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Prostaglandins in Gastroduodenal Mucosal Protection and Peptic Ulcer Therapy: A Comprehensive Review

S. Anand*[*1], V. Arunachalam[2], Dr. G. Mariyappan[3], Dr. J. Karthi[4]

[1]Bachelor of Pharmacy, Pallavan Pharmacy College, Kanchipuram.
[2]M.Pharm., Pallavan Pharmacy College, Kanchipuram.
[3]M.Pharm., Ph.D., Professor in Department of Pharmaceutics, Pallavan Pharmacy College, Kanchipuram.
[4]M.Pharm., Ph.D., Principal, Pallavan Pharmacy College, Kanchipuram.
Email ID: anandanand6841@gmail.com

ABSTRACT:

The development of peptic ulcers involves a delicate balance between aggressive factors like gastric acid and pepsin, and protective mechanisms mediated by prostaglandins. These natural compounds play a key role in safeguarding the gastroduodenal mucosa and facilitating healing by promoting the secretion of bicarbonate and mucus, and supporting the health of gastrointestinal epithelial cells. Reducing gastric acidity through acid inhibition is crucial for ulcer healing, but other processes like cytoprotection and mucosal defense also contribute to the recovery process. Some medications, such as NSAIDs, can cause mucosal damage by disrupting prostaglandin synthesis, underscoring their importance in maintaining gastroduodenal mucosal integrity. Although synthetic prostaglandin analogues have been developed for medical use, their effectiveness has been limited, and further study is needed to understand how they work and determine their potential benefits in treating peptic ulcers.

Keywords: Gastric acid secretory inhibition, Cytoprotection, Peptic ulcer, Peptic ulcer haemorrhage, Prostaglandin analogues.

Introduction:

Peptic ulcer disease is a complex and multifaceted condition characterized by an imbalance between aggressive factors and defensive mechanisms. Despite advances in medical treatment, current therapies, including H2 receptor antagonists and proton pump inhibitors, have limitations, with a significant proportion of ulcers persisting or recurring. Prostaglandin analogues offer a fresh perspective ontreatment by preserving gastroduodenal mucosa integrity, reducing gastric acid secretion, and promoting mucus and bicarbonate secretion. The concept of cytoprotection[(4)], where prostaglandins shield the gastric mucosa through acid-independent mechanisms, is a key aspect of their therapeutic potential. Prostaglandin analogues have shown promise in facilitating ulcer healing, stopping acute bleeding, and preventing rebleeding in peptic ulcer disease, making them a promising therapeutic option for managing this condition. This review aims to summarize the current evidence on the efficacy and clinical relevance of prostaglandin analogues in peptic ulcer disease, highlighting their potential benefits and limitations[(1)].

Ulcer:

Our understanding of the pathophysiology of peptic ulcers is still based on the oversimplified theory that they are caused by an imbalance between defensive and aggressive elements[(5)]. Relieving symptoms and avoiding complications like bleeding, perforation, and blockage are the goals of treatment for peptic ulcer disease. Despite the fact that the effectiveness of the existing medical treatment consensus has been questioned[(3)].

Figure 1. Peptic ulcer

The development and application of H2-receptor antagonists, which block the formation of acid by acting on the gastric parietal cell, significantly changed the way peptic ulcer disease is treated. Both ranitidine and cimetidine are currently prescribed all over the world, and their safety and effectiveness have been verified by a large number of controlled studies and a wealth of clinical experience. Other strong inhibitors of stomach acid output have recently been created and are presently being tested in clinical settings. These include new substituted imidazole H2-receptor antagonists that have longer half-life than ranitidine, prostaglandin (PG) analogues (PGE derivatives), and substituted benzimidazoles like omeprazole that reduce the production of gastric acid by blocking the parietal cell of H+/K+-ATPase[(1)].

Prostaglandin:

Lipid-based substances called prostaglandins influence a variety of physiological functions and work similarly to local hormones. They are crucial for maintaining the integrity of the duodenal and stomach linings and are important for preventing and curing peptic ulcers. These substances aid in the defenses of the gastrointestinal system, and their absence can result in ulcer development.Peptic ulcer disease can now be treated medically with synthetic prostaglandin (PG) analogues of the E class. By reducing acid secretion, increasing mucus and bicarbonate secretion, and regulating mucosal blood flow, PG are thought to preserve the integrity of the gastric mucosa[(3)].

Cell protection:

"Cytoprotection" refers to PG ability to shield the mucosa through processes other than acid secretion[(3)].The discovery that exogenous prostaglandins shield the stomach mucosa via mechanisms other than acid inhibition gives rise to the idea of cytoprotection[(2)]. "Cytoprotection" refers to an agents capacity to stop mucosal damage caused by harmful substances at non-antisecretory dosages. Both in humans and experimental animals, therefore it is called as "adaptive cytoprotection" has been shown to occur when PG production is triggered in response to a local irritation[(1)]. This phrase refers to prostaglandin relative ability to prevent mucosal injury when taken in dosages that do not reduce stomach secretion[(5)].Although they are currently marketed for the treatment of peptic ulcers due to their cytoprotective qualities, which are attained at lower dosages, the synthetic PG analogues currently being evaluated are delivered in acid inhibitory doses[(3)].

Biosynthesis of PG:

This phrase refers to prostaglandin relative ability to prevent mucosal injury when taken in dosages that do not reduce stomach secretion[(5)]. Although they are currently marketed for the treatment of peptic ulcers due to their cytoprotective qualities, which are attained at lower dosages, the synthetic PG analogues currently being evaluated are delivered in acid inhibitory doses[(3)].

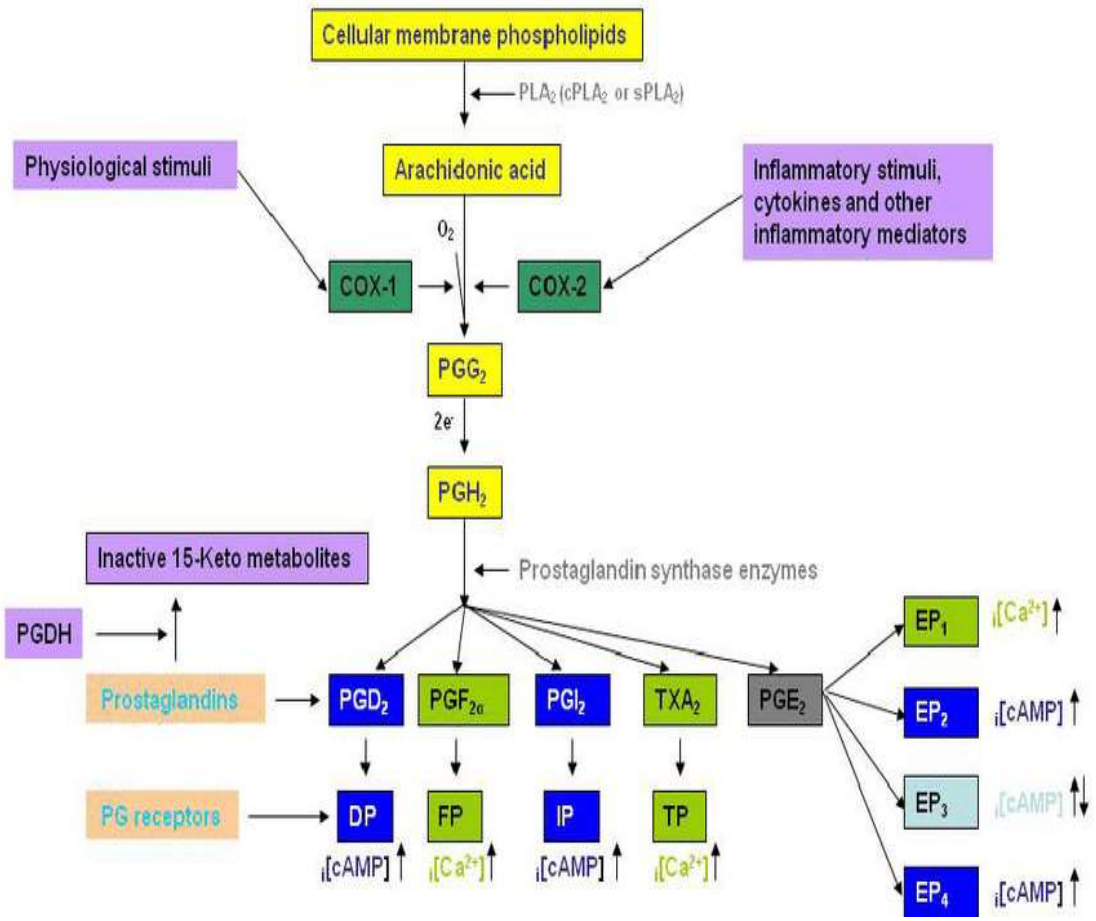

Figure 2. Biosynthesis of PG

Benefits of PG:

Gastric acid secretion is inhibited by a number of natural prostaglandins, especially those in the E series. The discovered PGE and PGEz analogues are strong inhibitors of acid secretion at a location near or at the parietal cell's adenylate cyclase. The largest potential benefit of these medicines is the protective nature of the analogues that have been evaluated in gastric injury models, when paired with gastric secretory inhibition[5]. In addition to having several additional effects on platelet, blood vascular, uterine, and bronchial function, many natural prostaglandins, especially those of the E series, also block the release of stomach acid[4].

Prostaglandins also have a role in cell kinetics, renal function, and inflammatory mediation. In addition to their antisecretory action, these medications also have "cytoprotection. The analogues that have been evaluated in gastric injury models are protective, and their greatest potential benefit is when they combine cytoprotection with stomach secretory suppression. They accomplish this by boosting the stomach's synthesis of bicarbonate and protecting mucus. They can also prevent ulcers brought on by NSAIDs or other conditions, as well as aid in the healing of ulcers that do not respond to other treatments[4].

Ulcer-related GI bleed:

A number of uncontrolled observations have indicated that PG analogues may have a therapeutic impact in bleeding peptic ulcers and acute hemorrhagic gastritis. In order to determine if arbaprostil, 50 mg taken orally four times a day for seven days, is effective in halting severe acute bleeding from erosive or ulcerative lesions of the stomach and duodenum and avoiding rebleeding, we conducted a prospective double blind, placebo controlled experiment.

The observed difference between arbaprostil and placebo in terms of halting bleeding within 48 hours had a 95% CI ranging from 6% for arbaprostil to 38% for the placebo. The same interval showed that the frequency of rebleeding varied from 6% in favor of arbaprostil to 32% in favor of a placebo. As a result, arbaprostil is unlikely to significantly impact the prognosis of individuals experiencing acute bleeding from duodenal or stomach ulcerative lesions. Additionally, it has been demonstrated that antacids are more effective than arbaprostil at preventing gastrointestinal bleeding in patients in intensive care units[3].

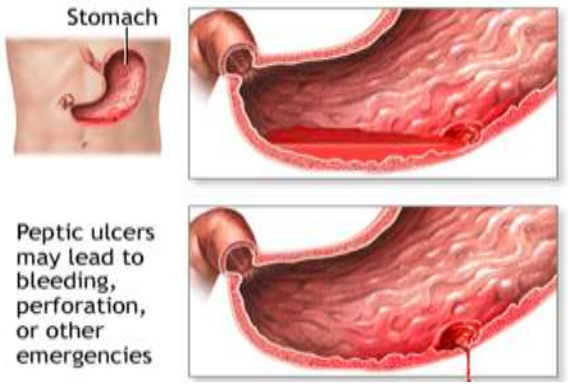

Figure 3. Peptic ulcer bleeding

Role of PG in peptic ulcer disease:

The argument that prostaglandins through cytoprotection offer a significant benefit over current first-line therapy for peptic ulcer healing is not supported by the findings of the trials mentioned. Instead, they are, if anything, less successful. The most frequently reported adverse effects are stomach pain and diarrhea. Although the incidence and severity of these effects varies from research to study, they are typically minor and infrequently result in patient withdrawal. If the medications were very effective, a frequency of diarrhoea (loose or more frequent than normal passage of stool) of 8% with misoprostol and between 10% and 18% with enprostil might be acceptable. Compared to the anticipated decrease observed following ranitidine, patients frequency of abdominal discomfort, which cannot be differentiated from ulcer pain, appeared to increase after beginning enprostil[(4)].

E-type prostaglandins special qualities, which combine stimulatory actions on mucosal factors with antisecretory effects on stomach acid, should make them ideal for treating mucosal lesions in the upper gastrointestinal tract. Therefore, natural PG and PGE analogues have been used to treat peptic ulcers, prevent NSAID-induced mucosal damage, and treat acute gastrointestinal bleeding. Below is a review of the literature on clinical trials using E type prostaglandins[(6)].

Stomach acid production:

The process by which specialized cells called parietal cells, which are found in the stomach lining, release hydrochloric acid (Hcl) into the stomach cavity is known as gastric acid secretion. A crucial component of gastric juice, this hydrochloric acid aids in digesting. It aids in the breakdown of food particles, produces the acidic environment required to transform pepsinogen into the protein-digesting enzyme pepsin, and acts as a defensive mechanism by eradicating or suppressing dangerous germs consumed with food. To preserve digestive effectiveness and shield the stomach lining from harm, the release of gastric acid is strictly controlled by neurological, hormonal, and chemical changes[(2)].

Peptic ulcer recovery:

It remains uncertain whether orally effective doses of PGE_2 have antisecretory effects in humans, but synthetic prostaglandin (PG) analogues clearly do. The PGE_1 and PGE_2 analogues currently in clinical trials. These compounds are among the most potent known antisecretory agents, based on the minimal doses needed for significant activity. At doses recommended for ulcer treatment, enprostil, and possibly arbaprostil, offer a combination of acid inhibition similar to conventional doses of cimetidine, cytoprotection (such as shielding the antral mucosa from aspirin-induced injury), and suppression of food-stimulated gastrin release. This combination of effects suggests they could be ideal anti-ulcer drugs. Given this, it would be expected that enprostil at antisecretory doses would promote rapid healing of duodenal ulcers. To evaluate this, we conducted a double-blind randomized trial comparing enprostil (35 µg twice daily) with ranitidine (150 mg twice daily) over a maximum of 6 weeks in 180 patients with endoscopically confirmed duodenal ulcers. Patients exhibited the study if their ulcer had healed and their pain was relieved within 2 to 4 weeks[(4)].

However, the enprostil group required longer treatment durations ($P < 0.05$), the cumulative healing rates were significantly higher in the ranitidine group on all study days ($P < 0.05$), and more patients treated with ranitidine experienced pain relief ($P < 0.05$). This superiority of ranitidine was unexpected, since enprostil (35 µg twice daily) has been reported to be as effective or even superior to cimetidine (600 mg twice daily) in acid suppression. Thus, any therapeutic effect of enprostil is likely due to its antisecretory action, rather than to any cytoprotective effect at lower doses. These results raise doubts about the short-term clinical relevance of the cytoprotective properties of anti-ulcer medications. Likewise, other double-blind comparative trials in duodenal and gastric ulcer healing most of which were multicenter and international have not shown PG analogues to be superior to H_2-receptor antagonists, even at antisecretory doses. Their effectiveness appears to correlate with their ability to inhibit acid, and the use of doses that are cytoprotective but not antisecretory usually leads to healing rates not significantly better than placebo[(3)].

Clinical applications of PG:

Naturally occurring PGs are rapidly metabolized when taken orally, which may cause abdominal cramps, diarrhea, and uterine contractions. Therefore, to produce PGs that are therapeutically helpful, structural and chemical modifications are required. To increase pharmacologic specificity, potency, and duration of action, several PG analogues have been developed[(1)]. Prostaglandin analogs are employed in many clinical contexts, primarily in ophthalmology and gastrointestinal disorders. In gastroenterology, they are used to treat persistent constipation and to shield the stomach lining when undergoing ulcer treatment. Numerous prostaglandin analogues have been created and are employed in a variety of medical fields. Analogs such as misoprostol, a prostaglandin E1 analogue, are used in gastroenterology to preserve the gastric lining by lowering the generation of gastric acid and increasing the secretion of mucus and bicarbonate. Because of this, they are very useful in treating and preventing stomach ulcers brought on by NSAIDs. Because of their stimulatory effects on intestinal motility, certain analogues are also used as laxatives to treat persistent constipation[(3)].

In ophthalmology, glaucoma and ocular hypertension are frequently treated with prostaglandin analogues such latanoprost, travoprost, and bimatoprost. They reduce the risk of optic nerve damage and vision loss by boosting the outflow of aqueous fluid from the eye, which lowers intraocular pressure.Because they can promote uterine contractions and cervical ripening, some prostaglandin analogues, such as dinoprostone and misoprostol are used in obstetrics and gynecology to induce labor, control postpartum bleeding, or end pregnancies. All things considered, prostaglandin analogues have emerged as crucial medicinal substances with specific uses, providing better safety and effectiveness profiles than their native equivalents[(4)].

Conclusion:

Research suggests a distinct role for prostaglandin analogues in preventing gastrointestinal damage, though their impact on the healing process is less clear. These compounds may aid in ulcer recovery by reducing gastric acid secretion, but there's limited evidence to support additional cytoprotective benefits. Existing anti-ulcer treatments are often just as effective with fewer adverse effects, making these compounds a secondary choice. More investigation is required to explore their potential in mitigating NSAID-induced damage. While they may provide an alternative therapeutic approach to managing peptic ulcer disease, it's unlikely they will replace established gastrointestinal medications as the primary option.

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