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REVIEW ARTICLE **OPEN ACCESS**

Emerging Role of Novel Anti Ulcers in Treatment of Gastric Diseases

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ABSTRACT
Over the last 25 years, a remarkable revolution in the pathophysiology and treatment of gastric and duodenal ulcers has occurred. Effective therapies were developed not only to heal ulcers but also to cure most patients. The two principles cause for gastric and duodenal ulcers are either infection with Helicobacter pylori or the use of non-steroidal anti-inflammatory drugs (NSAIDs). With H. pylori eradication, gastric and duodenal ulcers are rapidly becoming historical diseases. This communication reviews the salient pharmacology of the novel anti-ulcer drugs currently in development, with particular emphasis on the treatment of gastric and duodenal ulcers. Intense research is currently focused on the development of proton pump inhibitors primarily for the treatment and prevention of gastroesophageal reflux disease. The older proton pump inhibitors, omeprazole and lansoprazole, are effective in healing gastric and duodenal ulcers. Furthermore, both drugs are effective in eradicating H. pylori when given with various antibiotics. Pantoprazole, rabeprazole and esomeprazole are new proton pump inhibitors, which appear to have comparable therapeutic profiles with omeprazole and lansoprazole. Rebamipide is a new mucosal protective drug, which is effective in healing gastric ulcers. Polaprezinc and nocloprost are also mucosal protective drugs, which are in clinical development. However, none of these three cytoprotective drugs have been evaluated for their efficacy in eradication H. pylori when given in combination with antibiotics. With the rapid eradication of H. pylori currently happening in the developed world, the therapeutic challenge is now directed towards preventing NSAIDs from an associated ulcer. A significant reduction of NSAID-induced ulcers is achieved by using continuous prophylactic anti-ulcer therapy (Misoprostol or omeprazole).
Keywords:- physiology of gastric acid secretion, factors affecting gastric acid secretion, novel antiulcer drugs.

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INTRODUCTION

The gastric ulcer in the length of the gastrointestinal tract which is exposed or infects to gastric acid (stomach) and pepsin (duodenum). Gastric ulcer produce by the imbalance between aggressive factors (increases of acid, pepsin, *H. pylori*) and the defensive factors (decreases in bicarbonate, gastric mucus secretion, nitric oxide, prostaglandin, innate resistant of mucosal cells) to produce an ulcer.[1-3]

A hole in the lining of the stomach corroded by the acidic digestive juices which are secreted by the stomach cells. Ulcers formation is related to *H. pylori* bacteria in the stomach and anti-inflammatory medication.

Physiology of gastric secretion :

Three main factors are involved in gastric acid secretion

1) Acetylcholine (neuronal)
2) Gastrin (endocrine)
3) Histamine (pancrine)

The secretion of gastric acid is a complex and continuous process. The H+ secretion by the parietal cells. Acetylcholine, histamine, gastric they all control secretion of acid, their specific receptors are located on the membrane of the parietal cell in the body and fundus of stomach (M3, H2, CCK2 receptor respectively).

The H2 receptor of histamine is a GPCR (G-protein coupled receptor) that activates the Adenyl cyclase and adenyl cyclase increases Camp (cyclic AMP). [4-6].

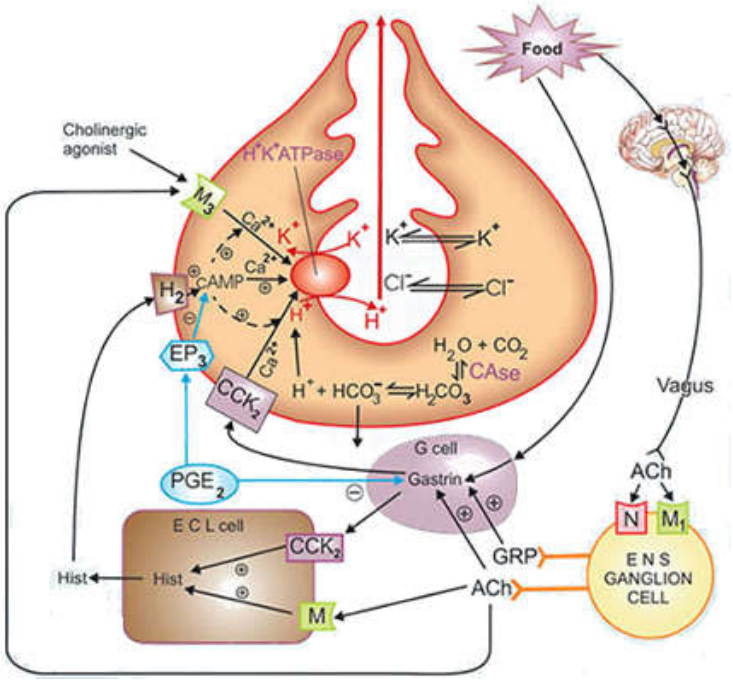


Fig. 1: Mechanism of gastric secretions

Acetylcholine and gastrin signals through GPCRs and that couple to (IP3) Ca+ pathway in parietal cells. The parietal cells in the cyclic AMP and Ca+ dependent pathway both activate H+, K+ ATPase (proton pump) which exchange H+ and K+ ions across the parietal cell membrane and secrete the acids.

Factors affecting gastric diseases:

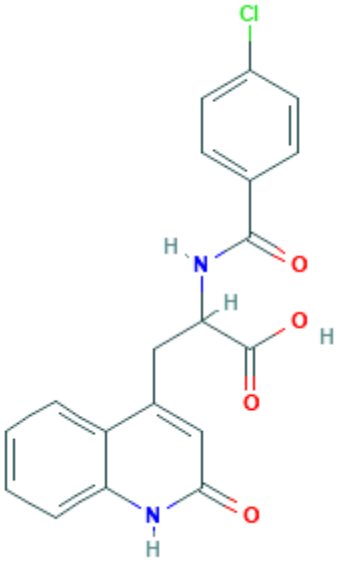
- *Helicobacter pylori* (*H. pylori*)
- NSAIDs – aspirin, ibuprofen
- Stomach cancer
- Drinking too much alcohol
- Radiation
- Gastrinoma
- Pancreatic enzyme reflux
- Staphylococcus aureus exotoxins
- Bile reflux
- Irregular meals and high intake of spicy foods [7-9]

Novel antiulcer drugs:

1) Rebamipide
2) Polaprezinc
3) Nocloprost
4) Ecabet sodium
5) Laufutidine

1) Rebamipide :

Rebamipide an amino acid derivative of 2-(1H)-quinolinone, is used for mucosal protection healing of gastroduodenal ulcers, and treatment of gastritis. It works by enhancing mucosal defense, scavenging free radicals, and temporarily activating genes encoding cyclooxygenase. Studies have shown that Rebamipide can fight the damaging effects of NSAIDs on the GIT mucosa, and more recently, the small intestine, but not for naproxen-induced gastric damage.



IUPAC Name: 2-[(4-chlorobenzoyl)amino]-3-(2-oxo-1H-quinolin-4yl) propanoic acid

Rebamipide a gastroprotective drug, is a compound selected from over 500 amino acid analogs of 2(1H)-quinolinone tested for gastroprotective action and for efficacy to heal experimental gastric ulcers. This drug stimulates prostaglandin generation in gastric mucosa and improves not only the speed but also the quality of ulcer healing. Besides, it protects the gastric mucosa against acute injury caused by various noxious and ulcerogenic factors. Based on these experimental results, Rebamipide had been subsequently tested in several clinical trials and approved in japan for therapeutic use in patients with gastric ulcers and patients with acute gastritis. The main purpose of developing this type of drug was to improve the quality of ulcer healing, especially in that antisecretory drugs lack this advantage. In a preliminary clinical study, Rebamipide improved the quality of gastric ulcer healing and reduced future ulcer recurrence. Several basic research studies have been performed to clarify the mechanisms of action of Rebamipide .these studies demonstrated unique properties of Rebamipide and convincingly showed that it increases gastric mucus glycoprotein compounds, stimulates migration and proliferation of wounded epithelial cell monolayers, increases expression of epidermal growth factor and its receptor in normal and ulcerated gastric mucosa, and scavenges active oxygen radicals. The drug also attenuates the activity of neutrophils and the production of inflammatory cytokines stimulated by NSAIDs and or *H. pylori*. Therefore, rebamipide can contribute to the management of patients who are taking NSAIDs or are infected with *H. pylori*. The inhibition of immune-inflammatory responses by Rebamipide in *H. pylori*-infected patients may prevent the development of gastritis, peptic ulcer disease, its recurrence, and possibly gastric cancer. Moreover, Rebamipide may enhance the eradication of *H. pylori*-infection using standard eradication therapy.

Indication: mucosal protective as antiulcer

Pharmacodynamic:

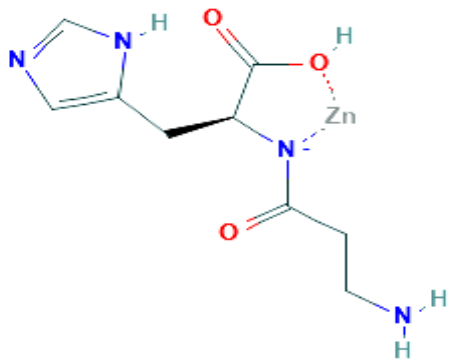
mucosal protection, healing of the gastroduodenal ulcer, it works by enhancing mucosal defense and scavenging free radicals.

Mechanism of action of Rebamipide:

The mechanism of action of Rebamipide in RAU is the preservation of existing cells and the replacement of lost tissue. The action of preservation of existing cells occurs through an increase in the content of soluble mucus, increase in the gastric concentrations of PGE2 and PGI2, downregulation of 15 hydroxyprostaglandins dehydrogenase, increase in the mucosal blood flow through enhanced nitric oxide synthase activity, decrease in the expression of neutrophil adhesion molecules (CD11b/CD18), and inhibition of the secretion of TNF-alpha by inhibiting the synthesis of inflammatory E-selectin and has a free radical scavenging effect on ROS. Rebamipide helps in the replacement of lost tissue by increasing the expression of epidermal growth factors (EGF) and EGF receptors. These EGF causes angiogenesis, increased production of granulation tissue and epithelization of ulcer healing. Rebamipide also used in the treatment of allergic conjunctivitis like VKC/AKC

Dosage: the adult dosage of rebamipide is 100 mg orally three times daily

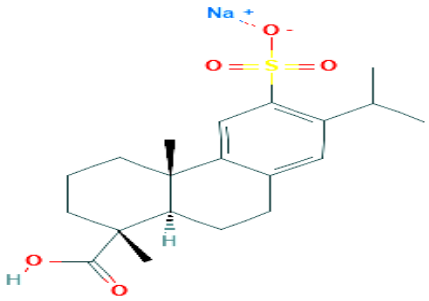
Pharmacokinetics:
The effective concentration of Rebamipide is in the range of 1-1000um. Up to 98.4% of ingested rebamipide is bound to plasma proteins. It is metabolized in the liver by the human cytochrome p450 enzyme. The cytochrome p450 enzyme acts on Rebamipide through hydroxylation and glucuronidation, resulting in the formation of 6-hydroxy and 8hydroxyrebamipide. The role of glucuronidation in the metabolism of Rebamipide is very low and nonsignificant. Drug interactions of Rebamipide with other drugs are very low and safely used concomitantly with other drugs.
Contraindication:
Rebamipide is contraindicated in patients with a known history of drug hypersensitivity.
Side effects:
Side effects seen are mild and can be corrected with dose adjustment. The common side effects noticed after Rebamipide use are gastrointestinal such as constipation, bloating, diarrhea, nausea, and vomiting. Hypersensitivity and rash were seen in <1% of patients. [10-13]
2) Polaprezinc:
Polaprezinc is a chelated form of zinc and L-carnosine. It is a zinc related medicine approved for the first time in Japan, which has been clinically used to treat gastric ulcers. It was determined that Polaprezinc may be effective in pressure ulcer treatment. A study in 2013 showed that co-administration of Polaprezinc may be effective against small intestine mucosal injury associated with long term aspirin therapy.



IUPAC Name: (4s)-3-(3-aminopropanoyl)-4-[(1H-imidazol-5-yl)methyl]-1-oxo-3aza-2-zincacyclopentan-5-one
Indication: peptic ulcer disease, dyspepsia
Pharmacodynamics:
It is used to treat/ manage peptic ulcer disease or irritation of the gastrointestinal tract by promoting tissue healing by the elimination of free radicals
Mechanism of action:
Polaprezinc increases the expression of various antioxidant enzymes, including superoxide dismutase 1 (SDO-1), SDO-2, heme oxygenase-1, glutathione s-transferase (GST), glutathione peroxidase (GSH-Px), peroxiredoxin-1 (PRDX1, PRXI) and PRXD5 (PRXV). This process occurs in the gastric mucosa, defending mucosal cells against reactive oxygen species. This drug inhibits the activity of the transcription factor nuclear factor-kappaB (NF-kB) and decreases the expression of various inflammatory cytokines including interleukin (IL) 1beta, IL-6m IL-8 and tumor necrosis factor-alpha (TNF-a). Polaprezinc also promotes the expression of numerous growth factors, including as platelet-derived growth factor-B(PDGF-B), vascular endothelial growth factor (VEGF), and nerve growth factor (NGF), in addition to various heat shock proteins (HSPs), including HSP90, HSP70, HSP60, HSP47, HSP27, and HSP10. This process promotes tissue growth and protects against damage the gastric mucosa.
Dose: the typical clinical oral dose is 150 mg/day, containing 34mg zinc and 116mg L-carnosine.
Pharmacokinetic: NA
Contraindication: Severe renal impairment, hypersensitivity to nitrofurans, G6PD deficiency, infants <3 month. Pregnancy at term, during labor and delivery, or when the onset of labor is imminent.
Side effects: nausea, vomiting, anorexia, abdominal pain, diarrhea, headache, drowsiness, vertigo, dizziness. [14-16].

3) Ecabet:

Ecabet is a prescription eye drop for the treatment of dry eye syndrome. Ecabet represents a new class of molecules that increases the quantity and quality of mucin produced by conjunctival goblet cells and corneal epithelia. Mucin is a glycoprotein component of the tear film that lubricates while retarding moisture loss from tear evaporation. Ecabet is currently marketed in Japan as an oral agent for the treatment of gastric ulcer and gastritis.



IUPAC Name: (1R,4aS,10aR)-1,4a-dimethyl-7-(propan-2-nyl)-6-sulfo-11,2,3,4,4a,9,10,10a-octahydrophena nthrene-1-carboxylic acid

Ecabet sodium, a dehydroabietic acid derivative from pine resin has been used clinically for the treatment of gastritis and gastric ulcer. Ecabet is a locally acting anti-ulcer agent with a high affinity for the stomach wall. It has also been shown, in animal experimental models of colorectal cancer, that ecabet sodium may slow the development of the mucosal dysplasia-invasive adenocarcinoma sequence. Ecabet is believed to exert its effect through a series of mechanisms.

1) Anti-bacterial effects. Triple therapy with amoxicillin, ecabet and a proton pump inhibitor effectively eradicated *H. pylori*. Ecabet prevents the survival of *H. pylori* in the stomach via inhibition of essential urease activity and inhibits the adhesion of *H. pylori* to gastric epithelia.

2) Enhanced mucosal protection and repair. Ecabet stimulates re-epithelization after mucosal damage and binds strongly to the gastric mucus layer.

3) Inhibition of pepsin activity. Ecabet binds to and precipitates pig pepsin and, by coating the mucus gel, can prevent its mucolytic by pepsin.

Ecabet sodium is a mucosal defensive agent. It is very safe and is in wide use as a locally acting antiulcer agent in Japan. Oral ecabet sodium has a high affinity for the gastric mucus and epithelial cells. Ecabet has been reported to prevent ulcer formation caused by various irritants that induce gastric mucosal damage, and to enhance gastric mucosal resistance by increasing mucus and HCO3 secretion and mucosal prostaglandins in animal models. Ecabet sodium is also reported to protect the integrity of the gastric mucosal gel layer. Urease is essential for *H. pylori* at pH 5, which is the optimal pH for urease. Ecabet sodium also exhibited a dose-dependent and rapid bactericidal effect against *H. pylori* in an acidic environment, although it did not affect the viability of H pylori in a neutral environment. Because the bactericidal effect of ecabet can be seen in the absence of urea, antiurease and antiATPase actions are considered to be involved in these bactericidal effects in an acidic condition.

H. pylori is a major cause of histological gastritis, gastric ulcer, duodenal ulcer, gastric carcinoma, and gastric mucosa-associated lymphoid tissue lymphoma. Treatment for *H. pylori* infection is available worldwide for the first-line therapy of peptic ulcer disease and low-grade gastric mucosa-associated lymphoid tissue lymphoma.

Indication: for the treatment of reflux oesophagitis and peptic ulcer disease.

Mechanism of action:

Ecabet reduces the survival of *H. pylori* in the stomach and inhibits pepsin activity in the gastric juice of experimental animals. Here we have investigated the effects of ecabet on some of the factors involved in the dynamics of the mucosal barrier, i.e. pepsins and mucins. Pepsin, acid and *Helicobacter pylori* are major factors in the pathophysiology of peptic ulcer disease and reflux oesophagitis. Ecabet also acts as an inhibitor of *H. pylori* NADPH oxidase as well as urease inhibition of these enzymes prevents bacterial adhesion to the gastric mucosa. [17-19]

CONCLUSION

The therapeutic importance of novel anti ulcers in the treatment of peptic ulcer or gastric ulcer and gastritis is highlighted. These drugs show anti-*Helicobacter pylori* activities. For eradication of peptic ulcer or gastritis one should avoid the NSAIDs, high intake of alcohol, irregular foods and spicy foods etc.

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