Zhongguo Kuangye Daxue Xuebao
Journal of China University of Mining and Technology

2024 | Vol 29 | Issue 4 | Page 329-332
Journal Homepage: https://zkdx.ch/
DOI: 10.1654/zkdx.2024.29.4-33

Evaluation of the Effectiveness of Some Proton Pump Inhibitors, Cytoprotectors and their Combinations on Nitric Oxide Synthesis in Gastric Mucosa in Indomethacin Gastropathy

Rakhmatullaeva Gulnoza Kutpitdinovna
Tashkent Medical Academy, University in Tashkent, Uzbekistan
*Corresponding author

Sadullaeva Umida Azimovna
Tashkent Medical Academy, University in Tashkent, Uzbekistan

Makhmudova Munira Sayfievna
Tashkent Medical Academy, University in Tashkent, Uzbekistan

Salimova Nargiza Djurabaevna
Tashkent Medical Academy, University in Tashkent, Uzbekistan

Abstract
Purpose: To evaluate the effectiveness of the action of certain proton pump inhibitors, cytoprotectors, and their combinations on the performance of the synthesis of nitric oxide in the gastric mucosa in indomethacin gastropathy.
Material and methods: Biochemical studies were conducted on 14 groups of animals: Group 1 - intact; Group 2 - animals with indomethacin gastropathy (IG); Group 3 - animals with IG treated with distilled water for 10 days (without treatment); Group 4 - animals with IG treated with omeprazole for 10 days; Group 5 - animals with IG treated with rabeprazole for 10 days; Group 6 - animals with IG + de-nol - 10 days; Group 7 - animals with IG + sucralfat 10 days; Group 8 - animals with IG + pepsan-R - 10 days; Group 9 - animals with IG + omeprazole + de-nol - 10 days; Group 10 - animals with IG + omeprazole + sucralfate - 10 days; Group 11 - animals with IG + omeprazole + pepsan-P - 10 days; Group 12 - animals with IG + rabeprazole + De-Nol - 10 days; Group 13 - animals with IG + rabeprazole + sucralfate - 10 days; Group 14 - animals with IG + rabeprazole + pepsan-P - 10 days. For biochemical studies, animals were scored under ether anesthesia by single-step decapitation. Removed the stomach, washed, scraped mucous and slurried.
Results: We found that de-nol and pepsan-P stimulate NO-formation, but sucralfate does not affect. Our results suggest that the effectiveness of De-Nol and pepsan-P is due to their inductive effect on the activity of the key enzyme NO-formation - NADPH diaphorase.
Conclusions: 1. Sucralfate does not affect these mechanisms. Rabeprazole, De-Nol and pepsan-P to a single degree stimulate NO in the mucous tissue of the stomach during IG. 2. For the stimulation of NO-formation in the mucous tissue of the stomach is more effective is the combined use of rabeprazole with pepsan-P and rabeprazole with De-Nol and less effective omeprazole with pepsan-R.

Keywords
Indomethacin gastropathy, NO formations, Cytoprotective drugs

1. Introduction
Today, nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most common drugs often used to treat various diseases. Many nonsteroidal anti-inflammatory drugs are included in over-the-counter lists in pharmacies, i.e. they are readily available to the public and many patients take them without prior consultation with their physician. The consequence of such uncontrolled intake of NSAIDs is the appearance of their side effects [14, 15]. Gastric or duodenal injury while taking NSAIDs is believed to occur in about one in five patients. The most serious complications are bleeding and perforation, mainly determining the mortality associated with the use of this group of drugs [10, 11].

In recent years, the study of the influence of NO on metabolic processes in the gastroduodenal mucosa and on its cytoprotection has been of great interest in gastroenterology. It has been found that NO interacts with prostaglandins in maintaining the integrity of the gastric mucosa. Nitric oxide should be attributed to the most important factors of protection of the gastroduodenal mucosa. The above-mentioned circumstances served as a basis for studying the

effectiveness of the effect of the drugs and their combinations on NO-formation in gastric mucosa in NSAID gastropathy [12, 13].

2. Material and Methods

We conducted experimental studies on 84 male white rats of sexually mature age with body weight 170-190 gr. Biochemical studies were performed on 14 groups of animals:1 group - intact; 2 group - animals with indomethacin gastropathy (IG); 3 group - animals with IG receiving distilled water for 10 days (without treatment); 4 group - animals with IG receiving omeprazole for 10 days; 5 group - animals with IG receiving rabeprazole for 10 days; 6 group - animals with IG + de-nol - 10 days; 7 group - animals with IG + sucralfate for 10 days; 8 group - animals with IG + pepsan-R for 10 days; 9 group - animals with IG + omeprazole + De-Nol for 10 days; 10 group - animals with IG + omeprazole + sucralfate for 10 days; 11 group - animals with IG + omeprazole + pepsan-R for 10 days; 12 group - animals with IG + rabeprazole + de-nol - 10 days; 13 group - animals with IG + rabeprazole + sucralfate - 10 days; 14 group - animals with IG + rabeprazole + pepsan-R - 10 days. For biochemical studies, animals were slaughtered under ether anesthesia by one-stage decapitation. The stomach was extracted, washed, mucosa scraped and suspended.

NO in mucosal tissue was studied by determining the content of its products nitrite, nitrate [7] in the supernatant fraction of mucosal homogenate. The method is based on the color change of the experimental sample upon addition of 0.6% solution of sulfanilic acid in 20% HCL solution and 0.1% solution of N-naphthyl ethylenediamine. The color intensity was measured on a spectrophotometer at a wavelength of 548 nm. The amount of products was expressed in μmol/mg protein.

The activity of NADPH diaphorase, a marker of NO-synthase enzyme, was determined according to the method of V.T. Hopa et al. Hopa et al. modified by A.S. Komarin et al [8]. The results were expressed in nmol/min/mg protein.

3. Results

The results of studying the effect of proton pump inhibitors and cytoprotective drugs on the indicators of NO synthesis in gastric mucosa in indomethacin gastropathy are presented in Table 1.

Table 1 Effect of proton pump inhibitors and cytoprotective drugs on NO synthesis parameters in gastric mucosa in indomethacin gastropathy

Group Animals	NO Products (μmol/mg protein)	P	NADPH-N diaphorase (nmol/min/mg protein)	P
Intact	12,40±1,10		18,53±1,12	
IG	5,82±0,54		7,46±0,60	
IG+ H2O	6,49±0,48		8,31±0,61	
IG + omeprozole	4,12±0,29	<0,001	4,85±0,31	<0,001
IG+rabeprazole	8,95±0,51	<0,01	12,39±0,97	<0,01
IG + de nol	7,88±0,30	<0,05	12,74±0,82	<0,001
IG+sucralfate	5,92±0,54	>0,05	8,88±0,69	>0,05
IG+pepsan-R	9,42±0,54	<0,001	14,69±1,01	<0,001
Note:	P-significance from that of the group without treatment			

It should be noted that one of the mechanisms of the damaging effect of indomethacin on the gastroduodenal mucosa is the negative effect of the drug on the activity of NADPH-N diaphorase [2, 16] . In the group of animals with IG, a decrease in the content of NO products more than 2-fold and in the activity of NADPH-N diaphorase (NO synthase) almost 2.5-fold was observed. In the untreated group (H_2 O) these changes were maintained.

In the group of animals treated with omeprazole, the inhibitory effect of the drug on NO formation was observed. A decrease in the content of NO products by 36.5% and enzyme activity by 41.7% from the untreated group was observed.

In the groups treated with rabeprazole, De-Nol and pepsan-P, a stimulating effect of the drugs was observed. When rabeprazole was used, the content of NO products increased by 37.9% and the enzyme activity by 49.1%. Almost the same results were obtained with De-Nol and Pepsan-P.

In animals treated with sucralfate, the results obtained were not significantly different from those of the untreated group (P<0.05). Table 2 presents the results of the study of the effect of combined use of omeprazole and rabeprazole with cytoprotective drugs on the indicators of NO synthesis in gastric mucosa in IG.

Table 2 Effect of proton pump inhibitors and cytoprotective drugs on NO synthesis parameters in gastric mucosa in indomethacin gastropathy

Group Animals	NO products (μmol/mg protein)	P	NADPH-N diaphorase (nmol/min/mg protein)	P
Intact	12,40±1,10		18,53±1,12	
IG	5,82±0,54		7,46±0,60	
IG+ H2O	6,49±0,48		8,31±0,61	
IG + omeprozole	4,12±0,29	<0,001	4,85±0,31	<0,001

IG+rabeprazole	8,95±0,51	<0,01	12,39±0,97	<0,01
IG + de nol	7,88±0,30	<0,05	12,74±0,82	<0,001
IG+sucralfate	5,92±0,54	>0,05	8,88±0,69	>0,05
IG+pepsan-R	9,42±0,54	<0,001	14,69±1,01	<0,001
Note:	P-significance from that of the group without treatment			

In the group of animals treated with omeprazole with De-Nol, the content of NO products and NADPH-N diaphorase activity remained significantly lower by 19.9% and 22.8%, respectively, than in the untreated group. These parameters were also significantly low in the omeprazole with sucralfate group. The results obtained in these groups did not differ from those of the group treated with omeprazole alone.

The combined use of omeprazole with pepsan-P was more effective. In this group, the NO content was high by 59.2% and NADPH-N diaphorase activity by 98.3% of the index of the group treated with omeprazole alone.

Potentiation of pharmacodynamic effect was observed in combinations of rabeprazole with De-Nol and pepsan-P. In the rabeprazole with de-nol group, NO product content increased by 80.5% and enzyme activity by 98.4% of the untreated group. These results were high by 30.9% and 33.1% of the results of the monotherapy group with rabeprazole ($P<0.05$). More pronounced enhancement of pharmacodynamic effect of rabeprazole was observed in its combined use with pepsan-P. In this group the indices we studied were high by 54.4% and by 55.3% of the results in the group with rabeprazole. When combined with sucralfate, the pharmacodynamic effect of rabeprazole was not altered.

4. Discussion

Our studies revealed an inhibitory effect of omeprazole on the processes of NO-formation in gastric mucosa in IG. There are different explanations for this effect of omeprazole in the literature. Fandriks L. et al. [1] suggest that the suppression of gastric secretion by omeprazole reduces the processes of chemical transformation of NO products. Slomiany B.L. et al. [5] believe that the inhibitory effect of the drug is associated with inhibition of caspase-3 activity. The authors in the treatment of acute gastritis with omeprazole and sucralfate found that omeprazole significantly reduces apoptosis of epithelial cells, which is accompanied by a decrease in the activity of caspase-3 key protease of apoptosis. A 46.7% decrease in the activity of NO synthase enzyme (NADPH.N diaphorase) was observed. In our studies we observed inhibition of this enzyme activity by 41.7%.

Rudenko S.A. [4] in studying the effect of nitric oxide on the motor and secretory function of the stomach and duodenum in patients with peptic ulcer disease and chronic gastroduodenitis found that omeprazole therapy causes a decrease in the intensity of systemic and tissue metabolism of nitric oxide, which is manifested by a decrease in urinary nitrite excretion, a decrease in the activity of oxidase and reductase domains of the neuronal nitric oxide system, the percentage of inducible nitric oxide synthase in the general structure of isoform activity distribution in the gastric submucosa.

Our results obtained during rabeprazole treatment are consistent with the data of Watanabe T. et al. [5], in the treatment of which the damage to the gastric mucosa caused by ethanol and the increase in the activity of NO-synthase and NO products in the mucosa are noted. Similar results are reported by other authors [3]. However, when analyzing the existing literature, we did not find a proper answer to the question why omeprazole and rabeprazole act differently on the NO system in the gastric mucosa in IG? Probably, it is to some extent related to the influence of these drugs on the mechanisms of POL initiation.

We found that De-Nol and pepsan-R stimulate NO-formation, while sucralfate has no effect. Unfortunately, there are no similar studies in the literature to study the system of NO- formation in gastric mucosa during monotherapy with cytoprotectors.

Our results suggest that the efficacy of De-Nol and pepsan-R is due to their inductive effect on the activity of the key enzyme of NO formation - NADPH diaphorase.

5. Conclusions

1. One of the mechanisms of the suppressive effect of omeprazole on the synthesis of the mucosal barrier in IH is its inhibitory effect on the processes of NO formation. Sucralfate does not affect these mechanisms. Rabeprazole, de nol and pepsan-R stimulate NO in gastric mucosa at AI to a single degree.
2. In combined use of omeprazole with De-Nol and sucralfate, rabeprazole with sucralfate pharmacodynamic effect of omeprazole and rabeprazole on NO-formation system does not change. The combined use of rabeprazole with pepsan-P and rabeprazole with De-Nol and less effective omeprazole with pepsan-P is more effective for stimulation of NO-formation in gastric mucosa.

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