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Assessment of the Impact of Some Inhibitors of Angiotensin-converting Ferment, Omeprazole and Their Combinations on the Frequency of Erosive Ulcerous Disorders of Gastric Mucosa When Administered with Indometacin

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Abstract. The examination of 144 white mature male rats of mixed population was conducted. Experimental rheumatoid arthritis model was used to study the impact of some ACE inhibitors: omeprazole, cytotek and combinations of omeprazole with ACE inhibitors and cytotek on frequency of erosive ulcerous injuries of gastric mucosa when administered within 5 and 10 days with indometacin. Drugs were administered per os in the form of water suspension.

It was established that the combined use of ACE inhibitors, omeprazole and cytotek with indometacin decreases the noci-influence of indometacin on gastric mucosa. Captopril is the most treatment medication among ACE inhibitors. Combined application of ACE inhibitors with omeprazole and cytotek increases the medicine efficacy. Com- bined use of omeprazole and captopril or omeprazole and cytotek is the most effective for prevention of side effect of indometacin on mucosa of gastroduodenal zone.

Keywords: stomach; indometacin; injury; damage; treatment.

Introduction. In the mean time it is obvious that early diagnosis, treatment and prevention of ulcers and erosion of the upper sections of gastrointestinal tract emerging in patients after taking non-steroid anti-inflammatory drugs (NSAID). Material expenditures on treatment of gastroduodenal complications are extremely high [1,2]. According to De Pawourvelle [3], total real cost of NSAID therapy is 1.5–2 times higher than nominal value of drugs due to expenses on treatment and prevention of NSAID-induced gastropathies.

Considering the above, the problem of safe application of NSAID, prevention and treatment of gastrointestinal side effects [4, 5] has attracted significant attention in recent years. New mechanisms of NSAID-gastropathy and therapeutic treatment and prevention drugs are under development, using the acquired data [6, 7, 8].

In the meantime, anti-secretory means and synthetic analogues of prostaglandins are mainly used for prevention and treatment of NSAID-gastropathies. Proton pump inhibitors are widely used out of these groups of drugs. Blockers of H2-histamine receptors do not affect the frequency of erosive ulcerous disorders in the stomach and are useless for prolonged use due to addicting property, caused by the phenomenon of receptors fatigue [9]. Efficiency of synthetic prostaglandin analogue E_2 – misoprostol in NSAID-gastropathies therapy is confirmed by clinical studies but it should be emphasized that the drug has not find its wide application due to high prices and frequent adverse effects [10, 11, 12].

To resolve this issue we consider as necessary to study the efficiency of inhi- bitors of angiotensin-converting enzyme (ACE inhibitors) for prevention of NSAID-induced gastropathy. Studies by O.M.Mikheyeva et al. [13], who established the ulcer-healing effects of enalapril in hypertension patients with concomitant ulcer disease served as primary prerequisite. Nafeeza Mohd Ismail et al. [14] studied the effects of captopril and ranitidine on composition of prostaglandin E_2, malon dialdehyde and activity of glutathione reductase on the model of aspirin-induced gastropathy in rats. It was established that captopril unlike ranitidine increases the activity of glutathione reductase, composition of prostaglandin E_2 and reliably decreases the composition of malon dialdehyde.

The research objective was aimed at studying the efficiency of some ACE inhibitors, omeprazole, cytotek and their combinations on the frequency of erosive ulcerous disorders of gastric mucosa in their combined application with indometacin.

Materials and methods. Experimental studies were carried out on 144 white male rats of mixed population with body mass of 160-200g by the start of the experiment. Twelve groups, each consisting of 6 animals have been investigated. This investigation was focused on the anti-ulcerous effects of enalapril, lysinopril, captopril, omeprazole and cytotek when administered within 5 and 10 days with indometacin. In addition, frequency and area of erosive ulcerous disturbances when indometacin is taken with omeprazole and enalapril, with omeprazole and lysinopril, with omeprazole and captopril, with omeprazole and cytotek have also been studied.

Frequency and area of erosive ulcerous disturbances were studied in the following groups of animals: 1st group – intact; 2nd group – animals with experimental rheumatoid arthritis (ERA); 3rd group – animals with ERA receiving indometacin; 4th group – ERA + indometacin+enalapril; 5th group – ERA + indometacin + lysinopril; 6th group – ERA +indometacin+captopril; 7th group – ERA +indometacin+omep- razole; 8th group – ERA +indometacin+cytotek; 9th group – ERA + indometacin + omeprazole+enalapril; 10th group – ERA + indometacin + omeprazole+lysinopril; 11th group – ERA + indometacin+omeprazole+captopril; 12th group – ERA +indo- metacin +omeprazole+cytotek.

Division of experimental animals into the above groups was determined by the desire to observe the protective effect of ACE inhibitors, omeprazole and cytotek against damaging effect of indometacin if taken simultaneously.

Commonly recognized model of experimental rheumatoid arthritis (ERA) in rats [15] was employed for investigation purposes. It was implemented by a single administration of 0.2 ml of Freund adjuvant into rear right leg. Severity of disease was assessed by circumference diameter of joints on posterior legs, development of secondary arthritis in joints of anterior legs and change in body mass of animals.

Indometacin was administered by 2.5 mg/kg dosage on experimental animals. By choosing such dosage of indometacin we relied on data from references where authors showed 100% erosive ulcerous damage of gastric mucosa when the drug is administered within 5 days [16]. Choosing the duration of research (5 and 10 days) was based on the fact that administration of indometacin within 5 days causes 100 % gastropathy in the form of erosive ulcerous disorders that progressively aggravates with continuous administration [16, 17].

Drug dosages were based on findings of experimental studies carried out on rats by other researchers. All drugs were administered per os in the form of water suspension in the following doses: enalapril in a dose of 10 mg/kg [18], lysinopril in a dose of 8 mg/kg [19], captopril in a dose of 7.5 mg/kg [20], omeprazole in a dose of 50 mg/kg [21], cytotek in a dose of 0.2 mg/kg [22, 23].

To examine the state of erosive ulcerous disorders and to determine the affected areas animals were decapitated by etherization. Extracted stomach was dissected on lesser curvature, cleaned and washed in saline solution. Stomach was fixed on sample surface. Damage from erosive

ulcerous, mainly located in antral section of the stomach was evaluated. Damaged areas had round shape 1-3 mm in diameter. Overall area of damages was expressed in mm².

Results and discussion. Table 1 exhibits results of the study of the frequency of erosive ulcerous disorders of gastric mucosa by indometacin when administered with ACE inhibitors, omeprazole and cytotek and their combinations.

Table 1: **Frequency of erosive ulcerous disorders of gastric mucosa by indometacin when administered with ACE inhibitors, omeprazole, cytotek and their combinations**

№	Groups of animals	Number of animals	Frequency of erosive ulcerous disorders (number of animals, %)	
			5 days	10 days
1	Intact	6	0	0
2	ERA	6	0	0
3	ERA+indometacin	6	6 (100,0%)	6 (100,0%)
4	ERA+indometacin+enalapril	6	6 (100,0%)	4 (66,6%)
5	ERA+indometacin+lysinopril	6	5 (83,3%)	3 (50,0%)
6	ERA+indometacin+captopril	6	4 (66,6%)	1 (16,7%)
7	ERA+indometacin+omeprazole	6	5 (83,3%)	3 (50,0%)
8	ERA+indometacin+cytotek	6	4 (66,6%)	2 (33,4%)
9	ERA+indometacin+omeprazole+ enalapril	6	5 (83,3%)	3(50%)
10	ERA+indometacin+omeprazole+ lysinopril	6	5 (83,3%)	2 (33,4%)
11	ERA+indometacin+omeprazole+ captopril	6	3 (50,0%)	0 (0%)
12	ERA+indometacin+omeprazole+ cytotek	6	3 (50,0%)	1 (16,7%)

Presented table indicates that administration of indometacin in a dose of 2.5 mg/kg within 5 day period provoked erosive ulcerous disorders of gastric mucosa in 100 % of animals. These changes were also observed within 10 day administration of drug. Frequency of formation of erosive ulcerous damages when indometacin and enalapril are used simultaneously within 5 day term remained the same, and mucosal damage was observed in only 66.6 % of animals within 10 day use.

More significant effect was observed when indometacin and lysinopril were administered simultaneously. Erosive ulcerous damages were observed in 83.3 % of animals on the fifth day when administered simultaneously and in 50 % of animals on the tenth day. Similar changes were also observed in the group of animals, receiving indometacin with omeprazole.

Preventive properties of captopril and cytotek are the best. Disorders were observed in 66.6 % of animals in the group with indometacin and captopril on the fifth day of administration, and in 16.7 % of animals on the tenth day. Similar changes were also observed in the group with cytotek. But the efficiency of 10 day administration was less than in the group with captopril.

Combined application of omeprazole with ACE inhibitors and cytotek substantially prevents the damage of gastric mucosa by indometacin. Results obtained from 5 day combined administration were less obvious. However, results obtained from 10 day administration were more convincing. Erosive ulcerous damages of stomach were observed in only 50 % of animals in

the group receiving indometacin+omeprazole+enalapril. Almost similar changes were observed in the group of animals receiving indometacin+omeprazole+lysinopril.

Damaged effect of indometacin was observed in 50 % of animals in the group receiving omeprazole and captopril within 5 day period, but the damaged effect of indometacin was not detected in animals treated within 10 days. Almost the same results were observed in the group of animals treated with omeprazole and cytotek. Only one animal (16.7 %) had erosions in gastric mucosa after 10 day administration of these drugs.

The obtained results of the study of the frequency of disorders also reflected on the area of erosive ulcerous damages.

Results of the study of the average area of erosive ulcerous destructions of gastric mucosa by indometacin when administered with ACE inhibitors, omeprazole and cytotek and their combinations are given in Table 2.

The data presented in Table 2 indicate that the preventive use of the studied drugs reliably reduces the average area of mucosal damage. Despite the 100 % damage to the area, 40 % less damage was observed in the group with indometacin and enalapril on the fifth day of administration if compared to the group with indometacin. The area of the damage decreased by 68 % if compared to the group with indometacin within 10 day combined administration. The area of damage decreased by 43.3 % and 77.2 % respectively in the group with indometacin and lysinopril on the fifth and tenth days of treatment. Similar results were observed in the group of indometacin and omeprazole.

Top results were observed when indometacin was administered with captopril and cytotek. The area of damage decreased by 72.3 % (on the fifth day) and by 86.1 % (on the tenth day) respectively in the group of indometacin and captopril. The area of injuries decreased by 66.3 % and 86.5 % respectively in the group of indometacin and cytotek if compared to the group with indometacin.

Combined application of omeprazole and enalapril within 5 day period reduced the area of damage 1.9 times and 10 day administration almost 4 times. The area of damage in omeprazole and lysinopril group reduced almost 2.5 and 5.5 times respectively on the fifth and the tenth day of treatment, whereas the frequency of destruction decreased only 1.2 and 3 times respectively. The obtained results were more significant in groups with omeprazole with captopril and omeprazole with cytotek. The area of damage reduced 3.9 and 4.9 times respectively on the fifth day of treatment. The efficiency of the use of such combinations was significant on the tenth day of treatment.

Table 2: **The area of erosive ulcerous damage of gastric mucosa by indometacin when administered with ACE inhibitors, omeprazole, cytotek and their combinations**

№	Groups of animals	Number of animals	Average area of erosive ulcerous injuries (мм²)	
			5 days	10 days
1	Intact	6	0	0
2	ERA	6	0	0
3	ERA+indometacin	6	15,21±0,572	22,31±0,907
4	ERA+indometacin+enalapril	6	9,15±0,357	5,10±0,170
5	ERA+indometacin+lysinopril	6	7,11±0,109	5,10±0,179
6	ERA+indometacin+captopril	6	4,22±0,151	3,11±0,128
7	ERA+indometacin+omeprazole	6	8,78±0,300	6,12±0,203
8	ERA+indometacin+cytotek	6	5,13±0,184	3,93±0,150
9	ERA+indometacin+omeprazole+ enalapril	6	8,12±0,287	5,65±0,238

10	ERA+indometacin+omeprazole+ Lysinopril	6	6,25±0,257	4,11±0,171
11	ERA+indometacin+omeprazole+ Captopril	6	3,93±0,154	0
12	ERA+indometacin+omeprazole+ Cytotek	6	3,13±0,135	1,78±0,105

We have detected that the cytoprotective effect of captopril is more significant than that of enalapril and lysinopril. It is likely caused by presence of sulfhydryl group in the structure of the drug. It is known that natural amino acids containing sulfhydryl (L-cysteine and methionine) as well as medicines, containing sulfhydril prevent gastric erosion induced by ethanol in rats. That suggests that sulfhydryls protect mucosal membrane of stomach and that endogen sulfhydryl compounds may mediate gastric cytoprotection induced by prostaglandins (PG). Sulfhydryl groups are necessary for synthesis of prostanoids and activation of PG receptors and may be directly responsible for protection of mucosal membrane affecting permeability of membranes, cellular adhesion and free radicals or they may bind receptors and prevent the release or acting of injury mediators of mucosal membrane [24, 25].

It should be noted that cytoprotective effect of ACE inhibitors is likely caused by their antioxidant and corrective effect on the system of NO-formation in stomach. Available data show that captopril inhibits lipid peroxidation and prevents the reduction in the activity of superoxide dismutase and catalyses. [26, 27]. The analysis of ascorbate, total glutathione, activity of glutathione peroxidase and glutathione reductase exhibited that captopril provokes the increase of antioxidant defense of the organism [28, 29], and in combination with natural antioxidants contributes to the normalization of indices of free radicals homeostasis [30]. The benefit of antioxidant effect of ACE inhibitors containing sulfhydryl group is also noted by other authors [31, 32]. It is commonly known that inhibition of angiotensin-converting enzyme restores balance between two vasoactive systems: angiotensin II and nitrogen oxide [33]. The latter, besides vasodilatation prevents thrombocytes aggregation and activation of a number of cells as well as inhibits proliferation of smooth muscular cells. It is necessary to note that correcting effect of I-ACE on system of NO-formation in stomach is caused by same mechanisms. ACE inhibitors contribute to the regulation of endothelial function, vascular system in general and increases the level of bradykinin that is a powerful stimulator of NO production. Besides, ACE inhibitors decrease oxidation stress resulting in activation of protective endothelial NO-system [34].

Literature contains contradictory proposals, concerning cytoprotective effect of omeprazole. Chandranath S.I. et al. [35] claim that inhibitors of proton pump impose cytoprotective action due to suppression of acid aggression and possibly due to other unknown mechanisms. Watanabe T. et al. [36] presume that protective action of IPP on the mucosal tissue of stomach when damaged by ethanol is accomplished by the regulation of formation system of nitrogen oxide while the quantity of prostaglandins does not change.

Our obtained results in application of cytotek conform to the data of other authors [37, 38]. As claimed by Abdulkhakov R.A., cytotek in analogy to endogen prostaglandins possesses the ability to amplify mucus formation and secretion of bicarbonates, improves blood stream, stimulates epithelial regeneration of gastric mucosal membrane and decreases the production of hydrochloric acid [39].

Conclusion. Consequently, the application of ACE inhibitors, omeprazole and cytotek reduces the damaging effect of indometacin on gastric mucosa. Captopril is the most efficient among ACE inhibitors. The combined use of ACE inhibitors with omeprazole and cytotek with omeprazole increases the efficiency of drugs. Combined use of omeprazole with captopril or omeprazole with cytotek is most reasonably aimed at the prevention of adverse effects of indometacin on mucosa of gastroduodenal zone.

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Оценка эффективности некоторых ингибиторов ангиотензинпревращающего фермента, омепразола и их комбинаций на частоту эрозивно-язвенных повреждений слизистой желудка при их совместном применении с индометацином

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Аннотация. Проводили экспериментальные исследования на 144 белых половозрелых крысах-самцах смешанной популяции. На модели экспериментального ревматоидного артрита изучали эффективность некоторых И-АПФ, омепразола, сайтотека и комбинаций омепразола с И-АПФ и с сайтотеком на частоту эрозивно-язвенных повреждений слизистой желудка при их совместном применении с индометацином при 5-ти и 10-ти дневном сроке введения. Препараты вводили per os в виде водной суспензии.

Установлено, что при совместном применении И-АПФ, омепразола и сайтотека с индометацином повреждающее действие индометацина на слизистую желудка снижается. Среди И-АПФ наиболее эффективным является каптоприл. При комбинированном применении И-АПФ с омепразолом и сайтотека с омепразолом эффективность препаратов увеличивается. В плане профилактики побочного действия индометацина на слизистую гастродуоденальной зоны наиболее целесообразным является комбинированное применение омепразола с каптоприлом или омепразола с сайтотеком.

Ключевые слова: желудок; индометацин; повреждение; лечение.