Review article

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REBOUND PHENOMENON OF PROTON PUMP INHIBITOR THERAPY

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Proton pump inhibitors (PPIs) are the most potent drugs for suppressing gastric acid secretion. They are used in the treatment of acid-peptic disorders, including peptic ulcer disease, gastroesophageal reflux disease, Zollinger Ellison syndrome, in the eradication of *Helicobacter pylori* infection and ulcer prophylaxis. In the pharmacotherapy of these disorders, they have significantly suppressed the use of H2 blockers, like other, older groups of antisecretory drugs.

Long-term PPI therapy leads to moderate hypergastrinemia (increased gastrin secretion) in 20-25% of patients. This hypergastrinemia results in rebound acid hypersecretion (RAHS) in 30-40% patients, who abruptly discontinue PPI. Most patients who abruptly discontinue PPI have symptoms of dyspepsia and gastroesophageal reflux, most commonly heartburn and a burning sensation in the esophagus.

Therefore, care should be taken to properly discontinue PPI and reduce the dose of the drug before complete discontinuation. A less effective acid blocker (H2 blocker) can be switched, since H2 receptor blockers cause less pronounced hypergastrinemia and hyperplasia of enterochromaffin-like cells (ECL cells) compared to PPI.

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Key words: *proton pump inhibitor, rebound, hypergastrinemia, gastric acid hypersecretion*

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Introduction

At present, there is plentiful evidence to suggest that short-term PPI therapy is well effective and relatively safe. Therefore, PPIs have become the drug of choice in all conditions accompanied by increased gastric acid secretion (1). Thus, in 2001 and 2008 they were the second group of drugs prescribed and dispensed in the United States (1). They significantly suppress the use of H2 blockers, as other, older groups of antisecretory drugs.

Indications for the use of PPI are short term treatment of gastroesophageal reflux disease (GERD) and long term treatment of severe esophagitis and Barrett's esophagus, dyspepsia caused by acid hypersecretion, Zollinger Ellison syndrome, healing of gastric and duodenal peptic ulcer disease, eradication of Helicobacter pylori infection (in combination with antibiotic therapy), prophylaxis of gastroduodenal lesions associated with the use of non-steroidal anti-inflammatory drugs (NSAID), aspirin or antiplatelet agents, as well as in critical patients in intensive care units (2).

Long-term PPI therapy increases the risk of developing "rebound" hypersecretion of gastric acid. Abrupt discontinuation of PPI in these patients can lead to a worsening of disease symptoms, even above the intensity of initial symptoms (3).

Regulation of gastric secretion

The proton pump (H+/K+ ATPase) located in the canalicular membrane of gastric parietal cells has a key role in acid secretion. It enables the transport of hydrogen ions into the gastric lumen (3). Three types of receptors have been identified on parietal cells whose activation leads to stimulation of acid secretion: receptors for acetylcholine, histamine and gastrin. Gastrin is the main hormonal mediator of the gastric phase of acid secretion released by antral neuroendocrine G-cells into peripheral blood in response to a variety of physical and neurohumoral stimuli such as gastric distension, histamine, presence of amino acids, and vagal stimulation. Gastrin stimulates histamine synthesis (via an increase in expression of histidine decarboxylase) and histamine secretion from fundic enterochromaffin-like (ECL)

cells (4). Histamine diffuses to interact with the H2-receptors and stimulate parietal cells to secrete HCL. This activation cascade usually named gastrin–ECL axis is considered as the main stimulatory pathway of gastric acid secretion. Gastrin might directly promote acid secretion to some extent inducing H+/K+-ATPase activation directly on parietal cells. This mechanism is considered to be less extensive (4). Vagal stimulation of acid secretion is mediated by acetylcholine which stimulates the parietal cells directly by binding to M3 receptors. Acetylcholine and gastrin stimulation leads to an increase in cytosolic calcium (Ca2+). Histamine induces the activation of adelynate cyclase which converts ATP to cyclic adenosine monophosphate (cAMP). An increase of cytosolic calcium (Ca2+) followed by accumulation of cAMP activates cAMP-dependent protein kinases and phosphorylation cascades which activate proton pump transport (H+/K+ ATPase). Activation of proton pump results in the exchange of intracellular H+ with extracellular K+-gastric acid secretion.

The inhibiting negative feedback prevents excessive gastric acid secretion which is potentially harmful to the integrity of the gastric mucosa. The main negative regulator of gastric acid secretion is somatostatin. It is produced in the antral mucosa by D cells in response to several stimuli. Gastrin is one of the stimuli which induce secretion of somatostatin by antral D cells and in turn inhibits secretions of gastrin from G cells. This constitutes the so-called gastrin-somatostatin axis which takes part in gastric levels and acid secretion. Another stimulus, low antral pH is considered as the most important inducer of somatostatin release which inhibits further gastrin secretion from G cells. Gastric food content or neutral gastric secretion inhibits somatostatin secretion (5).

Pharmacokinetics and pharmacodynamics of proton pump inhibitors

PPIs are acid-resistant capsules or tablets, which in inactive form pass through the esophagus and stomach. They are resorbed in the small intestine and reach the systemic circulation, and then by diffusion into the secretory canaliculus of parietal cells (6). The pH in the canalicular system of parietal cells is very low and activates PPI. After being activated, PPIs inhibit the active proton pump (H+/K+ ATPase) by covalent binding. Longer duration of the acid secretion inhibition, even after the PPIs levels in the blood have decreased, is enabled by this covalent binding. The duration of the inhibitory activity of PPIs is variable. The loss of covalently bound PPIs and pump turnover affect the inhibitory activity duration (7). The PPIs effect is most prominent when the proton pumps are active which occurs after a meal. This is the reason why patients should take PPIs before a meal (8).

PPIs inhibit acid secretion and lead to hypoacidity (higher pH level). The increase in pH inhibits antral D cells from somatostatin secretion which inhibits the negative feedback of gastrin secretion from antral G cells. The secretion of gastrin from the antral G cells is increased which is followed by an increase in gastrin blood concentration. Some increase in gastrin blood levels develops in patients who have been on long-term PPI therapy. Only a small number of them develop hypergastrinemia which defines gastrin levels higher than the upper limit of the reference range for fasting blood gastrin (9). Gastrin has a hypertrophic effect on the gastric mucosa and causes enterochromaffin-like (ECL) hyperplasia. The increase in gastrin is most pronounced in the first few months, but also up to 1-2 years in patients on PPI long-term treatment (10, 11).

Rebound phenomenon of proton pump inhibitors

After abrupt discontinuation of PPI treatment, a rebound phenomenon of acid hypersecretion can develop. It is believed that the rebound acid hypersecretion (RAHS) phenomenon results from hypertrophic effects of gastrin on ECL cells, which leads to an increase in acid production following discontinuation of PPIs therapy. The increased acid production causes rebound symptoms which may be followed by new inappropriate PPI prescribing (12). In 30-40% of patients who abruptly discontinue PPI therapy, there will be rebound acid hypersecretion and rebound symptoms. Most patients have rebound symptoms of dyspepsia and GERD: heartburn and a burning sensation in the esophagus (12).

Cellular hyperplasia leads to reversible excessive secretion of gastric acid and can last for weeks. There is no consensus on how long this hypersecretion lasts on average. It is estimated that it is a period of 6-8 weeks, but also up to 26 weeks.

The incidence of a rebound phenomenon depends on the intensity and duration of the drug and how long it has been applied, the individual sensitivity of the patient (severity of the primary disease and the present comorbidity), and the application of other co-therapy (13).

A gastric carcinogenic effect may be a consequence of long-term hypergastrinemia. (14). PPI therapy with secondary hypergastrinemia and ECL cell hyperplasia on a long term basis may lead to ECL cells neoplasia. In numerous case reports it has been described that gastric polyp formation with subsequent development of ECL carcinoids and carcinomas may appear in patients on long-term PPI therapy (15-18). It is debatable whether gastric cancer is induced by gastrin alone or gastrin acts as a co-factor with once triggered premalignant changes.

Proper dosing of proton pump inhibitors

Proton pump inhibitors are often inappropriately prescribed inconsistent with recommendations and guidelines, whether there is a poor indication, an overdose, or an excessive duration of therapy. For example, in therapeutic guidelines, short-term use of PPI in a duration of eight weeks is recommended for GERD and mild esophagitis to heal the inflammation and lose symptoms (19).

It has been reported that 51% of 901 Danish primary care patients on long-term PPI therapy had uninvestigated symptoms. This cross-sectional study

showed that 22% of these patients received PPI regardless of normal upper GI endoscopy (20).

If PPIs are prescribed without an appropriate indication or for longer than necessary, the dose and/or frequency of administration should be reduced. A proper way to quit PPI therapy seems to be halving the PPI dose for a month or two, and then ceasing PPI or switching to a less effective acid suppressant (H2 blocker). Antacids or H2 blockers should be prescribed to control rebound symptoms, for another 1-3 weeks after discontinuation of PPI (3). H2 blockers cause less pronounced hypergastrinemia and ECL cell hyperplasia compared with PPIs.

Studies have shown that about 30% of patients can discontinue long-term PPI therapy (21). The dose of PPI may be lower in up to 80% of patients on long term therapy (11).

If there is an appropriate indication for PPIs, PPIs should be continued with the lowest effective dose. Indications for long-term PPI therapy are severe esophagitis (LA grade C or D), Barret's esophagus, documented history of bleeding GI ulcer, chronic NSAIDs use with bleeding risk factors, Zollinger-Ellison syndrome (22).

Proper prescribing of PPI requires a documented indication, plan of the treatment duration, and patient control plan to decide on the need for further treatment.

Conclusion

Proton pump inhibitors are relatively safe drugs, with rare serious side effects.

However, it should be pointed out that these drugs are overprescribed, and it should be emphasized that they should be given only to patients with clear indications.

Long-term use of PPIs carries certain risks, insofar as their use is abruptly discontinued due to the possible rebound phenomenon of gastric hypersecretion and the appearance of rebound symptoms of dyspepsia and reflux disease.

Therefore, care should be taken to properly discontinue the use of PPIs by reducing the dose and frequency of drug administration before complete cessation, and if necessary, we can switch to H2 blockers.

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FENOMEN NAGLE OBUSTAVE TERAPIJE INHIBITORIMA PROTONSKE PUMPE

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Inhibitori protonske pumpe (IPP) najpotentniji su lekovi za suprimiranje sekrecije želudačne kiseline. Primenjuju se u terapiji acido-peptičkih poremećaja, uključujući peptičku ulkusnu bolest, gastroezofagusnu refluksnu bolest, Zollinger–Elissonov sindrom, infekciju izazvanu bakterijom *Helicobacter pylori* i profilaksu ulkusa. U farmakoterapiji ovih poremećaja, u značajnoj meri je potisnuta upotreba H2 blokatora, kao drugih, starijih grupa antisekretornih lekova.

Dugotrajna terapija IPP dovodi do umerene hipergastrinemije (pojačana sekrecija gastrina) kod 20% do 25% bolesnika. Ova hipergastrinemija rezultira povratnom hipersekrecijom želudačne kiseline (*rebound* fenomen) kod 30% do 40% bolesnika, koji su naglo prekinuli IPP. Većina bolesnika, koja je naglo prekinula IPP, ima simptome dispepsije i gastroezofagusnog refluksa, najčešće gorušicu i osećaj gorenja u jednjaku.

Zbog toga treba voditi računa o pravilnom prekidu upotrebe IPP i smanjiti dozu leka pre potpunog ukidanja. Može se preći na manje efikasan blokator kiseline (H2 blokator), s obzirom na to da blokatori H2 receptora izazivaju manje izraženu hipergastrinemiju i hiperplaziju ćelija sličnih enterohromafinu (ECL ćelija) u poređenju sa IPP.

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Ključne reči: *inhibitori protonske pumpe, rebound, hipergastrinemija, želudačna hipersekrecija*