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EFFICACY OF CIMETIDIN IN THE PREVENTION OF ULCER FORMATION IN THE STOMACH DURING IMMOBILIZATION STRESS

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EFFICACY OF CIMETIDIN IN PREVENTING ULCER  
FORMATION IN THE STOMACH DURING STRESSBy G. I. Dorofeyev, I. A. Litovskiy, L. K. Gavrovskaya,  
V. T. Ivashkin\*

Until now there has not been a completely clear assessment of the criteria for /24\*\* delimiting peptic ulcers and acute ulcers of the stomach and the duodenum. Some authors assume the possible formation of a chronic ulcer from an acute, and others believe that acute gastroduodenal ulcers (Cushing ulcers which develop after trauma to the brain, and Curling ulcers in patients with burn sickness, cortisone ulcers during overdosing of glucocorticoids, etc.) are the result of stress effects on the body. Numerous studies of the researchers from the school of S. V. Anichkov have shown the role of the central cerebral structures in closing the pathological reflexes during stress, and have also traced the centrifugal path of the stimuli which disrupt the trophism of the stomach, primarily in the sympathetic nervous system. Pathological stimuli which are disseminated on these paths, reaching the stomach, cause massive discharge of catecholamines from the tissues of the mucous membrane. This results in a subsequent depletion of the depot. These changes govern the decrease in energy metabolism in the cells. This is the main reason for the development of dystrophy [1]. Other humoral factors participate in the development of experimental gastric ulcers under the influence of stress, in particular, increased level of gastrin [9], corticosteroid hormones, as well as increased biosynthesis of histamine with its subsequent decrease [2, 10]. It has been established that the effect of histamine in the body is realized when it influences H<sub>1</sub>- and H<sub>2</sub>-receptors.

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\*\*Numbers in margin indicate pagination in original foreign text.

In studying the properties of new  $H_2$ -antagonists in experiments on animals, we found [4] a pronounced capacity to prevent the formation of lesions in the stomach caused by different factors (stress, pharmacological substances). In recent years, the blockers of  $H_2$  receptors have been used more extensively in clinical practice, mainly /25 to treat peptic ulcers. Cimetidin is currently the most popular of the analogs of this group [3, 5, 11]. The mechanism of action of cimetidin continues to be studied at present, however it has been established that one of its main effects in the stomach is the blockade of  $H_2$ -receptors of parietal cells. Consequently, it is very important to study the effect of this preparation on the metabolism in the stomach under stress conditions and to compare these data with ultrastructural changes in the parietal cells.

#### TECHNIQUE

We selected the stress model of formation of ulcers because it is precisely in this method that cimetidin shows its protector effect [8]. To solve this task we selected a model of formation of acute stress ulcers of the stomach in an experiment on rats under conditions of the effect of cold ( $4-8^{\circ}C$ ) in combination with immobilization. For this experiment we selected 36 albino rats, each weighing 250-300 g, 6 individuals in a group. As the control we used rats of the first group, fed, and second group, not fed for 2 days with unlimited water. Rats of the third group after second day fast were exposed to stress for 2 h, rats of the fourth group were exposed to a similar effect on the background of cimetidin injection. Rats of the fifth group after a 2-day fast were exposed to the effect of stress for 3 hours, and in the sixth group were exposed to hunger and 3-hour stress on the background of cimetidin injection. Hunger was prescribed in order to create more uniform conditions by the beginning of the experiment, since it is common knowledge that metabolic

activity in the gastric tissue can change depending on eating. The rats were decapitated. The following studies were made: 1) the total number of ulcerous lesions and erosions in the stomach were counted; 2) the content of cyclic adenosine monophosphate (cAMP) was defined in the tissues of all layers of the stomach body; 3) the distribution of mucopolysaccharides and lipids in the gastric mucous membrane was studied; 4) the ultrastructure of the lining cells was studied in rats of the 1, 2, 5 and 6th groups.

Cimetidin was injected intramuscularly in a dose of 25 mg/kg. The first injection was made 30 minutes before the beginning of the stress factor, the second was made in 90 minutes after the first, since it is known that the duration of preservation of the therapeutic concentration of the given preparation in the blood roughly equals 1 h 40 min. Thus, at the moment that the rats in the fourth group were killed, the therapeutic concentration of cimetidin was preserved in the blood, and in rats of the 6th group it disappeared in roughly 20 minutes before they were killed.

The cAMP content in the gastric tissue was determined according to the Gilman technique using domestic instruments (V. Yu. Vasil'yev) manufactured in the Leningrad University and not inferior in information content to the instruments of the firm "Amersham."

#### RESULTS AND DISCUSSION

In analyzing the obtained material it was established that the cAMP content in the stomach of the rats of the first group averaged  $2192 \pm 57.7$  pmole per 1 g of tissue, in the second, third, fourth, fifth and sixth groups,  $2070.6 \pm 177.8$ ,  $2148.9 \pm 188.3$ ,  $813 \pm 157$ ,  $3327 \pm 107$  and  $3749 \pm 153.6$  pmole/g respectively. No ulcers were found in the stomach of the rats of the first, second and fourth groups. At the same

time, ulcerous lesions were found in rats of the third group (2 rats) and small-spot erosions (2 rats) in rats of the fifth group, the number of ulcers averaged 6-7 per stomach, and in rats of the sixth group there were fewer, averaging 1-2 per stomach. In a comparison of the frequency of formation of ulcers by groups with the cAMP level in the gastric mucous membrane it was found that in rats exposed to the effect of stress without cimetidin, the cAMP level gradually increased, and consequently, the metabolic activity rose (by 60% as compared to the control). By the end of the study, this process ended in the formation of ulcers. As a result of the use of the blocker of H<sub>2</sub>-receptors, the metabolic activity in the stomach drastically diminished (roughly by 60%). The protector effect of it on the formation of ulcers in rats was simultaneously noted.

The presented factual material can be interpreted as follows. Since the cAMP level in the stomach drastically diminishes under the influence of cimetidin, consequently, the dynamics for the changes in the metabolic activity during stress is due to the histamine-sensitive cells (primarily lining cells). Since the mechanism for the effect of cimetidin is known, one can assume that the acid factor plays if not the main, then in any case, a significant role in the formation of stress ulcers in rats. In this case, the aggressive properties of hydrochloric acid are apparently not balanced to a sufficient degree by the activity of the protective mechanisms (increase in the production of mucus, proliferation of mucine-forming cells, etc.) which prevent reverse diffusion of the hydrogen ions. In addition to this it is important to note that after the effect of cimetidin stops, the level of cAMP in the stomach drastically rises (sixth group). It has been shown that with intraabdominal injection of rats with antagonists of H<sub>2</sub>-receptors of burimamide or metiamide, activation of histidine decarboxylase is observed in the mucous membrane of the stomach [6]. At the same time there was a significant increase in the concentration of the

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serum gastrin. In rats with removed distal half of the stomach, metiamide did not influence the activity of the enzyme and the serum concentration of gastrin. The authors hypothesize that the antagonists of H<sub>2</sub>-receptors stimulate the release of gastrin which governs the activation of histidine decarboxylase. By comparing the findings with the data of these authors, one can assume that during the blocking of H<sub>2</sub>-receptors, histamine is intensively produced (because of the activation of the gastrin mechanism). After the cessation of the effect of the blocker, the accumulated histamine binds the released H<sub>2</sub> receptors. This governs the rapid rise in the level of cAMP in the stomach and increase in the production of hydrochloric acid.

Histochemical study of the gastric mucous membrane by groups of animals demonstrated that in all groups the maximum content of mucopolysaccharides is mainly noted in the surface-fossal epithelium. In the remaining cells its content insignificantly or not at all changed under the influence of only stress and stress on the background of cimetidin. Study of the distribution of lipids showed their extremely low content or complete absence in the epithelium of the gastric glands. The content did not change at rest, in hunger, under the influence of stress alone, or stress on the background of the use of cimetidin. The effect of stress alone or its combination with the administration of cimetidin apparently does not result in a change in the content of mucopolysaccharides and lipids in the lining cells. This can be explained by the fact that glycogen and lipids, being the basic energy material, at least for the lining cells, are recovered by the cells immediately upon entering them.

Analysis of the ultrastructural changes in the parietal cells indicated that in the fed rats they contain a pronounced network of intracellular canaliculi with large quantity of mitochondria and a small number of tubulovesicles. With a drop in the level of cAMP in hungry rats, the length of the intracellular canaliculi diminishes



and the number of tubulovesicles rises. At the same time, in rats exposed to the stress effect for 3 h, not only are the intracellular canaliculi hypertrophied (as compared to those in rats of the first and second group), but their lumen is also dilated. The mitochondria adjoin each other so closely that the cytoplasm occupies a very small place. This change in the ratio between the volume of cytoplasm in the mitochondria has a physiological meaning, since in this case, the area of contact of the mitochondria with the system of intracellular canaliculi rises, and consequently the rate of transport of hydrogen ions. In rats of the sixth group during the 3-hour stress effect on the background of cimetidin administration, the lining cells also have a network of intracellular canaliculi, but less pronounced than in rats of the first and fifth groups, although the cAMP level in the gastric mucous membrane is higher in them than in rats of other groups. This can be explained by the fact that increase in the cAMP level precedes a morphological manifestation of high metabolic activity. One can therefore hypothesize that a further effect of the stress factor will induce the same changes as in rats of the fifth group, but by the moment of study they did not succeed in developing.

In making brief summaries, one can draw the conclusion that under the stress effect, ulcerous lesions develop in the stomach of rats, there is a parallel increase /27 in the level of cAMP in the gastric wall, and the length and width of the lumen of intracellular canaliculi increase in the lining cells. The use of blockers of H<sub>2</sub>-receptors prevents ulcer formation in the stomach while the therapeutic concentration is maintained in the blood. After the effect of cimetidin stops, a metabolic explosion seems to occur. It is manifest as an increase in the level of cAMP in the stomach as compared to the original by more than 3.5-fold.

Thus, the administration of cimetidin reliably prevents ulcer formation in the stomach of rats for the period of its action, however a drastic increase in metabolism

after the end of the effect of this blockeryields an unfavorable effect and can cause death of the animals [7]. The authors have established that as a result of using blockers of H<sub>2</sub> receptors in traumatic shock, the lethal outcome of mice increases. This makes it possible to draw an important conclusion for clinical practice that if cimetidin is used, and apparently other H<sub>2</sub>-antagonists to treat peptic ulcers, after an effect has been reached, in order to avoid relapse the preparation must be gradually removed.

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