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Review on Chronopharmacology of Peptic Ulcer

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ABSTRACT

Chronopharmacology is the exploring of effect of drug in consequences with the body`s biological rhythm, hormone and enzyme which enhances the effect of drug to treat the disease. Peptic ulcer is the lesion situated in the gastrointestinal mucosa which causes stomach pain due excess secretion of gastric acid. By using chronopharmacology the amount of production of acid secretion is reduced and suitable drug effect is achieved. By application of chronopharmacology Prompt diagnosis and treatment of gastric ulcers and their consequences are important to reduce morbidity and mortality.

Introduction:

Peptic ulcer disease is lesions located in gastroduodenal mucosa which causes stomach pain. By using chronopharmacology the amount of production of acid secretion is reduced and suitable drug effect is achieved. Peptic ulcer is disease of gastrointestinal tract in which perforation of mucosal membrane occurs in stomach and duodenal region due to aggressive factor like excessive acid secretion and *Helicobacter Pylori* and Defensive factor like decrease in mucin, prostaglandin, bicarbonate [1][2].

There are various forms of ulcer which include Zollinger Ellision Syndrome (ZES), stress induced ulcer, chronic gastric ulcer, drug induced ulcer. Peptic ulcer can be hazardous with indication like bleeding stool, stomach agony and spasms alongside heaving blood [3][4].

Pathogenesis:

Peptic ulcer disease is a chronic disease with 99% ulcer occurring in the region of duodenum and stomach in gastrointestinal tract. Under normal condition physiological balance between gastric acid secretion and gastroduodenal defence is concord. Injury to mucosa causing peptic ulcer occurs with disruption of statis between aggressive factor and defensive mechanism [5].

Hypersecretory acid environment mixed with dietary and stress are one of the major roots for the peptic ulcer disease. Prostanoid subordinates emerge from the transformation of arachidonic acid by cyclo-oxygenase (COX) isoenzymes following cell damage. There is a range of COX-1 and COX-2 restraint over the class of NSAID's [6]. H. Pylori have high urease movement which produces smelling salts to shield it from acidic condition in gut. It It induces an inflammatory response in the gastric mucosa and further develops an influx of lysosomal proteins, leukocyte influx, and neutrophil and macrophage influx which hampers the mucosal resistance of the mucosal coating [7][8].

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Aggressive Factor

- *Helicobacter Pylori* infections
- NSAIDS
- Corticosteroids
- Alcohol
- Smoking

Defensive Factors

- Surface mucus secretion
- Bicarbonate secretion into mucus
- Mucosal blood flow
- Apical epithelial cell transport
- Elaboration of prostaglandins

Physiological changes occurring in stomach

- Increased gastric acidity
- Impaired defenses
- Ischemic shock stress related (gastric ulcer)
- Delay gastric emptying (gastric ulcer)
- Duodenal gastric reflux (duodenal ulcer)

Associated disease

- Liver cirrhosis
- Renal failure
- Chronic pancreatitis
- Zollinger ellison syndrome
- hyperoarathyroidism

Peptic ulcer types:

• Duodenal ulcer Most common peptic ulcer Typically located in the proximal duodenum Multiple ulcers and/or ulcers distal to the second portion of the duodenum raise clinical suspicion of gastrinoma (Zollinger–Ellison syndrome)
• Gastric ulcer Generally, NSAID'S are not in use gastric ulcer is seen along the lesser Curvature of antrum.
• Esophageal ulcers Present at the distal esophagus, usually secondary to gastroesophageal reflux disease Seen also with gastrinoma
• Ectopic gastric mucosal ulceration Can develop with Meckel diverticulum

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Treatment:

Types of drugs	Mode of action	Practised
H2 receptor antagonists (roxatidine, cimetidine, famotidine, nizatidine, ranitidine)	Acid inhibition	H. pylori-negative stomach ulcer; Replaced with PPIs due to their inferiority in acid suppression.
PPI (rabeprazole, pantoprazole, lansoprazole, esomeprazole omeprazole)	Most potent acid inhibition	Standard treatment for all H. pylorinegative lesions, wound prophylaxis, NSAID or aspirin, is a key component of an eradication plan. Administered intravenously in bleeding wounds.
Prostaglandin analogues (misoprostol*)	Increase mucosal resistance; weak acid inhibition	H. pylori-negative stomach ulcer; protect wound caused by NSAID
H. pylori eradication regimens (PPI plus two antibiotics)	Cure of H. pylori infection	Standard treatment for all H. pylori-positive lesions
Bismuth salts (subcitrate, subsalicylate)	Weak antibacterial effect; increase of mucosal prostaglandin synthesis	In quadruple therapy to eliminate H. pylori

PPI = proton-pump inhibitor, NSAID = non-steroidal anti-inflammatory drug* Contraindicated in pregnancy

- **H2 receptor antagonists**:

These drugs work by blocking H2 receptors and thus reducing release. Stomach acid. It is very useful in reducing food-stimulated basiality by 90% and Eliminate stomach acid at night. Evidence from literature says it also helps in the prevention of gastric ulcers caused by stress. They are used in mixtures Antacids in the treatment of stress ulcers. These medications include: Ranitidine, cimetidine, famotidine and nizatidine. One of the major disadvantages is long hours of administration to treat ulcers, followed by recurrence of ulcers Recovery is a frequent complication [9][4].

- **Muscarinic receptor antagonist**:

Compared to histamine, perenzepine multicellular protection Receptor antagonists Helps prevent gastric mucinopathy Due to alcohol, sodium hydroxide (NAOH). To put it into practice those who are suppressed in the stomach have muscarinic receptors (M1) lower their groups and stimulate the secretion of acid [10][4].

- **Mucosal coating agents**:

Sucralphate is an essential sulfur disaccharide with an aluminum sulfate compound. This helps to create an adherent coating on the sites of the ulcerated mucosa. This one Pepsin works by reducing activity, absorbing bile salts and acting as a barrier to hydrogen Diffusion of ions. It also binds to both epidermal growth factor (EGF) and fibroblasts. Helps promote growth factor (FGF) and heal ulcers. It is effective in Helicobacter pylori infection [11][4].

- **H+ /K+ ATPase inhibitors**:

It acts by blocking the gastric proton pump directly instead of blocking Histamine and cholinergic receptors.There are many drugs available in this category, These are omeprazole, lansoprazole, rabeprazole and pantoprazole. They prevent the last step in the secretion of acid and thus better control of the foundation as well Nocturnal acid secretionHelicobacter is also known to inhibit the growth of Helicobacter. They are now used as a first-line treatment in the treatment of peptic ulcer. It has replaced H2 competitors [12][4].

- **Prostaglandins**:

Robert showed in 1979 that prostaglandins inhibit and help secrete stomach acid to protect against ulcers caused by nsaids, diet, alcohol, smoking, stress. Misoprostol, an analogue of prostaglandins, acts by increasing mucus secretion as well as bicarbonate and thus protects against chronic ulcers. But it only helps To protect against gastric ulcer and not duodenal ulcer. It is contraindicated in

pregnancy due to its aborted property. Enprostille, Rioprostil and Arbaprostil are other well-known compounds. Other drugs in clinical trials include Nocloprost, enisoprost and Mexiprost [13][4].

- **APPLICATION OF CHRONOTHERAPY**:

The treatment of gastric ulcers involves the use of chronotherapy, taking into account the body's natural rhythms and timing of medications to increase their effectiveness and reduce potential side effects [14][8].

➢ Optimal timing of drug administration:

- Proton pump inhibitors (PPIs):

PPI's are commonly prescribed to reduce stomach acid production and help ulcers heal. The effectiveness of PPI's may be influenced by the timing of administration. Taking ppis before breakfast or the biggest meal of the day can help suppress acid production when you need it most [15].

- H2 blockers:

Like PPI's, H2 blockers reduce the production of stomach acid. Taking these medications at bedtime may be beneficial because stomach acid production is usually greater at night. To reduce circadian rhythm disruption: Peptic ulcer and related disorders can be worsened by circadian rhythm disruptions caused by irregular sleep and shift work. Maintaining a regular sleep and eating schedule may reduce circadian rhythm disruptions and improve ulcer healing [16][17].

- Lifestyle modifications:

Adopting a healthy lifestyle that matches the circadian rhythm can have a positive effect on ulcer healing. Avoid heavy meals near bedtime, manage stress [18]. Absence of rest, inappropriate dietary patterns, alchol, smoking every one of these variables adds to this. Chronotherapy is the best alternative to bring back life on the track [19].

- Individualized Treatment Plans:

Chronotherapy acknowledges that individuals have different circadian rhythms and biological responses [8]. Tailoring treatment plans to each individual's rhythm might optimize medication absorption and healing.

- Analysis of factors affecting absorption:

Chronotherapy may involve monitoring how factors such as stomach pH and digestive system may affect drug absorption. Changing the time of taking the medicine in the same way can improve their benefits [8].

➢ CHRONOTHERAPY IN THE TREATMENT OF PEPTIC ULCER

Chronotherapy is one of the best alternatives to treat various diseases and to make life healthy [20]. Many features of the digestive system are under the biological clock rhythm: gastric acid secretion is highest at night. Small bowel and abdominal motility occur more slowly at night. Suppressing nocturnal acidity is an important factor in the duodenum Healing ulcers. So, with active duodenal ulcer once a day before bedtime is the recommended dose of H2 antagonists. Bedtime H2-receptor blockade using Chronotherapy overcome problems of sustained or profound decrease of 24-h intragastric acidity including the threat of enteric infection and infestation, potential bacterial overgrowth with possible N-nitrosamine formation [18][21].

➢ CHRONOPHARMACOLOGY OF PEPTIC ULCER DISEASE:

Gastric acid secretion:

Gastric motility is double in day time than night (morning 12.00 AM). Plasma concentration are higher in day than in night. Hepatic blood flow has been shown to be greater at 8.00am and metabolism to be reduced during the night. On an empty stomach, acid is excreted in relatively small amounts to maintain the pH in the stomach around 1.5. This low level is called basal acid secretion. A circadian rhythm of basal gastric acid secretion has been reported in healthy men with active gastric acid secretion [22][23][24].

The basal acid secretion rate is highest between 9pm and midnight. Increased acid secretion, usually associated with a transient increase in intragastric pH due to the buffering effect of food. Therefore, the pH of the stomach changes throughout the day, especially during meals [22][23][24].

At night, if there is no food, the intragastric pH remains low. Circadian changes in the rate of gastric emptying can delay the absorption of many oral medications taken at night. This delay is reflected in plasma (Cmax) and maximum plasma drug concentration (Tmax). It appears less when given at night than in the morning [25].

Conclusion:

By reviewing chrono-pharmacologic studies related to peptic ulcer, it becomes clear that the timing of drug administration can significantly affect treatment outcomes. Timed interventions to match the body's natural rhythm, such as administration of a proton pump inhibitor (PPI) during the nocturnal peak of acid secretion or the coordination of Helicobacter pylori eradication treatment with diurnal changes in bacterial activity, may improve treatment effectiveness. Could. Side effects are reduced. The review highlights the need for a personalized medication approach in peptic ulcer management, as different chronotype and environmental factors may influence response to treatment. Appropriate treatment planning that takes into account the chronobiologic profile of the patient may lead to more effective and efficient care.

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