ESTIMATION OF PHARMACODYNAMIC EFFECT OF ANTIULCER TREATMENT PREPARATIONS ON INDICATORS OF NO FORMATION SYSTEM AND ANAEROBIC GLYCOLYSIS IN GASTRIC MUCOSA.

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ANNOTATION

In an experimental model of gastric ulcer in rats, it was found that the components of antiulcer therapy omeprazole, metronidazole have a multidirectional effect on the NO formation system and increase the content of lactic acid in the mucous tissue. Among the components of antiulcer therapy, Bismuth subcitrate and rebamipide are the best.

Key words: experimental ulcer, components of antiulcer therapy, NO formation, lactic acid.

The urgency of protecting the mucous membrane of the gastrointestinal tract (gastrointestinal tract) is due to the variety of exogenous and endogenous factors of aggression. The gastrointestinal tract's own protective apparatus (dense intercellular connections, bicarbonate secretion, growth factors, a powerful blood supply system, etc.) does not always cope with this task, especially when several damaging factors are simultaneously exposed – hydrochloric acid, proteolytic enzymes, Helicobacter pylori, nonsteroidal anti-inflammatory drugs (NSAIDs), alcohol, nicotine, bile components, etc. [1, 2].

Due to the decrease in the effectiveness of classical schemes of eradication therapy, as well as the absence of fundamentally new drugs for the treatment of H. Pylori infection, aspects of optimizing existing schemes of eradication therapy are of particular relevance [3,4,5]. Based on this, and also taking into account the multifactorial development and systemic nature of peptic ulcer disease, an important component of the complex treatment of H. pylori-associated form of this disease is the use of drugs that have a cytoprotective effect on the mucous membrane of the stomach and duodenum [6].

There is evidence in the literature that the components of anti-ulcer therapy can negatively affect the protective mechanisms in the gastroduodenal zone. According to I.M. Belova et al. [7] eradication antimicrobial therapy delays the repair of ulcerative mucosal defects.

As the analysis of the literature data shows, from the point of view of studying the effect of anti-ulcer therapy components on protection factors, the study of the effect of drugs on the mechanisms of NO formation and on the state of hypoxia in the gastric mucosa is of particular interest. As is known, NO is one of the important factors of cytoprotection of the mucosa of the gastroduodenal zone. The NO education system is the main link in ensuring microcirculation and correction of hypoxia [8].

The purpose of the study. The aim of this work was to evaluate the pharmacodynamic effect of anti-ulcer therapy drugs in the treatment of peptic ulcer disease on the indicators of the NO formation system and anaerobic glycolysis in the gastric mucosa in experimental ulcers.

Materials and methods. The studies were conducted in 9 groups of animals. There were 6 animals in each group. The model of an experimental ulcer was reproduced by the method of V.A.Vertelkin in the modification of I.A. Losyev et al.[9]. After the simulation, the animals were divided into the following groups: 1st group intact; 2nd group animals with experimental ulcer (EU); 3rd group EU + H_2O (without treatment); 4-gr. EU+ omeprazole; 5-gr. EU+Bismuth subcitrate; 6-gr. EU+metronidazole; 7-gr. EU + tetracycline; 8-gr. EU + amoxicillin; 9-gr. EU+ rebamipid.

The drugs we used were administered orally as an aqueous suspension for 10 days in the following doses: omeprazole at a dose of 50 mg/kg [10], Bismuth subcitrate at a dose of 10 mg/kg [11], metronidazole at a dose of 50 mg/kg [12], tetracycline at a dose of 10 mg/kg [13], amoxicillin at a dose of 40 mg /kg [14]. rebamipid at a dose of 320 mg / kg / day [15].

The formation of NO in the gastric mucosa was studied by determining the content of its nitrite and nitrate products [16] in the microsomal fraction of the homogenate.

The content of the amino acid L-arginine in the supraventricular fraction of mucosal homogenate was determined by the method of A. Steven et al. [17].

The activity of NO-synthase markers - NADP*N-diaphorase was determined by the method of Hope V.T. et al. modified by S.A. Komarin et al. [18].

Changes in the L-arginine nitric oxide system may be a consequence of a lack of the main substrate-L-arginine in the mucosa, a decrease in the activity of NO-synthase, which, one way or another, contributes to tissue hypoxia. In this regard, to assess the blood flow in the mucosa, we limited ourselves to studying the content of the final product of anaerobic metabolism – lactic acid [19].

Results and their discussions. Table 1 presents the results of studying the effect of drugs of standard second-line therapy regimens on the indicators of the NO formation system and anaerobic glycolysis in the gastric mucosa in experimental ulcers.

As can be seen from the presented data, the experimental ulcer reduces the content of NO products by almost 3 times, the content of L-arginine by 2.1 times and the activity of NADP*N-diaphorase by 1.8 times, while an increase in lactic acid content by 2.5 times was observed.

When treated with omeprazole, there was a slight increase in NO products and a decrease in lactic acid content by 27.5%. The content of L-arginine increased by 35.0%, and the activity of NADP*N-diaphorase decreased by 31.6% of the value in the group without treatment.

In the group with Bismuth subcitrate, the content of NO products significantly increased by 84.1%, L-arginine by 81.2%, NADP*N-diaphorase by 49.6%, and the lactic acid content decreased by 43.5%.

Metronidazole inhibited the processes of NO formation, which was accompanied by an increase in the amount of lactic acid. Thus, in the group with metronidazole, the content of NO products decreased by 32.3%, and lactic acid increased by 34.9%. At the same time, the inhibitory effect of metronidazole on the activity of NADP·N-diaphorase was observed. In these groups, enzyme activity decreased by 24.6% and 35.8%, respectively. These drugs did not affect the content of L-arginine.

In the groups with tetracycline and amoxicillin, the results obtained did not significantly differ from the group without treatment.

In the group with rebamipid, the content of NO products significantly increased by 92.0%, L-arginine by 89.4%, NADP*N-diaphorase by 64.0%, and the lactic acid content decreased by 53.9%

Table 1
The effect of preparations of standard anti-ulcer therapy regimens on the indicators of the NO formation system and anaerobic glycolysis in the gastric mucosa in experimental ulcers.

Animal groups	Products NO mmol/mg protein	Lactic acid nmol/mg protein	L-arginine nmol/mg protein	NADP·N-diaphorase nmol/min/mg protein
1.Intact	9,41±0,65	0,114±0,01	19,55±0,68	8,40±0,63
2. Experimental ulcer (EU)	3,16±0,19	0,285±0,013	8,34±0,48	4,70±0,22
3. EU + H_2O	4,28±0,21	0,269±0,01	9,26±0,55	4,56±0,28
4. EU + Omeprazole	4,49±0,21	0,195±0.007*	12,51±0,62*	3,12±0,17*
5. EU + Bismuth subcitrate	7,88±0,28*	0,152±0,006*	16,78±0,91*	6,82±0,44*
6. EU + Metronidazole	2,90±0,17*	0,363±0,018*	8,69±0,42	3,45±0,17*
7. EU + Tetracycline	5,02±0,37	0,274±0,014	9,85±0,74	5,04±0,31
8. EU + Amoxicillin	4,78±0,256	0,235±0,014	8,92±0,37	4,87±0,25

9. EU+Rebamipid	8,22±0,27*	0,145±0,007*	17,54±0,92*	7,48±0,43*

Note: * - reliability of the indicator of the group without treatment (H2O)

In our studies, when omeprazole was used in animals, the content of NO products did not change, and lactic acid decreased. At the same time, a significant increase in the content of L-arginine and a decrease in the activity of NADP·N-diaphorase were observed. These results indicate that when using omeprazole, there is some imbalance in the NO formation system, which is accompanied by an increase in the NO substrate and a decrease in the activity of the main enzyme NADP*N-diaphorase. In the end, the amount of NO formed does not change and remains low. Omeprazole probably affects tissue hypoxia by other mechanisms, which is confirmed by a significant decrease in lactic acid. As some authors note, omeprazole reduces the intensity of systemic and tissue metabolism of nitric oxide in patients with chronic gastroduodenitis and peptic ulcer disease, which is manifested by a decrease in urinary excretion of nitrites, a decrease in the activity of the oxidase and reductase domains of neutral nitric oxide synthase (NADP*N-diaphorase), the percentage of induced nitric oxide synthase in the overall structure of the distribution of isoform activity in the submucosal layer of the stomach [20].

When using Bismuth subcitrate, an increase in the content of NO, L-arginine products and NADP·N-diaphorase activity was observed from the indicators of the group without treatment, and the lactic acid content decreased. It should be noted that the use of Bismuth subcitrate not only improves the synthesis of NO, but also significantly increases the content of the L-arginine substrate. Bismuth subcitrate is distinguished by the universality of the cytoprotection mechanism. Thus, it increases the synthesis of prostaglandins, has an antioxidant effect, reduces the content of pro-inflammatory cytokines and pepsin activity, partially binds bile acids, binds to proteins in the area of inflammation and necrosis, increases the synthesis of mucus and hydrocarbonates, improves microcirculation in the mucous membrane, increases the content of epidermal growth factor and inhibits bacterial adhesion [21].

When metronidazole was used, a significant increase in NO and lactic acid products was observed. At the same time, the content of L-arginine in the gastric mucosa did not change, and the activity of NADP·N-diaphorase decreased. It should be noted that there is no information in the literature concerning the study of the processes of NO formation during metronidazole peptic ulcer monotherapy.

Abasova A.S. [22] and Esedov E.M. [23] studying the content of nitric oxide in gastric juice when using various schemes of eradication therapy in patients with peptic ulcer disease noted that in terms of correction of NO synthesis, the best combination is triple therapy with omeprazole, clarithromycin and amoxicillin, and when using triple therapy with omeprazole clarithromycin and metronidazole, the content of NO products in gastric juice decreases. The authors claim that the regimens containing omeprazole and metronidazole inhibit the synthesis of NO. These statements were also established in our studies when using quadritherapy containing omeprazole, Bismuth subcitrate, tetracycline, metronidazole.

In the groups of animals treated with amoxicillin and tetracycline, the content of NO, lactic acid, L-arginine products and the activity of NADP*N-diaphorase in the gastric mucosa practically did not change.

When using rebamipid, we noted an increase in the content of NO, L-arginine products and the activity of NADP*N-diaphorase from the indicators of the group without treatment, and the lactic acid content decreased. This is probably due to the remarkable properties of rebamipid. As is known, the drug has a cytoprotective effect on the gastric and duodenal mucosa, reduces the inflammatory reaction associated with the action of tumor necrosis factor (TNF) alpha, stabilizes the macrophage cell line, reduces the activation of nuclear factor kappa B, interrupting the inflammatory signaling pathway [21].

These results are consistent with the data of Tomita [22] T. And co-author. Who, when prescribing rebamipid, noted a significant decrease in the concentration of reactive oxygen species, the number of damaged cells and activation of superoxide dismutase in the mucous membrane of the small intestine.

Conclusion. The components of the anti-ulcer therapy regimens have a multidirectional effect on the mechanisms of NO formation and anaerobic glycolysis in the gastric mucosa. Omeprazole, without affecting the NO content, reduces the lactic acid content in the mucous tissue. In terms of correcting disorders in the NO education system and anaerobic glycolysis, rebamipid and Bismuth subcitrate are the most effective. Metronidazole inhibits the mechanisms of NO formation and increases the lactic acid content. Tetracycline and amoxicillin do not affect these mechanisms.

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