Antiulcer Activity of Preparations Containing Ultralow Doses of Antibodies in Modeled Chronic Ulcer in Rats

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Screening of three potential antiulcer preparations containing ultralow doses of antibodies to endogenous regulators of ulcer formation (gastrin, histamine, and H2 histamine receptors) on the model of acetic acid-induced gastric ulcer in rats revealed pronounced antiulcer effect of ultralow doses of antibodies to histamine. The dynamics of regeneration of the ulcer focus by morphological and histological characteristics was similar during treatment with ultralow doses of antibodies to histamine and with famotidine.

Key Words: *ultralow doses of antibodies; acetic acid-induced ulcer; regeneration; gastric mucosa*

Ulcer disease of the stomach and duodenum is an urgent problem of modern medicine; it occurs in 5-10% population [2]. The polyetiological nature of ulcer disease is admitted by the majority of investigators [1]. The therapeutic effects of numerous drugs used in clinical practice (antacids, adsorbents, muscarinic receptor antagonists, anxiolytics, stimulators of regeneration, antibiotics, immunomodulators, proton pump inhibitors, H1 and H2 histamine receptor blockers) are directed at various mechanisms of ulcer formation [3]. Ulcer disease is characterized by protracted course; therefore the search for new preparations accelerating the process of ulcer regeneration and producing no side effects is in progress.

Increased gastric acidity and destruction of the mucous barrier are aggression factors in the development of ulcer defect [4,6]. Secretion of hydrochloric acid in the stomach is primarily determined by activation of the gastrin-histamine paracrine system: gastrin activates the production and secretion of histamine by enterochromaffin cells and histamine, in turn, stimulates secretion of hydrochloric acid via H2 receptors on parietal cells [7,8]. However, histamine plays a dual role in ulcer formation, because it can stimulate mucus production via activation of H1 and H2 receptors on mucocytes, thus producing a gastroprotective effect [7,9].

Here we studied the effects of three potential antiulcer preparations containing ultralow doses of antibodies (ULD AB) to mediators involved in the regulation of gastric acidity and homeostasis of the gastric mucosa (GM) [10]: ULD AB to gastrin, histamine, and H2 histamine receptors. Famotidine, a blocker of H2 histamine receptors, was used as the reference preparation in this study [4]. The test ULD AB preparations were studied on the model of acetic acid-induced gastric ulcer, a model of chronic ulcer in humans.

MATERIALS AND METHODS

Antiulcer activity of ULD AB was studied on male Wistar rats weighing 180-200 g and aging 1.5 months (n=200) using the model of chronic acetic acid-induced gastric ulcer.

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After 24-h food and water deprivation, laparotomy was performed under Nembutal narcosis (40 mg/kg) and then 0.05 ml 10% acetic acid was injected under the gastric serosa. Then, the wound was sutured layer-by-layer. The test preparations were administered intragastrically for 30 days starting from the next day after surgery: ULD AB to gastrin (group 1), ULD AB to histamine (group 2), and ULD AB to H2 histamine receptors (group 3) in a dose of 2.5 ml/kg or famotidine (group 4) in a dose of 20 mg/kg in an equivalent volume. Controls received distilled water in a volume of 2.5 ml/kg. Ten animals from each group were sacrificed on days 5, 10, 15, and 30 of treatment, the stomachs were isolated, the area of ulcers was measured, and morphological examination of the ulcer focus was performed for evaluation of the dynamics of tissue regeneration processes in the stomach.

The data were processed statistically using Student's *t* test,

RESULTS

In the control group, the area of the ulcer defect on day 5 was 78.9±2.2 mm^2. By day 30, epithelization of ulcers was observed in 70% rats of this group (Table 1). The dynamics of ulcer scarring in group 1 did not differ from that in the control group. In group 3, the rate of regeneration of the ulcer defect on days 10 and 15 significantly surpassed that in the control group, but was lower than in groups 2 and 4, where the most active regeneration of the ulcer focus was noted. Scarring of the ulcer defect by 30 days in all animals was observed in groups 2 and 4.

Histological analysis of the ulcer defect showed that ulcer formation in the control group and group 1 was accompanied by pronounced inflammatory reaction. On days 5 and 10 of the experiment, purulent and necrotic processes predominated in the control group and inflammatory reactions predominated in group 1. In both groups, these reactions weakened by days 15 and 30. Superficial erosive gastritis developed in all portions of the stomach in the control group and erosion of surface enterocytes was seen in group 1. Epithelization in the control group and group 1 was accompanied by rearrangement of GM by the pyloric type, in group 1 cystic cavities and glandular polyps were also formed. No complete epithelization of the ulcer defect was achieved in these groups by day 30. Cicatricial tissue appeared on the bottom of the ulcer.

In groups 2 and 4, ulcer formation was accompanied by moderate inflammatory changes. Epithelization processes were pronounced and were accompanied by GM rearrangement by the pyloric type. Regeneration of the ulcer in these groups was not associated with pronounced inflammatory and proliferative changes; in group 4, no complete recovery of GM was achieved, while in group 2, GM recovered completely but with the formation of cystic cavities and glandular polyps. Complete ulcer cicatrisation was observed in both groups.

In animals receiving ULD AB to H2 histamine receptors, the processes of ulcer formation were similar to those in group 1 animals. However, the degree of inflammatory changes in the ulcer on day 30 decreased compared to that in animals treated with ULD AB to gastrin and approached that in group 4. Epithelization and regeneration of the ulcer defect did not differ from those in group 1.

The observed antiulcer activity of ULD AB to histamine and, to a certain extent, ULD AB to H2 histamine receptors suggests that the antiulcer effects of these preparations are based on modification of histamine-dependent receptor transmission. The difference in the effect of these preparations is probably determined by activation of different gastroprotective processes.

TABLE 1. Effect of 30-Day Treatment with the Test Preparations on the Dynamics of Regeneration of Acetic Acid-Induced Gastric Ulcer (*M*±*m*)

Group	Ulcer area, mm^2			
	5 days	10 days	15 days	30 days
Control	78.9±2.2*	70.2±2.2*	47.9±4.4*	Cicatrisation in 70% animals
ULD AB to gastrin	75.1±2.6*	64.7±2.5*	39.7±3.6*	Cicatrisation in 80% animals
ULD AB to histamine	63.5±2.1$^+$	39.8±3.0$^+$	21.4±1.7$^+$	Cicatrisation in 100% animals
ULD AB to H2 histamine receptors	74.1±2.3*	61.9±1.9*$^+$	31.7±1.8*$^+$	Cicatrisation in 80% animals
Famotidine	59.7±2.1$^+$	42.7±1.8$^+$	20.9±1.0$^+$	Cicatrisation in 100% animals

Note. *p<0.0001 compared to: *famotidine, $^+$control.

Thus, our study of antiulcer activity of ULD AB to endogenous regulators of the gastrointestinal system, gastrin, histamine, and H2 histamine receptors on the model of chronic acetic acid-induced ulcer in rats demonstrated pronounced antiulcer activity of ULD AB to histamine comparable to that of H2 receptor blocker famotidine.

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