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Proton pump inhibitors - possible side effects of long-term therapy: a review

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Abstract

Introduction and purpose: Proton pump inhibitors (PPIs), which have been on the market for more than 30 years, are widely regarded as safe and effective medications. For this reason, they are very popular with both doctors and patients. PPIs find their use in the treatment of such ailments as gastroesophageal reflux, gastric ulcer disease or as a shielding therapy when taking non-steroidal anti-inflammatory drugs. Nevertheless, their long-term use may be associated with many side effects. The purpose of our review is to summarize the knowledge in the current medical literature on the possible complications of chronic use of PPIs.

A brief description of the state of knowledge: Although the use of PPIs in the short term is relatively safe, the number of people taking these drugs has increased significantly in recent years. They are prescribed not always as indicated, patients often take them for too long - this in turn leads to an increasing incidence of side effects. Some of them can permanently affect health and significantly reduce the comfort of life - such as kidney diseases, cardiovascular disorders or gastric cancer.

Summary: Considering the widespread availability and popularity of PPIs, it is important to adequately educate both patients and healthcare professionals of the possible side effects. It is crucial to use medications as prescribed, with an appropriate assessment of the risk-benefit ratio. It might result in reducing health care expenditures to deal with the consequences of IPP therapy.

Keywords: Proton Pump Inhibitors; Gastric Cancer; Vitamin Deficiency; Omeprazole

Introduction

Proton pump inhibitors (PPIs) took the pharmaceutical market by storm as soon as they were introduced into medicine in 1989. Drugs belonging to this group such as omeprazole, pantoprazole, esomeprazole and dexlansoprazole are well recognized for their highly effective mechanism of action, based on inhibition of hydrogen potassium ATPase - called the proton pump. This enzyme is located in the membranes of the parietal cells in the stomach. Thus

blocking the secretion of hydrochloric acid in the stomach, these medications have become the first choice for treating and preventing peptic ulcer disease, treating Zollinger-Ellison syndrome or as part of combination therapy in Helicobacter pylori eradication. Although they are widely regarded as safe when used in the short term, in recent years there have been increasing reports of side effects from their chronic intake - such as kidney disease, cardiovascular disorders as well as vitamin and mineral malabsorption. One reason for this is their increasing use, often outside of proper indications and for too long period of time. In our work, we focused on the most important side effects of chronic therapy with PPIs, which have been reported in the scientific literature and on which clinical studies have been conducted to prove the relationship between their occurrence and the intake of drugs belonging to this group [1,2].

Kidney diseases

In the scientific literature, as early as the beginning of the 1990s, the first case reports appeared that linked the use of PPIs to the possibility of developing acute interstitial nephritis (AIN) and acute kidney injury (AKI) [1]. In addition, in 2016 the results of two studies were published that indicated an increased risk of chronic kidney disease (CKD) in PPIs users (with the risk could not be explained only by an increased risk of developing AKI) [2]. One of these studies, in which 10,482 participants were actively observed, showed an increased risk of CKD in those taking drugs of this group in both unadjusted analysis and analysis adjusted for clinical, demographic and socioeconomic variables. In addition, the results indicated that a higher risk of CKD associated with the use of PPIs was carried by taking the medications twice a day compared to one dose per day [3]. In contrast, the second study mentioned above observed for 5 years a cohort of new PPIs users that included 173,321 people and a cohort of new H2 receptor antagonist users that included 20,270 people. The study showed a higher risk of CKD (which was defined as a drop in eGFR below 60ml/min/1.73m2) in those taking PPIs compared to the group taking H2 blockers. The results of the study also indicated a gradual increase in the risk of CKD and eventual progression to end-stage renal disease (ESRD) with longer duration of taking PPIs [4].

One of the hypothesized mechanisms of kidney damage in people taking PPIs may be caused by the accumulation of the group's drugs and their metabolic products within the interstitial tubules. As a consequence, this could lead to inflammatory changes leading to AIN, and this could potentially result in the development of AKI or tubular fibrosis. Subsequently, this could result in the development of CKD and possibly lead to criticality and progression to

ESRD. Another of the possible mechanisms of renal dysfunction in chronic PPIs users are changes in renal structures caused by hypomagnesemia - it causes endothelial dysfunction which exacerbates oxidative stress and can trigger inflammatory changes underlying the aforementioned disorders [5].

Excessive gastric acid secretion from rebound

Patients who take PPIs for a long period of time after abruptly discontinuing them may experience excessive gastric acid secretion and the onset of aggravated dyspeptic symptoms. In one randomized study, 120 participants were divided into two groups. The first group, for the entire period of the study, which was 12 weeks, took placebo only. In contrast, the second group took esomeprazole 40 mg/day for the first 8 weeks, followed by placebo for the remaining 4 weeks. In the group taking esomeprazole at the beginning, dyspeptic symptoms were significantly more common, occurring in 22% of participants, compared to 5% in the group taking placebo [6]. Another double-blind randomized placebo-controlled study involving 48 volunteers examined the presence of dyspeptic symptoms in two groups - the first taking pantoprazole 40mg/day and the second taking placebo for 28 days. The presence of symptoms was recorded both before, during and after treatment, and the Glasgow dyspepsia scale was used to determine their severity. Plasma gastrin levels were also measured at the same times. The result of the study indicated the occurrence of dyspeptic symptoms after a 4-week period of treatment with pantoprazole in people who had not previously suffered from this type of discomfort. There was also a correlation between the severity of symptoms and measured plasma gastrin levels. This strongly suggests a key role for excessive gastric acid secretion as a rebound effect after PPIs withdrawal in the mechanism of dyspeptic symptoms [7].

Long-term use of medications belonging to the PPIs is also associated with an increase in gastrin secretion, as well as affecting gene expression within gastric mucosal cells - which can result not only in dyspepsia but also in enteropathy [6].

However, hypergastrinemia, which is a result of long-term intake of PPIs, also leads to excessive proliferation of ECL cells, which are mainly located in the gastric body and fundus. These are histamine-producing gastrointestinal neuroendocrine cells, the proliferation of which, with the involvement of genetic and environmental factors, can be followed by dysplasia and the development of a gastrointestinal neuroendocrine tumor [8].

Vitamin deficiency

Both observational studies and numerous case reports indicate an association between long-term intake of PPIs and vitamin B12 and vitamin C deficiency [9].

Vitamin B12 ingested in foods is bound to proteins. In order for its absorption process to occur unhindered, it is first necessary to release it from this bond, which occurs in the acidic environment of gastric juice with the participation of the protein-digesting enzyme - pepsin. This is followed by the fusion of vitamin B12 with R protein (secreted by the salivary glands), which protects its chemical structure from damage - as it is sensitive to low pH. After that, already in the duodenum, where the environment is alkaline, proteolytic enzymes of pancreatic juice cause hydrolysis of the R protein, and the vitamin B12 released from this connection binds to the intrinsic factor (IF) produced by the parietal cells. Such a complex is eventually absorbed by the ileal epithelium [9, 10].

The above-mentioned pepsin is converted from its proenzyme, pepsinogen, also in the acidic environment provided by gastric juice. In chronic PPIs users, as a result of reduced hydrochloric acid production and increased gastric juice pH, the conversion of pepsinogen to pepsin may be impaired, preventing the release of vitamin B12 from its protein connections and its fusion with protein R. Without fusion with protein R, vitamin B12 will be damaged by pancreatic juices and fail to fuse with intrinsic factor [9].

In one cohort study conducted in Pakistan between May 2021 and May 2022, among 1225 participants of both sexes, aged 18-80 years who had been taking PPIs for at least a year, 55% of men had reduced blood levels of vitamin B12. Importantly, it was found that patients taking Omeprazole had noticeably lower blood levels of vitamin B12 compared to those participants taking Pantoprazole [11].

On the other hand, nevertheless, one meta-analysis, most of the 25 clinical trials considered, found no significant difference in blood levels of vitamin B12 between those not taking PPIs and those taking medications from this group on a long-term [12].

Also, results from a case-control study involving 125 participants taking long-term PPIs did not indicate that there was an association between taking PPIs and lowering vitamin B12 levels in the body. Despite this, it is nevertheless recommended that vitamin B12 levels be monitored in people who chronically use PPIs [9].

Taking PPIs can also lead to impaired absorption of vitamin C (ascorbic acid). Drugs in this group cause an increase in the pH of gastric juice, and vitamin C at a pH above 4 is characterized by significant instability. Under such conditions, the dehydroascorbic acid previously formed from ascorbic acid (as a result of reaction with reactive oxygen species or

free radicals) undergoes a hydrolysis reaction to 2,3-diketogluconic acid. The acid produced by this reaction cannot be converted back into vitamin C, and by this mechanism, taking PPIs reduces its bioavailability [9].

In 2005, the results of a clinical trial were published in which plasma vitamin C levels were measured after a 4-week supply of 40mg of omeprazole per day in 14 participants with positive Helicobacter pylori tests and in 15 participants not infected with Helicobacter pylori. After 28 days of omeprazole use, there was a decrease in mean plasma vitamin C levels (by 12.3%) in both Helicobacter Pylori positive and negative participants [13]. Similarly, in another study where omeprazole was used at the same dose for 4 weeks, there was a decrease in mean vitamin C levels in subjects from 5 μm/l before treatment to 3 μm/l after omeprazole treatment. [14].

Osteoporosis

An association has been shown in several meta-analyses, as well as systematic reviews, between taking PPIs and increased fracture risk. This was true for both sexes. It is likely to be related to the decrease in calcium bioavailability by this group of drugs, and to the increased resorption of calcium from bone as a result of an increase in parathormone produced by the parathyroid gland in response to the hypergastrinemia and hypomagnesemia that are side effects of PPIs. There is also a hypothesis that a potential mechanism underlying the increased risk of fractures with the use of PPIs is found in the intensification of osteoclast activity as a consequence of inhibition of the proton pumps of these cells by drugs of this group [15]. It should be mentioned, though, that a study published in 2017, which compared bone density as determined by densitometry and bone metabolic markers and measures of bone strength, found no differences between a group of subjects who had been taking PPIs for at least five years and a group that had not taken these drugs for that period [16].

Liver diseases

In people with cirrhosis, taking PPIs increases the risk of complications associated with the condition - such as hepatic encephalopathy and liver cancer. The increase in risk appears to primarily affect people who take PPIs long-term [1]. In 2020, a meta-analysis of 11 studies (involving a total of 173,894 patients) was published, and the results of 3 of these studies showed a 67% increase in the risk of hepatocellular carcinoma in people with chronic liver disease (CLD) who took PPIs, compared to people with CLD who were not treated with these drugs. In addition, pooled data from the other studies included in the aforementioned meta-analysis indicated an increased risk of death by 57% in patients with CLD and taking PPIs,

compared to patients suffering from CLD and not taking the drugs of this group [17]. The mechanism behind the liver damage with the use of PPIs is likely related to the proliferation of gut bacteria as a result of ATP'azy H+/K+ inhibition. This leads to a change in the composition of the intestinal microflora, followed by increased concentrations of bile acids and other substances that can lead to hepatocyte damage [1].

Dementia

The results of several studies suggest a link between the use of PPIs and an increased risk of dementia. Hypothetically, this would be due to the blocking of scavenging enzymes - which are responsible for removing free radicals - such as V-ATPase. Thus, this could lead to the accumulation of beta-amyloid and gradually cause the development of dementia. In one cohort study involving 3076 patients aged 75 and older who had not previously been diagnosed with dementia, the results indicated a 38% increased risk of developing dementia and, noteworthy, also a 44% greater risk of the onset of Alzheimer's disease in those taking PPIs [18]. Also published in 2024, a study on a Danish cohort of 1,983,785 people observed for a median of 10 years showed a link between the use of PPIs and the possibility of developing dementia. In the above group, there were 99,384 cases of dementia - among these people, PPIs were used in 21.2% of cases, while in the control group (consisting of 469,920 people) previously separated from the cohort in 18.9%. It is noteworthy that the association between the use of PPIs and the onset of dementia was stronger the younger the age at which a person was diagnosed with dementia [19]. It should be mentioned, that there are studies whose results do not indicate an association between the use of PPIs and an increase in the risk of dementia - such as large-scale cohort study that used electronic health data routinely collected from patients in Wales between 1999 and 2015. From the data of 3,765,744 people, a cohort of 183,968 (aged 55 and over) was created. This was matched with a cohort of non-exposed PPIs, which included 131,110 people. The results obtained did not allow confirmation of a relationship between the use of PPIs and an increased risk of developing dementia, which the results of some studies have indicated [20]. Also, another large study using pantoprazole showed no significant difference in terms of the incidence of dementia between those taking the drug and the group taking a placebo. The contradictory conclusions of these analyses mean that further studies, on large groups of patients, are needed to confirm or rule out a link between the incidence of dementia and the use of PPIs [18].

Cardiovascular risk

The outcomes of several research papers indicate a possible link between taking PPIs and an increased risk of cardiovascular events such as strokes, stent thrombosis and myocardial infarctions [5]. A retrospective study conducted in Taiwan, the results of which were published in 2014, showed the possibility of an association between PPIs use and an increased risk of myocardial infarction in users of these drugs. It was noted, however, that the benefits of PPIs therapy may greatly outweigh the risk of potential cardiovascular incidents. [21]. Similar conclusions were reached based on results from another retrospective study conducted using the Stanford University Hospital and Clinics system's database of 1.8 million people. The authors showed that PPIs users in this cohort had an approximately 20% higher risk of myocardial infarction compared to nonusers. However, it is important to keep in mind confounding factors due to the retrospective nature of the above two scientific papers, which may significantly affect the final results of the observations [22].

There are several postulated mechanisms that could lead to the aforementioned cardiovascular disorders and incidents associated with PPIs intake. Among these are, for example, the possibility of arrhythmias as a consequence of ionic disturbances or the inhibition of nitric oxide production in the vascular endothelium as a result of the PPIs-induced increased concentration of asymmetric dimethylarginine, which interferes with vasodilatory capacity [5].

Pneumonia

In a cohort study on a large group of patients, Laheij et al. based on their results determined that the risk of out-of-hospital pneumonia in the group of people taking PPIs was almost twice as high as in those who did not take drugs belonging to this group [6]. A nationwide study conducted in Sweden between 2005 and 2019, on the other hand, found that there were 307,709 periods of treatment with PPIs among 519,152 patients who were registered with at least one case of pneumonia. It was also determined that the use of PPIs was associated with an increase in the risk of pneumonia by more than 70%, while at the same time, based on the results obtained, there was no equally significant association between the incidence of this disease entity and the intake of histamine receptor type 2 blockers [23].

The likely mechanism that contributes to the increased risk of pneumonia in patients taking PPIs is related to an increase in the population of aerobic bacteria within the stomach and their microaspiration into the airways [6].

SIBO

Small intestinal bacterial overgrowth (SIBO) occurs when there is an excessive accumulation of intestinal microflora in the proximal segment of the small intestine. The condition

manifests itself through symptoms such as chronic constipation, diarrhea, weight loss, abdominal bloating and vitamin malabsorption. The main factors predisposing to SIBO are changes in pH and impaired gastrointestinal peristalsis [24]. The use of PPIs, by affecting the pH of the stomach, can lead to disruption of the bacterial flora of the initial part of the small intestine and result in the development of SIBO. In one meta-analysis, a review of scientific papers was conducted to evaluate the potential association between taking PPIs and the possibility of developing SIBO. They selected 11 clinical trials - involving a total of 3134 subjects - that compared the risk of SIBO between those who took PPIs and those who did not. The main parameter relied on to compare the risk of developing SIBO in the two groups was the odds ratio (OR). In a final analysis, the pooled OR of SIBO, in individuals who were treated with PPIs versus those who did not take the drugs belonging to this group, was 2,282 (the result fell within the 95% confidence interval of 1,238-4,205). Importantly, however, an association between SIBO and the use of PPIs group medications was found only in studies using highly accurate tests - cultures of duodenal aspirate and jejunum - to diagnose this clinical condition (OR: 7.587, with a 95% confidence interval of 1.805-31.894) Such an association was not found when using a less sensitive method in the form of the glucose hydrogen breath test (OR: 1.93, with a 95% confidence interval of 0.69-5.42) [25].

Simultaneous intake of prokinetic drugs may reduce the risk of SIBO in patients taking PPIs long-term, thanks to their ability to stimulate upper gastrointestinal motility, one study suggested [24].

Clostridium difficile infection

C. difficile infection leading to the development of pseudomembranous enteritis is associated with the occurrence of diarrhea, often of considerable severity, in extreme cases leading to dehydration, shock or even death. A meta-analysis that included 23 studies and a total group of 272,636 patients, after adjusting the results obtained by taking into account a possible publication error, noted the presence of a significant association between taking PPIs and the risk of developing C. difficile infection. In addition, the same study showed that the use of PPIs leads to an increased risk of recurrent C. difficile infection [15]. Similar conclusions can be drawn from the results of another meta-analysis, which was published in 2017. It included a total of 56 studies, of which 40 were case-control studies and 16 cohort studies. As a result of analyzing the above number of studies, there was a high probability of an association between the use of PPIs and an increased risk of developing C. difficile infection. Nonetheless,

the authors of this paper point out that further, thorough and large clinical studies are needed to confirm whether this is a causal link [26].

Gastric cancer

A Canadian population-based cohort study analyzed the relationship between the use of PPIs and H2 receptor antagonists and the risk of gastric cancer. The study used information collected from a UK database - The Clinical Practice Research Datalink. It identified a group of people taking PPIs for the first time (973,281 people) and a second group, where there were patients starting H2 receptor antagonist therapy for the first time. Finally, after a median follow-up of 5 years, it was found that patients taking PPIs had a 45% higher risk of developing gastric cancer compared to the second group. The number needed to harm (NNH) was 2121 for 5 years after starting PPIs therapy and 1191 after 10 years, respectively. In the end, however, the authors of this study pointed out that the absolute risk of gastric cancer with the use of drugs of this group is low [27].

By contrast, a cohort study published in 2023 and conducted in South Korea (a country where the incidence of gastric cancer is relatively high) concluded, based on the results obtained, that chronic intake of PPIs in people after Helicobacter Pylori eradication was associated with a significant and dose-dependent increase in the risk of gastric cancer [28].

Mineral deficiencies

Chronic use of PPIs can lead to mineral deficiencies, a problem that mainly affects iron, magnesium and calcium. Particularly vulnerable to deficiencies of these minerals, are the elderly, as well as the malnourished individuals. The risk is also increased in people taking drugs of this group and undergoing hemodialysis at the same time [14].

As for iron and calcium, the results of studies on the potential effect of PPIs on the impaired absorption of these elements are conflicting. The theoretical mechanism affecting the decreased efficiency of iron and calcium absorption would be based on an increase in pH within the stomach and proximal part of the duodenum, which would lead to a decrease in the absorption of non-heme iron and impaired dissociation of calcium contained in the ingested food [14].

Of the above minerals, by far, impaired magnesium absorption and consequent hypomagnesemia is the best documented side effect of chronic PPIs use, both by case reports and meta-analyses [14].

The results of two meta-analyses confirmed the association between PPIs use and increased risk of hypomagnesemia. Higher doses of PPIs were also associated with a higher likelihood

of developing this disorder compared to lower doses [29, 30]. The risk of this disturbance was also dependent on the type of PPI taken, with the lowest rates shown for those taking rabeprazole, while the highest rates were seen with omeprazole use. The risk of hypomagnesemia also increases with the age of PPIs users [29].

Conclusion

Given the widespread use of PPIs, their easy availability and the widespread reputation for their high safety, steps should be taken to educate patients, as well as health care personnel about the potential risks of using them for too long and unwisely. Although many of the described side effects of chronic therapy with these drugs are relatively rare, health care professionals should be aware of the possible risks and prescribe them as directed. The individual benefits and risks of therapy with PPIs should be assessed on a case-by-case basis, especially in cases requiring their long-term use. It should also be borne in mind that further, thorough, prospective studies are needed to gain a thorough understanding of the possible side effects of taking drugs belonging to this group.

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