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PROTON PUMP INHIBITORS: ASSESSMENT OF SIDE EFFECTS AND APPLICATION IN COVID-19 INFECTION

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Summary: Proton pump inhibitors (PPIs) are among the most commonly prescribed drugs. Their use is probably even higher than estimated due to the increase in the number of PPIs available over the counter. These medications are often prescribed for inappropriate indications or unnecessarily long treatment. The increased use of PPIs in the last two decades has called into question the long-term effects of these drugs. There are data from observational studies that indicate that long-term use of PPIs increases the risk of chronic kidney disease, dementia, osteoporosis, pneumonia, gastrointestinal tract infections, malabsorption of minerals and vitamin B12, as well as the risk of infection and a more severe course of the disease, COVID-19. However, the aforementioned suspicions do not yet have enough evidence to confirm a causal link between the disorder and PPI use, and even when there is a perceived risk, it is generally small. There is a need for better quality studies investigating this relationship. Proton pump inhibitors prescribed for the appropriate indication and for the appropriate duration of treatment are still safe drugs that bring more benefits to patients than risks.
Keywords: proton pump inhibitors, side effects, COVID-19

INTRODUCTION

Proton pump inhibitors (PPIs) are the most potent group of drugs used to suppress gastric acid secretion. With the appearance of these drugs at the end of the eighties of the last century, the treatment of acid peptic disorders has radically changed. PPIs are becoming one of the most prescribed drug groups in the world. In the pharmacotherapy of gastrointestinal disorders, they significantly suppressed the use of histamine H2 blockers, as another important or older group of antisecretory drugs.

The benzimidazole derivative - omeprazole was the first PPI introduced in 1988, and today there are others on the market: lansoprazole, rabeprazole, pantoprazole and esomeprazole (the active C-isomer of omeprazole). Their use in the world is growing year by year. PPIs are the second group of drugs in the number of prescribed and issued prescriptions in the USA in 2008, right after statins. The results of three different studies showed that 40-71.4% of patients treated in hospitals received PPIs, of which even 65-70% of patients had no real indication for their use [1]. In 2016, 839,548 PPI prescriptions were issued in Slovenia (4.7% of all prescriptions), and their representative drug pantoprazole is the second most commonly prescribed active ingredient after paracetamol. As PPIs are also available without a prescription, the actual consumption is probably even higher [2].

There are many indications for PPI treatment. Among them we include: peptic ulcer of the stomach and duodenum, dyspepsia, bleeding and prevention of bleeding from the upper parts of the gastrointestinal tract (due to non-steroidal anti-inflammatory drugs, antiplatelet, anticoagulant and corticosteroid therapy), prevention of bleeding in critically ill patients, eradication of Helicobacter pylori infection, gastroesophageal reflux disease, Barrett's esophagus, eosinophilic esophagitis and Zollinger-Ellison syndrome. Because of their exceptional efficacy and absence of serious side effects, the number of "indications" for PPIs gradually expanded to include various, even ill-defined problems without a convincing causal link to stomach acid. Regardless of the specialty of the doctor who prescribed the PPI, the proportion of inappropriately prescribed PPIs is alarmingly high, as it often exceeds 50% [3]. The following is a brief critical review of the possible side effects of long-term PPI use.

KIDNEY DISEASE

PPIs are a known trigger of acute interstitial nephritis, and recent research suggests an association between PPI treatment and the onset of chronic nephritis. In studies from 2014 and 2016, 72 cases of acute interstitial nephritis were diagnosed in a cohort of 572,661 patients with newly prescribed PPIs. The risk was fivefold higher in patients taking PPIs, the highest in patients older than 60 years [4,5]. A 2015 study involving 290,592 patients over 65 years of age taking PPIs and the same number of controls identified 40 cases of acute interstitial nephritis. The risk of acute kidney damage in patients treated with PPIs was 2.5 times higher [6]. Acute interstitial nephritis can be overlooked, and further treatment with the active substance that triggered the inflammation leads to the development of chronic kidney disease [5]. The relationship between PPI treatment and chronic kidney disease has been studied in four large studies [7–10].

In a study published in 2016, 10,482 patients were treated; PPIs were given to 3% of patients. Compared to patients who did not use PPIs, they had a statistically significantly higher body mass index and an increased prevalence of arterial hypertension. The absolute risk of chronic kidney disease in patients on PPIs was higher by 3.3% [7]. Xie et al. found a 1.22 times higher risk for chronic kidney disease when using PPIs [8]. A slightly higher risk was shown in PPI dosing twice a day, while no increased risk was observed in patients treated with histamine H2 receptor antagonists [9]. A 2017 study by Klatta et al showed that in patients treated with PPIs, prolonged duration of this therapy was associated with an increased risk of adverse renal outcomes, and that the risk of doubling serum creatinine concentration was 1.26 times higher than in users of histamine antagonists. H2 receptors [10]. Given the design of the mentioned research (retrospective, observational studies), we cannot unequivocally conclude about a cause-and-effect relationship between PPI treatment and the development of chronic kidney disease. These shortcomings can only be avoided by planning prospective randomized studies.

DEMENTIA

Research conducted on a population of mice showed that PPIs accelerate the formation of beta amyloid, and at the same time, by acting on the proton pumps of lysosomes, prevent its degradation [11]. In a German cohort study on a sample of 3,327 elderly people, during an 18-month follow-up with a structured neurological assessment, 431 cases of dementia were identified, including 260 cases of Alzheimer's disease [12]. Patients treated with PPIs had a 1.38 times higher score of any form of dementia and a 1.44 times higher risk of Alzheimer's disease. In an extended German cohort study with 73,679 elderly people, 29,510 cases of dementia were identified based on coded diagnoses in the insurance database, and PPI users were found to be 1.44 times more likely to have dementia [13]. Differences between groups in age, sex, number of regularly prescribed drugs and history of stroke, ischemic heart disease and diabetes were equalized using statistical methods. A similarly high risk was found in an Asian retrospective study, which was also based on insurance data [14]. The above findings are in contrast to the findings of the Finnish case-control study. The study included 70,718 patients diagnosed with Alzheimer's disease between 2005 and 2011 [15]. They found that PPI use was not associated with a higher incidence of Alzheimer's disease, and no higher risk was identified in patients taking higher doses of PPIs or taking them for longer periods of time.

A 2020 study from Great Britain based on a population of 3,765,744 people, using health data from multiple centers in Wales, could not confirm an association between PPI use and an increased risk of dementia. Previously reported associations may be related to uncertain data on PPI use or medications used for cardiovascular disease or depression. The results of two smaller studies with approximately 10,000 subjects also do not show a conclusive link between PPI use and dementia [17,18]. Although the mentioned studies indicate a possible safety risk when using PPIs in the elderly, the findings of the Finnish study with the most and most accurately diagnosed cases of Alzheimer's disease question the described causal relationship - the risk did not depend on the dose of PPIs or the duration of treatment.

OSTEOPOROSIS AND BONE FRACTURES

The mechanisms of bone damage associated with PPIs are still unclear, but impaired micronutrient absorption,

hypergastrinemia, and increased histamine secretion may play a role. During PPI treatment, the pH in the stomach increases (the acidity of the gastric fluid decreases), therefore the secretion of gastrin is compensatory increased.

Animal studies may indicate that hypergastrinemia is caused by hyperparathyroidism, if at the same time there is a disorder of vitamin B12 absorption, and at higher pH values of the stomach contents, the concentration of homocysteine increases, all of which can affect bone density [11]. In a study published in 2022, it was shown that long-term administration of lansoprazole caused symptoms of osteoporosis in mice, and lansoprazole triggered an increase in calcium in osteoblasts. Intracellular calcium persisted in high concentration, thus causing endoplasmic reticulum stress and inducing osteoblast apoptosis [19]. In a meta-analysis of 10 studies on a sample of 223,210 fracture cases, a slightly increased risk of hip and vertebral fractures was revealed (1.25 times) and (1.50 times), respectively, while the difference in cases of wrist fractures was not statistically significant [20]. In three of the four included cohort studies, no increased risk of fracture was demonstrated, while in five of the six case-control studies, an increased risk was found (up to 1.62 times). A difference in the level of risk regarding the duration of treatment was not determined in the meta-analysis [2]. A recent meta-analysis confirmed an increased risk of hip and vertebral fractures also taking into account only cohort studies, but the duration of PPI treatment did not affect the level of risk - namely, the increased risk was recognized already in the first year of use and it did not change over time [21]. In previous research, a convincing association between PPI treatment and reduction of bone density has not been proven [22,23]. Therefore, it was not possible to assess a causal relationship between taking PPIs and the effect on bone density, as the risk was only slightly increased. However, clinicians should exercise caution when prescribing PPIs to subjects with a pre-existing high fracture risk and consider the use of anti-osteoporotic drugs to control this additional effect of PPIs on bone.

GASTROINTESTINAL INFECTIONS

Gastric acid has a bactericidal effect on the ingested microbiome, and the intestinal microbiota changes during PPI treatment [24]. The effect of both mechanisms can increase the likelihood of Clostridium difficile infection and other gastrointestinal infections. The association between PPI treatment and C. difficile infection was discussed in three meta-analyses, which found that patients treated with PPIs were 1.7 times more at risk of developing C. difficile infection than those not using PPIs [23– 25]. The risk is further increased in patients receiving antibiotics at the same time as PPIs. The studies were mostly retrospective and differed from each other in terms of criteria within the groups. The duration of therapy and the dose were registered in only one study, so with the mentioned remarks, no conclusion can be drawn about the causal relationship between the frequency of C.difficile infection and the use of PPIs. In a recent retrospective cohort study on a sample of 18,134 intensive care unit patients at particular risk of C.difficile infection, no additional risk of C.difficile infection from PPI therapy was identified [26]. As expected, the most important risk factor for C. difficile infection was the use of antibiotics.

Research on the incidence of bacterial infections from the genera Salmonella and Campylobacter are significantly less frequent than studies on C.difficile infection. In two studies, they found that infection with these strains was 6 times higher when PPIs were used [27,28]. A large retrospective cohort study of 1,913,925 patients and nearly 7,000 cases of Salmonella and Campylobacter infections showed a slight increase in the risk of these infections in the PPI group, but infections with these bacteria were more common in these patients even before PPI administration [29].

INFECTIONS OF THE LOWER RESPIRATORY TRACT

An elevated pH value in gastric juice can allow bacterial growth, and microaspiration of gastric contents can lead to pneumonia [11]. An association between PPI use and the development of host lower respiratory tract infection has been identified in several observational studies. In two older meta-analyses, no differences were found [30,31]. In a recent meta-analysis, the risk of developing pneumonia in people using PPIs is 1.5 times higher [32]. According to the vast majority of research, when using PPIs, the risk of lower respiratory tract infection is higher in the first month, most pronounced in the first week of use.

The results of a double-blind, randomized controlled trial with esomeprazole that included more than 9,000 patients showed no association between PPI use and respiratory infections [33]. Based on the time interval between PPI prescriptions, it appears that the onset of respiratory infection symptoms is most likely attributable to gastroesophageal reflux disease (GERD) [34]. Despite the undeniable shortcomings of study randomization, it is unlikely that lower respiratory tract infections have any proven clinically relevant causal relationship with PPI use.

CLOPIDOGREL AND PROTON PUMP INHIBITORS

Clopidogrel is a prodrug that is activated in the liver by the action of cytochromes (mainly CIP2C19). These enzymes also metabolize PPIs, especially omeprazole, esomeprazole, and lansoprazole. Due to competition for enzyme binding sites, it is therefore theoretically possible that concurrently prescribed PPIs reduce the efficacy of clopidogrel and thereby increase the risk of cardiovascular events [11]. In a meta-analysis, which included research results up to February 2014 (39 studies with 214,851 patients, of which 73,731 received clopidogrel and PPIs simultaneously) [35,36] in patients who received both drugs simultaneously, an increased risk for death, myocardial infarction, blood vessel thrombosis and cerebrovascular event. If we consider only randomized trials and cohort studies with statistical equalization of initial differences between groups of patients, increased CV risk is not observed. However, whatever the study criteria included, it is evident that the risk of gastrointestinal bleeding in patients receiving clopidogrel and PPIs was significantly lower. Most authors conclude that the difference in conclusions between the randomized and nonrandomized studies is likely due to the underlying increase in cardiovascular risk in patients receiving PPIs in the nonrandomized studies. There is no convincing evidence to challenge the use of PPIs in combination with clopidogrel, but it may make sense to use pantoprazole or rabeprazole, which are metabolized by other pathways [37].

There is not much work to conclude on the interaction between PPIs and the newer antiplatelet agents, ticagrelor and prasugrel.

TUMORS OF THE GASTROINTESTINAL TRACT

Proton pump inhibitors cause compensatory hypergastrinemia and at the same time interfere with mucus secretion from the gland in the fundus of the stomach [11]. Long-term PPI treatment with concurrent H. pylori infection can worsen gastritis (caused by H. pylori infection) and lead to atrophy of the gastric mucosa, which is a possible pathophysiological mechanism of gastric carcinogenesis. In vitro studies have shown the trophic effect of gastrin on colon adenocarcinoma cells. A meta-analysis showed that long-term, at least one-year use of PPIs was associated with a 2.45-fold increased risk (range 1.03 to 10.7-fold) for the formation of gastric fundic gland polyps [38]. Fundic gastric polyps associated with PPI use are clinically insignificant and do not pose a risk of malignancy. The appearance of dysplasia in these polyps is extremely rare, therefore there is no need for endoscopic monitoring and polypectomy. Data on the association between PPIs and gastric adenocarcinoma are not consistent [39]. Two meta-analyses found that the risk of gastric cancer with PPI use was up to 1.5 times higher, but the possibility that PPIs were actually prescribed to treat early unrecognized symptoms of gastric cancer in these studies could not be excluded. Likewise, several studies did not provide data on the presence of H. pylori infection. Also, there is no convincing evidence of gastric neuroendocrine tumors as a consequence of PPI therapy, although moderate hypergastrinemia has been demonstrated with their use [40,41]. Individual examples of findings of neuroendocrine tumors when using PPIs are most likely coincidental without a proven cause-and-effect relationship with PPIs [41]. The link between long-term PPI use and colorectal cancer has not been proven either. An extensive post-marketing analysis at the request of the Food and Drug Administration (FDA) did not show a higher risk of developing tumors of the digestive organs in people who used PPIs [42,43].

Although the authors of the latest retrospective study of 973,000 new users of PPIs and 198,000 new users of histamine-2 receptor antagonists suggest that the absolute increase in gastric cancer risk with PPI use is very small, they support the need to avoid long-term PPI use when not medically indicated. [44]

VITAMIN AND MINERAL ABSORPTION DISORDERS

An elevated pH value in the stomach can reduce the absorption of iron and vitamin B12, while the pathophysiological mechanism of hypomagnesemia is unclear [11]. A retrospective cohort study [45] and a case-control study [46] identified an increased risk of iron deficiency depending on the dose and duration of PPI treatment. A risk for reduced iron absorption was also observed in a controlled study with histamine H2 receptor antagonist therapy. In the extended phase of two randomized trials (12 and 5 years, respectively) comparing the efficacy of PPIs and antireflux surgery, it was found that there were no differences in iron stores between these groups of subjects [47].

Although the cause-and-effect relationship and the influence of other variables on the reduction of iron levels in such designed studies cannot be reliably assessed, the influence of PPIs should also be considered if there is iron deficiency in people who use PPIs for a long time and regularly.

Data on hypovitaminosis B12 in people using PPIs are conflicting.

In a case-controlled study involving 25,956 patients with vitamin B12 deficiency and 184,199 controls, a 1.65-fold increased risk for hypovitaminosis B12 was found in patients receiving PPIs for more than two years [48]. In the previously mentioned randomized trials on the effectiveness of antireflux surgery or PPIs, there were no differences between groups regarding vitamin B12 deficiency [47].

There are completely different data on hypomagnesemia. The results of a meta-analysis of nine observational studies showed a 1.43-fold increased risk of hypomagnesemia [49], while a later prospective cohort study on a sample of 9,818 patients with long-term PPI use reported a clinically insignificant decrease in serum magnesium levels. At the same time, the risk of hypomagnesemia was highest in patients who simultaneously used a loop of Henle diuretic [48]. In a study of a sample of 414 patients who received PPIs for at least 6 months and were followed for an average of 5.7 years, 57 cases of hypomagnesemia were found. At least one additional causative factor of hypomagnesemia was present in 44 of them. In addition, hypomagnesemia was mild and asymptomatic in most cases [49].

Hypomagnesemia is probably an idiosyncratic effect of PPIs that we should consider in the absence of another clear cause of said electrolyte disturbance.

COVID-19 AND PROTON PUMP INHIBITORS

In early 2020, there were reports that PPIs could have a beneficial effect on the course of SARS-CoV-2 viral infection [50,51]. At the same time, there were reports of more severe disease progression in patients taking PPIs simultaneously, due to more frequent secondary infections and acute respiratory distress syndrome (ARDS) [52]. Reduced secretion in the stomach is "blamed" for that. Namely, the hypoacidic environment reduces the probability of eradication of introduced pathogens or allows them to grow in the intestines. Later published data from a meta-analysis of 5 studies suggested that there is a relationship between taking PPIs and a higher risk of severe disease from COVID-19 [53], as well as an increased likelihood of SARS-CoV-2 infection [54]. A pooled analysis of data from three of the five mentioned studies showed an almost 50% higher risk of a severe form of the disease, that is, of a fatal outcome of COVID-19 in patients receiving PPIs. [55–57]. Another pooled analysis showed a significantly increased risk of secondary infections in patients receiving PPIs [52,58].

A large meta-analysis published in February 2022 aimed to address the relationship between PPI use and severity of COVID-19 infection. A systematic literature search was conducted from December 2019 to January 2022. 14 studies were included. Susceptibility to infection with COVID-19, severity of COVID-19 (defined as a composite of adverse outcomes: admission to intensive care, need for oxygen therapy, need for ventilatory support, or death) and mortality from COVID-19 were assessed. It was concluded that PPI use was marginally associated with a nominal but statistically significant increase in the risk of infection with COVID-19. PPI use also increased the risk of complications and poor outcomes in patients with COVID-19. The study also concludes that the increased risk of COVID-19 infection in PPI users is only marginal and therefore does not merit prophylactic discontinuation of PPIs in patients for whom this drug is indicated. This study suggests that PPIs increase the risk of poor clinical outcomes in patients with COVID-19; therefore, PPIs should

be initiated with caution in this population. All patients with COVID-19 using PPIs should be closely monitored for severe or co-morbidities. Current evidence is insufficient to recommend discontinuation of PPIs in patients with COVID-19. Further studies are needed to consolidate the findings. Furthermore, future studies should investigate whether the variant of COVID-19 influences the association of PPI use with the susceptibility and prognosis of COVID-19 [59].

CONCLUSION

PPIs have an excellent safety profile marred by frequent prescribing for the wrong indication, or inappropriate and unnecessarily long duration of treatment. Despite the widespread use of PPIs, data on adverse effects are based almost exclusively on the results of observational studies, which are, however, unsuitable for defining causality. The identified levels of associated risk with the use of PPIs are generally small and insufficient to rule out the possibility of research bias. It is unrealistic to expect that randomized studies can be conducted for all potential side effects of PPIs, although only in this way can we reasonably conclude about possible causality.

Proton pump inhibitors are very effective if they are indicated for peptic ulcer, dyspepsia, prevention of bleeding from the upper gastrointestinal tract due to non-steroidal anti-inflammatory drugs, antiplatelet and anticoagulant drugs, in the prevention of bleeding in critical patients, eradication of Helicobacter pylori infection, gastroesophageal reflux disease, treatment of Barrett's esophagus, eosinophilic esophagitis and Zollinger-Ellison syndrome. For now, until we get the results of new qualitative research, which would show different results, and with a sober consideration of indications, doses and duration of treatment, we consider PPIs to be safe drugs where the benefits of the treatment outweigh the potential risks.

In patients with COVID-19, an individual assessment of the benefits and risks of taking PPIs is required or a regular check of the indications for taking PPIs in the lowest, still effective doses or substitution for otherwise less potent histamine-2 receptor inhibitors.

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