REVIEW ARTICLE

# Overuse of proton pump inhibitors

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**KEY WORDS**

hydrochloric acid, hypergastrinemia, hypersecretion, proton pump inhibitors

**ABSTRACT**

Proton pump inhibitors (PPIs) are currently the most effective drugs inhibiting hydrochloric acid secretion. They have replaced histamine type 2 receptor antagonists in the majority of clinical indications, for example, functional dyspepsia, gastroesophageal reflux disease, or drug-induced upper gastrointestinal tract injury. High prevalence of acid-related upper gastrointestinal tract diseases, as well as the potency, good tolerance, and acceptable costs of treatment with PPIs have largely increased their use in hospitals and outpatient clinics. At present, PPIs are used more frequently, often long-term and in high doses, and not necessarily according to the current recommendations. PPI-induced inhibition of hydrochloric acid secretion causes iatrogenic hypochlorhydria and hypergastrinemia, which may result in parietal cell hypertrophy and enterochromaffin-like cell hyperplasia, exposing patients to rebound hydrochloric acid hypersecretion. It is believed that this phenomenon may be responsible for failure to discontinue pharmacotherapy with PPIs and to their overuse. As a result, an inappropriate, especially chronic, treatment increases the risk of some side effects as well as individual and institutional expenditures. Therefore, a reasonable approach to clinical indications, dosing, and treatment regimen in each individual patient should be recommended.

**Introduction** Proton pump inhibitors (PPIs) proved to be an effective therapeutic option in a variety of upper gastrointestinal tract disorders including gastroesophageal reflux disease (GERD), peptic ulcer disease and its complications, *Helicobacter pylori* (*H. pylori*) eradication therapy, dyspepsia, lesions caused by nonsteroidal anti-inflammatory drugs (NSAIDs), stress-related mucosal bleeding, Zollinger–Ellison syndrome, and other hypersecretory conditions since omeprazole, the first representative of the group, emerged on the market in the late 1980s.

Acid-labile PPIs, administered orally as inactive prodrugs, are usually available as acid-resistant, delayed-release, enteric-coated capsules or tablets to protect them from destruction in the stomach. The prodrug is absorbed after dissolving the coating in the alkaline intestinal lumen. PPIs (lipophilic weak bases) diffuse easily into an acidified compartment of the oxyntic cell canaliculi, where the prodrug is protonated, concentrated, and converted into an active thiophilic sulfonamide cation, which forms a covalent disulfide bond with cysteines (813 and 892, omeprazole; 813 and 321, lansoprazole; 813 and 822, pantoprazole and tenatoprazole) of the α-subunit of $H^+/K^+$ ATPase, preventing its phosphorylation by adenosine triphosphate (ATP) and thus irreversibly inactivating the enzyme.[1,2]

PPIs should be administered on an empty stomach as their bioavailability may be decreased by food. At breakfast, about 70% of proton pumps are active and hence susceptible to inhibition (only 10% in a fasting state); therefore, PPIs should be administered approximately 30 to 60 minutes before meals (preferably breakfast), so that the peak serum concentration coincides with the maximum excretive activity of $H^+/K^+$ ATPase.[1]

Owing to the unique mechanism of action, PPIs suppress hydrochloric acid (HCl) secretion regardless of the type of stimuli affecting parietal cells as they inhibit the final step of the secretory pathway.[1] Therefore, PPIs interfere with both fasting and meal-induced HCl secretion, and, nowadays, they are the most potent antacid drugs. Despite a relatively short half-life (usually 0.5–2 hours), PPIs inhibit HCl secretion for much longer (48–72 hours). Although an increase in pH after a single dose of the drug is only temporal, continuous treatment markedly decreases 24-hour HCl output and acidity of the gastric

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**Received:** January 8, 2015.
**Revision accepted:** March 20, 2015.
**Published online:** March 20, 2015.
**Conflict of interest:** none declared.
Pol Arch Med Wewn. 2015;
125 (4): 289-298

content. Inhibition of HCl secretion is therefore progressive, and, as a result, long-term treatment with PPIs leads to therapeutic hypochlorhydria.

From the pharmacological perspective, PPIs are nearly perfect medicines: they are accumulated and activated close to their target site of action, they have a short serum half-life, but a long duration of action owing to an irreversible inactivation of the proton pumps, and they have hardly any severe clinically relevant adverse effects, especially in a short-term treatment.[1] In addition, unlike histamine 2 receptor antagonist ($H_2$RA), the lack of the direct effect on receptors means no risk of tachyphylaxis.

High efficacy, good tolerance and safety profile, acceptable costs of treatment with both original and generic preparations available nowadays favor PPIs over other gastric acid suppressive medications in the majority of reviews, meta-analyses, and evidence-based guidelines on the management of acid-related disorders.[3-6] On the other hand, PPIs are used more and more frequently off-label, often long-term and in above-standard doses, and apparently against the official up-to-date recommendations. Such an ample overuse of PPIs raises concern about the consequences of PPI-induced hypergastinemia and potential health hazard to long-term PPI users, as discussed in this review.

**Overuse of proton pump inhibitors** High prevalence of GERD, functional dyspepsia, and drug-induced upper gastrointestinal tract lesions, predominantly caused by NSAIDs,[7] have markedly increased the use of PPIs in ambulatory and clinical care settings,[8] in both adults and children.[9] The use of PPIs has risen by 456% in the 1990s since the introduction of omeprazole in the late 1980s.[10] In the United Kingdom, the total number of prescriptions for PPIs in the ambulatory setting increased 10-fold between 1991 and 1995, and repeated prescribing accounted for 77% of the total rate.[11] The use of omeprazole, esomeprazole, and pantoprazole increased largely over the years 2002–2009 in the outpatient setting in the United States, and PPIs were prescribed in 4% of outpatient visits in 2002 and 9.2%—in 2009; however, the rate of new prescriptions did not change significantly from 2006 to 2009.[12] According to IMS Health data (National Prescription Audit), the number of prescriptions for PPIs increased from 146 million in 2009 to 164 million in 2013 (the 8th position on the list of the top therapeutic classes by prescriptions) and for omeprazole—from 46.6 million in 2009 to 70.7 million in 2013 (the 8th position on the list of top medicines by prescriptions). In many countries, PPIs have been among the top 10 best-selling medicines for several years.

There is a growing number of publications on correct versus incorrect use of PPIs worldwide.[11-15] Postulated factors contributing to an inappropriate overutilization of PPIs include physician type, practice setting, formulary status, and consumer-oriented advertising.

There is evidence that PPIs are frequently prescribed to all elderly patients at the time of admission to the hospital as "gastroprotection" to avoid any potential prosecutions against physicians in charge for neglecting medical care.[8,16] In addition, PPIs overuse in the clinical setting is often the result of incorrect stress ulcer prophylaxis in non-intensive care unit patients, and failure to discontinue this therapy before hospital discharge. In a study by Nardino et al.,[17] 54% of non-intensive care unit patients were given acid-suppressive therapy, but 65% of prescriptions were not justified, and 55% of the patients receiving any form of prophylactic gastric acid inhibition were discharged on the therapy.

Some studies reported hospital overuse of PPIs in unlicensed indications. For example, Ntaios et al.[18] showed that PPIs (mainly omeprazole) were taken by 25.4% of the patients hospitalized in an internal medicine department of a tertiary hospital, but as many as 81.2% of them had no indications according to national regulations, and the patients were not given instructions concerning the duration of treatment in discharge letters. The three main indications ("prophylaxis") were as follows: concomitant use of antiplatelet drugs (31.8%), glucocorticosteroids (22.3%), and warfarin (21.6%), whereas the three least prescribed groups: *H. pylori* eradication therapy (2.5%), dyspepsia (2.5%), and GERD/esophagitis (2.3%), are, in fact, the unquestionable indications to the use PPIs. In a 800-bed Australian teaching hospital, the analysis of the pharmacy disposals for PPIs in 253 patients over 5 consecutive weeks disclosed that in 77.5% of the subjects, PPI prescriptions did not comply with the local guidelines.[19] In a study by Lai et al.,[14] unexplained abdominal pain was the main condition (76.4%) for empirical intravenous administration of PPIs, but finally, it was found that PPIs were incorrectly prescribed in more than half of the patients (52.8%) for indication, dose, or duration of treatment. A Spanish drug-utilization study[20] showed that out of 328 inpatients, 28.65% were prescribed a PPI on admission; 82.62%, during hospitalization; and 54.75%, at discharge; and incorrect indications for PPIs were found in 74.47%, 61.25%, and 80.24% of the cases, respectively. In a Colombian study,[21] the authors analyzed prescriptions for PPIs dispensed in 89 cities within 1 month. Unjustified use was disclosed in 23.1% of the prescriptions. The 1-year unjustified costs, calculated with reference to the lowest prices, were estimated to be more than 2 million United States dollars, contributing to the increasing expenditures of the health care system. In the recently published research from Singapore, nearly half of 1025 patients (46.5%) hospitalized on a randomly selected day were administered PPIs, the majority of them (54.1%) without indications recommended by the Food and Drug Administration (FDA).[22]

PPI overutilization in outpatients often occurs in the case of failure to reevaluate the need for continuous therapy in previously hospitalized individuals discharged on a PPI or when the step-down or on-demand therapeutic strategy is not adopted in practice. It is also a common practice to prescribe PPIs by general practitioners as symptomatic treatment without clear diagnosis or for unlicensed indications. Off-label use of lansoprazole was found in 358 000 prescriptions dispensed for infants in the United States in 2010.[13] In a British study by Bashford et al.,[11] nonspecific morbidity (nonspecific abdominal pain and nonulcer dyspepsia) accounted for 46% of new prescriptions for PPIs in 1995. Up to one-third of the patients who start treatment continue to refill their prescriptions without an evident indication for the maintenance therapy. Interestingly, in 62.9% outpatient visits by PPI users in the United States, no gastrointestinal diagnosis/complaints or other appropriate indications were documented.[12]

There is also little evidence to support a common use of PPIs in cirrhotic patients, except for specific indications related to upper gastrointestinal bleeding.[23,24] Nevertheless, many subjects with severe liver disease take PPIs for a long time only for symptomatic treatment of abdominal discomfort not associated with any documented lesions or a fear of peptic ulcer development.

Chavez-Tapia et al.[25] showed that 53.9% of inpatients with chronic liver disease taking PPIs had, in fact, no indications, and the major risk factor for an inappropriate use of PPIs in these population in an ambulatory setting was their previous administration in hospital. In a recent study, Dultz et al.[26] found coincidence between PPI treatment in cirrhotic patients and higher model of end-stage liver disease scores as well as ascites. Furthermore, the use of PPIs was an independent predictor of mortality in these subjects. The reasons for such a deleterious effect of PPIs may be the fact that these pharmaceuticals promote colonization of microorganisms, including multi-drug resistant bacteria in the upper gastrointestinal tract, small intestine bacterial overgrowth, impair gastrointestinal motility[27] and neutrophil function,[28] and favor infections including spontaneous bacterial peritonitis, *C. difficile* colitis, and pneumonia. In addition, patients with more advanced liver disease (more likely to be on PPIs) are also at higher risk of PPI accumulation (impaired liver metabolism by CYP450), adverse effects, and drug interactions.

The use of above-standard doses of PPIs (usually a double dose) for initial treatment of upper gastrointestinal tract symptoms is ubiquitous. However, Targownik et al.[29] showed that initial symptomatic pharmacotherapy with a double dose of PPIs in Canadian outpatients is not superior to the treatment with a standard dose in reducing resource utilization in a 1-year follow-up. In this study, no differences in duration of PPI use, upper gastrointestinal tract-related outpatient visits or hospital admissions were revealed, and the overall costs were higher for users of double-dose PPIs.

Only partial response to PPI therapy is observed in up to approximately 30% of outpatients with GERD.[30] On the other hand, there is evidence that many patients with GERD take too high doses of PPIs in the long term, whereas it is possible to reduce a double dose to a standard dose in 80% of the cases, and a standard dose to a half of the standard dose—in 58% .[31] Although current guidelines recommend step-down and on-demand strategies of treatment in selected subjects with GERD, some patients as well as clinicians seem to be reluctant to accept such instructions. In addition, certain individuals tend to continue pharmacotherapy with PPIs despite no evidence of pathology. For example, in a study by Gawron et al.,[32] as many as 45% of 90 patients evaluated for "refractory GERD" kept taking PPIs after exclusion of any form of reflux.

The fact that many PPIs are available as relatively cheap over-the-counter (OTC) preparations under different brand names in both a half of the standard and standard doses might also be a potential risk factor for overutilization of PPIs in the outpatient settings. Moreover, patients may take both PPIs and $H_2$RA, also available as OTC preparations, and such combined pharmacotherapy promotes tachyphylaxis to $H_2$RA.[33]

Besides, some pharmaceutical companies launched capsules containing a double-standard dose (40 mg) of omeprazole that may mistakenly substitute a standard dose of pantoprazole (40 mg) in case of unaware individuals. No professional consultations before the introduction of treatment or medical supervision as to the dose/duration of the pharmacotherapy may be another risk factor for the overuse of PPIs in outpatients.

It has been also proved that patients suffering from GERD who received prescriptions from gastroenterologists were more likely to be optimal PPI users with better symptom control than OTC consumers, in whom inappropriate use of PPIs, and, consequently, inadequate GERD symptoms control, were observed more frequently.[34]

**Safety concerns** Despite the fact that PPIs have been associated with an increased risk of intestinal dysbiosis, specific infections, including pneumonia and *C. difficile* infection (CDI), osteoporosis, nutritional deficiencies, and certain drug interactions, they are, in general, well-tolerated pharmaceuticals.[35,36] PPIs in a short-term treatment have an excellent safety profile, with extremely rare clinically relevant immediate adverse effects. The frequency of the most common side effects is only somewhat higher compared with placebo and does not exceed 6%.[37-39] Headache, the most frequent complaint in clinical trials, is declared by up to 5.5% of the subjects, and serious adverse reactions, for example, hepatitis (lansoprazole, omeprazole), interstitial nephritis (omeprazole), or visual disturbances, usually

following quick intravenous infusion (omeprazole, pantoprazole) are rarely reported.[38,39]

The current and short-term use (<30 days) of PPIs, particularly at high doses, was associated with community-acquired pneumonia[40,41]; however, these associations may be confounded.[42,43] A prophylactic administration of PPIs in new users of NSAIDs does not increase the risk of hospitalization for community--acquired pneumonia.[44] In terms of hospital--acquired pneumonia, the literature shows a slight tendency supporting the evidence for an association between the use of PPI and hospital--acquired pneumonia, and a higher risk with PPIs than with $H_2$RA.[45] Suggestions as to the pathomechanism of PPI-related pneumonia include increased intragastric pH stimulating colonization of acid-labile pathogens within the upper gastrointestinal tract that may be aspired or inhibition of extragastric $H^+/K^+$ ATPases and impaired neutrophil function resulting in microbial colonization of the airways.[45] Furthermore, the use of PPI use is associated with an increased risk of enteric infections such as community- and hospital-acquired CDI[46] as well as recurrent CDI.[47,48]

Some alarming publications raised concern about the risk of drug interactions in PPI users, especially in patients taking concomitantly clopidogrel, possibly as the result of lower conversion of clopidogrel (administered as a prodrug) to an active metabolite with antiplatelet action by cytochrome CYP2C19 moderately inhibited by some PPIs, mainly omeprazole.[49,50] Polish recommendations for medical practitioners that stressed the need to use preferentially weaker CYP2C19 inhibitors (esomeprazole) or pantoprazole, issued by the Working Group of national consultants (following American expert consensus) for internal medicine, gastroenterology and cardiology,[51] were soon generally negatively verified.[52] Data on clinically relevant interactions between omeprazole and antiplatelet drugs are still questionable.[53,54] Plavix prescribing information published on the FDA website (www.fda.gov; December 2011) warns as follows: "Avoid concomitant use of Plavix with omeprazole or esomeprazole because both significantly reduce the antiplatelet activity of Plavix", but later guidelines as to the choice of a PPI in patients taking clopidogrel do not recommend a switch to a non-omeprazole substitute in current omeprazole users.[3] On the other hand, PPIs may not be effective enough to prevent gastrointestinal bleeding in all at-risk patients because of, for example, patients' noncompliance, genetic polymorphism affecting drugs' action, other drug interactions, or NSAID-induced enteropathy.

The frequency of drug interactions reported to the FDA for pantoprazole, omeprazole, and lansoprazole is very low.[39] The most common interactions for vitamin K antagonists occur extremely rarely (0.09 and 0.11 per million packages for omeprazole and pantoprazole/lansoprazole, respectively). Reports on interactions with phenytoin or benzodiazepines were documented in less than 10 patients per each of these PPIs. It has been recently shown in Japanese patients that lansoprazole, but not rabeprazole, increases serum concentration of tacrolimus and cyclosporine A.[55]

It has not been fully explained why the prevalence of chronic pharmacotherapy with PPIs is raising, whereas the incidence of new prescriptions remains steady.[11,12] Anyway, there is evidence for overutilization of PPIs worldwide, so many recent publications show considerable concern not only about the background of this marked trend, but also prospective consequences of the long-term gastric acid suppression, namely, hypochlorhydria and hypergastrinemia.

**Rebound hydrochloric acid hypersecretion** Studies have shown that many people who start treatment with PPIs cannot stop taking these pharmaceuticals or other acid-suppressive agents despite no indications for maintenance therapy. Although not proven by all researchers,[56] rebound acid hypersecretion (RAHS), defined as an increased HCl secretion above pretreatment levels following antisecretory therapy, is one of the most important suggested reasons explaining the overutilization of PPIs.[57] It is believed that RAHS is responsible for the failure to discontinue PPI therapy and high annual individual and institutional expenditures estimated at over $11 billion in the USA and £2 billion worldwide.[58]

RAHS is observed within 14 days after discontinuation of pharmacotherapy. The withdrawal of PPIs may lead to rebound acid-related symptoms from the upper gastrointestinal tract such as heartburn, acidic regurgitations, or dyspepsia resulting in the reintroduction of therapy. In the aftermath of RAHS, continuous PPI use may be adopted to alleviate withdrawal symptoms.

Hyperacidity following discontinuation of PPIs is a well-known fact.[59-61] Typical symptoms, reported by 62% to 90% of the patients, are the most troublesome 5 to 6 days after PPI withdrawal and tend to diminish with time. The duration of RAHS seems to correlate with the duration of PPI therapy. In the case of treatment lasting less than 2 months, RAHS was present for less than 8 weeks, but in the case of chronic gastric acid suppression (≥1 year)—for 8 to 26 weeks.[61]

Interestingly, RAHS is not limited to patients and was observed in healthy volunteers taking less potent acid-suppressive drugs such as ranitidine.[62] In a randomized, double-blind, placebo-controlled trial, Reimer et al.[57] showed that rebound symptoms are also reported by healthy volunteers who discontinue taking a PPI (40 mg of esomeprazole daily for 8 weeks). Upper gastrointestinal tract symptoms assessed weekly according to the Gastrointestinal Symptom Rating Scale showed no difference between the groups at baseline, but a higher score in the PPI group after withdrawal of the drug was revealed. As many as 44% of the PPI group reported acid-related symptoms in

weeks 9 to 12 in comparison with 15% in the control group. At week 10 of the study, 22% of the subjects versus 7% of the controls suffered from dyspepsia, heartburn, and acidic regurgitations, and the incidence of symptoms decreased with time (21% vs 2% at week 12, respectively).

Niklasson et al.[63] confirmed previous observations. Her research team showed that RAHS was observed in healthy volunteers taking another PPI, which suggested a class effect. In this randomized, double-blind study, 48 *H. pylori*-negative healthy subjects had been taking either pantoprazole (40 mg/d) or placebo for 4 weeks, and than both groups were followed up for 6 consecutive weeks. The severity of symptoms was measured before, during, and after administration of a PPI or placebo according to the Glasgow dyspepsia score system. On the first week of the follow-up, 44% of the subjects taking a PPI reported symptoms versus 9% in the control group ($P$ <0.01). The authors found a correlation between the severity of dyspepsia and serum gastrin concentration that normalized within 6 weeks after a PPI had been discontinued.

It is generally believed that RAHS is associated with an elevated serum gastrin concentration on acid suppression therapy and a secondary increase in parietal and enterochromaffin-like (ECL) cell mass and activity.[61,63,64] Fossmark et al.[61] measured basal and pentagastrin-stimulated HCl output, serum gastrin, and chromogranin A (CgA) in GERD patients who discontinued long-term (>12 months) pharmacotherapy with PPIs after antireflux surgery at 4, 8, 16, and 26 weeks postoperatively. In addition, serum CgA and gastrin concentrations were measured before the operation. Mucosal biopsies were taken before and 26 weeks after the operation. Pentagastrin-stimulated HCl secretion was higher at 4 and 8 weeks than at 26 weeks after surgery. The number of oxyntic cells was reduced by 60% 26 weeks after surgery.

RAHS may have clinical implications because induced acid-related complaints may lead to "PPI dependency". Unpleasant symptoms of hyperacidity following discontinuation of PPIs might be more troublesome than the initial signs of the acid-related upper gastrointestinal disorder that were an indication for pharmacotherapy. Rebound symptoms cause anxiety and decrease the quality of life to such an extent that patients wish to ameliorate the symptoms as soon as possible ("PPI withdrawal syndrome"). The patient unaware of the pathogenesis and temporal nature of RAHS may seek professional help, but the random access to specialists, especially gastroenterologists, is limited. On the other hand, nowadays, PPIs are available as OTC preparations not only in a small but also in a standard dose. Therefore, the probability that the patient will reintroduce any form of antacid pharmacotherapy, including the most potent and widely advertised PPIs, seems to be quite high. Such a scenario leads to an overuse of PPIs as well as increases the costs of treatment, the risk of adverse effects of chronic HCl suppression, and "pseudotachyphylaxis" to PPIs due to an increased total mass of the parietal cells.

**Hypergastrinemia and its consequences** Serum gastrin levels are regulated by intragastric pH. Normal serum gastrin levels vary among studies, for example, <55 pmol/l (<212 pg/ml)[65] or 36 pmol/ml (±57 pg/ml).[66] Regardless of the etiology, HCl suppression modifies physiological feedback inhibition. Mild or modest hypergastrinemia is a typical reaction to the reduced gastric acid secretion no matter what is the cause. Therefore, an elevated serum gastrin concentration is, in fact, an anticipated effect secondary to pharmacotherapy with PPIs.

Although PPI-induced hypergastrinemia is a well-known fact, the data on its grade, duration, and clinical significance differs notably among researchers. It is generally believed that the serum gastrin concentration increases 2 to 4 times after 2 weeks of treatment with PPIs. In chronic treatment, it raises 3 to 4 times the baseline level through the first 1 to 2 months and then stabilizes or shows a discrete downturn. Some data report that in PPI users, the median serum gastrin levels increase 1.5- to 2-fold, but usually remain within the reference range (<100 pg/ml).[1] According to other studies, it is less than 103 pg/ml (±94 pg/ml)[65] or 250 pg/ml[66] in long-term treatment with PPIs. Typically, hypergastrinemia does not exceed 5 times the upper limit. Nevertheless, serum gastrin concentrations exceed 500 pg/ml in 3% of PPI users, which results in diagnostic dilemmas as such a concentration may be observed in pernicious anemia or gastrinoma.[1]

Hypergastrinemia follows treatment with all PPIs, although some data claims that this increase may be lower with omeprazole than with rabeprazole[67] and lansoprazole,[68] and lower with pantoprazole than with omeprazole,[69] but the differences seem to be clinically irrelevant.

Gastrin, released by G cells of the stomach, duodenum, and the pancreas, is a basic stimulus for postmeal HCl secretion. It activates parietal cells directly via CCK type B receptor and indirectly, through activation of receptors on the ECL cells and then histamine release.[70] Gastrin also stimulates the release of ghrelin that increases secretion of HCl through histamine release. Histamine from ECL cells acts as a paracrine signaling agent on the parietal cells via $H_2$ receptors. Gastrin is also a trophic agent toward parietal and ECL cells. This peptide hormone stimulates mitosis, synthesis of DNA, RNA, and structural proteins of cell membranes; therefore, an increased serum gastrin concentration in long-term users of PPIs raises at least theoretical concern about the clinical significance of prolonged hypergastinemia.

In physiological conditions, somatostatin acts as an inhibitory hormone that indirectly reduces HCl production by preventing the release of other hormones, including gastrin and histamine. Katagiri et al.[71] reported that an oral administration

of a single dose of omeprazole in healthy humans increased plasma somatostatin-immunoreactive substance levels at 60 to 240 minutes. On the other hand, as shown in animal studies, omeprazole-induced hypochlorhydria reduces somatostatin release from antral D cells that mediate a paracrine inhibition on gastrin gene expression in adjacent G cells.[72,73] Interestingly, it has been found that octreotide, a long-acting somatostatin analog (25 μg given subcutaneously 3 times per day), prevented baseline and meal-stimulated increases in serum gastrin levels during omeprazole therapy (40 mg daily for 5 days) in humans.[74]

Although PPIs have been regarded as safe pharmaceuticals, secondary hypergastrinemia rises concern about the risk of neoplastic transformation of the gastric mucous membrane.[75] As early as in 1996, Waldum et al.[59] reported a correlation between an increase in food-stimulated gastrin release on PPI therapy and an increased ECL cell mass. However, the issue whether PPI-associated hypergastinemia increases ECL cell hyperplasia still remains widely disputed. Some data support this correlation,[76,77] whereas other researchers deny it.[78,79] Studies in rats showed that omeprazole changes the expression of genes involved in cell proliferation, apoptosis, and defense (immune, inflammatory, and stress) response in gastric corpus mucosa.[80] Long-term treatment with omeprazole in children is associated with an increased number of G cells,[81] and chronic treatment with PPIs in *H. pylori*-positive adults was associated with small G cell-derived tumors in the duodenal bulb.[82] In female rats, a prolonged administration of PPIs promotes formation of gastric carcinoids, but it has been disputed whether long-term pharmacotherapy with PPIs induces ECL cell neoplasia in humans. A correlation between the level of hipergastrinemia and ECL cells hyperplasia was found in humans, but progression to carcinoids within altered mucous membrane has not been well documented,[36] despite the fact that in the last 20 years, the incidence of carcinoids has increased. Interestingly, even in cases of prolonged and marked hypergastrinemia related to Zollinger–Ellison syndrome, gastric carcinoids or cancer is rare (probably a chance association).[65]

In a study by Brunner et al.,[38] chronic treatment of adults with pantoprazole (40–160 mg daily) for up to 15 years proved to be effective, safe, and well-tolerated. The systemic assessment (clinical examination, laboratory tests including serum gastrin concentration, endoscopy with gastric mucosal histology, and endocrine cell quantification) of 142 patients showed that mean fasting gastrin levels increased from baseline to moderate concentrations throughout the study, but mean ECL cell density initially moderately increased during the first 3 years, and remained unchanged thereafter. No significant lesions of the gastric mucous membrane were associated with these alterations.

On the contrary, Jianu et al.[36] described gastric carcinoids found on a routine gastroscopy in 2 long-term (12–13 years) PPI users treated for GERD.[83] In both cases, histology of unchanged flat gastric mucosa showed no signs of atrophic gastritis, but hyperplasia of ECL cells was present. In 1 patient, the tumor was resected endoscopically, while in the other, it regressed after discontinuation of PPI therapy. In the latter case, normalization of serum gastrin and chromogranin A levels, previously elevated on PPI treatment, was documented. The ECL cell hyperplasia in the flat gastric mucosa regressed in both patients. Anyway, at present, there is a general consensus that routine monitoring of serum gastrin concentrations is not recommended in patients on long-term PPI treatment.[36]

Chronic acid suppression in *H. pylori*-positive patients may promote chronic gastritis in the gastric body that might precipitate atrophy and intestinal metaplasia as well as increase the risk of gastric adenocarcinoma. However, according to the current FDA position statement, there is no evidence that prolonged PPI therapy results in multifocal atrophic gastritis or intestinal metaplasia associated with an increased risk of adenocarcinoma. On the other hand, it should be stressed that PPIs may mask the symptoms of, especially early, gastric cancer and, therefore, delay an accurate diagnosis and treatment.

It has not been unequivocally proved that acid-suppressive pharmacotherapy increased the risk of carcinoma at any site in humans,[84-87] although some animal[88] and human studies[89,90] do not entirely exclude such an association. In addition, animal models showed conflicting data on the influence of the PPI-induced hypergastrinemia on the progression of Barrett's esophagus.[91] Obszynska et al.[66] addressed this controversial issue in 90 patients randomized to different doses of PPIs for 2 years and in cell models. Prolonged PPI therapy increased the mean serum gastrin concentration approximately 3-fold in comparison with the initial concentration, but no difference in the change in Barrett's esophagus segment length was shown regardless of the dose of PPIs over 2 years. Both migration and proliferation of cells in vitro were induced by gastrin at concentrations of 1 ng/ml and 100 ng/ml, respectively, but these effects were reversible, which suggests clinical safety of PPI therapy in Barrett's esophagus.

On the other hand, resent alarming findings, showing that omeprazole may act as a liver tumor promoter in rats, definitely deserves further interest.[92,93]

**Fundic gland polyps** PPI use is associated with an increased incidence of fundic gland polyps (FGPs), mainly in *H. pylori*-negative patients on long-term treatment with PPIs.[94,95] The analysis of the results of biopsies performed in 78 909 patients on gastroscopy over 1 year in the United States private centers showed gastric polyps in 6.35%, most of which were FGPs (77%).[96] The

authors concluded that an increased incidence of FGPs as compared with the previous years might be associated with an overutilization of PPIs. In a study by Zelter et al.,[93] PPI use was the most important risk factor for the presence of FGPs. Although chronic pharmacotherapy with PPIs increases the risk of FGPs 4-fold, FGPs develop in a small number of PPI users.[97] Interestingly, the level of PPI-induced hypergastinemia was not related to the development of FGPs.[98]

PPI-associated FGPs are usually asymptomatic, tiny, and benign with low-grade dysplasia found in less than 1% of FGPs.[97] Despite some case reports on high-grade dysplasia within FGPs in nonfamilial adenomatous poliposis patients,[99,100] it is believed that FGPs are not a risk factor for gastric malignancy. Nevertheless, their presence on endoscopy may cause patients' distress and demand regular (currently, in general, not recommended) endoscopic and histological follow-up. Discontinuation of PPIs may result in complete regression of FGPs.[93,101]

**Conclusions** Generally, in the clinical care setting, pharmacotherapy with PPIs should be initiated in conditions that deserve efficient inhibition of HCl secretion, for example, severe erosive esophagitis or peptic ulcer complicated with bleeding. The need to continue PPIs (duration/dosage) after hospitalization ought to be reevaluated at the time of discharge.

From the perspective of outpatient care, PPIs should be also used in specific subpopulations of patients with unquestionable indications for antacid treatment, in adequate doses, and for a certain time. The FDA recommends no more than 3 courses of treatment for heartburn with PPIs available as OTC preparations per year, no longer than 2 weeks each. The indications for long-term PPI therapy should be carefully assessed, including both the current guidelines and the risk-to-benefit ratio for individual patients.

The duration of treatment should be planned. The patient ought to be informed about the general schedule of pharmacotherapy, including the instructions (preferably written) on the dosage of the drug. If necessary, the follow-up visit should be scheduled, and the need to continue PPIs at the initial dose ought to be evaluated. In chronic treatment, the lowest effective dose, tailored to individual needs and therapeutic goals, should be used. In addition, chronic pharmacotherapy may require monitoring of potential adverse effects, especially in certain groups of patients (elderly patients, malnourished individuals, those with numerous comorbidities, etc.).

In the case of discontinuation, the drug dose should be first decreased slowly and then stopped. Sana et al.[102] recommended the following scheme of dose reduction over 16 weeks in case of extra-esophageal manifestations of GERD: withdrawal of $H_2$RA (if used) for the first 8 weeks, and concomitant decrease of the PPI dose to a single standard dose daily.[102] If there are no symptoms for the next 8 weeks, the PPI dose should be reduced to a single standard dose every other day and then discontinued. The decision on the need and the PPI dose in the maintenance therapy should consider the impact of residual symptoms on the patient's quality of life. Nevertheless, the patient should be informed that sometimes, despite taking all these precautions, discontinuation of treatment may cause some mild and usually temporal symptoms that do not necessarily mean a relapse of acid-related disease, and, therefore, an immediate reintroduction of acid-suppression therapy may not only be unnecessary, but even potentially harmful, and thus, contraindicated.

To conclude, PPIs, as any other medications, should be used only when indicated and as long as the maintenance of effective acid suppression is needed, according to evidence-based recommendations. A reduction in the rates of inappropriate administration of PPIs in the clinical and ambulatory settings should minimize both the risk of potential adverse effects and the health care costs.

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ARTYKUŁ POGLĄDOWY

# Nadużywanie inhibitorów pompy protonowej

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**SŁOWA KLUCZOWE**

hipergastrynemia, inhibitory pompy protonowej, kwas solny, nadmierne wydzielanie

**STRESZCZENIE**

Inhibitory pompy protonowej (IPP) są obecnie najskuteczniejszymi lekami hamującymi wydzielanie kwasu solnego. Zastąpiły antagonistów receptora histaminowego typu 2 w większości wskazań klinicznych, na przykład dyspepsji czynnościowej, chorobie refluksowej przełyku czy polekowych uszkodzeniach górnego odcinka przewodu pokarmowego. Duże rozpowszechnienie chorób górnego odcinka przewodu pokarmowego, których etiopatogeneza ma związek z wydzielaniem kwasu solnego, oraz skuteczność, dobra tolerancja i akceptowalne koszty leczenia znacznie zwiększyły zużycie IPP w lecznictwie zamkniętym i ambulatoryjnym. W tej chwili IPP stosuje się częściej, niejednokrotnie przewlekle i/lub w większych dawkach, a przy tym nie zawsze według aktualnych zaleceń. Hamowanie wydzielania kwasu solnego spowodowane przyjmowaniem IPP prowadzi do jatrogennej hipochlorhydrii i hipergastrynemii, co sprzyja przerostowi komórek okładzinowych i hiperplazji komórek enterochromafinopodobnych, narażając pacjentów na zwiększone wydzielanie kwasu solnego „z odbicia". Uważa się, że to zjawisko może być odpowiedzialne za nieudane próby zaprzestania leczenia farmakologicznego IPP i nadużywanie tej grupy leków. W następstwie, niewłaściwa, szczególnie przewlekła terapia zwiększa ryzyko niektórych działań ubocznych oraz indywidualne i instytucjonalne wydatki na leczenie. W związku z tym, w przypadku każdego pacjenta należy zalecać rozsądne podejście do wskazań klinicznych, dawki i schematu leczenia IPP.

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**Praca wpłynęła:** 08.01.2015.
**Przyjęta do druku:** 20.03.2015.
**Publikacja *online*:** 20.03.2015.
**Nie zgłoszono sprzeczności interesów.**
Pol Arch Med Wewn. 2015; 125 (4): 289-298