Original Article

Evaluation Of The Effectiveness Of Angiotensin-Converting Enzyme Inhibitors, Misoprostol, Omeprazole And Their Combinations On The State Of The Gastric Mucous Barrier In Indomethacin Gastropathy In Animals With Experimental Rheumatoid Arthritis

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Abstract

Annotation

Purpose. To study the effectiveness of ACEi, misoprostol, omeprazole and their combinations on the state of the gastric mucosal barrier in indomethacin gastropathy in animals with experimental rheumatoid arthritis.

Material and methods. Experimental studies were carried out on 78 male rats of mixed population weighing 160-200 g. For experimental studies we used a generally recognized model of experimental rheumatoid arthritis (ERA) in rats, which is carried out by a single injection of 0.2 ml of Freund's adjuvant into the hind right leg. After modeling ERA, NSAID gastropathy was induced in the animals by oral administration of indomethacin at a dose of 2.5 mg/kg. The study was conducted on 13 groups: 1 gr. - intact; 2 gr. animals with ERA; 3 gr. - animals with ERA and indomethacin gastropathy (GERA); 4 gr. - animals with GERA+H_2O; 5-9 groups: animals with GERA treated with enalapril, lisinopril, captopril, omeprazole, and misoprostol.

Groups 10-13 received a combination of omeprazole with ACEi and misoprostol. Each group consisted of 6 animals. The used drugs were administered for 10 days. The content of mucus-producing cells was calculated by counting the total number of cells in a standard field of view on light-optical preparations under magnification of 40x10.

For biochemical studies, animals were slaughtered by one-step decapitation under ether anesthesia, the stomach was extracted, cleaned, washed with cold physiological solution, and the pre-stomach was removed. Then the mucous layer was scraped out, weighed and suspended in distilled water in a porcelain mortar at the rate of 30 mg/ml. The content of sialic acids in the gastric mucosa suspension was determined by the method of L.I. Linevik.

Results. In experimental RA (ERA) the content of insoluble glycoprotein (IGP) fractions is practically unchanged.In animals with indomethacin-inducedgastropathyand ERA (GERA) a significant decrease in IGP fractions was observed. In ERA, the number of functioning cells decreased by only 5.8% ($p>0.05$). In indomethacin-induced gastropathy (GERA), along with a decrease in the content of IGP fractions, there is a significant decrease in the number of functioning mucus-producing cells.

ACE inhibitors, omeprazole, and misoprostol have a positive effect on the content of IGP fractions in the gastric mucosa. The use of captopril and misoprostol appeared to be more effective in the treatment of GERA. In the groups with captopril, omeprazole, and misoprostol, the content of functioning cells increased by 82.7%, 68%, and 99.1%, respectively, from that in the GERA group without treatment. Combined use of omeprazole with other drugs potentiates their cytoprotective effect in the form of additive pharmacodynamic interaction. In the groups omeprazole with captopril and omeprazole with misoprostol the drug interaction was more significant. The best results were obtained with the combined use of omeprazole with captopril and omeprazole with misoprostol. In this group, the number of cells increased by 204.2% from that of the group without treatment.

Conclusion. In experimental RA the state of the gastric mucosal barrier is practically unchanged. Treatment of RA with indomethacin significantly suppresses the synthesis of insoluble glycoproteins of the mucosal barrier and reduces the number of functioning mucus-

producing cells. ACE inhibitors has a cytoprotective effect in the treatment of indomethacin gastropathy. Among them, captopril is more effective, which increases the synthesis of the mucus barrier and the number of mucus-producing cells. By this effect, captopril is equal to omeprazole and misoprostol. When ACE inhibitors and misoprostol are combined with omeprazole, their pharmacodynamic effect increases in the form of additive synergism. Combinations of omeprazole with captopril and omeprazole with misoprostol are the most effective.

Keywords: ACE inhibitors, misoprostol, omeprazole, gastric mucosal barrier, indomethacin gastropathy, rheumatoid arthritis

Introduction. The number of nonsteroidal anti-inflammatory drugs (NSAIDs) and their dosage forms has increased enormously worldwide in recent decades. More than 40 aspirin-like drugs have been synthesized, which in itself has also led to a sharp increase in their consumption [1]. Globally, 6% of the population regularly takes NSAIDs: 30 million people take them daily, more than 300 million annually, including about 12 million adults. In Great Britain doctors annually make more than 24 million prescriptions for patients from the group of NSAIDs. Annually in the USA more than 100 million prescriptions for these drugs are written out, and the volume of annual sales of the specified means in this country reaches 6 billion dollars [2]. NSAIDs are often used in gerontological practice. Studies show that more than 60% of NSAID users are elderly and senile, and they take these drugs about 4 times more often than young people [2,3].

The consequence of significant increase in consumption and uncontrolled NSAIDs is the appearance of their adverse effects.

Even short-term intake of small doses of NSAIDs can cause gastrointestinal pathology, renal dysfunction, allergic reactions and other complications, which often pose a serious threat to the health and even life of patients [4].

Gastrointestinal (GI) damage is the most common side effect of NSAIDs. Gastrointestinal or duodenal damage is thought to occur in about one in five patients when taking NSAIDs [5]. The most serious complications are bleeding and perforation, which mainly determine the mortality associated with the use of these drugs [6]. In England, 2,000 people a year die from such complications, and in the United States taking these drugs causes 100,000 hospitalizations each year [7].

The recurrent nature of NSAID gastropathy determines the need for prevention of this pathology during the entire period of NSAIDs use, regardless of its duration [8]. Therefore, issues of prevention and treatment of gastroduodenal complications deserve special attention.

Anti-secretory drugs currently play amajor role in the prevention and treatment of NSAID gastropathies. Powerful suppression of acid-peptic factor has made these drugs one of the basic means for the therapeutic treatment of gastrointestinal bleedings and prevention of bleeding and ulcer perforations[9].

However, in recent years, evidence has accumulated that proton pump inhibitors (PPIs) in NSAID-induced gastropathies do not always produce the expected effect.

In the literature, there are reports on the positive effect of angiotensin-converting enzyme inhibitors (ACEi) on gastric mucosa (GM) in patients with cardiovascular disease with concomitant gastroduodenal pathology. In particular, Gidoyatov A.A. and auth. [10] established ulcer healing effect of ednit and renitec when treating patients with cardiac insufficiency with concomitant peptic ulcer disease.

Similar results are given in the studies of Alekseenko S.A. and auth. [11], who showed that enalapril and lisinopril promoted normalization of proliferative processes in gastric mucosal epithelium in AH patients with concomitant chronic gastritis. Also, Medvedev V.N. and auth. [12] recommend to include ACEi in complex treatment of peptic ulcer, combined with hypertension or coronary heart disease, which significantly improves general condition of the patient, hemodynamic parameters, motor and evacuatory function of the stomach, reduces terms of ulcer scarring and does not cause metabolic disorders.

The stated circumstances were the grounds of the present investigation.

Purpose of work. To study efficacy of ACEi, misoprostol, omeprazole and their combinations on stomach mucous barrier condition at indomethacin gastropathy in animals with experimental rheumatoid arthritis

Materials and methods of investigation. Experimental studies were performed on 78 male rats of mixed population weighing 160-200 g. For experimental studies, we used a generally recognized model of experimental rheumatoid arthritis (ERA) in rats [13], which is carried out by a single injection of 0.2 ml of Freund's adjuvant into the hind right leg. After modeling ERA in animals, NSAID gastropathy was induced by oral administration of indomethacin at a dose of 2.5 mg/kg for 5 days. The choice of this dose of indomethacin was based on the literature data, where the authors indicate 100% development of erosive and ulcerative lesions in the gastric mucosa when injected for 5 days [14].

The animals were divided into 13 groups:

Each group consisted of 6 animals.

Group 1 - intact.

Group 2 - animals with experimental rheumatoid arthritis (ERA).

Group 3 - animals with ERA and indomethacin gastropathy (GERA).

Group 4 - animals with GERA+H_2O.

Group 5 - animals with GERA treated with enalapril.

Group 6 - animals with GERA treated with lisinopril.

Group 7 - animals with GERA who received captopril.

Group 8 - animals with GERA treated with omeprazole.

Group 9 - animals with GERA treated with misoprostol.

Group 10 - animals with GERA receiving omeprazole and enalapril.

Group 11 - animals with GERA treated with omeprazole and lisinopril.

Group 12 - animals with GERA treated with omeprazole and captopril.

Group 13 - animals with GERA treated with omeprazole and misoprostol

Each group consisted of 6 animals. The used drugs were administered for 10 days. When selecting the doses of the drugs used, we were guided by the data from experimental studies conducted by other researchers in rats. All drugs were given orally in aqueous suspension in the following doses: enalapril 10 mg/kg, lisinopril 8 mg/kg, captopril 7.5 mg/kg, omeprazole 50 mg/kg, misoprostol 0.2 mg/kg.

The animals were kept in conditions of natural light, with free access to food and water, 2-3 individuals per cage, and were kept on a standard vivarium diet. The studies were conducted according to the European Convention on the Protection of Vertebrate Animals Used for Experimental or Other Scientific Purposes ETS N 123 [Strasbourg, 1986]. The basic provisions of the Declaration of Helsinki and the principles of animal husbandry ethics were observed during the studies. According to the Helsinki Declaration on the Humane Treatment of Animals, a one-step decapitation was performed within the rules of euthanasia.

For biochemical studies, the animals were slaughtered by one-step decapitation under ether anesthesia, the stomach was extracted, cleaned, washed with cold physiological solution, and the pre-stomach was removed. Then the mucous layer was scraped out, weighed, and suspended in distilled water in a porcelain mortar at the rate of 30 mg/ml [15]. The content of sialic acids in the gastric mucosa suspension was determined according to the method of L.I. Linevik [16].

To determine fucose in insoluble mucous gel (IMG) suspension we used the method suggested by RabinovichP.D.and auth. [17]. Total protein content was determined by the method of Lowry O.N. and auth. [18] and expressed in mg per ml of suspension.

It is established that the content of mucus-producing cells in antral part of the stomach is the main index indicating the state of functioning of protective mucous barrier [19]. Therefore, we considered it expedient to compare

the results of studying biochemical parameters of IGP gastric mucosa with the number of functionally active mucus-producing cells. For this purpose we took pieces of gastric tissue from antral part of the stomach with fixation in 10% formalin for light microscopy. The content of mucus-producing cells was calculated by counting the total number of cells in a standard field of view on light-optical preparations under magnification of 40x10.

Results. Table 1 presents the results of the study of the content of insoluble glycoprotein fractions in indomethacin-induced GP in animals with experimental RA. As can be seen from the data presented in experimental RA (ERA) the content of insoluble glycoprotein fractions (IGP) is virtually unchanged. There was a slight decrease in the content of sialic acids, fucose and total protein. However, these changes were not significant.In indomethacin-induced HA in animals with ERA (GERA), a significant decrease in the fraction of IGP was observed. The content of sialic acids was low by 69.5% of that in the group with ERA. Fucose and total protein content were reduced by 55.5% and 48.1%, respectively. These results were also significantly low from those of the control group. A study of the number of functioning mucus-producing cells in the gastric mucosa showed that in animals with ERA the number of functioning cells decreased by only 5.8% ($p>0.05$). In indomethacin-induced HP (GERA), along with a decrease in the content of IGP fractions, there is a significant decrease in the number of functioning mucus-producing cells. In this group, there was a 64.7% decrease in the number of cells from the control group and a 62.5% decrease from the figure in the ERA group (Table 2).

Table 1. Content of insoluble glycoprotein fractions in gastric mucosa during indomethacin gastropathy in animals with experimental rheumatoid arthritis

№	Animalgroups	Sialic acids μgper ml of suspension	Fucose mg per ml of suspension	Total protein mg per ml of suspension
1	Control	4,12±0,158	6,73±0,125	15,22±0,655
	Animals with experimental RA (ERA)	3,84±0,155	6,25±0,153	14,72±0,593
3	Indomethacin gastropathy in ERA (GERA)	1,22±0,067*	2,78±0,100*	7,65±0,257*

Note: * - $p<0.05$ from control and ERA groups

Table 2. Content of mucus-producing cells in gastric mucosa in indomethacin gastropathy animals with ERA

№	Animalgroups	Sialic acids μgper ml of suspension	Fucose mg per ml of suspension	Total protein mg per ml of suspension
1	Control	4,12±0,158	6,73±0,125	15,22±0,655
	Animals with experimental RA (ERA)	3,84±0,155	6,25±0,153	14,72±0,593
3	Indomethacin gastropathy in ERA (GERA)	1,22±0,067*	2,78±0,100*	7,65±0,257*

Note: * - $p<0.05$ from control and ERA groups

Table 3. presents the results of a comparative study of the efficacy of some ACEi, omeprazole and sitotec on the content of IGP fractions in the gastric mucosa during GERA.

Our studies have shown that ACEi, omeprazole and misoprostol have a positive effect on the content of IGP fractions in the gastric mucosa. In the enalapril-treated group, a 60.8% increase in sialic acid content, a 34.5% increase in fucose content, and a 29.7% increase in total protein content were observed compared with the untreated group. Almost similar results were observed in the group treated with lisinopril and omeprazole.

The use of captopril and misoprostol appeared to be more effective in treating GERA. In the group with captopril, sialic acid content increased by 136.2%, fucose by 69.7%, and total protein by 37.4% from those in the untreated group. Despite a significant increase in fractions in this group, the results obtained remained low from the

values in the control group. In the group with misoprostol an increase in sialic acids of 183.3%, in fucose of 87.3% and in total protein of 44.1% was noted.

Table 3. Effect of ACEi, omeprazole and misoprostol on insoluble glycoprotein content in gastric tissue during indomethacin gastropathy in animals with ERA.

№	Animalgroups	Sialic acids μgper ml of suspension	Fucose mg per ml of suspension	Total protein mg per ml of suspension
1	Control	4,12±0,158	6,73±0,125	15,22±0,655
2	GERA	1,22±0,067	2,78±0,100	7,65±0,257
3	GERA +H_2O	1,38±0,072	2,85±0,121	8,55±0,352
4	GERA +enalapril	2,22±0,047*	3,82±0,089*	9,92±0,400
5	GERA +lisinopril	2,47±0,085*	4,12±0,051*	10,12+0,397*
6	GERA+captopril	3,27±0,041*	4,82±0,106*	11,75±0,546*
7	GERA + omeprazole	3,52±0,089*	4,12±0,076*	10,22±0,343*
8	GERA + misoprostol	3,92±0,122*	5,32±0,089*	12,32±0,483*

Note * - $p<0.05$ from the GERA group without treatment (GERA+H_2O)

Table 4 shows the results of the comparative effectiveness of our preparations on the content of mucus-producing cells in the gastric mucosa.

From the data presented in the table we can see that from the drugs used the most effective are captopril, omeprazole and misoprostol. In the groups with enalapril and lisinopril an increase in the content of functioning cells by 34% and 48,4% was observed, respectively. In the groups with captopril, omeprazole, and misoprostol, the content of functioning cells increased by 82.7%, 68%, and 99.1%, respectively, from that in the GERA group without treatment.

Table 4.Effect of ACEi, omeprazole, and misoprostol on the number of mucus-producing cells in gastric tissue in animals with indomethacin gastropathy in ERA

№	Animalgroups	Number of mucus-producing cells in the field of view
1	Control	60,33±1,726
2	GERA	21,35±0,835
3	GERA+H_2O (without treatment)	25,68±0,963
4	GERA +enalapril	34,42±1,79
5	GERA +lisinopril	38,13±1,37*
6	GERA+captopril	46,92±1,70*
7	GERA + omeprazole	43,17±1,72*
8	GERA + misoprostol	51,13±1,54*

Note * - p<0.05 from the GERA group without treatment (GERA+H_2O)

The results of the study of combined use of omeprazole with ACEi and misoprostol on the content of IGP fractions in the gastric mucosa are presented in Table 5.

According to the results given in the table we can state that the combined use of omeprazole with other drugs potentiates their cytoprotective effect in the form of additive pharmacodynamic interaction.

Table 5. Effect of combination of omeprazole with ACEi and misoprostol on the content of insoluble glycoprotein fractions in gastric mucosa at indomethacin gastropathy in animals with ERA.

№	Animalgroups	Sialic acids μgper ml of suspension	Fucose mg per ml of suspension	Total protein mg per ml of suspension
1	Control	4,12±0,158	6,73±0,125	15,22±0,655
2	GERA	1,22±0,067	2,78±0,100	7,65±0,257
3	GERA+H_2O	1,38±0,072	2,85±0,121	8,55±0,352
4	GERA + omeprazole +enalapril	4,32±0,074*	5,98±0,147*	12,88±0,584*
5	GERA + omeprazole +lisinopril	4,52±0,105*	6,72±0,220*	13,98±0,625*
6	GERA + omeprazole+captopril	5,98±0,155*	8,72±0,173*	16,78±0,500*
7	GERA + omeprazole + misoprostol	7,37±0,133*	10,85±0,466*	19,62±0,569

Note * - p<0.05 from the group without treatment (GERA+H_2O)

In the GERA group of animals treated with omeprazole with enalapril there was an increase in sialic acid content by 213%, fucose by 110.5% and total protein by 50.8% of those in the GERA+H_2O group. Almost the same interaction was observed in the group treated with omeprazole and lisinopril.

In the groups omeprazole with captopril and omeprazole with misoprostol, the drug interaction was more significant. The results obtained were high even from those in the control group. In the omeprazole with captopril group, sialic acid, fucose, and total protein content increased by 333.3%, 207%, and 96.5%, respectively, from those in the untreated group. In the group with misoprostol, the increases in these fractions were 433.3%, 281.7%, and 129.6%, respectively. These results were reliably high even from those of the control group.

Table 6 shows the results of a study of the effectiveness of combined use of omeprazole with ACEi and misoprostol on the number of functioning mucus-producing cells in GERA.

Table 6. content of mucus-producing cells in gastric tissue during combined use of omeprazole with ACEi and misoprostol in animals with indomethacin gastropathy in ERA

№	Animalgroups	Number of mucus-producing cells in the field of view
1	Control	60,33±1,726
2	GERA	21,35±0,835
3	GERA+H_2O (without treatment)	25,68±0,963
4	GERA + omeprazole +enalapril	48,55±1,35*
5	GERA + omeprazole +lisinopril	55,60±1,59*

6	GERA + omeprazole+captopril	78,15±1,91*
7	GERA + omeprazole + misoprostol	85,37±1,43*

Note * - $p<0.05$ from the group of animals without treatment

As can be seen from the data presented, when omeprazole was combined with enalapril, the number of mucus-forming cells increased by 89% of that in the untreated group, whereas when monotherapy with enalapril was used, the number of cells increased by 57%.

Identical changes were observed with the combined use of omeprazole with lisinopril. The best results were obtained with the combined use of omeprazole with captopril and omeprazole with misoprostol. In this group, the number of cells increased by 204.2% from the untreated group and this increase was 29.4% higher than in the control group. In the group with misoprostol, the cell count increased 232.3% and was 41.4% high from the control group, whereas in themonotherapy with misoprostol, the cell count remained 15% lower from the control values (Table 7).

Table 7. Content of mucus-producing cells in the gastric mucosa in indomethacin-induced gastropathy in animals with ERA

№	Animalgroups	Number of mucus-producing cells in the field of view
1	Control	60,33±1,72
2	ERA	56,85±2,10
3	GERA	21,35±0,835*

Discussion. It is known that water-insoluble mucous gel, lining the gastroduodenal mucosa in a continuous layer, due to its high viscosity, adhesiveness and ability to self-repair forms a kind of mucous barrier preventing mucous membrane damage by acid, pepsin and numerous exogenous substances. Insoluble glycoproteins are the main component of the mucous gel. It is known that the protective properties of gastric mucus are provided mainly by glycoproteins. The structure and spatial orientation of glycoprotein macromolecules provide viscous and gel-forming properties of the mucus [20]. Functional fullness of glycoproteins is provided by a certain content of carbohydrate components in them - sialic acids, fucose, hexosamines, hexoses, and protein. Therefore, evaluation of the content of insoluble glycoproteins in mucus by determining its individual chemical components is considered a reliable method [21].

It has been established that sialic acids and fucose play a special role in the complete functioning of the IGP. These carbohydrate components provide elasticity and viscosity of the mucosal barrier [22]. The obtained results of the group with indomethacin suggest that the damage to the gastric mucosal barrier is provided by a decrease in the synthesis of IGP and its functional insufficiency characterized by a change in its rheological properties. In the existing literature, the negative effect of indomethacin on the mucosal barrier is explained by inhibition of COX enzymes, suppression of prostaglandin production with subsequent disruption of microcirculation. We assume that this mechanism is not the only one. Probably one of the causes of the damaging effect of the drug is a disruption in the bioregulatory system of L-arginine-nitric oxide as a universal mechanism in triggering mutually reinforcing pathogenetic mechanisms of cell damage.

There are convincing data in the literature claiming the ulcer-healing effect of enalapril [23]. The authors attribute this effect to the stimulation of prostaglandin synthesis. We suggest that this is one of the mechanisms of the positive effect of the drug, which is a consequence of the corrective action of the drug on the NO-forming system. Mikheeva O.M. et al. [24] in clinical and experimental studies established ulcer healing effect of enalapril on gastric mucosal defect in peptic ulcer disease. The authors argue that this effect of enalapril is due to improvement of microcirculation in the gastric mucosa. Nikonov E.L. studied the effect of captopril and lisinopril on the state of gastric mucosa in patients with arterial hypertension and osteoarthritis taking NSAIDs for a long time [25]. The author found that I-APP has a positive effect not only on the cardiovascular system, but also improves the morpho-functional parameters of the gastric mucosa. Alexeenko S.A. et al. [26] state that the mechanisms of positive influence of ACEi group drugs on gastric mucosal epithelium require further investigation. Probably, they are connected with the increase

of the level of endogenous prostaglandin E2 and its cytoprotective action. According to some authors, angiotensin II increases the proliferative processes in the target organ tissues, as well as in the epithelium of gastric mucosal by stimulating the synthesis of DNA and proteins [27]. One of the mechanisms of this process is the activation by angiotensin II of growth factor receptors, including epidermal growth factor [28]. The ability of ACEi to normalize proliferation processes, as well as to prevent the post-stressor activation of DNA synthesis in the gastric mucosal epithelium has been demonstrated in an animal experiment [50]. The ability of ACEi to reduce the proliferative activity of target organ cells can explain the phenomenon of decreased incidence of cancers of various localizations in AH patients during long-term treatment with ACEi [29].

We found a positive effect of omeprazole on the synthesis of insoluble glycoproteins and on the number of functioning mucus-producing cells. There are controversial assumptions in the literature about the cytoprotective effect of omeprazole. Chandranath S.I. et al. [30] state that proton pump inhibitors have cytoprotective effect due to the suppression of acid aggression and, probably, due to other unknown mechanisms. Watanabe T. et al. [31] suggest that the protective action of PPI on gastric mucosa in case of its damage by ethanol is performed through regulation of nitric oxide formation system, and the amount of prostaglandins does not change.

The results we obtained when using misoprostol agree with the data of other authors [32]. According to Abdulkhakov R.A. misoprostol similarly to endogenous prostaglandins has the ability to increase mucus formation and bicarbonate secretion, improve blood flow, stimulate regeneration of gastric mucosal epithelium, reduce hydrochloric acid production [33].

Conclusions. 1. In experimental RA the state of gastric mucosal barrier practically does not change. The use of indomethacin in the treatment of RA significantly suppresses the synthesis of insoluble glycoproteins of the mucosal barrier and reduces the number of functioning mucus-producing cells.

2. ACEi has a cytoprotective effect in the treatment of indomethacin gastropathy. Among them, captopril is more effective, which increases the synthesis of the mucus barrier and the number of mucus-producing cells. By this effect, captopril is equal to omeprazole and misoprostol.

3. When ACEi and misoprostol are combined with omeprazole, their pharmacodynamic effect increases in the form of additive synergism. Combinations of omeprazole with captopril and omeprazole with misoprostol are the most effective.

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