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Review Article

Pharmacology of Gastric Acid Suppression and Regulation: Past, Present, and Future

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Abstract

It has been less than two centuries since the discovery of hydrochloric acid in the stomach. The understanding of the molecular pathways enabled efficient therapeutic reduction of stomach acid secretion. The remarkable advancements in the treatment of acid-related illnesses are the result of the combined efforts of several excellent pharmacologists, basic scientists, and clinical physicians. Effective stomach acid suppression therapy has significantly improved acid-related disorder treatment and prognosis. The use of proton pump inhibitors (PPIs) in clinical practice has revolutionized the medical treatment of upper gastrointestinal disorders dramatically. PPIs are the "gold standard" treatment for acid-related disorders. However, several issues persist in the treatment of acid-related disorders, such as the management of patients who do not respond adequately to PPI therapy, more effective gastroprotection, or more potent antisecretory treatment for the eradication of *Helicobacter pylori* infection. New ant secretory medications are continuously being developed and investigated to give a more effective and profound inhibition of stomach acid secretion. The development of acid pump antagonists, or potassium channel acid-blocking drugs (P-CABs), has been a significant step ahead.

Keywords: Gastric Acid Suppression; H2-receptor Blocker; Proton Pump Inhibitor; Potassium-competitive acid Blocker; Acid-related Disorder; *Helicobacter pylori*; Gastroesophageal Reflux Disease; Gastroprotection; Safety

Abbreviations

PPIs: Proton Pump Inhibitors; P-CABs: Potassium Channel Acid-Blocking Drugs; PUD: Peptic Ulcer Disease; H2Ras: H2-Receptor Antagonists; GERD: Gastroesophageal Reflux Disease

Introduction

For centuries, the function and secretion of the stomach have remained a complete mystery. Before the 17th century, there was considerable uncertainty about the role of the stomach in the digestion process. For a long period, the formulation of numerous concepts about the nature of the gastric liquid was fraught with debate. The ancient Greeks only recognized acid as bitter-sour liquids [1].

The stomach, according to Paracelsus (1493-1541), contains acid, which is necessary for digestion, but the source and nature of the acid remained unknown. He believed that the acid in the human stomach was caused by drinking acidic spa water ("hungry acid") [2].

Lazzaro Spallanzani (1729-1799), a professor of the natural power of saliva, recognized the solvent capabilities of gastric juice. In 1780, he published his discoveries in this field, but he was unsure about his findings regarding the acidity of gastric fluid. William Prout revealed the precise conclusion to the exact nature of stomach acid in 1823. He had specifically detected hydrochloric acid in human and other animal stomach fluids and was able to quantify the total and free hydrochloric acid and chloride present [3,4].

The scientific investigation was enhanced with the first description of gastric glands as the source of stomach acid (Purkinje and Golgi, mid and late 19th century). Pavlov discovered the involvement of the Vagus nerves in the control of gastric acid secretion and the theory of "nervism" (the neuro-reflex stimulation of gastric secretion by the vagal nerve) (early 20th century). The histamine-mediated concept of gastric secretion contributed to this theory (Popielski and Code, mid-20th century). Schwann completed the complexity of gastric secretion in 1836 when he developed a water-soluble component called "pepsin," stating that gastric acid and pepsin are requisite for digestion [5,6]. Prostaglandins have been shown to regulate all components of the stomach mucosal defensive barriers (Vane, the 1970s).

Barry Marshall and Robin Warren (1984), who later received the Nobel Prize for their discovery that bacteria might cause diseases previously thought to be caused by human factors, were the first to identify *Helicobacter pylori* as the causative agent of peptic ulcers. Many experts have been persuaded by the discovery to conclude that psychological elements, notably Hans Selye's famous stress theory, are of secondary importance [7]. The discovery of *H. pylori*'s major pathological function in peptic ulcer disease (PUD) revolutionized our understanding of mucosal ulcers and allowed us to cure the disease [8,9]. For decades, antacids, protective agents, anticholinergics, gastrin antagonists, and prostaglandins were primarily used to treat PUD, with insufficient results and common adverse effects.

Regulation of gastric acid secretion

Gastric acid secretion is controlled centrally and peripherally by neural (acetylcholine), hormonal (gastrin), and paracrine (histamine, somatostatin) pathways. Acetylcholine and gastrin stimulate the body by increasing cytosolic calcium, whereas histamine stimulates the body by activating adenylate cyclase and producing cyclic adenosine monophosphate.

Potentiation of histamine by gastrin or acetylcholine could be due to post-receptor interactions between different pathways and the ability of gastrin or acetylcholine to release histamine from mucosal enterochromaffin-like cells. Gastrin, which does not directly activate parietal cells but mobilizes histamine from oxyntic mucosa via enterochromaffin-like cells, is the principal circulating trigger of acid secretion. The rigorous regulation of parietal cells ensures that HCl is secreted properly. The stimulation of the proton pump (H+, K+- ATPase) enzyme expressed in parietal cells, which regulates the exchange of cytoplasmic H+ for extracellular K+, is the final factor in acid secretion. The H+, K+- ATPase released into the stomach lumen interacts with luminal Cl- to generate gastric acid.

Following gastric acid secretion, a feedback process wraps up gastric acid secretion. Somatostatin is the primary inhibitor of acid secretion. Somatostatin release from antral D cells is stimulated by a fall in intragastrical PH.

Somatostatin not only decreases stomach acid secretion but also slows gastrin release. Furthermore, duodenal acidity can trigger the production of secretin, which limits stomach acid release [10-12].

H2-receptor antagonists

The mainstay of treatment for acid-related disorders has been the control of stomach acid secretion with antisecretory drugs. The discovery of the histamine (H2)-receptor (James Black, 1970s) laid a solid foundation for the creation of powerful H2-receptor antagonists (H2RAs), which partially reduce basal and meal-stimulated acid production. When taken twice daily at prescribed doses, some of these medicines can cause an intragastrical pH >3 that lasts for roughly 10 hours. H2RAs are very selective and have no effect on H1-receptors; they are also not anticholinergic drugs.

The level of gastric acid suppression can aid in the healing of duodenal ulcers; however, the inhibition of gastric acid secretion achieved with H2RAs is suboptimal for effectively controlling more severe acid-related disorders, particularly in the healing of severe erosive esophagitis, and has limited efficacy for other indications (e.g., upper gastrointestinal bleeding). Furthermore, the development of tolerance to H2RAs restricts their extensive clinical usage. Despite this, H2RAs can be used as part of a step-down strategy for gastroesophageal reflux disease (GERD) treatment for self-control (on-demand treatment) of acid-related symptoms. It has also been proposed that the efficiency of a nighttime dose of H2RA can be beneficial in the eradication of nocturnal acid breakout [13-15].

Proton pump inhibitors

The final stage in acid secretion is the activation of the proton pump (H+, K+-ATPase), which secretes hydrogen ions into the stomach lumen in exchange for potassium ions. The discovery of proton pumps in parietal cells (Ganser, Forte, and Sachs, late 1970s) and the recognition that proton pump (H+, K+-ATPase) is

the final step of acid secretion cleared the way for more potent and profound acid inhibition, culminating in the development of proton pump inhibitors (PPIs; late 1980s) that target this enzyme directly [16-18].

PPIs revolutionized the treatment of acid-related disorders and are now one of the most routinely prescribed drug classes. After 5 days, once-daily PPI dosage reduces maximal acid output by around 66%. After once-daily oral administration of appropriate doses, PPIs can cause an intragastrical pH above 3 that lasts roughly 17 hours and an intragastrical pH over 5 and last around 9 hours. With higher doses and continuous intravenous administration of PPIs, it is possible to achieve even higher target pH values. They are most efficient when the parietal cell is activated postprandially to release stomach acid. This phenomenon has clinical significance for administration timing. After discontinuing PPI medication, maximum stomach acid secretory capacity may not be regained for up to 24-48 hours [19,20].

All known PPIs are chemically composed of a benzimidazole ring and a pyridine ring, but the ring substitution varies. The mechanism of action of all PPIs is generally similar. However, there are some discrepancies in the pharmacokinetics, pharmacodynamics, and potential for pharmacological interactions among the PPIs. Although individual PPIs have equal efficacy in many circumstances, variations should be noted when determining a care plan [21,22]. table 1 summarizes the key messages regarding primary indications and appropriate use of PPIs [23-25].

Short term PPI therapy appropriate • Healing of erosive esophagitis (Los Angeles grade A and B) • Helicobacter pylori eradication (in combination with antibiotics) • Functional dyspepsia • Peptic ulcer disease • Acute upper gastrointestinal bleeding • Stress ulcer prophylaxis in high-risk patients • Eosinophilic esophagitis
Long term PPI appropriate • Barrett's esophagus • Severe erosive esophagitis (Los Angeles grades C and D) • Zollinger Ellison syndrome • Idiopathic peptic ulcer disease • Gastroprotection in high-risk patients (long term nonselective NSAID users) • Anti-platelet therapy in patients at high risk for upper GI complications • PPI responsive Eosinophilic esophagitis
PPI use no benefit • Corticosteroid treatment (unless used in combination with NSAIDs) • Acute pancreatitis (no benefit from acid inhibition) • Hypertensive gastropathy (no need for acid suppression) • Chronic pancreatitis (standard dose of PPI only in patients with steatorrhea, refractory to enzyme replacement treatment) • Stress ulcer prophylaxis in noncritically ill hospitalized patients and low risk for upper GI complications • Anticoagulant therapy (no need for gastroprotection unless used in combination with NSAIDs)
PPI, proton pump inhibitor; NSAID, nonsteroidal anti-inflammatory drug; GI, gastrointestinal.

Table 1: Current indications and appropriate use of PPI therapy.

Safety of long-term PPI therapy

PPI therapy is usually utilized outside of clear-cut indications, resulting in widespread unnecessary use or for causes with little benefit; thus, incorrect long-term treatment is a major concern [23].

Although overuse and misuse may impair the safety profile, PPIs have a remarkable tolerance. Adverse events occur at a rate of 1-3 percent in most cases. Long-term trials indicate a tolerability rate like that reported in short-term trials [24,25]. PPIs have been linked to an increased risk of pneumonia, osteoporosis, Clostridium difficile-associated diarrhea, cardiovascular illness, liver disease, chronic renal disease, microscopic colitis, dementia, or stomach carcinoid, according to observational studies.

Despite the significant number of research, the overall level of evidence indicating PPI toxicity is low. With 53,000 patient-years of follow-up, a major placebo-controlled randomized trial of 17,598 individuals found that long-term adverse effects in the PPI (pantoprazole) group were equivalent to placebo arms. When administered for three years, pantoprazole was not linked with any major adverse events, except for an elevated risk of enteric infections (1.4 v 1.0% in the placebo group; OR 1.33; % CI 1.01-1.75) [26].

Although the overall therapeutic benefits of PPI medication outweigh the potential hazards, people who do not have a clear indication are only exposed to the minimal risks of PPI treatment. As a result, following evidence-based guidelines is essential for safe and efficient PPI treatment. Reducing inappropriate PPI prescribing can help to reduce the risk of adverse events.

New drug development

Several new strategies for addressing PPIs' pharmacological limitations are being investigated. To address these concerns, researchers have created powerful H2-receptor agonists, gastrin agonists, non-benzimidazole PPIs, prolonged and delayed-release PPIs, PPI combinations, novel agents with longer half-lives, and a new generation of PPIs. It remains to be examined whether these new strategies provide a meaningful clinical advantage or introduce new and unexpected adverse effects (Table 2) [27-29].

Potassium-competitive acid blockers

The development of acid pump antagonists, potassium channel acid-blocking medications (P-CABs), which block the K+, H+-ATPase K+ channel, has been a significant step forward. P-CABs limit stomach acid secretion by blocking the proton pump's K-exchange channel, resulting in competitive, reversible, food-independent suppression. They have a fast onset of action and sustain a prolonged and consistent increase of intragastrical PH. Table 3 shows the main variations in the mechanisms of action of PPIs and P-CABs.

Group	Drug
H2Ras	Lavoltidine
CCK/gastrin receptor antagonist	Loxitidine
	Loxiglumide, spiroglumide, itriglumide
PPI	Pantoprazole magnesium
Delayed release	Dexlansoprazole (MR; modified release)
	Rabeprazole (ER; extended release)
	Esomeprazole stronium delayed release
New agents	IR-omeprazole (instant release)
	Ilaprazole
	Tenatoprazol (non-benzimidazole PPI)
	AGN-201904-Z (omeprazole pro-drug)
PPI combination	Omeprazole + lansoprazole

H2RAs, H2-receptor antagonists; PPIs, proton pump inhibitors.

Table 2: New drug development for gastric acid inhibition.

Vonoprazan fumarate (Takecab®) is a first-in-class potassium-competitive acid blocker that has been licensed in Japan since February 2015 and has been introduced only in a few Asian countries [30-33] table 4. summarizes the key pharmacological features of vonoprazan.

In terms of endoscopic erosive esophagitis healing rate after 8 weeks, vonoprazan 20 mg was proven to be efficacious and non-inferior to lansoprazole 30 mg. Furthermore, at 2 and 4 weeks, vonoprazan 20 mg treatment resulted in slightly higher esophagitis healing rates than lansoprazole 30 mg treatment. Vonoprazan 20 mg had a similar safety profile to once-daily lansoprazole 30 mg [34].

PPIs	P-CABs
Requires transformation to the active sulfonamide form	Acts directly on the proton pump (K+, H+-ATPase)
The lower concentration in parietal cell acid space (1,000-fold higher than those in plasma)	Super concentration in parietal cell acid space (100,000-fold higher than those in plasma)
Covalent binding to K+, H+-ATPase	Competitive binding to K+, H+-ATPase
Irreversible binding to K+, H+-ATPase	Reversible binding to K+, H+-ATPase
Duration of effect related to the half-life of the sulphonamide-enzyme complex	Duration of effect related to the half-life of the drug in plasma
Delay onset of action	The full effect from the first dose
Food-dependent inhibition of gastric acid	Food independent acid inhibition
Incomplete acid suppression	Complete, prolonged acid suppression

PPIs, proton pump inhibitors; P-CABs, potassium channel acid-blocking drugs.

Table 3: The main differences in the mechanisms of action between PPIs and P-CABs.

First in class potassium competitive acid blocker
It inhibits the H+, K+ ATPase mediated gastric acid secretion in a selective, reversible, and potassium competitive manner with a slow dissociation rate
Food independent
Rapid onset of action
It possesses approximately 350 times more potent inhibitory effect than lansoprazole (*in vitro* experiments)
Stronger and longer lasting effect than lansoprazole
Prolonged and consistent elevation of gastric pH
A single oral dose of 20 mg increases the gastric pH above 4.0 as early as 4 h after and maintained the gastric pH above 4.0 until 24 h post dose.
It undergoes important metabolic elimination, but the influence of genetic polymorphism is limited.

Table 4: The main pharmacological properties of vonoprazan.

Vonoprazan's exceptionally robust antisecretory activity may be especially beneficial in the long-term therapy of patients with severe esophagitis and Barrett's esophagus. Indeed, vonoprazan is more efficacious than most PPIs in patients with severe erosive esophagitis, and its efficacy in GERD maintenance treatment may be higher than that of other PPIs [35,36].

Vonoprazan may also be a new therapy option for the prevention of NSAID or aspirin-related gastroduodenal mucosal adverse events in high-risk individuals [37].

Finally, the use of vonoprazan as an alternative to PPI therapy for *H. pylori* eradication, particularly in resistant and difficult-to-treat populations, has been investigated. In terms of *H. pylori* eradication, the vonoprazan-based triple therapy surpassed the PPI-based triple therapy. Furthermore, vonoprazan appears to be superior to traditional PPI-based therapy for the eradication of clarithromycin-resistant *H. pylori* bacteria.

The tolerance and incidence of adverse events for the vonoprazan-based triple therapy were comparable. It has also been proposed that dual therapy with vonoprazan and amoxicillin is as effective as triple therapy with vonoprazan, amoxicillin, and clarithromycin, implying that vonoprazan-based dual therapy can provide an acceptable eradication rate of *H. pylori* infection (92.9% intention-to-treat analysis, % CI 82.7-98.0%) without the need for additional antimicrobial agents, such as clarithromycin [38-40].

Long-term trials comparing P-CABs versus PPIs will aid in identifying the exact role and safety profile of this novel class of medication in the treatment of acid-related disorders.

Conclusion

Stomach acid suppression has been given special attention for decades. The development of different PPIs and H2RAs has posi-

tively impacted on management of several acid-related disorders. However, there were limitations and adverse effects for the use of these medications especially in conditions requiring long-term therapy. Vonoprazan, a recently developed C-CCB, is proven to surpass traditional PPI for the management of acid-related disorders. The tolerance and incidence of adverse events for the vonoprazan-based therapy are comparable with traditional PPI. Long-term clinical trials are required to further study the safety profile of this novel medication.

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