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RECENT ADVANCES IN FORMULATION AND DEVELOPMENT OF PROTON PUMP INHIBITORS

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INTRODUCTION

Peptic ulcer is a chronic disease that affects about 10% of total population in the world. Ulcer is an acid-induced lesion of the gastrointestinal (GI) tract which causes an open and painful sore. Peptic ulcers are mainly arisen in stomach or proximal duodenum.[1] *Helicobacter pylori* (*H.Pylori*) play an important role in the pathogenesis of peptic ulcer mainly involving antral mucosa or muscularis propria. The human immune system is incapable to eradicate this infection without affecting the antibody production. As a result, the bacterium can consequently lead to form a chronic active gastritis. It may cause an increase in gastrin production or more frequently gastrin formation may hamper. Gastrin increase the production of gastric acid formation and *H.Pylori* increases the gastrin formation by colonization. These excess amounts of acid formation lead to erosion of mucosal membrane, which leads to formation of ulcer. The use of non-steroidal anti-inflammatory drugs (NSAIDs) are the another major causative reason for ulcer formation. The gastric mucosa itself protects with a layer of mucus from gastric acid. Mucus secretion is inspired by the prostaglandins. Cyclooxygenase is the main source for production of prostaglandins. Which function is blocked by the using of NSAID .The duodenal ulcers has decreased significantly in last 30 years, while the incidence of gastric ulcer is increase in last few years due the use of NSAIDs. Younger patient with ulcer treated with antacids or H2 antagonists. Patients those are taking nonsteroidal anti-inflammatory also prescribed with prostaglandin analog to prevent peptic ulcer.

Most effective treatments for *H.Pylori* infection are combination of two antibiotics with one proton pump inhibitor. In intricated cases, three antibiotics and proton pump inhibitors used for the treatment of ulcer. Ulcer treatment generally clears the *H.Pylori* and relieves the symptoms.[2]

GASTRO OEOSOPHAGEAL REFLUX

Overtime, gastro esophageal reflux disease (GERD) and peptic ulcer (PU) rarely diagnosed among the most frequently diagnosed diseases.[3] This disease is very common in developed countries, affecting 18-27% of the North Americans, 23% of South Americans, 8-25% of Europeans, 11% of Australians, and 2-7% of eastern Asians.[4] This high frequency effect not only quality of life but also economy of the country. The high number of GERD in the USA may arrived 9-10 billion dollars in direct cost per year.[5] Approximately 50 million Americans notice heartburn two or three days per week.[6]

Gastro esophageal reflux disease (GERD) is such a condition, which develops when the reflux of stomach contents causes uncomfortable symptoms and complications.[7] Although GERD increase esophageal injury, which leads to damage in structure. The symptoms for GERD include chronic cough, hoarseness, asthma and dental erosion.[8]

The mucosal inflammation formed due to injury into the tight junction proteins in the esophagealepithelium which increased permeability in Para-cellular and dilated intracellular space (DIS).With DIS, toxic agents (gastric acid, bile, and pepsin) entire into deep basal layers of esophageal mucosa which produce damages in esophagus through the toxic agent. This inflammation may act on nociceptors to produce symptoms.[9, 10, 11, 12,13]

Esophageal mucosa has three different protective barriers such as pre-epithelial, epithelial, and post- epithelial layer. Pre-epithelial defense is producing very minute amount of mucus by esophagus but it contains protective agent like prostaglandin E2, epidermal growth factor, transforming growth factor-A, mucin. In three instances epithelial defense consists of dealing with hydrogen like (a) prevented from entering the cells; (b) Once inside the cell, buffer it with bicarbonate, protein and phosphate; (c) cell membranes move from the cell to the ion

transport mechanism (i.e., the Na+/H+ exchanger and the Na+ dependent Cl-/HCO3-exchanger). Bicarbonate obtained from capillaries neutralized blood born acid that helps in post epithelial defense.[14, 15,16]

PROTONS PUMP INHIBITOR

Since 1980s, Protons pump inhibitor was first introducing in and have been the cornerstone for acid suppression.[17] The Food and Drug Administration (FDA) in USA[18] and the national institute for clinical excellence (NICE) in UK[19] published guidance on the use of PPIs in the following well-defined indication.

1. Healing of erosive esophagitis and maintenance of this healing.
2. GERD with its various clinical manifestations (non-erosive reflux disease =NERD, ascertained extra esophageal symptoms, esophageal strictures and Barrett's esophagus).
3. Treatment of *H.Pylori* infection in combination with antibiotics.
4. Short term treatment of *H.Pylori* negative peptic ulcer and maintenance of healed ulcer.
5. Non-steroidal anti-inflammatory drug (NSAID) induced dyspepsia.
6. Healing of NSAID associated gastric ulcer.
7. Risk reduction of NSAID associated gastric ulcer.
8. Pathologic hypersecretory conditions (Zollinger-Ellison syndrome=ZES).
9. Critically ill patients on prolonged mechanical ventilation.
10. Short term treatment with regular review of patients with functional dyspepsia.

Proton pump inhibitors mainly inhibits gastric acid secretion. Meta-analysis of PPIs founds that there is negligible difference in efficacy between PPIs in the anticipated therapeutic effect.[20]

The first PPI is Omeprazole that was available in 1989, simultaneously Lansoprazole (1995), Rabeprazole (1999), Esomeprazole (2001), Pantoprazole (2002), Dexalnsoprazole (2009) were arrived. The PPIs are most effective and safe in treating of GERD, peptic ulcer and other acid related disorders. The PPIs impact the management of acid related disorders in last few years. This development is due to some changes in PPIs from the initial to make them more clinically efficient.[21]

All the PPIs are mainly benzimidazole derivatives. Mainly these agents decrease the gastric H+K+ adenosine triphosphate part of the proton pump by selectively and irreversibly blocking.[22]

All PPIs undergo acid accumulation and acid activation and inhibit the H+K+ ATPase pump via covalent binding. There are two types of acid dissociation constant (PKa) present for PPIs. The pKa for first type leads to accumulation of PPIs in the parietal cell (pKa1) where the pH ranges from 3.8-4.5. The selective accumulation of PPIs in parietal cell occurs where the pH is below four depends on pKa1 of pyridine ring by which it influences the pKa1 are similar among the PPIs.[23]

There is no large range in pKa1 value but difference in pKa1 value within PPIs can affect their operation. For example, Lansoprazole and Rabeprazole have the same benzimidazole group which structurally different in their pyridine ring alternatives. In such cases, a higher pKa1 value related to the greater nucleophilicity of the pyridine mutation and may therefore convert to the active from of the drug. However, when the benzimidazole of PPI activation in the parietal cells. For this step pKa value (pKa2) is<1, occurring rapidly in the acidic space of the parietal cell or on the surface of the active acid producing H+K+ -ATPase pump (pH-0.8). The comparison of Lansoprazole and Pantoprazole serves to illustrate the effect of pKa2 on the activation rate, as these two PPIs have similar pKa1 (3.83).Value pKa2 of Lansoprazole (0.62) is higher than Pantoprazole (0.11), pKa1 affects PPL activation rate of current PPIs generally depends on the second protonation, pKa2, especially acidic conditions. Selective synthesis of PPIs in the parietalcell and the requirement for acid activation confirm that gastric acid excretion is stimulated whenthe modification of the voluntary in excited highly acidic conditions is specific to activated H+K+ ATPase pump. PKa2 as a key determinant of activation rate also thought to have an impact on the stability of gastric acid emission.[24]

Proton pump inhibitor form a covalent bond with cysteine residues of proton pump to inhibit the H+/K+-ATPase pump and cause prolonged inhibition of gastric acid secretion. All proton pump inhibitor undergo acid accumulation in the parietal cell through protonation, followed by activation mediated by a second protonation at the active secretory canaliculus of the parietal cell.[25]

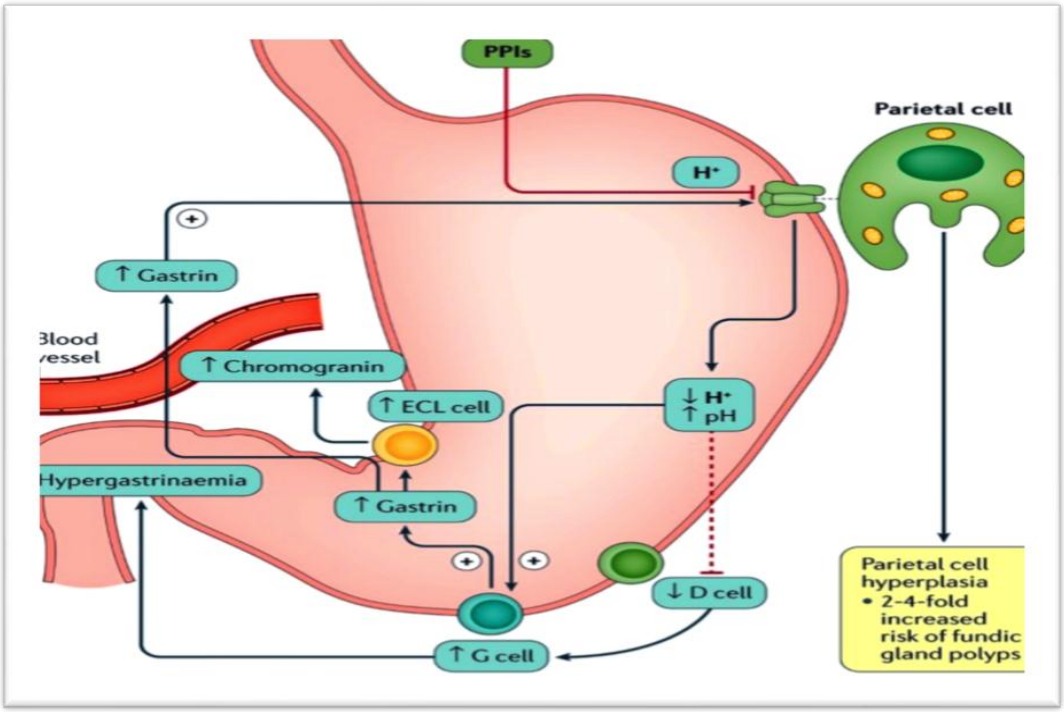

Figure.1: Effect of proton pump inhibitors on gastro physiology.

The ease with which these steps take place with different proton pump inhibitors depends on the difference in their activation rate, which in turn affects the position of the covalent binding and the barrier stability. Slow activation involves the involvement of cysteine residues involved in proton transport located deep in the membrane. However, it is accessible to the endogenous reducing agents responsible for restoring H+/K+-ATPase activity, based a longer duration of gastric acid inhibition.[26]

PHARMACOKINETICS OF PPIs

The maximum plasma concentration (C_{max}) of PPIs depends upon the rate of passage in the gastrointestinal tract, release of drug and intraduodenal pH.

PPIs are slow to achieve stable state resistance to gastric acid and take about 3 days to repress most acid.

The area under the plasma concentration time curve (AUC) correlates with acid suppression, and the area under the same curves for Rabeprazole 20mg or 40mg, Omeprazole 20 mg are lower than the Pantoprazole 20mg and Lansoprazole 30mg.

PPIs have very short plasma half-life of elimination, which allows it for rapid restoration of gastric acid secretion of uninhibited proton pumps. The duration of acid inhibition is relatively long because irreversible binding of the sulphanilamde to the H+K+ ATPase pump.

Different PPIs having different oral bioavailability (BA).Incase of Omeprazole the oral BA is initially low may be 35-40% but it increases to about 65% on repeated dosing. Pantoprazole has constant BA of 77%. Lansoprazole have also high BA of 80-91% at independent of dose. All PPIs are highly protein bound and rapidly metabolized in the liver and have negligible renal clearance.[27,28 & 29]

ANTI-ULCER DRUGS CLASSIFICATION[30]

Classification	Drugs
1.Reduction of Gastric acid secretion	
Histamines (H2) antagonist	Cimetidine, Ranitidine, Famotidine, Roxatidine
Proton Pump Inhibitors	Omeprazole, Esomeprazole, Lansoprazole,Pantoprazole, Rabeprazole, Dexrabeprazole
Anticholinergic drugs	Pirenzepine, Propantheline, Oxyphenonium
Prostaglandin analogue	Misoprostol, Rioprostol, Enprostil
2.Neutralisation of Gastric acid	
Systemic	Sodium bicarbonate, Aluminum hydroxide gel
Non systemic	Magaltrate, Calcium carbonate
3.Ulcer Protective agent	Sucralfate, Colloidal bismuth subcitrate
4. Anti H-pylori drugs	Amoxicillin, Clarithromycin, Metronidazole,Tinidazole

MEDICINAL PLANTS HAVING ANTI-ULCERPROPERTY.

Common Name	Botanical Name	Part Used	Effects	Reference
Tulsi	*Ocimum Sanctum*	All parts	Antiulcer, Antibacterial	[31]
Tippani	*Allophylus serratus*	Leaves	Antiulcer	[32]
Shaparni	*Desmodium gangeticum*	Root extract	Inflammation, typhoid, Anti ulcer	[33]
Neem	*Azadirachta indica*	Dried Bark	GIT disorder	[34]
Indian Sarsaparilla	*Hemidesmus indicus*	Extract of leaves	Anti-diarrheal, Anti- Ulcer	[35]
Satavari	*Asparagus racemosus*	Root extract	Anti-diarrheal, Anti- Ulcer	[36]
Triphala	*Terminalia pallid*	Plant extract	Anti-ulcer	[37]
Aamala	*Embilica officinalis*	Fruit extract	Anti-ulcer	[38]
Gotu Kola	*Centella asiatica*	Fresh juice	Anti-ulcer	[39]
Brahmi	*Bacopa monniera*	Fresh juice	Anti-ulcer	[40]
Apple Bananas	*Musa sapientum*	Fruits	Anti-ulcer	[41]
Pappeta	*Carica papaya*	Seeds	Anti-amoebic, Anti-Ulcer	[42]
Pausanto	*Kielmeyera coriacea*	Steam	Anxiolytic, Anti-ulcer	[43]
Brindle Berry	*Garcinia cambogia*	Fruit extract	Anti-ulcer	[44]
Winter Melon	*Banincasa hispida*	Fruits	Anti-ulcer, epilepsy	[45]
Wild Pipal	*Ficus arnottiana*	Fruits	Anti-ulcer, Demulcent	[46]
Indian devil tree	*Alstonia scholaris*	Whole plant	Anti-ulcer	[47]
Indian mulberry	*Morinda citrifolia*	Fruit	Anti-ulcer, Anti-diabetic	[48]
Indian borage	*Plectranthusamboinicus*	Whole plant	Diuretic, Anti-ulcer	[49]
Babul	*Acacia Arabica*	Leaves, Gums	Ulcer, Wound	[50]
Boabab	*Allium sativum*	Leaves and bark	Anti-ulcer, syphiliticulcer, irritable inflammatory ulcerdisease	[51]
Bael tree	*Aegle marmelos*	Fruits	Anti-ulcer	[52]
Kattalai	*Aloe vera*	Leaves and power	Anti-ulcer	[53]
Custard apple	*Annona squamosal*	Leaves	Anti-ulcer	[54]
Kannchanara/ Orchid tree	*Bauhinia variegate*	Bark and roots	Anti-ulcer	[55]
Indian or Nepalarberry	*Berberis aristata*	Root and wood	Anti-ulcer	[56]
Beetroot	*Beta vulgaris*	Roots	Anti-ulcer	[57]
Slow match tree	*Careya arborea*	Leaves, Steam andbark	Anti-ulcer	[58]
Arasha maram	*Ficus religiosa*	Bark and leaves	Anti-ulcer	[59]
Garlic	*Allium sativum*	Bulb juice	Anti-ulcer	[60]

RESEARCH ARTICLES FOR FORMULATION ANDDEVELOPMENT OF PPIs.

Sl No	Name of formulation	Method	Reagent	Reference
1.	omeprazole	UV-Vis spectrophotometry	colored species in reaction with 3-methyl-2-benzothiazolinone hydrazone (MBTH)	[61]
2.	lansoprazole	LC-MS/MS	mobile phase water:acetonitrile with 0.1% formic acid (60:40); IT-TOF detection; linearity in the range of 5.0–25.0 µg/mL	[62]
3.	rabeprazole	LC-ESI-MS/MS	LC mobile phase methanol:water (50:50) with addition of 0.1% of formic acid in water; transition m/z 359.95→241.96; linearity in the range of 0.2–200 ng/mL	[63]
4.	dexrabeprazole sodium	RP-UPLC	UV-Vis detection at λ = 284 nm; mobile phaseA—phosphate buffer (pH = 7.0):acetonitrile (99:1) and mobile phaseB methanol:acetonitrile (95:5) (gradient elution)	[64]
5.	lansoprazole	RP-HPLC	UV-Vis detection at λ = 284 nm; mobile phase methanol:water (80:20); linearity in the range of 50.0–30.0 µg/mL	[65]

CONCLUSION

Antacids use as Proton pump inhibitor. PPIs have demonstrated superiority over all previously prescribed medications, including H2-antagonists. The main difficulties with PPI medication were long-term acid suppression and Gastroesophageal reflux disease. The pharmaceutical companies can apply this technology to additional PPIs as a delivery platform, supplying generic-formulated medications and promoting patient compliance. The new development is immediate release omeprazole formulation and Dexlansoprazole MR dual delayed release. Dual delayed release is more advantageous technology and make PPIs more affordable.

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