IN-0

NASA TECHNICAL MEMORANDUM NASA TM-76864

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

G. I. Dorofeyev, I.A. Litovskiy, L.K. Gavrovskaya and V.T. Ivashkin

(NASA-TM-76864) EFFICACY OF CIMETIDIN IN THE PREVENTION OF ULCER FORMATION IN THE STOMACH DURING IMMOBILIZATION STRESS (National Aeronautics and Space Administration) 9 p HC A02/MF A01 CSCL 06E G3/52

N82-30923

Unclas 30445

Translation of "Effektivnost' tsimetidina v preduprezhdenii yazvoobrazovaniya v zheludke pri stresse". Patologicheskaya fiziologiya i eksperimental'naya terapiya, No. 6, November-December 1980, pp 24-27.

NATIONAL AERONAUTICS AND SPACE ADMINISTRATION
WASHINGTON D.C. 20546 MAY 1982

STANDARD TITLE PAGE

1. Report No. NASA TM-76864	2. Government Accession No.	3. Recipient's Catalog No.
4. Title and Subtitle EFFICACY OF CIMETIDIN IN THE PREVENTION OF ULCER FORMATION IN THE STOMACH DURING IMMOBILIZATION STRESS		5. Report Date MAY, 1982 6. Performing Organization Code
7. Author(s) G. I. Dorofeyev, I.A. Litovskiy, L.K. Gavrovskaya and V.T. Ivashkin		8. Performing Organization Report No. 10. Work Unit No.
9. Performing Organization Name and Address SCITRAN Box 5456 Santa Barbara, CA 93108		11. Contract or Grant No. NASw-3542 13. Type of Report and Period Covered Translation
12. Sponsoring Agency Name and Address National Aeronautics and Space Administration Washington, D.C. 20546		14. Sponsoring Agency Code

15. Supplementary Notes

Translation of "Effektivnost' tsimetidina v preduprezhdenii yazvoobrazovaniya v zheludke pri stresse". Patologicheskaya fiziologiya i eksperimental'naya terapiya, No. 6, November-December 1980, pp 24-27.

16. Abstract

Discussion of the effect of stress on the formation of ulcers in the mucous membrane of the stomach, the increase in cyclic adenosine monophosphate level in the gastric tissues and parietal cell structure alteration. Use of cimetidin prevents this.

17. Key Words (Selected by Author(s))

18. Distribution Statement

19. Security Classif. (of this report)	20. Security Classif. (of this page)	21. No. of Pages	22. Price
Unclassified	Unclassified	7	

UDC 616.33-002.44-02:616.45-001.1/.3]-085.218.2-039.71

EFFICACY OF CIMETIDIN IN PREVENTING ULCER FORMATION IN THE STOMACH DURING STRESS

By 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_1-and H_2-receptors.

*Department of Hospital Therapy (head, Professor G. I. Dorofeyev) of the S. M. Kirov Military Medical Academy, Leningrad.

**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°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_2-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 /26 (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_2-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

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_2-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_2-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 bonds the released H_2 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_2-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 blocker yields an unfavorable effect and can cause death of the animals [7]. The authors have established that as a result of using blockers of H_2 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_2-antagonists to treat peptic ulcers, after an effect has been reached, in order to avoid relapse the preparation must be gradually removed.

BIBLIOGRAPHY

1. Anichkov, S. V. Izbiratel'noye deystviye mediatornykh sredstv ["Selective Effect of Mediator Substances"], Leningrad, 1974, p 212.
2. Grechishkin, L. L.; and Mustafina, T. K. Byull. eksper. biol., No 3, 1970, p 31.
3. Aadland, E.; and Berstad, A. Scand. J. Gastroent., vol 13, 1978, pp 193-197.
4. Bugaiski, I.; Havo, I.; and Danek, L. Europ. J. Pharmacol., vol 36, 1976, p 237.
5. Gillies, R. R.; Archambanet, A.; Kinnear, D. G., et al. Gastroenterology, vol 74, 1978, No 2, pt. 2, p 396.
6. Hakanson, R.; Hedenbro, J.; Liedberg, G. et al., Brit. J. Pharmacol., vol 53, 1975, pp 127-130.
7. Halevy, S.; and Altura, B. M. Pros. Soc. Exp. Biol. (N.Y.), vol 154, 1977, pp 453-456.
8. Hayden, L. I.; Thomas, G.; and West, G. B. J. Pharm. Pharmacol., vol 30, 1978, pp 244-246.
9. Konturek, S. I.; Damitrescu, T.; Radeeki, T. et al., In: International Symposium on Histamine H_2-Receptor Antagonists, London, 1973, p 247.
10. Levine, R. I.; and Sennay, E. C. Am. J. Physiol., vol 214, 1968, p 892.
11. Winship, D. H. Gastroenterology, vol 74, No 2, part 2, 1978, pp 402-406.