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Updates in Drug Development Strategies against Peptic ulcer

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Introduction:
An ulcer occurring in the lower end of oesophagus, in the stomach usually along the less curvature and in duodenum is known as peptic ulcer or duodenal ulcer. It is associated with symptoms including epigastric gnawing, heart burn, acid eructations, nausea, vomiting, belching, bloating, anorexia, haemorrhage and anaemia. Peptic ulcer occurs due to an imbalance between mucosal damaging (acid, pepsin) and protecting (mucus, bicarbonate, Prostaglandin E2 and I2) mechanisms. Acid secretion is a physiologically important process of the stomach as gastric acid induces pepsinogen activation to initiate digestive process and kills bacteria and other microbes ensuring a stable intragastric environment. There are three endogenous secretagogues called positive regulators of acid secretion. They are acetyl choline, histamine and gastrin. Prostaglandins (PG E2 and I2) act as negative regulators of acid secretion. An imbalance in these regulators leads to peptic ulcer. Another cause of Peptic ulcer is the Helicobacter pylori infection. This infection has no direct role but can induce the immune system which results in superficial gastritis and when it becomes chronic it gradually results in peptic ulcer. The secretion of gastric acid occurs at the level of parietal cells of oxyntic glands in the gastric mucosa, producing 2-3 liters of gastric juice per day (HCl of pH 1). Based on the involvement of multiple factors in peptic ulcer, several therapeutic strategies have been adopted against it. These, include suppression of the aggressive factors with use of antacids, specific antagonists of muscarinic -M1 receptors, gastrin receptors, histamine-H2 receptors, proton pump inhibitors (PPIs), mucoprotective agents, eradication of H. pylori and analogues of prostaglandins. Research for development of antiulcer agent, aims to address one or the other of these issues.

Objectives:
Therapeutic strategy for treating ulcer at the molecular level generally involves reducing acid secretion by inhibiting receptors/ mediators at the initial level, intermediate level and final level of acid secretion. In the initial level, the strategy aims to reduce secretion by preventing stimulation to transmitters including histamine, acetylcholine and gastrin. The intermediate level mainly involves interference on the role of carbonic anhydrase in promoting acid secretion. In the final stage it is the proton pump (H+ K+ ATPase) which has been the target for inhibition to reduce acid secretion.

Results:
Inhibition of H+/K+-ATPase as a means of controlling gastric pH has attracted considerable attention in recent years with the discovery of benzimidazole sulfoxide class of antisecretory agents. Timoprazole, as one of the first well-defined inhibitor of gastric proton pump which was followed by more potent picoprazole and omeprazole. Chemically, the basic structure consists of substituted benzimidazole ring and a substituted pyridine ring connected to each other by a methylsulfinyl chain. Clinically used PPIs include Omeprazole, Lansoprazole, Rabeprazole, Pantoprazole and Esomeprazole. Irreversible inhibition of H+/K+-ATPase occurs following acid activation of these compounds within the acidic compartments in the parietal cells and covalent binding, with C813 residue of gastric H+/K +-ATPase. The draw backs relating to use of irreversible proton pump inhibitors includes extreme acid suppression sometimes leads to achlorohydria at recommended doses and that may produce enteric infections like typhoid, cholera, and dysentery. Significant drug interactions can lead to decreased absorption of some drugs like griseofulvin, ketoconazole, vit.B12, iron salts. Other side effect includes abdominal pain, diarrhea, nausea, and headache. Acute interstitial nephritis progressing to acute renal failure has also been reported to be associated with the use of PPIs. Prolonged inhibition of gastric acid secretion has been associated with the formation of precancerous changes in human gastric mucosa and gastric carcinoids in long term animal studies.

So the research efforts are currently targeting to obtain reversible proton pump antagonists. Imidazopyridine based compound SCH28080 was the prototype of this class and the anti-secretory effect of this compound is mediated through gastric proton pump. SCH 28080 is a protonable weak base (pKa -5.6); hence like omeprazole it accumulates in the acidic compartments of the parietal cells in its protonated form. SCH 28080 is chemically stable even after protonation, is itself active and does not need an acid-induced transformation, as required by omeprazole and its congeners. SCH28080 binds non- covalently with gastric H+/K+-ATPase but was withdrawn due to serious hepatotoxicity.

Conclusions:
The growth of peptic ulcer disease with time is complex and interesting. Although its incidences were rare before 1800 century, with time and change in life style its incidences have increased significantly. Several therapeutic strategies have evolved over time for its management. However, considering the involvement of multiple factor in its etiology, it has not been possible to provide an ideal solution to completely cure its occurrence. Traditional use of antacids and use of histamine inhibitors have become insufficient in the management of peptic ulcer. Irreversible inhibition of proton pump although reduces ulceration, in the long run leads to adverse issues. It has not been possible to develop an ideal proton pump inhibitor. In this scenario, search for alternatives by capitalizing on the multifactorial etiology of ulceration holds promise. However, these searches are far from over and require further investigations to develop ideal antiulcer agents.