

УДК 616.711-018.3-002:616.33-002-07-08

*O.I.Fediv, L.M.Hresko, S.O.Hresko, R.R.Boichuk***MODERN ASPECTS OF DIAGNOSTICS AND TREATMENT OF NONSTEROID GASTROPATHIES IN PATIENTS WITH OSTEOARTHRISIS**Department of Internal Medicine and Endocrinology (Head – Prof. O.I. Fediv)
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Abstract. A bibliographical review deals with modern data, concerning the diagnosis and treatment of gastropathies induced by nonsteroidal anti-inflammatory drugs in patients with osteoarthritis.

Key words: nonsteroidal gastropathies, diagnosis, treatment.

Osteoarthritis (OA) is an important medico-social problem that results in temporary disability, invalidism and an essential decline of patients' quality of life. In Ukraine OA is detected in 47,7 % of women aged 40-49 years, in 62,8 % – 50-59 years of age, in 74,9 % – 60-69 years of age, in 79,9 % – older than 65 years. These indices in men make up respectively 56,6 %; 72,3 %; 83,7 % and 88,6 % [13]. OA makes up 60 % within the framework of the disease incidence and according to the findings of the state statistics its prevalence constituted 2351,9 per 100 thousand of the population in 2002. The pathology in question ranks second and third as far as the disease incidence is concerned after coronary disease and cerebrovascular disease in persons aged 45-59 years in the countries of Europe [19]. In the USA OA of the knee joints occurs in about 6 % of residents over 30 years of age, whereas that of the coxal joint – in 3 % [9]. Up to 2020 an increase of the disease incidence is expected by 57 % according to forecasts of specialists, whereas cases with a restricted activity associated with this disease – up to 66 % [5]. By now nonsteroidal anti-inflammatory drugs (NSAIDs) make up the basis of OA treatment. This particular group of drugs has a broad spectrum of the curative effect, uniquely combining the anti-inflammatory, analgesic, antifebrile and antithrombotic effects, they influence on the processes of neogenesis, cell adhesion and apoptosis. Just because of that NSAIDs are the most widely used preparations in medicine. Annually 500 million prescriptions for these drugs are written out, around 30 million people take them daily, 2/3 of the patients – without a prescription and doctor's supervision [7]. However, along with the curative effect NSAIDs exert a toxic action on the alimentary canal (AC), liver, central nervous system, cardio-vascular and respiratory system, the renal filtration activity, teratogenicity and embryotoxicity. According to bibliographical findings 46,5 % of side effects in Ukraine are due to NSAIDs [7]. The curative and side aspects are provided by the pathogenetic mechanism of suppressing the activity of the enzyme of cyclooxygenase (COX), in the metabolism of the arachidonic acid, as a result of which the synthesis of prostaglandins (PGs) is reduced. Two isoforms of cyclooxygenase have been revealed by now – COX-1 and COX-2. The COX-1 enzyme is permanently present in the AC, kidneys,

thrombocytes and insures the synthesis of thromboxane A₂, PG E₂ and prostacyclin that perform a cytoprotective action. COX-2 in health exists in a small amount in the brain and kidneys, it is detected in other tissues only in case of a pathological process and it induces the synthesis of PGs which participate in an inflammation, cellular proliferation and destruction. The level of COX-2 is regulated by cytokines, the growth factors and factors that induce tumor growth [4]. There is bibliographical evidence of the existence of the 3^d isoform – COX-3 which is a derivative of COX-1, when it is inhibited there occurs a decrease of the content of prostaglandin E₂ which exerts an antipyretic and analgesic action [1]. In addition, the antiinflammatory and analgesic actions of NSAIDs are associated with a suppression of the activation and chemotaxis of neutrophilic granulocytes and a diminished production of toxic free radicals in activated neutrophilic granulocytes. NSAIDs also inhibit the stimulation of monoxide nitrogen. Via inhibiting the synthesis of prostaglandins NSAIDs influence on apoptosis and enable to normalize the life cycle of cells in the focus of inflammation [4]. Just the ability of NSAIDs to inhibit the functional activity of COX-2 insures a therapeutic action, but simultaneously they also reduce the activity of COX-1, bringing about concurrent reactions. On the other hand, a physiological role of COX-2 that induced the synthesis of PGs participation in the regulation of ovulation, the renal and cardio-vascular function, a reparation of fractured skeletal bones has been established [14]. However, even a short-term intake of NSAIDs may result in the development of severe complications, on the part of the AC, above all. About 20 % of all gastric ulcers and 10 % of duodenal ulcers are associated with NSAIDs intake, more than half of them being complicated by bleeding and perforation [18]. Some authors believe that the use of NSAIDs in the treatment is directly proportional to the frequency of the onset of hemorrhages from the upper portions of the gastrointestinal tract (GIT). The specific characteristics of these erosions and ulcers are their multiple character, an asymptomatic or scantily symptomatic course, the most frequent localization is in the antral portion of the stomach, a high risk of the onset of bleeding, the absence of an inflammatory swelling around the ulcer, foveolar hyperplasia of the mucous tunic, a

rapid repair upon NSAIDs withdrawal [15]. In 1986 S. Roth suggested a term "NSAID-gastropathy" in order to determine injuries of the stomach due to the intake of this group of agents.

Two mechanisms of an immediate and mediated effect of NSAIDs are singled out in the pathogenesis of an injurious effect on the mucous coat of the stomach and the duodenum. A direct injury of the AC mucous coat is inflicted by NSAIDs which manifest themselves as weak organic acids that are to be found in a nonionized form in the acidic medium of the stomach, therefore they act directly on the superficial epithelium, destruct it, enhance permeability of hydrogen ions and favour their excessive retrodiffusion. An acute injury of the stomach arises already in a few hours in the form of submucous hemorrhages and erosions following NSAIDs ingestion. Further NSAIDs intake results in a healing of surface erosions in the majority of cases that is accounted for in the literature by the phenomenon of adaptation to the drug action. The mediated action of NSAIDs on the mucous coat is provided via a sharp inhibition of the activity of COX-1, as a result of which the activity of PGs, insuring the cytoprotection of the mucous coat of the stomach, decreases. PG I₂ deficiency leads to an impaired blood flow in the wall of the stomach, disturbed stabilization of the membranes of the mast cells of lysosomes, an elevated production of oxygen radicals and enzymes by neutrophils, an impaired regulation of the vascular endothelium. A reduction of PG E₂ is conducive to a decrease of the secretion of bicarbonates and gastric mucus in consequence of which an increase of the gastric secretion ensues. NSAIDs are also capable of switching the metabolism of the arachidonic acid from the prostaglandin pathway to the lipoxygenase pathway and promoting the synthesis of leukotrienes that exert a toxic effect on the AC and induce the development of a local inflammation at the expense of the adhesion of neutrophils to the endothelium [6, 15]. On inhibiting COX-1 thrombocyte aggregation is also impaired, accounting for an increased risk of gastrointestinal hemorrhages [8]. A great role in the pathogenesis of NSAID-gastropathies is played by nitric oxide (NO) which maintains the gastrointestinal blood circulation, inhibiting the adhesion and activation of neutrophils, captures free radicals, prevents leukocyte adhesion to the vascular wall and an injury of the stomach in hemorrhagic shock. An inhibition of its production results in a deteriorated condition of the mucous coat of the stomach and duodenum, stimulates the adhesion of leukocytes to the vascular epithelium and a blood flow disturbance of the AC. It has a direct effect on the secretory properties of the stomach, on the properties of its mucous coat to interfere with the action of the aggression factors, on the onset and healing of erosions and ulcers [6]. As a result of proving the physiological role of nitric oxide in the AC modified NSAIDs have been created, containing the sources of nitric oxide that point out their antiulcerous activity [2]. A change of lipid peroxidation (LPO) plays a certain role in the mechanism of the

ulcerogenic action of NSAIDs. The products of lipid free radical oxidation, forming as a result of the toxic effect of NSAIDs, participate in damaging the mucous coat of the stomach, as well as in ruining mucopolysaccharides. The activation of POL is regarded by many researchers as a leading mechanism of the development of erosive – ulcerous damages of the stomach and duodenum and as a side effect of treating with NSAIDs.

G.Yetkin et al. [33] mark a protective impact of the transforming growth factor- α (TGF- α) on the AC mucous coat in case of ulcers induced by NSAIDs. TGF- α intensifies the healing of the ulcerous defect [22].

The problem of an association of *Helicobacter pylori* (Hp) and AC pathology caused by the intake of NSAIDs has not been cleared up to the end up till now. It is known that Hp may protect the upper parts of the AC by means of elevating the level of prostaglandins, however, clinical studies of this question indicate that the elimination of Hp leads to a diminished risk of pathology of the stomach and duodenum in persons who are treated with NSAIDs and a combination of a prolonged ingestion of NSAIDs and Hp essentially enhances the risk of hemorrhages [20]. There are bibliographical findings pertaining to an intensification of apoptosis of the epithelial cells of the stomach in patients with Hp who take NSAIDs and a decrease of this index following Hp eradication that may be indicative of a synergic action of the AC damage [26].

Some investigators consider that Hp and NSAIDs exert an influence on the mucous coat of the stomach independently of each other and do not enhance the action of one another [27]. It is noted in the Maasstricht consensus 2- 2000 that the eradication of Hp lowers the risk of new ulcers in the presence of already existing ones in patients whose anamnesis includes a prolonged treatment with NSAIDs. According to the findings of the consensus of Maasstricht-2003 the correlation between Hp and NSAIDs is complex, almost all peptic ulcers are associated with these two factors, they are independent factors of the incipience of both peptic ulcers and ulcerous bleedings.

The management of NSAIDs-gastroduodenopathies in patients with osteoporosis is rather a complicated and topical problem, so long as the cessation of NSAID therapy as the principal cause of the occurrence of gastroduodenopathies in these patients is impossible on account of an exacerbation of the underlying disease. Having studied the mechanisms of the adverse reaction of NSAIDs, new approaches to the treatment of gastric and duodenal lesions under the influence of these drugs have been elaborated. During the period from 1990 through 2000 new NSAIDs – selective COX-2 inhibitors were introduced into medical practice. They don't differ from the classical NSAIDs as far as efficacy is concerned, but they are almost free of side effects on the part of the AC. Large-scale numerous trials (VIGOR, CLASS and others) note a lower rate of erosive-ulcerous lesions and their complications, while taking selective COX-2 inhibitors compared to those

observed, while taking traditional NSAIDs. The same findings were obtained by many other researchers [29, 30]. In accordance with the NISE recommendations of 2001 selective NSAIDs are prescribed if risk factors of NSAIDs-induced gastropathies are available. In 2001 it was confirmed by FDA that the risk of the onset of erosive-ulcerous lesions of the stomach and duodenum preserved, when using selective COX-2 inhibitors as well. Some authors believe that selective NSAIDs cause gastric and duodenal ulcers 3-4 times less seldom, as well as lesions of the small intestine [11]. C.I.Hawkey et al. point out that selective COX-2 inhibitors, likewise nonselective ones, cause the same dangerous side effects under the action of two and more risk factors [24]. Nowadays, the central place among medical agents used for the treatment of gastroduodenopathies induced by NSAIDs is occupied by proton pump inhibitors (PPIs) [21]. On the basis of some experimental findings (ASTRONAUT, OMNIUM, SCUR, OPPULENT) PPIs are more effective than other drugs in exerting a protective effect on the mucous coat of the gastrointestinal tract (GIT), preventing its damage and contributing to a rapid healing of ulcers and erosions following the intake of NSAIDs [10, 17]. An additional prescription of safe PPIs suppresses the acid production, they don't enter into competitive interdrug interactions with NSAIDs that is regarded to be the basis of preventing and treating NSAIDs-associated gastroduodenopathies, particularly, active gastric ulcers [15]. J.Greenberg's studies showed that in 2005 following "coxib crisis" selective NSAIDs are taken by 36,1 % of patients, whereas PPIs – 53,7 %. This ratio makes up 37,2 % and 57,1 % among patients without risk factors, with one risk factor – 37,2 % and 57,1 %, with two and more risk factors – 41,5 % and 65,4 % respectively [23]. An analysis of the results of 32 researches, studying the efficacy of PPIs in the treatment of peptic ulcer and gastroesophageal disease, has demonstrated that, regardless of some distinctions among PPIs, there are no data in favour of one PPI having greater efficacy compared to others [31]. As to the use of H₂-blockers in standard doses to prevent the development and relapses of gastric ulcers and erosions they are not effective, however, they reliably lower the risk of the development of duodenal pathology, whereas high doses may be used to prevent NSAIDs-induced gastric ulcers [12]. Trials were carried out in Japan among patients who took NSAIDs protractedly and where the prophylactic efficacy of the intake of PPIs, H₂-blockers and misoprostol was evaluated. The rate of the origin was essentially lower, when using H₂-blockers [28]. There is bibliographical evidence to the effect that misoprostol (a synthetic analog of prostaglandin E₂) endowed with cytoprotective properties in relation to the gastrointestinal mucous membrane and in combination with nonselective NSAIDs reduces the rate of the development of gastric and duodenal ulcers, as well as the risk of the onset of ulcerous complica-

tions, at least half as much [11]. This medication suppresses the acid and pepsin production by the stomach, increases the amount of mucus and the density of the mucous gel, elevates the release of bicarbonates and improves the blood circulation in the gastric mucosa, favours the restoration of the cells of the mucous coat and diminishes a reverse diffusion of hydrogen ions. It may be used for the treatment of NSAID-gastropathies, but the bulk of investigations are devoted to its prophylactic action. In the trials of OMNIUM in which misoprostol was administered to 125 patients with gastric ulcers 60 – with duodenal ulcers and 97 – with multiple ulcers, a healing of the ulcers was noted in 62 %, 61 % and 75 % in 4 weeks, whereas in 8 weeks – in 72 %, 77 % and 87 % of patients respectively [10]. However, it is not advisable to take misoprostol combined with antacids, since they reduce essentially its plasma concentration [3]. The American Association of Gastroenterologists has recommended to use misoprostol in the treatment of patients with ulcerous anamnesis who take NSAIDs together with anticoagulants or glucocorticoids, or they have concomitant severe diseases [6]. Some researchers point out that nowadays American doctors prescribe misoprostol considerably less frequently and give preference to PPIs [21, 25]. A promising prospect for a successful treatment is creating drugs enriched with NO that protects the mucous coat from the damaging action [32].

Of late in order to treat and prevent NSAIDs-induced gastropathies they have started to use a new preparation Rebamipid ("Mucogen", Macleods Pharmaceuticals Limited), which elevates the content of endogenous PG E₂ and I₂ in the mucous coat of the stomach and therethrough raises the regenerative properties of the gastric mucosa, insures its protection from damaging factors. Mucogen stimulates the secretion of bicarbonates to maintain the pH gradient, improves the blood circulation in the mucous coat and intensifies cell proliferation. The amount of the superficial gastric mucus under the influence of treating with Rebamipid increases by 160 %. Mucogen also inhibits the migration and activation of neutrophils, diminishes the adhesion of Hp to the gastric mucosa and does not influence on the basal and stimulated gastric secretion of the hydrochloric acid. Mucogen is used to prevent the development of recurrences following the treatment of erosive-ulcerous lesions of the gastric mucosa and duodenum by forming a flat scar with diminished remodelling of the gastric wall, a normalization of the microcirculation and a restoration of adequate epithelization [16].

Thus, the question of gastropathies induced by nonsteroidal anti-inflammatory drugs in patients with osteoarthritis continues to remain one of the most pressing problems of gastroenterology. A promising perspective is further in-depth research of the pathogenetic specific features of gastroduodenopathies induced by NSAIDs in patients with osteoarthritis via studying the mechanisms of dysadaptation of the mucous coat of the stomach and duodenum.

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СОВРЕМЕННЫЕ АСПЕКТЫ ДИАГНОСТИКИ И ЛЕЧЕНИЯ НЕСТЕРОИДНЫХ ГАСТРОПАТИЙ У БОЛЬНЫХ ОСТЕОАРТРОЗОМ

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Резюме. В обзоре литературы приведены современные данные по диагностике и лечению гастропатий, индуцированных нестероидными противовоспалительными препаратами, у больных остеоартрозом.

Ключевые слова: нестероидные гастропатии, остеоартроз, диагностика, лечение.

СУЧАСНІ АСПЕКТИ ДІАГНОСТИКИ І ЛІКУВАННЯ НЕСТЕРОЇДНИХ ГАСТРОПАТІЙ У ХВОРИХ НА ОСТЕОАРТРОЗ

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Резюме. В огляді літератури наведені сучасні дані щодо діагностики і лікування гастропатій, індукованих нестероїдними протизапальними препаратами, у хворих на остеоартроз.

Ключові слова: нестероїдні гастропатії, остеоартроз, діагностика, лікування.

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Vuk. Med. Herald. – 2009. – Vol.13, №2.–P.109-113

Надійшла до редакції 21.04.2009 року