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Research Article

Study of the Cytoprotective Effect of Low Molecular Weight Chitosan on a Model of Indomethacin Gastropathy in Rats

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Abstract

The gastroprotective effect of low molecular weight chitosan was studied on a model of indomethacin gastropathy in Wistar rats. An assessment of the areas of ribbon and point erosions in the gastric mucosa in rats after intragastric administration of indomethacin suspension at a dose of 60 mg per 1 kg of body weight showed that intragastric administration of 0.2% aqueous solution of low molecular weight chitosan (50 kDa) 1 hour after administration of indomethacin significantly reduces the areas of erosion in the gastric mucosa. This effect is especially pronounced in the analysis of band erosions, as the most severe form of nonsteroidal gastropathy. The data obtained may be of significant interest for the creation of combined dosage forms of NSAIDs with minimal damaging effect on the gastric mucosa.

Keywords: Nonsteroidal Gastropathy; Chitosan; Indomethacin Gastropathy

Relevance

Nonsteroidal anti-inflammatory drugs (NSAIDs) are currently one of the most common groups of pharmacological agents. This is mainly due to a wide range of diseases in which NSAIDs are used to relieve inflammatory reactions [1]. The most common medical indications for taking NSAIDs are various acute respiratory viral infections and rheumatoid diseases (systemic vasculitis, polyarthritis, systemic lupus erythematosus, etc.). It should be noted that in the treatment of rheumatoid diseases, NSAIDs are used in long courses, and in the treatment of acute respiratory infections in very high doses [1]. Due to this, when treating these diseases with NSAIDs, the most common complications are nonsteroidal gastropathy, which manifests itself in the form of point and band erosions on the gastric mucosa [1]. As these lesions progress, they can merge and pass into the stage of classic gastric ulcer with the development of dangerous gastric bleeding and a high probability of malignancy. The pathophysiological mechanism of the development of non-steroidal gastropathy is very complex and not fully understood, but is mainly associated with inhibition of cyclooxygenase type 1 (COX-1), which is responsible for the synthesis of prostaglandins in the gastric mucosa and the formation of mucus, which protects the cells of the gastric mucosa from the damaging effects of acid and pepsin [2,3]. Almost all NSAIDs inhibit both COX-1 and COX-2 [4]. But only through inhibition of COX-2 is the systemic anti-inflammatory effect of NSAIDs achieved. There have been attempts to synthesize specific COX-2 inhibitors, but they

turned out to be less effective anti-inflammatory drugs than COX-1 and COX-2 inhibitors. Nevertheless, the problem of preventing nonsteroidal gastropathy is extremely relevant due to very wide prevalence of NSAIDs. In USA, 25% of people over 65 years of age use NSAIDs daily, and about 70% at least once a week [11,12]. The incidence of gastric and duodenal erosions when taking NSAIDs reaches 50%. Currently, there are no specific means of preventing nonsteroidal gastropathy. Symptomatic remedies are mainly used: antacids, mineral and herbal remedies, peptides [5-10]. In this regard, our attention was drawn to low molecular weight chitosan (50 kDa), which, due to the activation of tissue macrophages, can create an active anti-inflammatory background at the level of the gastric mucosa when taking NSAIDs. An additional factor for the study was that low molecular weight chitosan is non-toxic and can be used per os for a long time without any side effects.

The purpose of the study was to evaluate the effectiveness of low molecular weight chitosan (50 kDa) as a means of preventing damage to the gastric mucosa when taking NSAIDs in a model of indomethacin gastropathy in rats.

Materials and Methods

The work used 14 male Wistar rats, 3 months old with an average body weight of 240 – 250 g.

24 hours before the start of the study, all rats were put on a fasting diet. After 24 hours, under light ether anesthesia, all rats were injected intramuscularly with a suspension of indomethacin at the rate of 60 mg per 1 kg of body weight. 1 hour after administration of the indomethacin suspension (this period is sufficient for complete absorption of indomethacin into the systemic circulation), animals in the control group (K1-5) under light ether anesthesia were injected with 2 ml of 0.9% sodium chloride solution intravenously, and animals in the experimental group (O1-9) 2 ml of 0.2% aqueous solution of low molecular weight chitosan (50 kDa). 24 hours after administration of the test substances, all rats were euthanized by an overdose of ether anesthesia. The stomachs of the animals in the experimental and control groups were removed, cut along the lesser curvature, washed with saline, and the gastric mucosa was scanned with a resolution of 1200 dpi. The area of erosions in the gastric mucosa (band and point) in mm^2 and the area of the mucous membrane in mm^2 were calculated in the Corel Draw 13 after selecting their outline with Bezier curves. Statistical processing of the results was carried out in Gnumeric 1.12.17 spreadsheets.

Research Results

The results of the study are presented in Figures 1-5 (scans of the mucous membranes of the stomachs of rats with isolated band and point erosions) and Tables 1-6 (areas of erosion of rat stomachs).

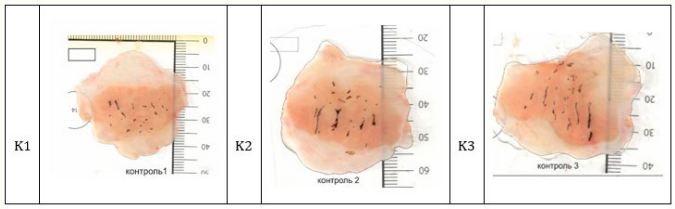

Figure 1: Scans of the mucous membranes of the stomachs of rats with isolated band and point erosions (K1-K3).

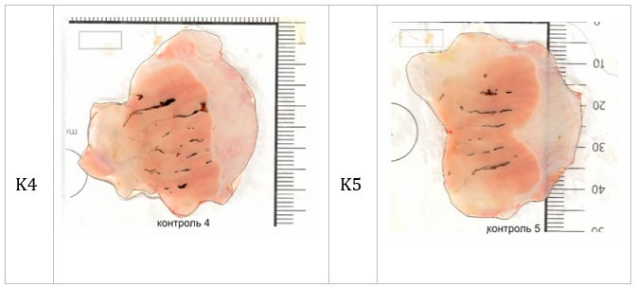

Figure 2: Scans of the mucous membranes of the stomachs of rats with isolated band and point erosions (K4-K5).

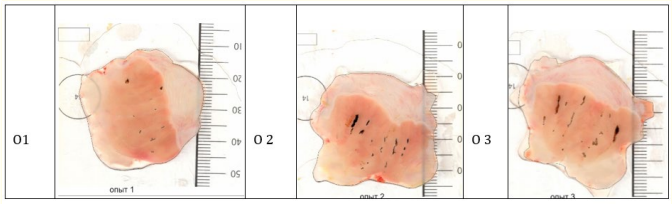

Figure 3: Scans of the mucous membranes of the stomachs of rats with isolated band and point erosions (O1-O3).

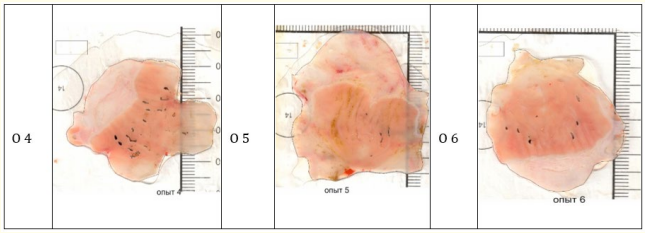

Figure 4: Scans of the mucous membranes of the stomachs of rats with isolated band and point erosions (O4-O6).

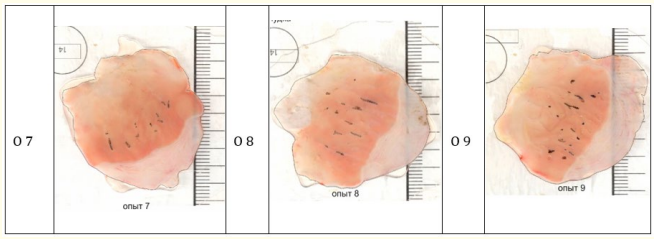

Figure 5: Scans of the mucous membranes of the stomachs of rats with isolated band and point erosions (O7-O9).

K1		K2		K3	
Area of the gastric mucosa, mm^2	1553.2	Area of the gastric mucosa, mm^2	1531.34	Area of the gastric mucosa, mm^2	1556.67
Area of tape erosion, mm^2	3.72	Area of tape erosion, mm^2	18.21	Area of tape erosion, mm^2	17.48
Area of point erosions, mm^2	4.0	Area of point erosions, mm^2	3.34	Area of point erosions, mm^2	4.2
Erosive damage to the mucosa, %	0.5	Erosive damage to the mucosa, %	1.41	Erosive damage to the mucosa, %	1.39

Table 1: Areas of erosion of rat stomachs (K1-K3).

K4		K5	
Mucosal area stomach, mm^2	1565.8	Mucosal area stomach, mm^2	1621.15
Area of tape erosion, mm^2	24.26	Area of tape erosion, mm^2	17.82
Point area erosion, mm^2	3.46	Point area erosion, mm^2	1.95
Erosive damage to the mucosa, %	1.77	Erosive damage to the mucosa, %	1.22

Table 2: Areas of erosion of rat stomachs (K4-K5).

O1		O2		O3	
Area of the gastric mucosa, mm^2	1443.65	Area of the gastric mucosa, mm^2	1561.40	Area of the gastric mucosa, mm^2	1581.32
Area of tape erosion, mm^2	0	Area of tape erosion, mm^2	11.65	Area of tape erosion, mm^2	12.75
Area of point erosions, mm^2	3.87	Area of point erosions, mm^2	1.43	Area of point erosions, mm^2	3.37
Erosive damage to the mucosa, %	0.27	Erosive damage to the mucosa, %	0.84	Erosive damage to the mucosa, %	1.02

Table 3: Areas of erosion of rat stomachs (O1-O3).

O7		O8		O9	
Area of the gastric mucosa, mm^2	1563.17	Area of the gastric mucosa, mm^2	1565.31	Area of the gastric mucosa, mm^2	1603.93
Area of tape erosion, mm^2	4.57	Area of tape erosion, mm^2	4.51	Area of tape erosion, mm^2	6.64
Area of point erosions, mm^2	1.15	Area of point erosions, mm^2	3.84	Area of point erosions, mm^2	4.59
Erosive damage to the mucosa, %	0.37	Erosive damage to the mucosa, %	0.53	Erosive damage to the mucosa, %	0.7

Table 5: Areas of erosion of rat stomachs (O7-O9).

Experimental group	Area of the gastric mucosa, mm^2	Relative area of erosive damage to the gastric mucosa, %	Area of tape erosions of the gastric mucosa, mm^2	Area of point erosions of the gastric mucosa, mm^2
K (n = 5)	1565.63 ± 14.9	1.26 ± 0.21	16.29 ± 3.38	3.39 ± 0.39
O (n = 9)	1588.39 ± 58.66	0.53 ± 0.1	5.41 ± 1.48	2.9 ± 0.57

Table 6: Average values (x ± SE) of damage to the gastric mucosa in the indomethacin model of gastropathy in Wistar rats with a single intravenous injection of 2 ml of 0.9% sodium chloride solution (K) and 2 ml of low molecular weight chitosan (O).

Discussions

Our studies have shown that low molecular weight chitosan (50 kDa) has a pronounced cytoprotective effect and reduces the percentage of damage to the gastric mucosa in a model of indomethacin gastropathy in rats. Moreover, with intragastric administration of low molecular weight chitosan, not only the total area of erosive damage to the stomach is reduced, but also the area of band erosions is significantly (more than five times) reduced. Band erosions are more severe forms of damage to the gastric mucosa when using NSAIDs. It should also be noted that we introduced low molecular weight chitosan 1 hour after the administration of indomethacin. If we take into account that the evacuation of stomach contents in rats into the duodenum occurs on average no later than 30 minutes, then the cytoprotective effect of low molecular weight chitosan is not associated with its local effect on the gastric mucosa. We believe that the mechanism of the described therapeutic effect of low molecular weight chitosan is due to the activation of macrophages and the expression of their synthesis of anti-inflammatory cytokines. It is also possible that against such a background, activated macrophages may participate in compensating for the blockage of COX-1 synthesis caused by NSAIDs. In comparison with other approaches to reduce NSAID-induced gastropathy based on the search for selective COX-2 inhibitors, this study differs in that the chemical structure of NSAIDs does not change and their anti-inflammatory activity does not change. Existing selective COX-2 inhibitors have lower anti-inflammatory activity than non-selective ones. In this aspect, low molecular weight chitosan can be considered as an additional component in the dosage forms of NSAIDs, which reduces their side effect on the gastric mucosa and at the same time does not affect their anti-inflammatory activity. As a result, the existing therapeutic regimens of NSAIDs may remain unchanged, which is very important from a clinical point of view. But low-molecular-weight chitosan can also be used as a separate pharmacological agent in therapeutic regimens using NSAIDs.

Conclusions

Low molecular weight chitosan has a clear gastroprotective effect when administered with indomethacin and can be considered as a promising drug for the prevention of non-steroidal gastropathy. At the same time, low-molecular chitosan can be a very promising additional component in the manufacture of dosage forms of NSAIDs with a reduced side effect on the gastric mucosa.

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