The choice of proton pump inhibitor in terms of efficacy and safety in a particular patient

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ABSTRACT

Proton pump inhibitors are a diverse class of drugs with unique acid suppression properties . The aim of this work was to present the therapeutic benefits of rabeprazole and pantoprazole in clinical practice. Numerous studies have demonstrated the high efficacy of proton pump inhibitors and the relative safety of taking these drugs. However, it is necessary to increase the awareness of doctors and pharmacists about the possibility of complications during therapy with proton pump inhibitors in a polymorbid patient. The choice of proton pump inhibitors should be based on the clinical situation, comorbidity and therapy, the presence of risk factors in the patient, the speed and stability of the drug effect.

Keywords: proton pump inhibitors, rabeprozole , pantaprazole , clinical efficacy

Introduction. Rabeprazole is converted from prodrug to drug faster than other drugs , and thus a greater gradient of prodrug concentrations is created across the membrane of the secretory tubules. Pharmacodynamics rabeprazole does not depend on gene polymorphism, in this regard, there is no need for dose adjustment in fast metabolizers. In addition, a distinctive feature of rabeprazole is the ability to stimulate the production of mucin to a greater extent, thereby providing an additional cytoprotective effect. A feature of the metabolism of pantoprazole is that, in addition to binding to cysteine 813, there is an additional bond with cysteine 822, which ensures the restoration of acid secretion only after the synthesis of a new protein and, as a result, the longest lasting effect of the drug. High pH selectivity characterizes a low probability of proton pump inhibition in tissues with a less acidic pH , i.e., it determines the specificity of action only in the parietal cells of the stomach and the greatest safety of long-term use in patients with comorbid pathology.

pantoprazole and rabeprazole have the lowest affinity for the cytochrome P450 system and lower inhibitory activity against CYP2C19 , demonstrating a minimal risk of drug interactions. The need to suppress the acid production of the stomach arises in a number of widespread diseases. The suppression of gastric secretion has become so successful that surgical interventions for certain diseases, such as gastroesophageal reflux disease and peptic ulcer disease have practically ceased to be used. Currently, proton pump inhibitors (PPIs) are the most effective means of basic acid-suppressive therapy, and the range of indications for their use is expanding every year [1].

The first APIs were developed between 1980 and 1990 [1]. The drug class currently includes forms such as omeprazole , lansoprazole , rabeprazole , pantoprazole , esomeprazole , dexlansoprazole , dexrabeprazole , tenatoprazole * . The effective therapeutic effect of each individual form of PPI is achieved through the use of various strategies, taking into account the pharmacokinetics and pharmacodynamics of a particular PPI and the clinical situation.

Purpose of the study. The purpose of this report is the therapeutic aspects of the use of

rabeprazole and pantoprazole in clinical practice.

The current indications for PPI therapy are [1]:

• stomach and duodenal ulcers, erosive gastritis, duodenitis;

• gastroesophageal reflux disease including Barrett's esophagus ;

• Helycobacterpylori -associated gastritis (as part of complex therapy);

• prevention and treatment of gastrointestinal complications, including gastrointestinal bleeding, in patients with risk factors while taking non-steroidal anti-inflammatory drugs, antiplatelet , anticoagulant therapy.

Pharmacotherapy with PPIs is successful provided that the target pH values can be maintained over a certain period of time. In 1990, W. Burget et al . published for the first time the data of a meta-analysis of more than 300 works, on the basis of which they came to the conclusion that gastric and duodenal ulcers are scarred in almost all cases, if during the day it is possible to maintain the pH of the intragastric contents> 3 for about 18 hours a day (Bourget's rule) [2] .

Further studies have determined the degree of pH increase and the duration of this increase as a prognostic factor in the treatment of other acid-related diseases. So, the pH value > 4 is optimal for the healing of reflux esophagitis. Eradication of Helycobacter infection py^ n (H. pylori) is successful at intragastric pH values > 5 (worst conditions are created for bacteria and better for realizing the effect of antibiotics).

Modern proton pump inhibitors make it possible to achieve optimal pH values (> 3) even with a single dose of a standard dose; for fast metabolizers , an increase in the frequency of taking first-generation drugs (twice a day of a standard dose of omeprazole or lansoprazole) is required [2].

The most recent data on the therapeutic and prophylactic efficacy of the PPI class are due to B. Scally et al . the effect of gastroprotectors (PPIs, H2-receptor blockers, prostaglandin analogs) in reducing the risk of ulcers, bleeding and mortality, in general, for individual drugs in the class of gastroprotectors [3]. Comparison of gastroprotective and control groups in 849 studies (142,485 participants): 580 prophylactic studies (110,626 participants), 233 therapeutic studies (24,033 participants), and 36 studies separately for the treatment of acute upper bleeding gastrointestinal tract (7826 participants). Comparisons of one gastroprotective drug against another were available in 345 studies (64,905 participants), including 160 prevention studies (32,959 participants), 167 therapeutic studies (28,306 participants), and 18 studies for the treatment of acute upper gastrointestinal bleeding (3640 participants). The mean number of patients per group was 78 (44210) participants. The average duration of taking gastroprotectors was 1.4 months (0.9-2.8). The results of the meta-analysis showed that, overall, gastroprotective agents were significantly more effective than placebo in preventing endoscopic ulcers (OR, 0.27; 95% CI, 0.25–0.29; p < 0.0001); symptomatic ulcers (OR — 0.25 (0.22-0.29; p < 0.0001); bleeding from the upper gastrointestinal tract (OR — 0.4 (0.32-0.50); p < 0.0001) However, a stronger proportional reduction in upper gastrointestinal bleeding was observed with PPIs (OR 0.21, 99% CI 0.12–0.36) compared with other gastroprotective agents: prostaglandin analogs (OR — 0.63 (0.35–1.12); p < 0.0005) and H2 receptor blockers (OR — 0.49 (0.30–0.80); p < 0.0005) [3].

Gastro-protectors were significantly more effective than placebo and in the conservative treatment of endoscopic ulcers (OR - 3.49, 95% CI 3.28-3.72; p < 0.0001), while again PPIs showed higher efficacy (OR - 5 .22; 99% CI 4.00-6.80) than prostaglandin analogs (OR 2.27 (1.91-2.70)) and H2 receptor blockers (3.80 (3.44-4. 20); p < 0.0001). In studies among patients with acute bleeding, gastroprotectors reduced the risk of further bleeding (OR 0.68, 95% CI 0.60–0.78; p <0.0001), blood transfusion (OR 0.75 (0.65–0 .88); p = 0.0003), further endoscopic intervention (OR — 0.56 (0.45-0.70); p < 0.0001) and surgical intervention (OR — 0.72 (0.61- 0.84); p < 0.0001), but did not significantly reduce

mortality (OR — 0.90 (0.72–1.11); p = 0.31). PPIs showed more pronounced protective effects in preventing further bleeding than H2 receptor blockers (p = 0.0107) and blood transfusions (p = 0.0130) [3].

Features of the metabolism of rabeprazole and pantoprazole

benzimidazole derivatives - are weak bases that accumulate in the acidic environment of the secretory tubules of the parietal cell in close proximity to the target molecule - the proton pump, directly block the work of H +, K + -ATPase - the proton pump of the parietal cell, which turns out to be "out of control" of the receptors of its basolateral membrane (Fig. 1). Approximately 25% of proton pumps are replaced by newly synthesized ones within 24 hours [4].

All PPIs are also prodrugs , but when exposed to an acidic environment, they can turn from a prodrug into a drug, which is a cyclic sulfenamide [5, 6].

The main pharmacokinetic characteristics of proton pump inhibitors and the effectiveness of their action include: absorption from the intestine with penetration into the systemic circulation; concentration in the secretory tubules of parietal cells; proton binding in the acidic environment of the tubules; conversion from prodrug to drug (activation of PPI by acid); covalent binding to SH groups of the proton pump and its inhibition [5, 6].

The mechanism of action of all the PPIs mentioned above on the proton pump is approximately the same. The differences lie in the metabolic rate of these compounds. For PPI, among the pharmacokinetic parameters on which the value of the calculated parameter A and C depends, Cmax (the maximum concentration of the drug in the blood), which correlates with the number of blocked proton pump molecules in the secretory tubules of the parietal cells at the maximum concentration of the drug, has the greatest value . T^/2 - the retention time of the drug in the blood is less important, since PPIs are drugs with a short half-life and the rate of their elimination is much higher than the rate of replacement of blocked proton pump molecules with newly synthesized active enzyme molecules [5, 6]. PPIs act on the proton pump not from the side of the blood or extracellular fluid, but from the side of the secretory tubules, and the effect depends not so much on the concentration of the PPI (i.e. prodrug) in the blood, but on the concentration of the active form, i.e. the corresponding cyclic sulfenamide in secretory tubules [5, 6].

The concentration of PPIs in the secretory tubules, in turn, depends not only on pharmacokinetic parameters, but also on the rate of conversion of the prodrug into the drug: as this conversion occurs, the rate of accumulation of PPIs in the secretory tubules may increase. Thus, the faster the conversion of the prodrug into the drug, the more the drug can accumulate in the secretory tubules, the more pump molecules will be blocked. And the inhibitory effect persists for a long time after a decrease in the concentration of PPIs in blood plasma [5, 6].

The rate of accumulation of PPI in the tubules of parietal cells for different PPIs is different and is determined by the ionization (dissociation) constant pKa : the larger the constant, the greater the rate of PPI transformation into the active form. Rabeprazole has the highest pKa among PPIs , 4.8. Rabeprazole in the in system vitro provides 80% inhibition within 5 minutes (Fig. 2) [5, 6].

Rabeprazole is converted from a prodrug to a drug faster than other drugs , and thus a greater concentration gradient of the prodrug is created on the membrane of the secretory tubules [7, 8]. In addition, a distinctive feature of rabeprazole is the ability to stimulate the production of mucin to a greater extent (more than 5 times within 8 weeks) and thereby restore the protective barrier of the stomach and esophagus, providing an additional cytoprotective effect [7, 8].

Duration of secretion inhibition

Recovery of acid secretion after PPI inhibition may be due to the synthesis of de novo pump protein and/or disulfide reduction and reactivation of the inhibited pump. Whereas all PPIs bind to cysteine 813, pantoprazole additionally binds to cysteine 822

deeper in the TM6 membrane domain. Recovery of acid secretion after pantoprazole is entirely dependent on new protein synthesis. For pantoprazole, this period is the longest and is about 46 hours [5, 6].

Features of interaction with the cytochrome P450 system

When using PPIs metabolized by the cytochrome P450 system , issues of competitive drug interactions with drugs that are also metabolized using this system can be acute. For all PPIs, except for rabeprazole and pantoprazole , the inhibitory effect on CYP2C19 is quite large [5, 6]. In 2009 and 2010, the U.S. Food and Drug Administration (Food and drug Administration of the United States , FDA) [22] and the European Agency for Evaluation of Medicines (European Medicines Agency , EMA) [23] did not recommend the use of clopidogrel in combination with drugs such as omeprazole and esomeprazole . Unlike other PPIs, the transformations of rabeprazole and pantoprazole occur in addition to the cytochrome system along the " non-enzymatic pathway", during which a thioester is formed rabeprazole , which also has antisecretory activity, and pantoprazole is metabolized by sulfotransferase cytosol [5, 6].

Thus, among all PPIs, pantoprazole and rabeprazole show the lowest affinity for the cytochrome P450 system with lower inhibitory activity against CYP2C19 , demonstrating a minimal risk of drug interactions. In addition, it should be emphasized that the pharmacodynamics rabeprazole does not depend on gene polymorphism, in this regard, there is no need for dose adjustment in fast metabolizers [5, 6].

Safety Issues for PPI Therapy

Numerous randomized controlled trials have demonstrated the high efficacy of PPIs and their relative safety (the number of side effects does not exceed 3%) [9, 10]. However, the safety of long-term PPI therapy should be discussed. Currently, there is evidence of the possible development of malabsorption and malabsorption of micronutrients. Data were obtained on an increase in the risk of developing hypomagnesemia by 1.54 times [9]. It has been shown that PPI therapy for 2 or more years can lead to vitamin B12 deficiency (OR — 1.65; 95% CI 1.58-1.73) [10]. A higher risk of fractures has been confirmed, especially in the elderly on long-term PPI therapy, and therefore the risk -benefit ratio should be carefully weighed before prescribing PPIs to elderly patients [11].

A relationship was found between the duration of PPI intake and the risk of developing intestinal bacterial overgrowth syndrome (3 times when taken for more than 13 months) [12], with an increased risk of developing collagen colitis (risk coefficient - 4.5) [13]. Some observational studies have shown that PPIs increase the risk of gastric cancer in patients infected with H. pylori , while others present conflicting results [14-16]. More research will be needed to determine whether PPIs increase the risk of gastric cancer in patients with H. pylori infection , as well as in those who have successfully undergone eradication .

Long-term use of PPIs can cause hyperplasia of the fundic glands [14-16]. The published results of a large meta-analysis , including a total of 785 patients, showed that long-term use of PPIs to maintain remission in patients with gastroesophageal reflux disease is not accompanied by an increase in the frequency of atrophic changes in the gastric mucosa, as well as hyperplasia of enterochromaffin-like cells for at least 3 years of continuous treatment based on the results of randomized clinical trials [17].

These results of individual studies indicate PPI nephrotoxicity , manifested by the development of acute tubulointerstitial nephritis (ATIN), chronic kidney disease [18, 19]. In this regard, when prescribing PPIs, the presence of risk factors for ATIN should be taken into account, including older age, heart failure, chronic kidney disease, diabetes mellitus, liver cirrhosis, and diuretics. An increase in serum creatinine , a decrease in glomerular filtration rate, electrolyte disturbances (hyperkalemia , hyponatremia), proteinuria, leukocyturia , hematuria, cylindruria , eosinophiluria make it possible to

diagnose ATIN with a high probability [18, 19]. A recent study showed that PPI therapy is an independent risk factor for myocardial infarction: after 120 days of taking PPIs, the risk increased by 1.58 times [18, 19].

If it is necessary to prescribe PPIs to patients with a high risk of gastrointestinal bleeding during antiplatelet and anticoagulant therapy, PPI therapy with the lowest affinity for CYP2C19 with a minimal risk of drug interactions (pantoprazole or rabeprazole) is considered the safest [20].

The frequency of prescribing PPIs and the duration of use formed the basis for large-scale population studies. The longest safety study is available for pantoprazole (15 years of continuous use of the drug) [21]. The absence of clinically significant adverse events over a long period of treatment is apparently due to the high pH -selectivity of the pantoprazole molecule . High pH selectivity characterizes a low probability of proton pump inhibition in tissues with a less acidic pH , i.e., it determines the specificity of action only in the parietal cells of the stomach and the greatest safety of long-term use in patients with comorbid pathology.

Conclusion . Thus, it is necessary to increase the awareness of physicians and pharmacists about the possibility of complications during PPI therapy, which will reduce the incidence of their development and improve prognosis. The choice of PPI should depend on the clinical situation, comorbidity and therapy, the presence of risk factors in the patient, the speed and stability of the PPI effect.

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