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Proton pump inhibitors overuse - consequences among patients

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Abstract

Introduction

Omeprazole was first proton pump inhibitor (PPI) approved for use by patients. Thirty years have passed since then. Due to their effectiveness, low price and safety proton pump inhibitors have become one of the most frequently prescribed medicines in the world. In recent years, more attention has been paid to the problem of their overuse.

Aim of the study

The aim of our study was to investigate the scale of proton pump inhibitors overprescription and possible resulting side effects.

State of knowledge

Analyzed observational studies proves that problem is present both in hospitals and ambulatory clinics. Research shows increasingly frequent use of this medicines in case of

non-specific abdominal discomfort or in many cases without any indications. This results in prolonged and unnecessary therapy. The possibility of obtaining medicines over the counter and patients non-compliance, are also a challenge in maintaining high-quality therapy. In many cases patients taking drugs irregularly or do not stop therapy, even being free from symptoms.

Conclusions

Despite the fact that proton pump inhibitors are considered safe drugs, more attention should be paid to the compatibility of their use with recommendations. There are also evidences about the possibility of side effects associated with long-term proton pump inhibitor therapy, which can be particularly dangerous for older patients with multiple diseases. It is necessary to inform patients about the need of discontinuation therapy in case of recovery, which will reduce the risk of adverse effects.

Keywords: Proton Pump Inhibitors; PPI; Proton pump

Introduction

On 1977 in Gastroenterology was published an article describing secretion mechanism of hydrochloric acid into the stomach, associated with membrane enzyme of the parietal cells. This enzyme turned out to be K+ stimulated ATPase, which transport H+ into the vesicular lumen under presence of ATP, Mg 2+ and KCl. [1] This was another step which made possible to understand mechanism of action medicines used in acid related diseases, which have been worked on since the early seventies. In 1973 was discovered a compound with antisecretory effect and reduced toxicity compared to other substances - benzimidazole H 124/26, but due to his patent protection, and registration in the treatment of tuberculosis could not be used. His metabolite - timoprazole had even more antisecretory properties, but because of inhibition of iodine absorption in the thyroid gland, as well as atrophy of the thymus also was replaced by picoprazole. Optimization of benzimidazole derivatives by increasing antisecretory properties led to omeprazole, which was released in Europe as Losec in 1988, and Prilosec two years later in United States. [2] Finding mechanisms of blocking gastric proton pump enabled effective treatment of diseases caused by excess hydrochloric acid, treated up to this point by drugs influencing cholinergic, gastrin and histamine receptors. Further research led to release lansoprazole (1995), rabeprazole (1999), pantoprazole (2000), and the stereoisomeric compounds esomeprazole and dexlansoprazole (2001). [3] PPIs are weak bases, packed in protective systems to prevent their premature activation and degradation in gastric acid. After absorption in small bowel, they accumulate in the acid cavity of the parietal cells, where they are activated by cyclic sulfonamide tetramer (except esomeprazole and dexlansoprazole which are non chiral). Then they covalently bind to cysteine of ATPase, and cause irreversible inactivation of the enzyme. There are also intravenous forms with ability to act immediately, available for patients who can’t take medicines orally. The half-life of PPIs is short and last one to two hours. The exception among this group of drugs is tenatoprazole belonging to imidazopyridines with prolonged half-life reaching 7 hours. During this time about 70% of proton pumps are inhibited. Achieving a stable state of inhibition of acid secretion takes about 2 to 3 days. Omeprazole and esomeprazole are metabolized mainly by CYP2C19, which is associated with high risk of interaction with other drugs. Despite CYP2C19, rabeprazole, lansoprazole and dexlansoprazole have an affinity for CYP3A4, which results in less frequent interactions. Pantoprazole is degraded by CYP2C19 O-demethylation and sulfate conjugation, which leads to the lowest cytochrome induction. Pantoprazole, lansoprazole and dexlansoprazole are recommended for patients burdened by many diseases requiring multidrug therapy. [4] There are three phenotypes of the metabolizers due to the polymorphism of cytochrome P450 2C19:

extensive metabolizers (homEM), poor metabolizers (PM), and persons having one wild-type and one mutant allele (hetEM). [5] Proton pump inhibitors have revolutionized the treatment of diseases related with hydrochloric acid and have found application in the treatment of gastric and duodenal ulcer disease, gastrointestinal bleeding, eradication of H. pylori, prevention of NSAID induced gastroduodenal ulcers, Zollinger-Ellison syndrome, functional dyspepsia, erosive esophagitis and nonerosive reflux disease. [4] In recent years, attention has been paid to the problem of their too frequent use, in many cases without any indications.

Aim of the study

The aim of our study was to analyze the scale of proton pump inhibitors overprescription, and possible side effects.

State of the knowledge

The problem associated with over-prescription of proton pump inhibitors was noticed more than 20 years ago. Bashford's retrospective study determined the relation between new prescriptions for proton pump inhibitors, and recorded upper gastrointestinal morbidity in General Practice Research Database. The total number of analyzed patients accounted for 612 700 cases. During the analyzed period of the study the number of prescription increased 10 times and repeat prescribing accounted for 77% of the total. Results showed that number of prescriptions for non-specific indications increased from 32% in 1991 to 46% in 1995. [6] Heidelbaugh's study evaluated prevalence of proton pump inhibitors inappropriate use, and its economic effect in ambulatory care setting. Retrospective medical record review revealed that from among 946 patients 35.4 % had appropriately documented indications for PPIs therapy, 10.1% received PPIs empirically, 18.4% received PPIs for gastroprotective purpose and 36.1% had no documented appropriate indication for PPIs treatment. [7] It is claim that one of the reasons for incorrect prescription of PPIs in primary care is an incorrect recommendation from the hospital. The study summarized compatibility of prescribing proton pump inhibitors with recommendations during discharge from hospital and the influence of these recommendations on general practitioners. From among 506 patients, in 263 cases (58%) there were no indications. Two thirds of cases without indications were initiated in the hospital. Taking PPIs before admission to hospital, was the strongest factor associated with non-indicated continuation of this medicines (OR: 3.0; 95% confidence interval (CI): 1.7–5.4). [8] The problem of too frequent use of proton pump inhibitors has also been noticed in hospitals. The study conducted by Eid et al. compared the predictors of proton pump inhibitor overuse among academic and non-academic hospitalists. Out of 400 prescriptions 39% were compatible with the guidelines. Authors drew attention to the significant difference in correct prescriptions in favor of academic centers, compared to non-academic (50% compared to 29%, $p<0.05$). The most common indication for non-compliant prescriptions was gastrointestinal ulcer bleeding prophylaxis for low risk patients. [9] Administration of drugs which inhibit secretion of hydrochloric acid is one of the elements of stress ulcer prophylaxis in patients on intensive care units, but this practice has been transferred to other hospital wards. To examine stress ulcer prophylaxis in non-intensive care units patients, American scientists conducted a study on 1,769 patients. It turned out that 391 patients (22.1% of total, 95% confidence interval (CI): 20–24%) received stress ulcer prophylaxis, and more than half of them were discharged home on antisecretory therapy. None of these patients had appropriate symptoms to receive this medicines according to the American Society of Health-System Pharmacists. The most frequently used antisecretory medication was pantoprazole (89.4% of total pills). [10] In recent years, more attention has been paid to the problem of non-compliance with medical recommendations among patients. A study conducted at Northwestern University determined prevalence of PPIs use among

patients without evidence of reflux disease after conducting Bravo pH or multichannel intraluminal impedance-pH test. From 90 patients who participated in the study 38 (42.2%) declared current PPI use, despite negative test result. Only 17 patients (18.9%) declared being informed to stop taking PPIs. [11] One of the reasons for the incorrect use of PPIs can be the possibility of receiving this medicines at low doses without prescription. In the American study, patients with PPIs prescription from gastroenterologist were the most optimal users (71%) and they also had a better symptom control. On the other hand, patients receiving prescriptions from primary care physician were optimal in 47%. Patients taking PPIs over the counter were the least optimal (39%). [12] Discontinuation of proton pump inhibitors is an important issue, which allows avoid problem associated with too long unnecessary use of the drug, and the resulting side effects. According to review of studies concerning the methods of discontinuation of PPIs therapy authors recommend that patients who don't have indications for their admission should stop treatment, which should not result in worsening of symptom control. It is also recommended to gradually discontinue proton pump inhibitors therapy to avoid the possibility of hypergastrinemia and hypersecretion after long-term use of PPIs. [13] For many years proton pump inhibitors have been considered safe and effective in the treatment of acid related diseases, but in recent years, there have been many reports about possible side effects resulting from their chronic, and in many cases unjustified use. One of them is higher risk of Clostridium difficile infection (CDI). It is claimed that inhibiting the secretion of hydrochloric acid may cause reduction of microbial diversity, which is characteristic feature of CDI. Results of Seto et al. research proved to be consistent with this thesis. Regardless of the dose taking PPIs caused reduction of microbial diversity. [14] Meta-analysis of 42 studies, showed in 39 cases statistically significant association between PPI use and risk of developing CDI, (OR: 1.74; 95% confidence interval (CI): 1.47 – 2.85) compared to non-receiving patients. Additionally, in three studies, there was a association between the use of PPIs and recurrent CDI, (OR: 2.51; 95% confidence interval (CI): 1.16 – 5.44). PPIs were associated with greater risk of CDI compared to histamine-2-receptor antagonists (H2RA). Taking antibiotics during PPI therapy, had greater risk of CDI compared to using only PPIs [15]. Growing number of such reports resulted in a statement from the American Food and Drug Administration (FDA) in which they inform about possible relation between use of proton pump inhibitors (PPIs) and increased risk of Clostridium difficile diarrhea (CDAD). [16] Research also points to the relation between acid suppression, and increased risk of not only C. difficile but also Salmonella, Shigella and Campylobacter infections. [17] Community-acquired pneumonia is another serious side effect that has been investigated for this class of drugs. The study whose aim was to determine the association between use of acid-suppressive drugs, and occurrence of community-acquired pneumonia, (CAP) revealed greater incidence rates among patients received acid-suppressive drug, than patients who do not take these medicines. In Laheij et al. study took part 364 683 patients. The incidence rates of pneumonia in acid-suppressive drug users and non–acid-suppressive drug users were 2.45 and 0.6 per 100 person-years. [18] Vitamin B12 deficiency may lead to pernicious anemia, manifested by smoothing and redness of the tongue due to its atrophic inflammation, megaloblastosis of small intestine epithelial cells, leading to diarrhea, poor absorption of nutrients and irreversible neurological disorders. [19] In research evaluated the association between vitamin B12 deficiency and use of acid-suppressing medication, patients who taking PPIs or H2RAs had increased risk for vitamin B12 deficiency. Higher doses of drugs, were associated with greater risk of B12 vitamin deficiency. [20] In recent years many reports are also being made about possible adverse effects regarding kidney disease and dementia. [21, 22] Due to the growing number of papers related with consequences of prolonged PPI therapy, research of Jaynes and Kumar draw attention to low quality of research including mostly observational studies and meta-analyses, which frequently include the same

observational studies. [23]

Conclusions

Proton pump inhibitors are one of the most widely prescribed medicines in the world. Their discovery was a great progress in treating diseases related with hydrochloric acid. In recent years a lot of research concerned the problem of their overprescription and possible adverse effects. According to our analysis, reduction of their occurrence could be reached by critical evaluation of patients' hospital and pre-hospital recommendations which could avoid unnecessary therapy of (PPIs). It is also claimed that patients should be properly informed about rules for taking medications and a need to terminate their treatment after recovery.

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