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THE MAIN ASPECTS OF THE PATHOGENESIS OF GASTRODUODENOPATHY ASSOCIATED WITH NON-STEROIDAL ANTI-INFLAMMATORY DRUGS IN PATIENTS WITH OSTEOARTHRITIS

ОСНОВНІ АСПЕКТИ ПАТОГЕНЕЗУ ГАСТРОДУОДЕНОПАТІЙ, АСОЦІЙОВАНИХ ІЗ НЕСТЕРОЇДНИМИ ПРОТИЗАПАЛЬНИМИ ПРЕПАРАТАМИ, У ХВОРИХ НА ОСТЕОАРТРОЗ

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Abstract. *The largest group of users of non-steroidal anti-inflammatory drugs are patients with rheumatoid arthritis and osteoarthritis. Nonsteroidal gastropathies are diagnosed in approximately 70% of patients who systematically use these drugs. The article provides modern literary data and results of long-term research on the mechanisms of pathogenesis of gastroduodenopathy induced by non-steroidal anti-inflammatory drugs in patients with osteoarthritis.*

Key words*: nonsteroidal anti-inflammatory drugs, osteoarthritis, gastroduodenopathy.*

Introduction.

Osteoarthritis (OA) is an important medico-social problem that leads to temporary incapacity, disability and a significant decrease in the quality of life of patients. According to official statistics, the prevalence of OA in Ukraine is 2,515.7 cases per 100,000 population, the incidence is 527.0 cases per 100,000 population. The rate of primary disability of the adult population due to OA is 0.6 per 10,000 people, and 0.7 per 10,000 people of the able-bodied population [1].

The main text.

Today, the mainstay of OA treatment is non-steroidal anti-inflammatory drugs (NSAIDs). This group of drugs has a wide range of therapeutic effects, uniquely combining anti-inflammatory, analgesic, antipyretic and antithrombotic effects, affecting the processes of neogenesis, cell adhesion and apoptosis. That is why NSAIDs are the most widely used drugs in medicine. Every year, 500 million prescriptions for these drugs are written in the world, about 30 million people take them every day, 2/3 of patients - without a prescription and medical supervision [2]. In Great Britain, more than 24 million prescriptions of these drugs are registered annually, the largest number of which is for the treatment of arthritis (in more than

60% of cases) and much less often (up to 20%) - for the relief of pain of other origin [3]. According to world statistics [4], almost 5-7% of the world's population, among whom the share of elderly people reaches 40-60%, constantly take NSAIDs, the use of which is associated with a number of side effects and risks, among which the leader is damage mucosa of the gastrointestinal tract (GI) from the esophagus to the rectum. However, the frequency of damage to the gastroduodenal zone develops approximately 6 times more often, which justifies the relevance of the problem of gastrosafety when using non-selective NSAIDs, the use of which is associated with the development of NSAIDs-gastropathy and an increased risk of bleeding and perforations of the gastrointestinal tract [5-9].

Two mechanisms of direct and indirect action of NSAIDs are distinguished in the pathogenesis of the damaging effect on the gastric mucosa (GM) and GM of the gastric mucosa. NSAIDs cause direct damage to GM of the GI tract as weak organic acids that are in non-ionized form in the acidic environment of the stomach, therefore they directly act on the surface epithelium, destroy it, increase the permeability of hydrogen ions and contribute to their excessive retrodiffusion. A few hours after taking NSAIDs, acute damage to the stomach occurs in the form of submucosal bleeding and erosions. Further use of NSAIDs in most cases leads to the healing of surface erosions, which is explained in the literature by the phenomenon of adaptation to the action of drugs. The mediated effect of NSAIDs on GM is provided by a sharp inhibition of the activity of cyclooxygenase-1, as a result of which the activity of prostaglandins (PGs), which provide cytoprotection of GM, decreases. Deficiency of PG I2 leads to the deterioration of blood flow in the stomach wall, disruption of the stabilization of mast cell membranes by lysosomes, increased production of oxygen radicals and enzymes by neutrophils, and disruption of vascular endothelium regulation. A decrease in PG E2 contributes to a decrease in the secretion of bicarbonates and gastric mucus, as a result of which there is an increase in gastric secretion. NSAIDs are also able to switch the metabolism of arachidonic acid from the prostaglandin to the lipoxygenase pathway and promote the synthesis of leukotrienes, which have a toxic effect on the gastrointestinal tract and induce the development of local inflammation due to the adhesion of neutrophils to the endothelium [10-12]. Inhibition of cyclooxygenase-1 also disrupts platelet aggregation, which explains the increased risk of gastrointestinal bleeding [13].

Endothelium-derived relaxing factor (EDFR), discovered in 1980 by R. Furchgott and J. Zawadzki, later named nitrogen monoxide (NO), plays an important role in the pathogenesis of NSAID gastropathy. PG I2 (prostacyclin) and nitric oxide are the most powerful vasodilators known today, produced by a multifunctional endocrine organ - the vascular endothelium. A normally functioning endothelium is both an endocrine and a paracrine cell monolayer, which ensures the maintenance of a balance between the processes of vasodilation and vasoconstriction, anti- and prothrombosis, growth inhibitors and promoters, pro- and anti-inflammatory factors, anti- and pro-oxidants [14]. One of the main antagonists of NO is endothelin. In 1988, M.Yanagisawa et al. discovered a vasoconstrictor of endothelial origin and called it endothelin. It is one of the most studied bioactive mediators and is a powerful vasoconstrictor substance synthesized in the endothelium. The main

manifestations of endothelial dysfunction are a decrease in the secretion of NO, prostacyclin, an increase in the level of endoperoxides and the production of reactive oxygen species, an increase in the synthesis of endothelin-1, as well as cytokines and tumor necrosis factor-α, which inhibit the production of nitric oxide [14-17]. NO participates in the functioning of the central and autonomic nervous system, cardiovascular, respiratory and genitourinary systems, affects the processes of initiation and progression of apoptosis.Nitric oxide can be considered as a signal molecule of the digestive system, since NO stimulates the relaxation of smooth muscles of the esophagus, stomach, small and large intestines, and gall bladder. NO, contained in GM, is one of the mediators of duodenal bicarbonate secretion in response to acid irritation of GM. NO is classified as a mediator of non-specific protection of GM (as PG) against chemical and mechanical factors that damage GM [18]. It supports gastrointestinal blood circulation, suppressing the adhesion and activation of neutrophils, captures free radicals, prevents the adhesion of leukocytes to the vascular wall and damage to the stomach during hemorrhagic shock. Suppression of its production leads to a deterioration of the state of SOS and SO of the DPC, stimulates the adhesion of leukocytes to the epithelium of vessels and disruption of blood flow in the gastrointestinal tract. It directly affects the secretory properties of the stomach, the properties of its GM to prevent the action of factors of aggression, the occurrence and healing of erosions and ulcers [11]. It should be noted that the increase in NO production, which has a very large adaptive value, can turn from a link of adaptation into a link of pathogenesis and be no less dangerous a damaging factor than a deficiency of nitrogen monoxide. Hyperproduction of NO is caused by the expression of inducible NO-synthase under the influence of cytokines (γ-interferon, interleukin-1, tumor necrosis factor-α, transforming growth factor β, platelet activation factor, etc.). Inducible NO-synthase and NO play an important role in the intensification of the processes of lipid peroxidation (POL) and oxidation of sulfhydryl groups, development and progression of pathological processes.In the presence of peroxynitrite or its decomposition products, glutathione radicals are formed, as a result of which the last antioxidant turns into a pro-oxidant, which initiates the processes of POL. A number of researchers also note the possibility of NSAIDs to stimulate inducible NO-synthase, which leads to hemorrhagic damage to the mucous membrane [19,20]. In addition, NO combines with oxygen radicals to form peroxynitrite, which in high concentrations is very toxic and causes apoptosis [21]. In the mechanism of the ulcerogenic effect of NSAIDs, a certain role is played by a change in LOP. The products formed as a result of the toxic effect of NSAIDs are involved in the damage of the SOS, as well as in the destruction of mucopolysaccharides [22]. It is known that LPO reactions are decisive among the processes of free radical oxidation in a living cell. On the one hand, this is a normal metabolic process that regulates the transport of substances through the membrane, the transfer of electrons in the chain of respiratory enzymes. The synthesis of PG and leukotrienes, the metabolism of catecholamines and steroid hormones, the transmission of genetic information, the regulation of the speed of cell division and their differentiation, and the formation of the body's immune-protective reactions take place with the participation of POL. On the other hand, excessive activation of POL

has a universal cytotoxic effect, and this leads to a decrease in GM resistance of the gastrointestinal tract and depletion of the bioantioxidant system. The loss of protein coating membranes by lipid molecules leads to increased penetration of oxygen and pro-oxidants, which contributes to the back diffusion of hydrogen ions through GM of the GI tract. Reactive oxygen species, interacting with the membrane of cells of the GI tract, start an autocatalytic chain reaction of lipid peroxidation with the formation of primary and secondary products. As a result, oxidative stress occurs, which is an important link in the development of the pathological process. POL activation is considered by many researchers to be the leading mechanism for the development of erosive-ulcerative lesions of the stomach and gastrointestinal tract, as a side effect of NSAID treatment.

Conclusion and findings

Increasing the effectiveness of NSAIDs treatment, availability and acceptability for the patient, safety of use is of significant practical importance. The problem of safe use of NSAIDs remains relevant and will require further research and research.

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Анотація. *Найбільшу групу споживачів нестероїдних протизапальних препаратів становлять хворі на ревматоїдний артрит та остеоартроз. Нестероїдні гастропатії діагностують приблизно у 70% хворих, які систематично вживають ці засоби. У статті наведено сучасні літературні дані та результати багаторічних досліджень щодо вивчення механізмів патогенезу гастродуоденопатій, індукованих нестероїдними протизапальними препаратами у хворих на остеоартроз.*

Ключові слова: *нестероїдні протизапальні препарати, остеоартроз, гастродуоденопатії.*