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EDUCATION AND SCIENCE: THEORY&PRAXIS

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CONTENT

ECONOMIC SCIENCES

ENERGY

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KEY ISSUES OF BALANCING THE BENEFITS AND RISKS OF PROTON PUMP INHIBITORS IN ACID-DEPENDENT CONDITIONS

Meta-analyses of recent randomized clinical trials have shown that proton pump inhibitors (PPIs) have clinical benefits in reducing acidity. In the presence of Helicobacter pylori infection, eradication therapy is recommended, and if necessary, an increase in the dose and duration of PPIs[1]. The focus of attention is on patients with reflux disease, Barrett's esophagus, peptic ulcer disease, and comorbid conditions that require long-term use of nonsteroidal anti-inflammatory drugs (NSAIDs). It is known that the proliferation of histamine-producing cells (histamine, which under normal circumstances stimulates parietal cells, activating H^+/K^+-ATPase and producing acid in the stomach) is a negative consequence of long-term PPI use[2]. The problem is that after stopping long-term PPI use, in some cases, acid levels increase to levels higher than before the PPI was started.

Here you need to know the physiology of acid production.

What cells affect the secretion of hydrochloric acid in the stomach? The work of the parietal cells of the stomach is a consequence of stimulation by neurocrine, paracrine and hormonal stimuli after the binding of the main secretagogues (including gastrin, acetylcholine, PACAP-hypothalamic peptide and histamine) with the corresponding receptors on the cell surface. Today, it is possible to experimentally test the level of hydrochloric acid production

1 Dutta, AK; Jain A, Jearth, V; Mahajan, R; Reddy, DN; et al. (2023). Guidelines on optimizing the use of proton pump inhibitors: PPI stewardship. 42(5): 601–628.PubMed ID: 37698821: Jenkins, D & Modolell, I. (2023). Proton pump inhibitors. BMJ. 383. DOI: 10.1136/bmj-2022-070752. PubMed ID: 37957000.

2 Susman, F; Niec, R & Katz, Ph. (2020). Proton pumb ingibitors. The good, bad, and ugly. Gastrointest. Endosc. Clin. N. Am.,. 30(2):239–251. PubMed ID: 32146944. DOI: 10.1016/j.giec.2019.12.005.

(gastric acid outputs – GAO). PPIs inhibit the release of hydrochloric acid by parietal cells.

How to maintain intracellular homeostasis? With the help of a proton pump. After the generation of intracellular second messengers that activate protein kinases, acid secretion is stimulated by activating the enzyme H^+/K^+-ATPase of the parietal cells (proton pump). To maintain intracellular homeostasis, intracellular hydrogen ions and extracellular potassium ions are exchanged in a 1:1 ratio through proton pumps. The drugs of choice may be PPIs. However, long-term use of PPIs leads to vitamin B12 deficiency (it binds to the protein molecule R-factor, and to release it from R-factor, protease activation is required, which is possible only in an acidic environment), iron deficiency (anemia), impaired absorption of insoluble calcium from food (osteoporosis). There is an opinion that hypergastrinemia can lead to malignancy (cancer process).

Is there a connection between PPIs and the development of tumors of the digestive system? Regarding the risk of pancreatic cancer in patients taking PPIs, convincing conclusions were obtained in the corresponding systematic review and meta-analysis of the fixed or random effects model. Nine studies (three cohorts and six case-control studies) involving 1,036,438 patients were selected. Overall, no statistically significant association was identified between PPI use and the risk of cancer.

What ensures the safety of PPIs? pH selectivity. It is known that, in addition to parietal cells, many other cells where proton pumps work can become targets for non-selective PPIs: the epithelial lining of the intestine, bile ducts, blood-brain barrier, renal tubules, cornea, endothelium of smooth muscle vessels, immunocompetent cells, osteoclasts, as well as cellular organelles with an acidic environment – lysosomes, neurosecretory granules and endosomes, in which pH=4.5–5. At pH=1–2, all PPIs act equally quickly. However, at intracellular pH=3, the rate of PPI activation decreases, at pH=4, PPIs practically do not convert to the active form. The order of decreasing pH level of PPI activation is distributed as follows: rabeprazole > omeprazole = esomeprazole = lansoprazole > pantoprazole.

What are the undesirable side effects of PPIs? If a PPI is a selective PPI, then the side effects are minimized. Non-selective PPIs can cause undesirable side effects in the form of inhibition of many important cellular functions.

For example, rabeprazole, being implemented in the lysosomes of cells of the nonspecific immune system, which constitute the first line of defense against bacterial and viral infections, leads to an increase in the frequency of infectious and inflammatory side effects (rhinitis, pharyngitis, acute respiratory viral infections) by 2–5 %. From the perspective of the possible effect of PPIs on neutrophil function, the development of spontaneous bacterial peritonitis (SBP) in patients with cirrhosis of the liver (CP) is discussed, i.e. infection of ascitic fluid without an obvious source.

What is the role of PPIs in different seasonal intervals? It is in the autumn period that both the frequency of viral and gastroenterological diseases increases. In case of peptic ulcer disease against the background of a viral infection, PPI treatment should be continued. But remember: when used concomitantly with omeprazole, the serum concentrations of atazanavir and nelfinavir decreased, so their simultaneous use is not recommended.

How do PPIs affect magnesium levels? PPIs can lower blood magnesium levels. Hypomagnesemia, which is associated with reduced active intestinal magnesium absorption by transient receptor potential protein channels (TRPM 6/7), which are stimulated by extracellular protons, leads to decreased immunity. If the patient is acidic, this leads to bacterial overgrowth syndrome and an increased risk of bacterial aspiration.

Do PPIs provoke the development of hepatic encephalopathy (PE)? PPIs significantly increase the risk of PE. PPIs are metabolized almost exclusively in the liver. The main metabolic pathway is demethylation by CYP2C19 with subsequent sulfate conjugation, other metabolic pathways include oxidation by CYP3A4. In patients with CP and PE, it is recommended to use PPIs strictly according to clinical need with careful monitoring for signs of PE even after short-term exposure.

Can gastroesophageal reflux disease (GERD) cause bleeding from esophageal varices, and what is the role of PPIs in this? It is known that ascites can exacerbate GERD symptoms, but several clinical trials have shown that PPIs (including Ezonexa) have not been shown to reduce the risk of bleeding associated with portal hypertension.

Are there any negative effects of PPIs on the antiplatelet effect of clopidogrel? When several drugs are used simultaneously, the metabolism of which occurs with the participation of cytochrome P450, their effectiveness may vary, the

negative effect of omeprazole and esomeprazole on the antiplatelet effect of clopidogrel is discussed, as a result of which the prognosis for patients receiving such parallel therapy after acute myocardial infarction or with a coronary stent installed for the prevention of gastrointestinal bleeding is worsened. This phenomenon is believed to occur due to competition between 1st generation PPIs and clopidogrel for the same CYP2C19 enzyme, which allows these compounds to be metabolized in the liver with the transition to the active form. As a precautionary measure, the simultaneous use of esomeprazole and clopidogrel should be avoided.

Can hypergastrinemia occur with long-term PPI therapy? What to do in this case? During long-term PPI therapy, an increase in the number of enterochromaffin-like cells (ECL) was observed in both children and adults, which was probably caused by an increase in serum gastrin levels. These results are considered clinically insignificant. However, such patients should undergo EGD with biopsy (!): against the background of long-term treatment with antisecretory drugs, the frequency of formation of gastric glandular cysts increases. Such changes are a physiological consequence of pronounced inhibition of gastric juice secretion, they are benign in nature and disappear after the end of treatment.

Do PPIs increase the number of bacteria normally present in the stomach in the gastrointestinal tract? The reduction in gastric acid secretion caused by any PPI increases the number of bacteria normally present in the stomach. Treatment with PPIs may increase the risk of gastrointestinal infections, such as Salmonella or Campylobacter, and in hospitalized patients, possibly also Clostridium difficile. In case of defecation disorders, a bacterial culture of feces for pathogenic flora should be performed.

Are there any precautions regarding the use of PPIs in active rheumatoid arthritis in adults, widespread chronic psoriasis, especially in elderly and disabled patients, and acute lymphocytic leukemia? Methotrexate is prescribed in the pathogenetic treatment of these diseases. There are reports that the concomitant use of methotrexate and omeprazole prolongs the renal excretion of methotrexate. With the concomitant use of PPIs, their interaction may occur. When prescribing high doses of methotrexate, temporary withdrawal of esomeprazole should be considered. Many patients take PPIs, and it is important to recognize when the indication for use no longer exists or

when they are ineffective for the patient. For example, approximately 50% of patients taking PPIs for the treatment of non-erosive GERD do not experience symptoms. In these cases, it becomes important to inform the patient that increasing the dose of the PPI may be a viable option. To do this, you need to decide - this is empirical therapy: prescribing a PPI 40 mg half an hour before breakfast for 4–8 weeks, with proper symptom control - on-demand therapy at a dose of 20 mg, non-erosive reflux disease and mild (LA A/B): prescribing a PPI 40 mg half an hour before breakfast for 6–8 weeks, with proper symptom control - on-demand therapy at a dose of 20 mg, severe erosive reflux disease (LA C/D), Barrett's esophagus: 40-80 mg half an hour before breakfast for 8 weeks, control VEGDS to decide on further management of the patient. However, given the number of potential side effects associated with long-term PPI, the Enhancing Healthcare Team Outcomes believes that to improve outcomes, it is advisable to prescribe the lowest effective dose for the shortest possible period and maintain an adequate level of understanding with patients to adapt according to their needs.

The formulations and delivery methods of PPIs should also be considered: often specifically designed to prevent premature activation by gastric acid: enteric-coated tablets, gelatin capsules, coated granules, suspensions, solutions for injection and infusion, combined with bicarbonate for temporary neutralization of luminal gastric acid.

What is the place of PPIs according to Maastricht VI? The Maastricht Consensus is a key document that summarizes the basic principles of diagnosis and treatment from the standpoint of evidence-based medicine. According to the updated consensus, the first-line therapy for H. pylori eradication remains the triple combination of a proton pump inhibitor (PPI), amoxicillin, and clarithromycin. Grade 1 corresponds to a strong recommendation and indicates a clear expert position on the use or non-use of the formulated position.

Thus, the use of PPIs is based on high-quality evidence and implies a high level of confidence that the benefits of using the position outweigh the potential risks.

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