WHAT IS THE MECHANISM OF ACTION OF A PROTON PUMP INHIBITOR?

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https://doi.org/10.5281/zenodo.7954120

Abstract. *Pariet - PPI proton pump inhibitors with the active ingredient rabeprazole, after passing through the stomach, enter the small intestine, where they dissolve, after which they first enter the liver through the bloodstream, and then penetrate the membrane of the parietal cells of the gastric mucosa. goes and there they accumulate in the secretion. tubules. Here, at acidic pH, proton pump inhibitors are activated and become tetracyclic mechanism of action of proton pump inhibitors (Maev I.V. et al.)*

Keywords: *proton pump inhibitor, action, mechanism, types of proton pump inhibitors.*

Mechanism of action of proton pump inhibitors

(Maev I.V. et al.) sulfenamide, it is charged and therefore cannot cross the membranes and does not leave the acidic compartment inside the secretory tubules of the parietal cell. In this form, proton pump inhibitors form strong covalent bonds with the mercapto groups of cysteine residues of H + / K + -ATPase, which blocks conformational transitions of the proton pump, and it is irreversibly removed from the hydrochloric acid process. secretion. New H + / K + -ATPases must be synthesized to restart acid production. Half H + / K +Human α-ATPase is renewed within 30-48 hours, and this process determines the duration of the therapeutic effect of PPI. At the first or single dose of PPI, its effect is not maximal, because by this time not all proton pumps are installed in the secretory membrane, some of them are located in the cytosol. When these molecules, as well as newly synthesized H + /K + -ATPases appear in the membrane, they interact with subsequent doses of PPI, and its antisecretory effect is fully realized (Lapina T.L. , Vasiliev Yu. .V.).

Types of proton pump inhibitors

The Anatomical Therapeutic Chemical Classification (ATC) in section A02B includes two groups of anti-ulcer and anti-gastroesophageal reflux drugs, proton pump inhibitors. A02BC "Proton pump inhibitors" group lists the International Non-State Names (INN) of seven PPIs (the first six types of which are approved for use in the United States and the Russian Federation, the seventh, dexrabeprazole, is not approved for use): Nexium is a PPI with the active ingredient esomeprazole

Esomeprazole, dexlansoprazole, and dexarabeprazole are optical isomers of omeprazole, lansoprazole, and rabeprazole, respectively, and have high biological activity. This group also includes:

There are a number of new proton pump inhibitors in various stages of development and clinical trials. Tenatoprazole is the most famous of them and its trials are nearing completion. However, some clinicians believe that it does not have clear pharmacodynamic advantages compared to its predecessors, and the differences are only related to the pharmacokinetics of the active substance (Zakharova N.V.). Among the advantages of Ilaprazole, it is less dependent on the polymorphism of the CYP2C19 gene and its half-life (T 1/2) is 3.6 hours (Maev I.V. et al.)

In January 2009, the US Food and Drug Administration (FDA) approved the sixth proton pump inhibitor, dexlansoprazole, an optical isomer of lansoprazole, for use in the treatment of GERD; In May 2014, it was approved in Russia. In Pharmacological Index

Zulbex 10 mg (rabeprazole) In the section of gastrointestinal preparations there is a group "Proton pump inhibitors". According to the decision of the Government of the Russian Federation No. 2135 of December 30, 2009, one of the proton pump inhibitors is omeprazole (capsules; lyophilizate for the preparation of a solution for intravenous administration; lyophilizate for the preparation of a solution). infusion; coated tablets) are included in the list of vital and essential drugs.

Currently, 5 standard doses of proton pump inhibitors (esomeprazole 40 mg, lansoprazole 30 mg, omeprazole 20 mg, rabeprazole 20 mg, pantoprazole 40 mg) and one double dose (omeprazole 40 mg) Noflux (rabeprazole) are licensed for the treatment of GERD in Europe. Standard doses of proton pump inhibitors are licensed for 4-8 weeks for the treatment of erosive esophagitis, and double-doses are licensed for up to 8 weeks in refractory patients previously treated with standard doses. Standard doses are prescribed once a day, twice - twice a day (V.D. Pasechnikov and others).

OTC proton pump

In the first decades after their introduction, antisecretory drugs and proton pump inhibitors were generally prescription drugs in the United States, Russia, and many other countries. In 1995, the FDA approved the H2 blocker Zantac 75, and in 2003, the first OTC PPI, Prilosec OTC (omeprazole magnesium), was approved for over-the-counter sales. Later OTC PPIs were registered in the US: Omeprazole (omeprazole), Prevacid 24HR (lansoprazole), Nexium 24HR (esomeprazole magnesium), Zegerid OTCNexium 24HR (esomeprazole) 20 mg OTC (omeprazole + sodium bicarbonate). All over-the-counter forms have no active ingredient and are intended to "treat frequent heart palpitations."

Pantoprazole 20 mg European Union (EU) 12.6.2009, approved for OTC in Australia in 2008 Esomeprazole 20 mg - in the European Union 26.8.2013 Lansoprazole - in Sweden since 2004, then allowed in other EU countries, Australia. and New Zealand. Omeprazole - since 1999 in Sweden, later in Australia and New Zealand, other EU countries, Canada and a number of Latin American countries. Rabeprazole has been approved in Australia since 2010 and later in the UK (Boardman HF, Heeley G. The pharmacist's role in the selection and use of over-the-counter proton pump inhibitors. Int J Clin Pharm (2015) 37: 709–716 DOI 10.1007/s11096-015-0150-z).

The following PPI dosage forms are allowed for OTC sale in Russia, namely Rabiet (rabeprazole) 10 mg OTC:

Gastrozol, Omez, Ortanol, Omeprazole-Teva, Ultop, capsules containing 10 mg of omeprazole

Beret, Noflux, Pariet, Rabiet, capsules containing 10 mg sodium rabeprazole (or rabeprazole)

Controloc, capsules containing 20 mg of pantoprazole

As a general rule, when taking non-prescription PPIs, it is necessary to consult a specialist if there is no effect within the first three days. The maximum duration of non-prescription PPI treatment without consulting a doctor is 14 days (for Controloc - 4 weeks). The interval between 14-day courses should be at least 4 months.

Proton pump inhibitors in the treatment of gastrointestinal diseases

lanzoptol (lansoprazole) Proton pump inhibitors are the most effective drugs that suppress hydrochloric acid, although they are not without some drawbacks. In this case, they found wide use in the treatment of acid-related diseases of the gastrointestinal tract, including, if necessary, the eradication of Helicobacter pylori.

Diseases and conditions indicated for the treatment of proton pump inhibitors (Lapina T.L.): Dexilant (declansoprazole)

gastroesophageal reflux disease (GERD)

stomach and / or duodenal ulcer

Zollinger-Ellison syndrome

damage to the gastric mucosa due to the use of non-steroidal anti-inflammatory drugs (NSAIDs).

Diseases and conditions in which eradication of Helicobacter pylori is indicated.

Many studies have shown a correlation between the duration of maintaining gastric acidity at pH > 4.0 and the rate of healing of ulcers and erosions in the esophagus, stomach and duodenum, the frequency of Helicobacter pylori eradication and the reduction of characteristic symptoms. showed a direct correlation. extraesophageal manifestations of gastroesophageal reflux.

The lower the acidity of the stomach contents (that is, the higher the pH value), the faster the therapeutic effect is achieved. In general, it can be said that for most acid-related diseases, it is important to have a pH level in the stomach above 4.0 for at least 16 hours a day. More detailed studies have shown that each of the acid-related diseases has its own critical level of acidity that must be maintained for at least 16 hours a day (Isakov V.A.):

A crucial link in the pathogenesis of gastric or duodenal ulcers is the imbalance between factors of aggression and factors of mucosal protection. Currently, among the factors of aggression, in addition to the high secretion of hydrochloric acid: high production of pepsin, Helicobacter pylori, gastroduodenal motility disorders, bile acids and lysolicetin on the mucous membrane of the stomach and duodenum, the effect of the pancreas. the presence of duodenogastric reflux, as well as ischemia of the mucous membrane, smoking, drinking solid liquids, taking certain medications, such as non-steroidal anti-inflammatory drugs. Losek MAPS (omeprazole) Protective factors include: secretion of the gastric mucosa, the production of bicarbonates on the surface of the gastric mucosa, which help to neutralize intragastric acidity up to 7 units. pH, the ability of the latter to regenerate, the synthesis of prostaglandins that have a protective effect and are involved in ensuring adequate blood flow in the mucous membrane of the stomach and duodenum. It is important that many of these aggressive and defensive factors are determined genetically and that the balance between them is ensured by the coordinated interaction of the neuroendocrine system, including the cerebral cortex, hypothalamus, peripheral endocrine glands, gastrointestinal hormones and polypeptides. The most important role of high acidity in the genesis of gastric ulcer is confirmed by the high clinical effectiveness of antisecretory drugs widely used in modern therapy of gastric ulcer, among which proton pump inhibitors play a leading role (Maev IV).

Proton pump inhibitors in Helicobacter pylori eradication regimens

Eliminating Helicobacter pylori is not always successful. Widespread and incorrect use of common antibacterial agents has led to increased resistance of Helicobacter pylori to them. Helol (omeprazole) In different countries (different regions) of the world, it is recognized that it is appropriate to use different schemes. In most schemes, one of the proton pump inhibitors is

definitely available in the so-called standard dose (omeprazole 20 mg, lansoprazole 30 mg, pantoprazole 40 mg, esomeprazole 20 mg, rabeprazole 20 mg 2 times a day). The presence of a proton pump inhibitor in the regimen significantly increases the effectiveness of antibiotics and dramatically increases the percentage of successful eradication. Except for cases where proton pump inhibitors are not used - this is atrophy of the gastric mucosa with achlorhydria confirmed by a pH meter. The choice of one or another proton pump inhibitor affects the probability of elimination, but the substitution of other drugs (antibiotics, cytoprotectors) has a much greater effect than PPI. Exact recommendations for the elimination of Helicobacter pylori are given in the standards of diagnosis and treatment of acid-dependent and Helicobacter pylori-related diseases adopted by the Scientific Society of Gastroenterologists of Russia in 2010.

Proton pump inhibitors increase the risk of fractures, possibly cause Clostridium difficile-associated diarrhea, and may cause hypomagnesemia and dementia in the elderly, and possibly increase the risk of pneumonia in the elderly.

Neo-Zext (esomeprazole) 40 mg Tablets The US Food and Drug Administration (FDA) has published a series of reports on the potential risks of long-term or high doses of proton pump inhibitors:

In May 2010, the FDA issued a warning about the increased risk of hip, wrist, and spine fractures with long-term or high-dose use of proton pump inhibitors ("FDA Warning").

In February 2012, an FDA advisory warned patients and physicians that proton pump inhibitor therapy may increase the risk of Clostridium difficile-associated diarrhea (FDA Communication, 2/8/2012).

Based on these and similar data, the FDA believes that when prescribing proton pump inhibitors, the clinician should select the lowest dose or shortest course of treatment appropriate for the patient's condition.

Omeprazole Davur is a generic prescription drug of omeprazole sold in Spain. Several cases of life-threatening hypomagnesemia (lack of magnesium in the blood) associated with the use of proton pump inhibitors have been described (Yang Y.-X., Metz DC.). Proton pump inhibitors slightly increase the risk of hospitalization for hypomagnesemia when taken with diuretics in elderly patients. However, this fact should not affect the rationality of prescribing proton pump inhibitors, and the low level of risk does not require determination of blood magnesium levels (Zipursky J el al. Proton Pump Inhibitors and Hospitalization with Hypomagnesemia: A Population Based Case). -Control Study / PLOS Medicine - September 30, 2014).

According to studies conducted in Germany (German Center for Neurodegenerative Diseases, Bonn), long-term use of proton pump inhibitors increases the risk of dementia in old age by 44% (Gomm W. et al. Associacion of Proton Pump Inhibitors With Risk of Dementia. Pharmacoepidemiologic analysis of claims data JAMA Neurol Published online February 15, 2016 doi:10.1001/jamaneurol.2015.4791).

UK researchers found that elderly people who took PPIs for two years had a higher risk of pneumonia. The logic of the authors of the study is as follows: the acid in the stomach creates a barrier to the intestinal microbiota, which is pathogenic for the lungs. Therefore, if acid production is reduced due to PPI consumption, then more pathogens may enter the airways due to higher refluxes (J. Zirk-Sadowski, et al. Proton-Pump Inhibitors and Long-Term Risk of Community-

pneumonia in Older Adults. Journal of the American Geriatrics Society, 2018; DOI: 10.1111/jgs.15385).

Simanenkov V.I. Acid suppression therapy for refractory forms of GERD

Still from the video: Simanenkov V.I. Acid-suppressive therapy of refractory GERD shows how many and what adverse events (AEs) occur when taking PPIs.

Taking proton pump inhibitors during pregnancy

According to the FDA, different proton pump inhibitors have different fetal risk categories:

About Marcus Gerards Jr. Portrait of an unknown woman. 1595 pantoprazole, lansoprazole, dexlansoprazole - B (animal studies did not show the risk of adverse effects on the fetus, relevant studies in pregnant women were not conducted)

omeprazole, rabeprazole, esomeprazole - C (animal studies have shown adverse effects of the drug on the fetus, and appropriate studies have not been conducted in pregnant women, but the potential benefit associated with the use of this drug in pregnant women justifies its use possible, despite the risk)

Taking proton pump inhibitors to treat gastroesophageal reflux disease during the first trimester of pregnancy doubles the risk of having a baby with a heart defect (GI & Hepatology News, August 2010).

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