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PANTOPRAZOLE WITHDRAWAL AND REBOUND ACID HYPERSECRETION: PATHOPHYSIOLOGY, CLINICAL MANIFESTATIONS, AND MANAGEMENT

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ABSTRACT

Pantoprazole is a proton pump inhibitor (PPI) that irreversibly inhibits the gastric H^+/K^+-ATPase enzyme in parietal cells, thereby suppressing gastric acid secretion. Prolonged acid suppression may lead to compensatory hypergastrinemia and parietal cell hyperplasia, increasing the stomach's acid-secretory capacity. Upon abrupt discontinuation, this enhanced capacity can result in rebound acid hypersecretion (RAHS) and recurrence of acid-related symptoms. RAHS may cause patients to resume therapy, mistaking rebound symptoms for disease relapse. Understanding the underlying mechanisms and clinical implications of RAHS is essential to promote appropriate deprescribing strategies and prevent unnecessary long-term PPI use.

KEYWORDS: Pantoprazole; Proton pump inhibitors; Rebound acid hypersecretion; Hypergastrinemia; Deprescribing; Gastric acid secretion; PPI withdrawal.

INTRODUCTION

Pantoprazole is a first-generation proton pump inhibitor (PPI) utilized in treating gastroesophageal reflux disease (GERD), offering gastric protection to prevent the recurrence of stomach ulcers or damage from prolonged NSAID use, and addressing pathological hypersecretory conditions like Zollinger-Ellison (ZE) Syndrome. It is also included in quadruple therapy regimens for H. pylori infections, alongside antibiotics such as amoxicillin,

clarithromycin, and metronidazole. Owing to its strong acid suppressive effects and favourable safety profile, it is frequently prescribed for long-term therapy[1,4]

Pantoprazole is a prodrug that becomes activated in the acidic environment of parietal cell canaliculi. It suppresses stomach acid by inhibiting the final stage of gastric acid production by binding covalently to on cysteine residues of the (H+, K+)-ATPase enzyme at the gastric parietal cell's secretory surface. This action inhibits basal and stimulated acid secretion, regardless of the stimulus. Since pantoprazole's binding to the (H+, K+)-ATPase enzyme is irreversible, new enzyme expression is required to resume acid secretion, resulting in an antisecretory effect lasting over 24 hours. [4]

This prolonged suppression of gastric acid has important physiological consequences on the regulation of gastrin secretion. Gastric parietal cell acid secretion is a complex process involving various stimulatory and inhibitory mediators, with gastrin being a key mediator that indirectly stimulates acid secretion by releasing histamine from enterochromaffin-like (ECL) cells. Antisecretory therapy can lead to hypergastrinemia, mucosal hyperplasia, and increased ECL cell mass, enhancing gastric acid secretion capacity. This increased capacity can manifest as rebound acid hypersecretion (RAHS) after stopping antisecretory therapy.[2,3]

Long-term PPI use, including pantoprazole, has been linked to potential adverse effects, such as increased susceptibility to bacterial infections (including gastrointestinal C. difficile), reduced absorption of micronutrients like iron and B12, and a higher risk of hypomagnesemia and hypocalcemia, which may contribute to osteoporosis and bone fractures later in life.

Recent studies have also indicated that prolonged use is associated with a higher risk of gastric cancer compared to those not on therapy. Therefore, unnecessary long-term use should be avoided. However, discontinuing PPIs presents its own challenges, as abrupt withdrawal of PPIs can elevate gastric acid production beyond pre-treatment levels, related to persistent hypergastrinemia. This phenomenon contributes to rebound acid hypersecretion and may complicate appropriate deprescribing.[3]

This biological mechanism and pathophysiology have been established in both animal and human studies and are known as rebound acid hypersecretion (RAHS). Pantoprazole doses should be gradually reduced, or tapered, before discontinuation, as rapid cessation may cause a rebound effect and a temporary increase in hypersecretion.

Definition

Rebound acid hypersecretion (RAHS) refers to a temporary surge in stomach acid levels that exceeds those before treatment, typically manifesting after discontinuing prolonged (use for

more than 8 weeks) use of proton pump inhibitors (PPI) or H2 blockers. This condition results in symptoms such as heartburn and indigestion, which generally emerge 5 to 14 days after stopping the medication and can persist for up to 2 weeks. This may often lead patients to incorrectly assume recurrence or worsening of the underlying reflux disease.[1]

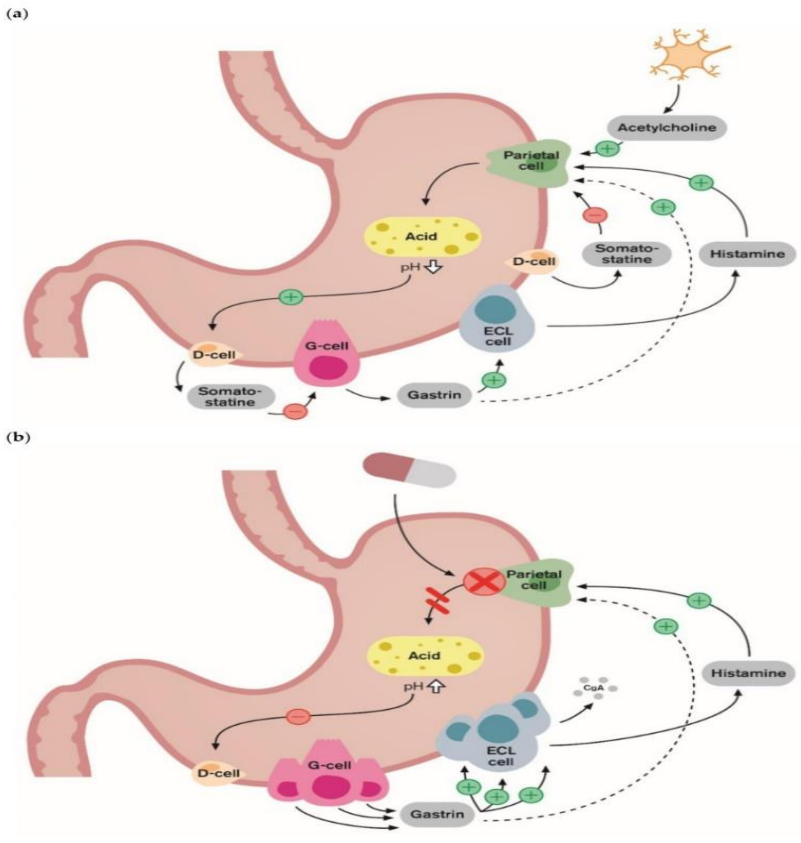
Pathophysiology

The stomach's lining consists of mucous cells, parietal cells, chief cells, and neuroendocrine cells, including G-cells, ECL-like cells, and D-cells. Each cell has its distinct role. Parietal cells are responsible for secreting intrinsic factor and hydrochloric acid (HCl); the latter aids in protein digestion and eliminates bacteria in food. Chief cells release the pro-enzyme pepsinogen, which becomes pepsin through the action of HCl, playing a crucial role in protein digestion. G-cells produce gastrin, a neuroendocrine hormone that enhances HCl production both directly and indirectly. ECL-like cells secrete histamine, which also indirectly boosts HCl production. D-cells release somatostatin (SST), an inhibitory hormone that reduces gastric acid production by inhibiting gastrin secretion.[6]

The secretion of gastric acid is a complex, multi-step process. Acetylcholine (ACh), histamine, and gastrin work together to stimulate acid release. Vagal stimulation, triggered by the sight, smell, or presence of food, leads to ACh release. This neurotransmitter activates nicotinic (N) and muscarinic (M1) receptors on parietal cells, while gastrin from G-cells stimulates cholecystokinin-2 (CCK2) receptors on both parietal and enterochromaffin-like (ECL) cells. Gastrin and ACh facilitate HCl production. Histamine, secreted by ECL cells upon M and CCK2 receptor stimulation, activates H2 receptors on parietal cells, thereby stimulating adenylate cyclase (AC) and generating cAMP in the parietal cell lumen, indirectly aiding HCl secretion. The main mechanism involves the stimulation of parietal cells. The activated M3 receptor increases intracellular calcium, and CCK2 receptors activate phospholipase C to enhance cytosolic calcium release. Both pathways increase the activity of the H+K+ ATPase proton pump located on the apical membrane of parietal cells, resulting in hydrochloric acid secretion into the gastric lumen.[7]

Proton pump inhibitor (PPI) therapy is designed to reduce stomach acid production. These inhibitors are absorbed in the upper small intestine and, once in the bloodstream, they target the stomach's parietal cells. PPIs work by binding to and blocking the H+/K+ ATPase enzyme, also known as the gastric proton pump, which is crucial for moving hydrogen ions into the stomach's lumen. When gastric acidity is consistently lowered due to prolonged PPI use, serum gastrin levels rise because of a disrupted negative feedback mechanism caused by

antral G-cell hyperplasia. This increase in gastrin, known as hypergastrinemia, is a compensatory mechanism that leads to ECL cell hyperplasia, which in turn boosts histamine release. Extended periods of elevated gastrin levels have a stimulating effect on the gastric lining, causing an increase in enterochromaffin-like (ECL) cell hyperplasia and a rise in histamine release. Gastrin also encourages the multiplication of parietal cells, which boosts the stomach's ability to secrete acid. When proton pump inhibitor (PPI) treatment is stopped, the previously inhibited proton pumps become active again, while gastrin levels stay temporarily high, leading to an excessive stimulation of parietal cells and a surge in gastric acid production. This occurrence is known as rebound acid hypersecretion (RAHS). The elevation in gastrin levels due to PPI use is believed to contribute to rebound acid hypersecretion(RAHS) once PPIs are stopped. Although PPI therapy interrupts the stimulation of parietal cell acid secretion by increased histamine through hypergastrinemia, the acid secretion capacity can become exaggerated after discontinuation of PPIs. In patients with GERD, both gastrin and CgA levels rise during PPI treatment, and after stopping PPIs, both basal and pentagastrin-stimulated acid secretion significantly increase compared to pre-treatment levels.[1,8]



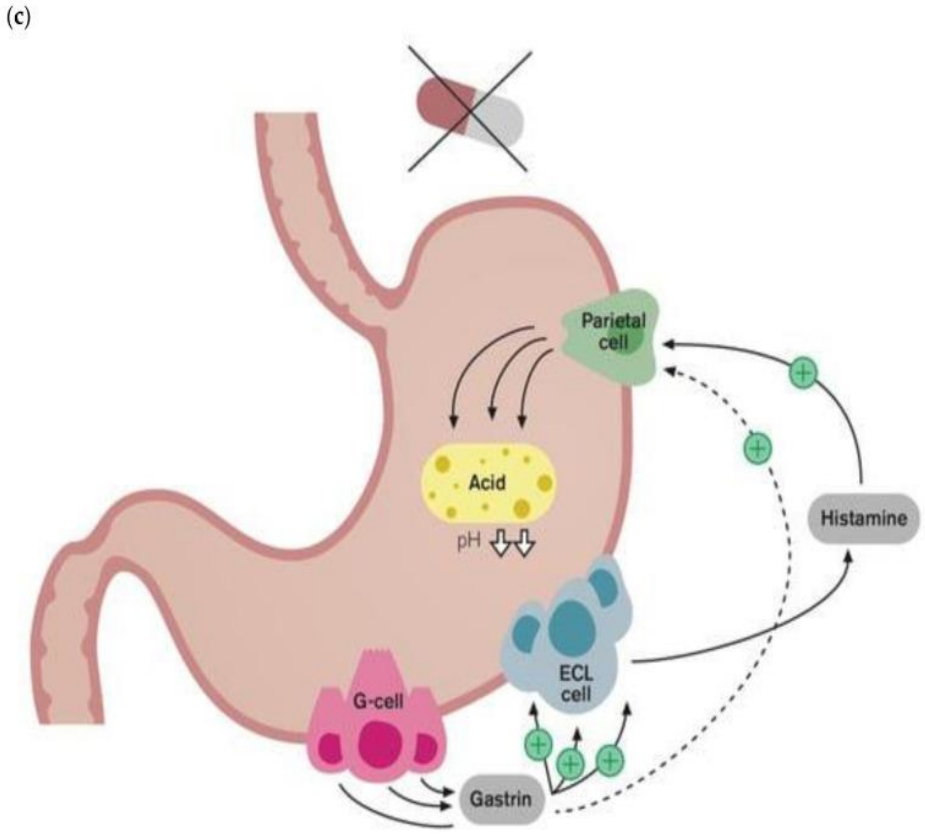


Figure 1. Mechanism of rebound acid hypersecretion following proton pump inhibitor therapy.

(a) Normal regulation of gastric acid secretion involving gastrin, histamine, and acetylcholine.
(b) During PPI therapy, inhibition of the H^+/K^+-ATPase proton pump reduces gastric acid secretion, leading to compensatory hypergastrinemia and ECL cell stimulation.
(c) After discontinuation of PPI therapy, persistent hypergastrinemia and increased ECL cell activity cause excessive stimulation of parietal cells, resulting in rebound acid hypersecretion.
Source: Adapted from Namikawa K, Björnsson ES. Rebound Acid Hypersecretion after Withdrawal of Long-Term Proton Pump Inhibitor Treatment—Are PPIs Addictive? Int J Mol Sci. 2024;25(10):5459.

Clinical Manifestations

RAHS in Healthy Volunteers

RAHS in Healthy Volunteers. Research has shown that RAHS can manifest following the cessation of PPI treatment. For example, a randomized, double-blind, placebo-controlled study with 120 healthy participants revealed that 44% of those who had used esomeprazole for eight weeks experienced significant acid-related symptoms, such as heartburn, acid

regurgitation, or dyspepsia, within four weeks of stopping the drug [10]. This indicates that RAHS can trigger symptoms that might result in a dependency on PPIs.

RAHS in GERD Patients

RAHS in GERD Patients. In individuals with GERD, stopping PPI therapy can worsen reflux symptoms and elevate esophageal acid exposure. GERD patients who ceased PPI use showed a marked increase in symptoms and acid exposure, especially during the first 20 days after discontinuation [9]. This suggests that RAHS can have a more significant effect on those with existing acid-related issues.

After stopping the use of proton pump inhibitors such as Pantoprazole, rebound acid hypersecretion (RAHS) can cause various gastrointestinal symptoms.

The most frequently observed symptoms are heartburn, acid regurgitation, indigestion, and discomfort in the upper stomach area. Additionally, some individuals might experience pain and discomfort in the upper abdomen, bloating, nausea, and a feeling of fullness after eating. The increased stomach acid production can also lead to frequent belching and a sour taste in the mouth. [1]

In some instances, patients may experience symptoms related to reflux, such as chest discomfort and night time reflux episodes, due to the esophagus being exposed to more stomach acid. These symptoms typically emerge within one to two weeks after stopping PPI treatment. For those who were previously without symptoms, the rebound in gastric acid secretion might mimic a return of gastroesophageal reflux disease (GERD). Consequently, many patients resume PPI therapy, mistakenly believing their initial condition has returned, rather than recognizing it as a temporary physiological reaction to stopping the medication.[10]

Besides the typical signs of rebound acid hypersecretion, there are several less commonly reported symptoms that can occur after stopping proton pump inhibitor treatment.

These symptoms might include excessive burping, feeling full quickly, bloating, and discomfort after eating. Some individuals may also experience unusual reflux symptoms such as a persistent cough, hoarseness, a sore throat, or a sensation of a lump in the throat due to laryngopharyngeal reflux. Rare symptoms like water brash, nighttime reflux episodes, and a lasting acidic taste in the mouth have also been noted. Although these symptoms are usually mild and temporary, they might lead patients to think that their original acid-related condition has returned.[11]

Factors influencing rebound acid hypersecretion

Not everyone who stops taking a proton pump inhibitor, like pantoprazole, experiences rebound acid hypersecretion. The likelihood and intensity of this rebound phenomenon can be influenced by a number of physiological and treatment-related factors. These factors are primarily linked to the compensatory alterations that take place in the gastric mucosa during PPI therapy and the extended suppression of gastric acid secretion.

Hypochlorhydria: Proton pump inhibitor therapy over an extended period of time causes significant acid suppression (PPI-induced hypochlorhydria). Compensatory hypergastrinemia and ECL-cell stimulation, which boosts the ability of the stomach to secrete acid, may be linked to this condition. This has been linked to a higher risk of osteoporotic fractures, malabsorption of vitamins, minerals, and nutrients, and infections.[13,14]

Hypergastrinemia: Hypergastrinemia: Gastrin's hypertrophic effects on the stomach's ECL cells are thought to be the cause of the rebound acid hypersecretion (RAHS) phenomenon. High levels of gastrin promote the growth of ECL cells and the release of histamine, which intensifies the stimulation of parietal cells. resulting in rebound symptoms, increased acid production even after therapy has been stopped, and potentially fueling the cycle of improper prescribing.[15]

PPI Therapy Duration: Rebound acid hypersecretion is largely influenced by the length of proton pump inhibitor therapy. Sustained hypergastrinemia and adaptive changes in the gastric mucosa may result from prolonged suppression of gastric acid, especially for durations longer than eight weeks. Long-term PPI therapy has been shown to promote the growth of enterochromaffin-like (ECL) cells and boost the stomach's ability to secrete acid. These alterations may cause an excessive rise in gastric acid secretion when treatment is stopped. [15]

ECL-cell hyperplasia: Prolonged hypergastrinemia, which increases gastric acid secretion, causes an increase in the number of ECL cells in the gastric mucosa. This condition is brought on by PPI treatment.[15]

PPI Therapy at High Doses: Gastric acid secretion may be more severely suppressed by higher dosages of proton pump inhibitors. Because the normal negative feedback mechanism is disrupted, this severe acid suppression may further increase the release of gastrin. Once PPI therapy is discontinued, elevated gastrin levels can increase parietal cell stimulation by promoting ECL cell activity and histamine release.[14,15]

Abrupt Therapy Cessation: Rebound acid hypersecretion has also been linked to abrupt PPI therapy cessation. The previously suppressed proton pumps become active again when

treatment is abruptly stopped, and gastrin levels briefly stay elevated. This combination may result in increased production of gastric acid and excessive stimulation of parietal cells.

Gender: Only a small number of studies have looked into how gender affects PPI treatment, and some of the results suggest that women may be more susceptible to the inhibitory effects of PPIs on acid secretion and that they cause more gastrin release than men. However, there is still little data on gender differences.[15]

MANAGEMENT

Deprescribing guidelines

Guidelines for reducing PPI therapy have been created to offer valuable advice to both patients and healthcare providers on the timing and method for tapering off PPIs.

The Australian algorithm, developed by the National Prescribing Service, suggests a gradual approach for GERD patients, where symptom management dictates whether to decrease or increase treatment for controlling reflux symptoms. This algorithm advises slowly lowering the dosage before discontinuation to address RAHS.

In contrast, the Canadian algorithm proposes various methods for deprescribing, such as reducing to a lower dose, stopping and using as needed, or ceasing abruptly, without endorsing a single best approach. It also suggests follow-ups at four and 12 weeks. Despite this, these guidelines can serve as a helpful reminder for clinicians to consider stopping therapy when the justification for PPIs is weak, as prolonged PPI use without proper monitoring and reassessment appears to be common.[15]

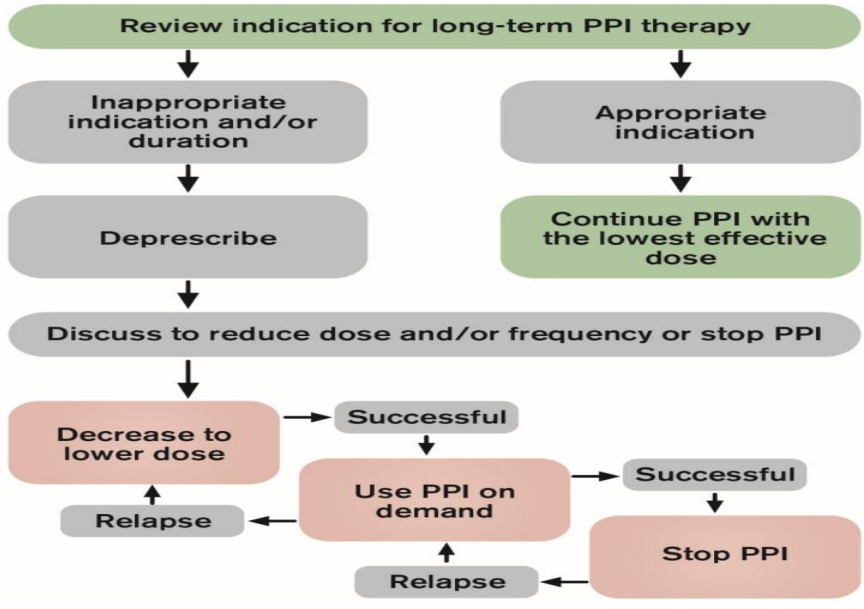


Figure 2. Deprescribing algorithm for long-term proton pump inhibitor (PPI) therapy.

The algorithm illustrates the clinical decision-making process for reviewing long-term PPI use and guiding deprescribing strategies, including dose reduction, on-demand therapy, or discontinuation depending on symptom control.

Source: Adapted from Helgadottir H, Björnsson ES. Int J Mol Sci. 2019;20(21):5469.

PPI tapering strategies

Tapering of PPI therapy has been proposed as a strategy to prevent the possible effects of RAHS. Consequently, some experts have advocated for tapering the dosage or using PPIs on-demand to lower the risk of acid rebound, citing studies that show their effectiveness in managing symptoms or successfully stopping PPIs [16]. Nonetheless, there is insufficient evidence to confirm its effectiveness. Hendricks et al. recently carried out a randomized controlled trial in the USA involving 38 GERD patients to explore the difference in successful PPI discontinuation after 12 months between those who stopped abruptly and those who tapered off. Although no significant difference was observed between the groups, the tapering approach was associated with fewer symptoms. Conversely, in the RCT conducted by Björnsson et al., no difference was found in the proportion of patients who resumed PPI use after 6 months between those who withdrew abruptly and those who tapered over three weeks. It is possible that extending the tapering period could be beneficial, but there is a lack of evidence supporting this method. To fill this gap, more structured studies on tapering methods are necessary [1].

Alternative therapies

In recent years, efforts have been made to identify effective methods for stopping PPIs to avoid acid rebound.

The use of H2 blockers has been linked to the successful cessation of PPIs. Alginate, which alleviates reflux symptoms by creating a protective barrier for the sensitive esophageal lining, has been reported to be beneficial in preventing symptom flare-ups during the pre-investigation PPI wash-out phase.

Coyle et al. [17] found that combining an educational program with alginate management for rebound symptoms facilitated the successful reduction or discontinuation of PPIs. In this prospective interventional study, trained nurse advisers delivered a 20-minute educational session on PPI management for de-prescription, including acid rebound, and provided alginate for self-management of rebound symptoms [1].

Bridge therapy can be employed to address rebound symptoms that arise after stopping proton pump inhibitors. In this approach, alternative medications like H2 receptor blockers, antacids, or alginate-based products may be temporarily used to decrease stomach acidity and alleviate reflux symptoms. These drugs help manage symptoms while the body's gastric acid production gradually normalizes following the cessation of PPIs. This supportive treatment can enhance patient comfort and improve the chances of successfully discontinuing PPIs.

Lifestyle modifications

Lifestyle modifications and dietary adjustments can also help reduce reflux and heartburn symptoms linked to GERD. Suggested lifestyle changes include weight loss for those who are overweight, quitting smoking for smokers, and elevating the head of the bed or using extra pillows at night. Dietary recommendations involve avoiding high-fat meals, consuming smaller portions, steering clear of citrus fruits, opting for decaffeinated drinks, avoiding spicy foods, and refraining from alcohol. Individuals may identify specific foods that trigger their GERD symptoms, such as heartburn and food regurgitation, so recognizing and avoiding these foods when possible is crucial.

Prevention of rebound acid hypersecretion

Prevention of rebound acid hypersecretion involves appropriate use of proton pump inhibitors and adherence to strategies that optimize their therapeutic effectiveness.

Appropriate timing of PPI administration plays an important role in preventing inadequate acid suppression and minimizing rebound symptoms. Enteric-coated PPIs regulate intra-gastric pH best when administered prior to a meal (30–60 minutes before breakfast for once-daily dosing, 30–60 minutes before breakfast and dinner for twice-daily dosing) because meals increase proton pump activity. Since a pre-dinner dose is more effective at controlling acidity, bedtime dosing is discouraged. Regardless of meal timing, dexlansoprazole, a dual delayed-release PPI that is first absorbed in the duodenum and then partially further down the small bowel, seems to be equally effective in controlling pH. When taken at bedtime, an omeprazole-sodium bicarbonate combination that is not enteric-coated offers good control of intragastric pH during the first four hours of sleep. In somecases, switching to alternative PPIs such as rabeprazole may be considered, a PPI that does not rely on CYP2C19 for primary metabolism. Patients with GERD complications, such as Barrett's esophagus and severe erosive esophagitis (LA C or D), should receive maintenance PPI therapy. On-demand therapy, in which PPIs are taken only when symptoms arise and stopped when they are

relieved, may be considered for patients without erosive esophagitis or Barrett's esophagus who still experience symptoms after stopping PPI therapy. On-demand or intermittent PPI therapy may be effective in treating patients with NERD and otherwise uncomplicated GERD. Another viable management strategy, especially for NERD patients, is step-down therapy to H2RAs.[19]

To effectively prevent rebound acid hypersecretion, it is crucial to follow proper prescribing guidelines and implement careful strategies for discontinuation. Healthcare providers should prescribe proton pump inhibitors (PPIs) only when absolutely necessary and for the shortest duration that is effective. It is advisable to periodically reassess the necessity of ongoing PPI therapy, especially for patients on long-term treatment. Gradually reducing the dose or employing step-down therapy can help mitigate the sudden surge in gastric acid production that may occur with abrupt cessation. Additionally, educating patients about the possibility of temporary rebound symptoms and advising the use of supportive measures like antacids or H_2-receptor antagonists can enhance adherence to deprescribing plans and decrease unnecessary prolonged PPI use.

CONCLUSION

Rebound acid hypersecretion (RAHS) is a significant clinical concern that can occur after discontinuing proton pump inhibitors like Pantoprazole, particularly after extended or high-dose use. This condition primarily results from compensatory physiological changes during acid suppression, such as hypergastrinemia and the activation of enterochromaffin-like (ECL) cells, which enhance gastric acid secretion capacity once the medication is stopped. Clinically, RAHS may present as heartburn, dyspepsia, and acid regurgitation, sometimes leading patients to mistakenly believe that their original condition has returned. To manage rebound acid hypersecretion effectively, it is essential to devise careful deprescribing plans and supportive measures to minimize the chances of symptoms reappearing. The focus on deprescribing proton pump inhibitors has grown due to their extensive and often prolonged use. Research indicates that many patients on long-term PPI therapy can successfully reduce their dosage or stop treatment with the right strategies. However, the success of deprescribing can vary based on patient characteristics and clinical indications. A comprehensive understanding of the mechanisms, clinical symptoms, and available management options is crucial for optimizing patient outcomes and preventing unnecessary long-term use of proton pump inhibitors. Factors like the duration of therapy, dosage, and abrupt discontinuation can

influence the onset and severity of rebound symptoms. Although rebound acid hypersecretion has been reported after stopping proton pump inhibitors, its clinical significance in patients with GERD remains uncertain. Some studies have not shown clear evidence of symptoms directly caused by acid rebound. Additionally, distinguishing symptoms of rebound hypersecretion from the recurrence of GERD can be challenging. Therefore, further well-designed studies are needed to clarify its true clinical importance. Effective management strategies, including the gradual reduction of PPIs, alternative therapies, lifestyle changes, and evidence-based deprescribing guidelines, can help reduce rebound symptoms and facilitate successful discontinuation. Raising awareness among healthcare providers about rational prescribing practices and regularly reassessing long-term PPI therapy is crucial to prevent unnecessary medication use and lower the risk of rebound acid hypersecretion.

Ultimately, careful prescribing practices and appropriate deprescribing strategies are essential to minimize the risk of rebound acid hypersecretion and ensure the safe use of proton pump inhibitors.

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