integral member of the bc1 complex of the respiratory electron transport chain[54]. QcrB forms the target protein for the action of LPZS. QcrB is an emerging, highly vulnerable target for M.tuberclosis and LPZS represents a novel class of QcrB inhibitors. LPZS is highly safe and promising anti tubercular lead compound which does not inhibit gastric H^+K^+ATPase. Thus differential pro drug activation of LPZ in gastric parietal cells [sulfenic acid and sulfenamide intermediates]and myocobacterial host cells [sulfoxide reduction of LPZ in to LPZs] makes LPZS as a novel, specific and highly effective anti tubercular drug[12].

Thus targeting bc1 complex and QcrB of M.tuberculosis is the new mechanism of action of anti TB drugs along with existing mechanisms like inhibition of mycolic acid synthesis, arabinoglycan, DNA dependent RNA polymerase, peptide synthesis and binding to DNA gyrase.

Anti malarial action of PPIs

Drug like atovaquone and several other anti malarial drugs target the cytochrome b of plasmodium. Despite the presence of human mitochondrial orthologues, targeting the parasitic cytochrome bc1 complex is quite safe[55]. Recently it is observed that LPZ is a potent inhibitor of plasmodial growth only when they have infected metabolically active liver cells. It is likely that intracellular sulfoxide reduction results in to anti plasmodial activity[56]. Thus, PPI like LPZ becomes an important pharmacological tool to control malaria and tuberculosis, both being very important causes of mortality.

Anti viral action of PPI

When LPZ was tried on the rhinovirus infected tracheal epithelial cell culture, it inhibited this infection by reducing ICAM-1 and by reducing endogenous production of Interleukin-l beta and also by blocking the entry of rhinovirus RNA in to endosomes[11].

Antibacterial action of PPIs on other bacteria

Antibacterial effect of omeprazole was observed in vitro to be more effective on the inhibition of Gram positive bacteria like enterococcus fecalis and staphylococcus aureus than on Gram negative bacteria like E.coli and K.pneuminae[57]. Variation in the action of omeprazole on these bacteria could be explained on the basis of the number or accessibility of SH group and cysteine content in them which are located in the outer membrane proteins of bacteria. Also, a degree of cysteine dependence of these bacteria governs the growth inhibition of these organisms by omeprazole[58]. Antibacterial actions of PPI on other bacteria in vivo studies are not very significant.

CONCLUSION

PPI are extensively used due to their safety profile in acid peptic disorders and in NSAID induced gastro intestinal injuries. The beneficial effects of these drugs to treat H. pylori infection is proved beyond doubt. They also have been found to possess antifungal, antiviral and in vitro antibacterial properties. Pro drug lansoprazole gets converted in to lansoprazole sulfide within mycobacteria, which has been found to inhibit bacterial cytochrome bc1 complex ,reduce ATP synthesis and affects its energy metabolism. This results in to mycobacteriocidal activity. Lansoprazole was observed to have anti plasmodial action by same mechanism as that in mycobacteria. These beneficial actions of lansoprazole on mycobacterium and plasmodium makes it a promising drug to treat MDR tuberculosis and malaria. Further studies regarding the actions of lansoprazole and its metaoblites or derivatives would prove as boon in the treatment of drug resistant tuberculosis and malaria.

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