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DRUGS THAT REDUCE GASTRIC SECRETION, THE NEED AND PROSPECTS FOR THEIR USE

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Abstract. The most common treatment for GERD is still medical therapy. Although interest in GERD drug development has decreased in recent years, mainly because most proton pump inhibitors (PPIs) have been converted to generic and over-the-counter compounds, there are still many unmet needs in GERD. Potent histamine type 2 receptor antagonists, extended release PPIs, PPI combinations, potassium-competitive acid blockers, prokinetics, mucosal protectants, and esophageal pain modulators have been the focus of drug development. It is likely that these compounds will be niched for specific unmet needs in GERD rather than competing with the currently available anti-reflux therapies. Due to their strong inhibition of gastric acid output, PPIs are frequently used to treat acid-related conditions such as gastroesophageal reflux disease and to potentially prevent ulcers caused by aspirin or NSAIDs. Like other medications, PPIs can have clinically significant side effects, however these are rarely noticed during or after treatment. PPIs are therefore thought to be clinically helpful and reasonably safe. Although PPIs' positive effects for functional gastrointestinal illnesses and primary prevention of drug-related gastroduodenal damage have not been thoroughly established, they have recently become often prescribed to patients with these conditions. Only patients who will have a significant clinical benefit should be given PPIs, and high-quality prospective studies should be conducted to further examine any negative side effects.

Keywords. Heartburn, gastroesophageal reflux, erosive esophagitis, proton pump inhibitors, gastric acid, ulcer.

Introduction. The stomach is the only organ that secretes acidic fluid as low as pH. This secretion is necessary not only for the sterilization of bacteria found in food, but also for the digestion and absorption of various nutrients, such as protein, iron, calcium, and vitamin B12. However, because secreted acid can harm the gastrointestinal tract, there are a number of protective mechanisms, such as mucosal mucous/bicarbonate secretion and sphincter contraction of the gastroesophageal junction, to prevent gastric secretion-induced gastroesophageal damage. When these protective mechanisms are compromised by acid secretion, the gastrointestinal mucosa can become irritated and damaged, leading to unpleasant symptoms or even

organic disease. These pathological conditions are known as acid-related diseases and include Barrett's esophagus, gastroduodenal ulcers, GERD, Barrett's esophagus, and functional dyspepsia [1,2,3,4]. In the United States (US), GERD is the most common outpatient diagnosis in gastroenterology, affecting 20% of the adult population weekly and 7% daily. The majority of patients with GERD fall into one of three categories: non-erosive reflux disease (NERD), erosive esophagitis (EE), or Barrett's esophagus (BE). GERD is defined clinically as at least weekly heartburn and/or acid regurgitation. Additionally, it is evident that NERD and EE react differently to antireflux medication [5-9]. Proton pump inhibitors (PPIs) and histamine type 2 receptor antagonists (H2RAs) are currently the primary medical treatment options for GERD. Although the potencies of the two medication types differ, they both work by suppressing stomach acid. Additional underlying methods for treating GERD include reducing stomach acidity (antacids), preventing or replacing gastric acid reflux by forming a foamy raft in the stomach (alginate-based formulations), and enhancing esophageal clearance and gastric emptying (prokinetics). Relieving symptoms, healing and maintaining EE remission, avoiding complications, and enhancing health-related quality of life are the primary objectives of GERD treatment [10,11,12]. Because of their strong inhibitory effect on acid release, PPIs currently provide GERD patients unparalleled clinical efficacy. The remission of esophageal mucosal inflammation, however, is far more predictable than the resolution of symptoms, even in individuals undergoing PPI medication. The response to antireflux medication varies among the various GERD phenotypes. For instance, NERD patients make up the bulk of patients with refractory heartburn because they respond to PPI medication at a considerably lower rate than other GERD categories. In gastroenterology practice today, the most frequent manifestation of GERD is failure of PPI therapy [13,14,15,16]. After beginning clinical use for the treatment of acid-related diseases, PPIs' employment increased steadily and remarkably, and they are currently among the most commonly prescribed medications worldwide, with many affected patients receiving continuous treatment with PPI administration for years. Accompanying their popularity are adverse events that may be related to long-term PPI administration, though the level of risk is low. In this review, we describe the pharmacological characteristics of PPIs and compare them with those of H2RAs, as well as providing a balanced interpretation of reports regarding the benefits and drawbacks of PPI use [17,18,19].

The main purpose of this analytical manuscript is to provide a brief overview based on scientific research on drugs that reduce gastric secretion, their range of use, necessity and prospects.

It has been less than two centuries since the stomach's hydrochloric acid was discovered. The successful therapeutic reduction of stomach acid secretion was made possible by the elucidation of the molecular processes. Numerous outstanding pharmacologists, basic scientists, and clinical physicians have contributed to the remarkable advancements in the treatment of acid-related illnesses. The treatment and results of acid-related disorders have significantly improved with the use of effective stomach acid suppression medication. The way upper gastrointestinal problems are treated medically has altered dramatically since proton pump inhibitors (PPIs) were first used in clinical settings. PPIs are the "gold-standard" treatment for conditions involving acid reflux [9-12]. The development of acid pump antagonists, potassium channel acid blocking drugs (-P-CABs), has been a major advancement in the treatment of acid-related diseases; long-term studies comparing P-CABs with PPIs will help define the precise place and safety profile of this class of drug in the management of acid-related disorders. Other problems still exist, such as the management of patients who do not respond well to PPI therapy, more effective gastroprotection, or more potent antisecretory treatment for the eradication of Helicobacter pylori infection [6,7,11,18,19].

Antagonists of Histamine Type 2 Receptors. By competitively inhibiting the connection between histamine and H2 receptors on parietal cells, H2RAs lower the release of stomach acid. H2RAs also lower the volume of stomach acid and pepsin. Cimetidine, famatodine, nizatidine, and ranitidine are the four H2RAs that are currently licensed by the Food and Drug Administration (FDA) in the United States. When given in equipotent quantities, the various H2RAs are thought to be equally effective at inhibiting the production of stomach acid. It appears that there are no clinically relevant changes in the pharmacokinetic and pharmacodynamic properties of the H2RAs. H2RAs have minimal effectiveness in decreasing postprandial acid secretion, despite their effectiveness in regulating baseline acid secretion. H2RAs are now used to treat mild to moderate EE (LA-A and LA-B) and manage symptoms [12-17]. Furthermore, a number of studies have shown that after taking an H2RA twice a day for four weeks, about 30% of NERD patients report a reduction in their symptoms. For up to 12 hours, H2RAs are especially beneficial in reducing postprandial heartburn. If taken half an hour before eating, they also help avoid postprandial heartburn. Furthermore, H2RA before bed considerably shortens the time of nocturnal acid breakthrough [16-20].

Proton pump inhibitors' pharmacological properties. Since histamine-stimulated acid secretion is crucial during the nocturnal period, H2RAs competitively bind to histamine H2 receptors on the basolateral plasma membrane of parietal cells and prevent histamine from binding to these receptors. This inhibits gastric acid secretion primarily during the nocturnal period. When it comes to post-

prandial acid secretion, H2RAs are ineffective at blocking the stimulation of stomach acid secretion by gastrin or acetylcholine. After the initial dosage, an H2RA's acid-suppressive action becomes evident as soon as its plasma concentration rises. Nevertheless, after only about two weeks of repeated dosing, H2RAs exhibit progressively diminished acid suppression, a tolerance phenomena, similar to that of many other receptor antagonist types [4-10]. As a result, H2RAs are regarded as short-distance track sprinters rather than long-distance marathon runners. P-CABs, or potassium competitive acid blockers, inhibit acid secretion by binding to the potassium binding site of the alpha-subunit of proton pumps with iron bonds. While P-CABs exhibit a rapid acid suppression effect when taken orally, their superior clinical benefits over conventional PPIs have not been confirmed, with the exception of Helicobacter pylori eradication therapy and PPI-resistant GERD. While several P-CABs have been found to have therapeutic effects comparable to those of standard PPIs when used for the treatment of uncomplicated GERD, revaprazan and vonoprazan, P-CABs that are now only used in a few countries, such as Korea and Japan, in contrast to standard PPIs [11-16]. Since only a portion of the proton pump is in an active state of secreting acid when a PPI is administered, repeated doses of the drug are required to ensure adequate and complete inhibition of proton pumps. Even during the period of stable acid inhibition after multiple initial oral doses, the nocturnal period acid inhibition is weaker with a once daily morning dose because approximately 25% of proton pumps are replaced by newly synthesized ones within 24 hours, and the newly synthesized pumps after the morning PPI administration will start to secrete acid during the nocturnal period. Since PPIs are almost entirely metabolized by the liver and not the kidneys, impaired renal function has no effect on the potency of the drug [7,12,17].

Potassium-competitive Acid Blockers (P-CABs) are a diverse class of medications that have a common final mechanism of action: they inhibit gastric H+/K+-ATPase in a K+ competitive but reversible manner, so they don't require prior proton pump activation to achieve their antisecretory effect. Due to their rapid rise in peak plasma concentration, P-CABs exhibit an early onset of acid-secretion inhibition. Based on their pharmacokinetic and pharmacodynamic profile, P-CABs are likely to be useful as an on-demand treatment for GERD symptoms [1-5].

Temporary Relaxants for the Lower Esophageal Sphincter. The majority (55–80%) of reflux episodes in GERD patients and all reflux episodes in healthy people are caused by TLESR, the primary mechanism of both acidic and nonacidic gastroesophageal reflux. 65 Gamma-aminobutiric acid B (GABAB), metabotropic glutamate receptor 5 (mGlucR5), cannabinoid (CB), cholecystokinin (CCK), 5-hydroxytryptamine 4 (5-HT4), muscarinic, and opioid receptors are among the several receptors that activate TLESR [7-11].

Discussion. The stomach is the only organ that secretes acidic fluid as low as pH 2, which is necessary for the sterilization of bacteria found in food as well as for the digestion and absorption of various nutrients, including protein, iron, calcium, and vitamin B12. However, because secreted acid can harm the gastrointestinal tract, there are a number of protective mechanisms, such as mucosal mucous/bicarbonate secretion and sphincter contraction of the gastroesophageal junction, to prevent gastric secretion-induced gastroesophageal damage. When these protective mechanisms are compromised by acid secretion, the gastrointestinal mucosa can become damaged and irritated, leading to unpleasant symptoms or even organic disease. These pathological conditions are known as acid-related diseases and include gastroduodenal ulcers, GERD, Barrett's esophagus, and functional dyspepsia [1-11]. Numerous neutralizing agents and inhibitors of stomach acid release have been discovered for the treatment of acid-related disorders. At first, anticholinergic medicines and neutralizing medications with magnesium or aluminum were used. However, those for acid inhibition have limited effects, and using them often results in negative side effects such constipation, diarrhea, and cardiovascular problems. Acid-neutralizing medications are also likely to alter the bioavailability of concurrently delivered medications by interacting with other medications in the gastrointestinal system. As a result, histamine H2 receptor antagonists (H2RAs), created in the late 1970s, have essentially supplanted those initially used for acid-related disorders. Histamine's acid-secretory actions are neutralized by an H2RA [4,5,6]. An H2RA is most effective at inhibiting gastric acid secretion during the nocturnal period due to the stimulating effects of gastrin and acetylcholine, particularly during the post-prandial period. As a result, H2RAs are not strong enough to treat GERD with post-prandial reflux, but they are effective for gastroduodenal ulcers. Proton pump inhibitors (PPIs) were developed for more potent acid inhibition during the daytime period, and they are used as the first-line treatment for acid-related diseases [11,14,15]. PPIs are the most commonly prescribed drug for the suppression of stomach acid worldwide. The benzimidazole nucleus and different kinds of branch structures are present in all of the PPIs that are sold in Japan, including omeprazole, esomeprazole, lansoprazole, and rabeprazole. These medications disrupt the acid secretory activity of the alpha-subunit of proton pumps on the secretary canalicular membranes of gastric parietal cells by covalently binding to the SH residues of cysteine molecules in those pumps. This, in turn, inhibits the secretion of gastric acid. All of the PPIs that are currently on the market have comparable pharmacological properties since they all have the same chemical structure. In an acidic environment, a PPI becomes unstable [11-17]. Since PPIs are usually used for conditions for which the requirement of the medicine has not been proved, rare side effects are referred to as clinically relevant. The evidence offered

in those studies is not high enough to assess the therapeutic value of the numerous PPI-related side effects that have been documented because the majority of the research is based on retrospective observational studies with low reported hazard ratios. PPIs should only be administered to patients who will significantly improve their clinical condition, and any adverse side effects should be further investigated through high-quality prospective research [7-12].

Conclusions. PPIs have continued to be the cornerstone of treatment for GERD patients, and drug development in this condition has slowed down significantly since the majority of PPIs are now generic and available over-the-counter. Nevertheless, there are still a lot of unmet needs in GERDs, necessitating the need for new therapies. Currently, compounds under development include improved PPIs, TLESR reducers, esophageal-specific pain modulators, and mucosal protectants.

Because treatment failure has become the most common presentation of GERD in GI practice, drug development has primarily focused on this particular area of unmet need. It would be a serious mistake to ignore other significant areas of unmet need in GERD, as they offer a unique opportunity for drug development for a large number of patients in dire need of a therapeutic solution. In any case, the number of new medical treatment choices for GERD is probably going to keep going down during the next ten years.

Rare side effects are described as clinically relevant since PPIs are typically used for diseases for which the drug's necessity has not been established. Since most of the research are based on retrospective observational studies and the reported hazard ratios are low, the evidence presented in those studies is not at a high enough level to determine the therapeutic relevance of the many PPI-related adverse effects that have been described. Only patients who will have a significant clinical benefit should be given PPIs, and high-quality prospective studies should be conducted to further examine any negative side effects.

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