Problem of NSAID gastropathies and their treatment

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According to the official data, non-steroid anti-inflammatory drugs (NSAID) compose one of the main groups of medicines that are sold in Ukraine. For instance, the bestseller medicine in pharmaceutical and hospital segments is acetylsalicylic acid (ASA), which is on the fifth place in the sales structure of all medicines – 24.1 million of packages in 2009 and 21.1 million in 2010. Similar data is observed in other countries, in particular in Denmark in 2009 acetylsalicylic acid was the second bestseller, paracetamol and ibuprofen were third and eleventh respectively.

NSAID is applied in treatment of arthropathy, cardiovascular system pathology, in neurology etc. An anti-inflammatory action of NSAID consists in suppression of synthesis of prostaglandins through the reduction of cyclooxygenase products (COX-1 and COX-2). Suppression of prostaglandins synthesis creates conditions for gastropathies development. Besides, there is a direct damaging effect of these agents on gastric mucous membrane (MM). NSAID properties, duration of their administration, constitutional peculiarities of patients influence the risk of NSAID gastropathies, which are characterized by the development of grave and life threatening complications that develop in 1-5% of patients, who administer NSAID longer than a year.

About 107 000 of the US patients are hospitalized every year because of complications, connected with NSAID administration. 16 500 deaths occur in patients with arthritis because of such complications.

Aiming to determine frequency of gastropathy development, Japanese scientists (Tamura I. et al., 2010) conducted a retrospective research that included 400 patients with atherosclerosis, who administered low doses of ASA. The results of endoscopy showed that 62% (249 patients) had inflammatory and erosive lesions of mucosa of the gastroduodenal zone and 10% (41 patients) had gastroduodenal ulcers. The frequency of NSAID gastropathies detection was significantly higher in those patients, who had two or more out of five risk factors of gastrointestinal complications (aged more than 65, administration of anticoagulants, NSAID, glucocorticosteroids (GCS)).

Determination of risk factors is very important to define how to manage a patient. Such factors include elderly age (>65 years old), concurrent use of systemic corticosteroids or anticoagulants, presence of ulcer in a patient's history, aggravated by hemorrhage, presence of rheumatoid arthritis, cardiovascular diseases, smoking habit, gastrointestinal dyspeptic disorders, which are associated with NSAID administration. The analysis of the results of the research, conducted in Korea by Sung-Hun Lee et al. in 2008, that included 3140 patients with arthropathy, who had been prescribed NSAID, showed that 45% of the patients pertained to the group of high and very high risk of gastrointestinal complications development. About 54% of the patients with complications development were older than 65, with comorbid conditions – 46%. Herewith, diseases of cardiovascular system, kidneys, and liver, diabetes mellitus and hypertensive disease have been determined among the concurrent illnesses. Uptitration of NSAID caused complications in 43% of patients; gastrointestinal hemorrhages in the patients' histories were noted in 36% of cases. Complications were detected in 15% of patients, who had administered ASA. Uptitration of NSAID caused complications in 43% of patients.

It is known that there are three MM protection levels: superepithelial layer that includes mucus barrier, bicarbonates, superficial active phospholipids; epithelial layer – growth factors, cell proliferation, regeneration; and subepithelial layer - blood microcirculation and leucocytes.

Study of MM protection system has been conducted since 80-s, right at that time an important role of prostaglandins, as a protective factor, was proved. The role of prostaglandins in the protection of mucous membrane includes reduction of acid production, increase of mucus and bicarbonates production, increase of the blood flow, regulation of protein synthesis – factors that are important for maintenance of homeostasis in MM.

Also MM protection depends a lot on nitrogen oxides (NO) synthesis, which modulates a range of protective properties (blood flow, mucus and bicarbonates synthesis) and together with prostaglandins plays a significant role in ulcer and erosion cicatrization.

Pathophysiological mechanisms of NSAID gastropathies development are connected with isoenzymes of cyclooxygenase – COX-1 and COX-2, which were separated in 1990-s. Nowadays it is known that COX-1 is a constitutional enzyme, whereas synthesis of COX-2 is induced when an inflammation develops. Traditional NSAID suppress the actions of both cyclooxygenase isoforms that causes the reduction of their functional capabilities in the synthesis of prostaglandins and, consequently, the decrease of protective properties of stomach MM. There are NSAID at the pharmaceutical market that pertain to the coxibs group and are capable of selective COX-2 inhibition.

However, there are some aspects of development mechanism of stomach MM lesion, which need further studying. Theory of NSAID “accumulation” in cells with their eventual destruction tries to explain precisely these aspects. Most NSAID are weak organic acids. They are unionized and lipophilic in gastric juice, when they get into the stomach they come through MM, epithelium and cell membrane to the cytoplasm, where pH-factor is neutral. In neutral pH NSAID ionize, become hydrophilous and, thus, accumulate within a cell that consequently leads to epithelium discontinuity and development of mucous membrane lesions.

The results of these studies potentiate scientists to search for new medicines, capable of leveling a damaging potential of NSAID. In particular, they study the effectiveness of the combination of ASA and γ-tocopherol. H. Matsui with coauthors [7] point at the presence of antioxidant potential of inhibitors of proton pump (IPP). The researches of C. Desai with coauthors (2009), based on studying of expression of genes, coding proteins that are responsible for the development of inflammatory processes in MM, show that an expression level of anti-inflammatory cytokine IL-8 in MM was higher in patients, who had the development of erosive and ulcer lesions of the stomach at a time when NSAID were administered against the background of naproxen administration during 7 days. According to the data of Handa O. with coauthors (2006) and K. Higuchi with coauthors (2009) IPP can decrease synthesis of IL-8 by cells that gives them the possibility to reduce proinflammatory processes in MM and induce gastroprotective action.

At present there is no doubt that it is necessary to prescribe, first of all, antisecretory agents – IPP to patients with the risk of gastroduodenal complications development when administering NSAID. A number of studies demonstrate their effectiveness. When choosing IPP, it is necessary to take into account the peculiarities of metabolism of different drugs of this group, as each of them has pharmacokinetic characteristics. It is known that IPP pantoprazole possesses high bioavailability, the highest pH-selectivity among other IPP molecules. Pantoprazole has the longest time of proton pumps’ recovery after administration of a single dose, which constitutes 92 hours. Many scientists favor pantoprazole in their

studies. Taking into account a long IPP treatment period, it is necessary to note the importance of economic constituent of the therapy. The inhibitor of the proton pump Panocid® (pantoprazole) pertains to the category of drugs affordable to a broad spectrum of patients and, with regard to clinical advantages, when the research was conducted, Panocid® appeared reasonable to be used.

Research objective: to study the effectiveness of IPP Panocid® (pantoprazole, 40mg), "Ananta Medicare" company (UK), in treatment of gastroduodenal zone lesions, associated with NSAID administration.

Materials and methods of research: 23 patients have been examined during their treatment at the department of stomach and dodecadactylon diseases of the Institute of Gastroenterology of Academy of Medical Sciences of Ukraine. The average age of patients was 58,3 ± 4,8 years. The criterion for inclusion into the examination was the administration of NSAID at least once a week during at least a month. Clinical examination of patient has been conducted with studying the drug history, symptoms, patient's complains and physical examination data.

Macroscopic state of MM of ezophagogastroduodenal zone (EGDZ) has been studied with the help of esophagogastroduodenoscopy (EGDS) according to the standard practice using fibrogastroduodenoscope "Olympus". To standardize the results of endoscopy of EGDZ organs "Minimal standard terminology in endoscopy of the digestive system" was used (it is recommended for use by the World Organization for Digestive Endoscopy). The patients' therapy scheme included IPP Panocid® (pantoprazole, 40mg), "Ananta Medicare" company (UK). Duration of therapy has been calculated depending on the MM involvement: if there was superficial erosion, Panocid® was prescribed in 40 mg dose ance a day during 4 weeks; if there were MM ulcers of gastroduodenal zone – 40 mg dose once a day during 4-8 weeks with following continuation of Panocid® administration 40 mg once a day if the continuation of NSAID administration is required. The drug has been prescribed for administration 1 hour before meal. Therapy effectiveness has been assessed through the analysis of dyspepsic presentations and pain syndrome. Endoscopic control on healing the MM defects in gastroduodenal zone was conducted on the 14^{th} and 28^{th} day of the treatment.

Statistical analysis of the results of the researches has been conducted using methods of variation statistics and has been realized using standard package of application programs SPSS 13.0 for Windows.

Results of research: Dyspepsic 21 (91.3%) and pain 20 (87%) syndromes appeared most characteristic for the patients (fig. 1)

Fig. 1 frequency rate of dyspepsic and pain syndromes in the examined patients, %

Pain syndrome has been assessed by localization, intensity and correlation with mealtime and time of the day (table 1).

Table 1

Frequency and character of pain syndrome in the examined patients

Clinical aspects	Before treatment (n=23)	
	n	%
Total	20	87,0

Pain localization:		
retrosternal	14	60,9
epigastrium	19	82,6
Pyloroduodenal zone	15	65,2
Pain character:		
Increased pain at night	17	73,9
Co-relation of pain syndrome with food intake:	13	56,5
Pain on an empty stomach	19	82,6
At a time of food intake	6	26,1
30 min after food intake	7	30,4
Not connected with food intake	4	17,4

As the given data shows, the examined patients more often complained of pain syndrome in epigastrium, with an increased pain mainly on empty stomach and at night. About one third of the patients suffered pain with food intake and 30 min after food intake that can be explained with the irritation of the distal part of the stomach and the duodenum by the dietary fibers and/or disorders of antroduodenal coordination against the background of MM involvement in the gastroduodenal zone. Slightly less than in one fifth of the patients pain syndrome wasn't connected with food intake and was of permanent character. The analysis of constituents of the dyspepsic syndrome is represented in table 2.

Table 2

Frequency and character of dyspepsic symptoms in the examined patients

Dyspepsic aspects	Before treatment (n=23)	
	n	%
Total	21	91,3
epigastric burning:	19	82,6
1-2 timesa week	7	36,8
More than two times a week	12	63,2
eructation:	15	65,2
Gaseous	12	80,0
Gaseous with food additive	3	20,0
Epigastric discomfort after food intake	18	85,7
Nausea	12	57,1
dry mouth	8	38,1
Bitterness in mouth	10	47,6
abdominal distention	14	66,7

The results of the analysis showed that, first of all, it is necessary to pay attention to such symptoms as epigastric burning, epigastric discomfort after food intake and gaseous eructation, which together with the presence of NSAID administration in treatment history require profound further examination and EGDS.

When macroscopic state of the mucous membrane of the stomach and the duodenum was assessed in the examined patients, erythematic changes of the stomach MM were detected in all the patients. The erythema expression of the MM of the antral part of the stomach in most patients corresponded to the third level – 69.6%. Diffuse erythema of the stomach MM more often corresponded to the second level and was detected in 56.5% of the examined patients. Acute erosions of the stomach MM were detected in the antral part in 17 patients (73.9%) Almost in a half of the cases they were associated with acute erosions in a

duodenal bulb – 8 (34.8%) patients. In 6 (26.1%) cases EGDS detected antral stomach ulcer, whereas two of them (8.7%) already against the background of cicatricial deformity of the prepyloric part.

After the prescribed treatment pain syndrome was fully arrested on the 5,4 ± 1,1 day of the treatment. It is necessary to mention that most patients with erosive changes of the MM noted the absence of pain already on the 2-3 treatment day. Pain syndrome in the patients with gastric ulcers pain syndrome lasted longer. On the first days of the treatment the intensity of epigastric burning significantly decreased and it was arrested in average on 4,2 ± 1,9 day of the treatment. On the whole during 7-8 days we managed to level dyspepsic and pain syndromes in the majority of cases. The terms of improvement in one case were longstanding because of headache presence, due to what it was difficult for the patient to give up NSAID.

On the 14th day of the treatment adhesion of ulcer defect in the antral part of the stomach occurred in 5 (21.7%) examined patients. An ulcer in one of the cases was registered in a cicatrisation stage that made us enhance the cytoprotective therapy. Erosive chanhes in the stomach and the duodenum weren't detected in any patients, expression of the MM diffuse erythema and the MM erythema of the antral part of the stomach reduced to 1 and 2 levels respectively.

In the process of treatment with Panocid there wasn't noted clinically significant interaction with other drugs, which had been used in a complex treatment. Apparently, it is connected with the fact that Panocid® has lower affinity with the P450 cytochrome system than other IPP molecules do.

No side effects were detected against the background of the provided treatment.

Clinical example. Patient M-ko, born in 1951, applied to the Institute of Gastroenterology of Academy of Medical Sciences of Ukraine in June 2011 with complains of continuous epigastric pain that significantly increased on an empty stomach and 20-30 min after food intake, bitterness in mouth, frequent gaseous eructation, abdominal distention. About 10 years of duodenal ulcer are mentioned in the patient's history. Last aggravation was 2 years ago; he was under treatment in his place of residence with improvement. Worsening of the state of health he has been noting for 2 months, when the pain became so intensive that made it difficult to fulfill ordinary duties. The detailed examination elicited that during a year because of a frequent headache he has been self-administering up to 10-12 pills of NSAID-Citramonum, Sedalgin and others per day. He has been smoking for 23 years, up to 2 packs a day. Under physical examination: asthenic bodybuild. Skin tightness is reduced; skin and mucous membrane color is common. Moist tongue, plastered with white fur. When examination of the abdomen was conducted, palpation tenderness in epigastrium, projection of the pyloroduodenal zone, was noted. There were no symptoms of peritoneal irritation. According to the data of EGDS (15.06.2011): pylorobulbar ulcer. Flagrant deformity of pylorobulbar section upon the signs of fractional stricture formation. Duodenal reflux. Erosive bulbopathy.

The results of histologic examination of biopsies (24.06.2011): intestinal metaplasia of gastric superficial-foveolar epithelium by colic type in biopsies from the edges of the ulcer defect, fibroblastic reaction of the own MM plate. According to the data of the ultrasound examination of the abdominal cavity organs, signs of chronic pancreatitis, chronic cholecystitis and diffusive changes in the liver were detected. X-ray examination of the stomach did not detect any signs of

stricture formation. The patient got the therapy that included administration of Panocid 40 mg once a day, cytoprotector rebamipide 100 mg three times a day.

Additional laboratory studies detected cholesterine level increase in blood serum, and the examination of vessels showed atherosclerotic changes. To specify the genesis of the headache the patient was examinated by the neuropathologist, consulted by psychotherapist that made it possible to implement an integrated approach to his treatment. As the result, the patient's state improved much, due to significant reduction of headache we managed to minimize and then to refuse of NSAID administration.

The EGDS results as of 11.07.2011 testify the ulcer defect cicatrization. The patient has been prescribed a supporting therapy with Panocid of 40 mg dose a day; the recommendations on further observation have been given.

Discussion of the results. NSAID gastropathies' development is a very important medical problem, which requires profound approach to studying of main mechanisms of their origination, as well as to development of management standards for patients, who extremely need NSAID. It is necessary to explain to patients risks and importance of observation of all the recommendation given by a doctor, constant administration of the prescribed gastrocytoprotectors, as the achievement of therapy compliance makes it possible to decrease grave complications development. The recommended medications for decrease of development of MM involvements in the gastroduodenal zone are IPP due to their acid reducing, anti-inflammatory and anti-oxidant properties. The peculiarities of Panocid metabolism make it the right drug for prevention and treatment of NSAID gastropathies.

Administration of Panocid in a complex treatment of patients with NSAID gastropathies allows to achieve a desired positive effect: leveling of pain and dyspepsic syndromes, ulcer and erosion cicatrization at early stages of treatment.

Conclusions:

- Patients with erosive and ulcer lesions of the gastroduodenal zone need a profound collection of a drug history to determine the genesis of these lesions and to recommend a treatment strategy.
- Use of Panocid in a complex treatment of patients with NSAID gastropathies allows to achieve good clinical effect: early leveling of pain and dyspepsic syndromes, MM defects cicatrization in the gastroduodenal zone provided there are no side effects.
- The calculation of therapy duration with Panocid should be made in accordance with the extent of MM lesion: in case of superficial erosion – 40 mg a day during 4 weeks, in case of ulcers – 40 mg a day during 4-8 weeks, if it is necessary to comntinue NSAID administration it is recommended to administer Panocid 40 mg a day 1 hour before food intake.

The bibliography is currently on editing.