

Clarification of the irritating and toxic effects of bentonite-like clays

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Abstract—This article studies the action and biocompatibility of the developed montmorillonite-containing preparation “Sor bent” on experimental animals with its long-term use. The local irritating effect of the “Sor bent” preparation was evaluated by its effect on the gastric mucosa of animals with experimental ulcerative pathology. The size of the most common particles in the suspension is 5-8 microns. The experiments were carried out on white rats of the Wistar line and non-linear Hartley guinea pigs.

To identify the irritating effect, the drug was administered to animals in therapeutic doses of 200 mg/kg and three times the conditionally therapeutic dose - 600 mg/kg of body weight. Destructive changes in the stomachs of experimental animals were studied macroscopically. The ulcerogenic effect was evaluated by calculating the Pauls index.

Keywords—*enterosorbent, montmorillonite, ulcerative pathology, inflammatory process*

I. INTRODUCTION

Constantly increasing environmental pollution determines the excessive content of toxic substances in drinking water, food, feed and livestock products. In this situation, the search for ways to reduce the content of potentially hazardous substances by binding and eliminating various xenobiotics, microorganisms, their toxins, endogenous intermediate and final metabolic products that can accumulate or penetrate into the cavity of the gastrointestinal tract during various diseases [1].

Enterosorbents (gr. enteron - gut; lat. sorbens - absorbing) are substances that have a high sorption capacity, are not destroyed in the digestive tract, effectively bind and excrete endogenous and exogenous toxic compounds, supramolecular structures and cells used for treatment and disease prevention [2-4]. In mild and moderate forms of acute intestinal infections, the therapeutic effectiveness of individual enterosorbents is not inferior to antibacterial drugs widely used in clinical practice (furazolidone, gentamicin, ceftriaxone, etc.) [5-8].

The direct action of enterosorbents is aimed at binding and elimination of the trophic chain pollutants, toxic metabolic products and the inflammatory process, pathogenic bacteria and their toxins, viruses, biologically active substances from the digestive system, the binding of gases formed in excess during the putrefactive process. As a rule, the detoxification process begins to appear in the stomach and continues to be carried out in the small intestine. The indirect effect is due to the prevention or weakening of the clinical manifestations of endotoxemia, toxic-allergic reactions, diarrhea syndrome, as well as the elimination of flatulence, improvement of trophism of the intestinal wall and stimulation of intestinal motility. The use of enterosorbents reduces the metabolic load on the liver and kidneys, helps to normalize the motor, evacuation and digestive functions of the gastrointestinal tract, positively affects the resistance and functional state of the immune system [4, 9-11].

Enterosorbents, located within the digestive tract and not having their own pharmacodynamics, have a powerful systemic (distant) effect on the body - eliminate lipid metabolism disorders, suppress the elements of the systemic inflammatory reaction, promote compensation and improve the function of internal organs [9, 10-13]. They practically do not change the composition of normal intestinal autoflora [9, 10]. In addition to the high sorption capacity in relation to the removed components and the above mechanisms of action, modern enterosorbents must meet the basic medical requirements: not to have toxic and traumatic effects on the mucous membranes of the digestive system; must well eliminate from the intestines and not cause loss of useful ingredients. Enterosorption preparations should have an acceptable cost, a convenient oral form and have good organoleptic properties [4].

The processes of interaction of sorbents with removed components are carried out in four main ways, such as adsorption, absorption, ion exchange, and complex formation [9, 12].

The classification of modern enterosorbents is based on several principles: the shape, structure, nature of the material (in addition to synthetic materials for enterosorption, natural polymers based on lignin, chitin, cellulose, clays (aluminosilicates), zeolites, etc. can be used), as well as the type of interaction between the sorbent material (sorbent) and related substance (sorbate).

Most modern enterosorbents are known to practitioners of various specialties. However, many registered enterosorbents have not yet found widespread use for various reasons: due to the lack of awareness of doctors about the role of enterosorbents in the treatment of infectious and non-infectious diseases of the digestive system, the lack of awareness of the advantages and disadvantages of certain sorbents for a specific pathology and the skeptic actually existing attitudes of doctors to enterosorption.

The bulk of the sorbents used in the Russian Federation are not specific to specific toxins and metabolites. Due to the porous structure, substances fixed in them are tropic to the surface of the sorbent and have the corresponding molecular sizes, which allow penetration into pores of different sizes. Potentially hazardous substances vary in relative molecular weight - from hundreds to a million daltons, hydrophilic or hydrophobic properties, features of blood circulation, transport through membranes, and ways of excretion from the body. Their effective removal is determined by the selection of appropriate sorbents with different pore size and volume, surface size and chemical composition, and other indicators [14]. Enterosorbents should not be combined with other medicines. The interval between their doses should be at least 1.5-2 hours. A negative factor, especially coal sorbents, is the sorption of vitamins, mineral salts and other nutrients, as well as non-specific sorption of enzymes (pepsin, trypsin, amylase), which requires the replacement of substitution therapy with enzyme preparations. At the same time, coal enterosorbents have a damaging effect on the mucosa, and they should not be used for a long time in the presence of an erosive or ulcerative process in the gastrointestinal tract [2].

II. EXPERIMENTAL

In recent years, there have been reports of the use of minerals, in particular, montmorillonite-containing clays from the group of smectites with serious intoxication of the body, both humans and animals. No worse than modern antibiotics, they cope with pathogenic bacteria. But, unlike medicines, clay itself remains chemically inert, and, therefore, completely harmless to the body, clay inactivates only harmful microbes and toxins, renewing cells, and strengthens the immune system. Due to the wide range of applications for various diseases, physical ability to regenerate tissues, antitoxic, antiseptic, bactericidal and preservative properties, clay is an indispensable health aid. Montmorillonite is a clay mineral of the layered silicates group. It occurs in nature in the form of small imperfect crystals. The mineral structure is a three-layer packet of the type (2:1): two layers of silicon-oxygen $[\text{SiO}_4]^{4-}$ tetrahedra facing each other with their vertices create a network of the

composition $[\text{Si}_2\text{O}_5]^{2-}$, covering the layer of aluminum-hydroxyl octahedra $[\text{Al}(\text{O},\text{OH})_6]$. The connection between the packets is weak, the interpacket distance is large, and water molecules or other polar molecules, as well as exchange cations and anions, can penetrate into it.

The therapeutic effect of montmorillonite-containing clays (bentonite-like) is based on their sorption-adhesive, ion-selective properties and saturation with various chemical elements, some of which are in a bioavailable form. The minerals of the montmorillonite group exhibit a detoxifying function, adsorbing and removing toxins from the intestines, products of incomplete metabolism, pathogenic and conditionally pathogenic bacteria, allergens [15].

Moreover, mineral adsorbents contribute to a more complete absorption of vitamins. Being in the composition of food, mineral adsorbents slow down the passage of food through the gastrointestinal tract, that is, extend the time the food spends in the intestines. Naturally, for a longer period of time, the nutrients of the food, including vitamins, are absorbed in larger quantities. Knowing this, pharmacologists have long been using mineral carriers for drugs and vitamins in order to prolong their action. Mineral adsorbents efficiently bind mycotoxins, which are characterized by poor solubility in water. The adsorption capacity of certain types of clays is due to their layered structure and high sorption area [16-20].

The distance between the microscopic layers that make up the structural basis of clay is a fraction of a nanometer. If you increase this distance, you can significantly increase the specific surface of the clay and thereby its adsorption properties. [21, 22].

Based on nanostructured modified montmorillonite containing clays, the preparation "Sorbent" developed by us [23] suppressed the ability of *Escherichia* and *Salmonella* to exhibit their pathogenic properties, and reduced the absorption of bacterial toxins, as well as decay products of intestinal contents. The revealed adsorption ability of "Sorbent" on the surface of fimbriae and the cell wall of *Escherichia* and *Salmonella* prevented the adhesion and colonization of these microorganisms to the epithelial cells of the gastrointestinal tract of laboratory animals and further prevented their reproduction. On broiler chickens experimentally infected with colibacteriosis, its therapeutic efficacy in combination with preparations of the fluoroquinolone group has been clarified. After the course of treatment, the expense of expensive fluoroquinolones was halved.

The information presented in the scientific literature clearly shows that therapy with modern enterosorbents is of particular importance both in healthcare and veterinary medicine in almost any acute and chronic diseases accompanied by exo- and endogenous intoxication syndrome, of which dysfunctions of the microbiocenosis and intestinal barrier are critical. In this regard, the use of bentonite-like clays containing montmorillonite is of particular importance. The mineral binds and removes toxic substances from the body, optimizes the metabolism of proteins, lipids, vital microelements, promotes the absorption

of vitamins by the digestive system, normalizes intestinal function, increases the nonspecific resistance of the body, and positively affects the productivity, production quality and reproductive functions of animals.

From the considered data, close attention should be paid to the issue of aluminum content in montmorillonite-containing clays. Since in the world literature the concentration of aluminum in food products and its decrease in diets is given great importance [24].

The fact is that aluminum can cross the placental barrier and can be found in breast milk. With an increase in the aluminum content in tissues, the iron concentration in the body decreases. In turn, a deficiency of calcium and magnesium leads to the accumulation of aluminum in brain tissues and bones.

The negative effect of aluminum compounds on the chromosomes of bacterial cells and the reproductive system of dogs has been experimentally confirmed, its neurotoxic effect on mice and rats has been established at doses exceeding the conditionally acceptable level of aluminum consumption per week (provisional tolerable weekly intake - PTWI), [25, 26].

According to the European Food Safety Authority (EFSA) [27], the acceptable level of its receipt from all sources per week is 0–1 mg/kg body weight (TWI), as well as the established level of PTWI (0.1–2.0 mg/kg body weight per week).

According to WHO estimates, the average intake of aluminum in the human body from all possible sources is from 11 to 136 mg/person per week. In this case, a significant amount in the total supply of aluminum belonged to aluminum containing food additives used in the food industry.

Based on the repeated toxicity assessments of these compounds, the requirements of EU Decisions No. 1129/2011, EU No. 380/2012, it was decided to exclude from the list of approved for use a number of aluminum containing food additives E554 (Sodium Aluminosilicate), E555 (Potassium Aluminosilicate), E556 (Calcium Aluminosilicate), E558 (Bentonite), E559 (Kaolin), etc.

For this time period, according to EU Regulation No. 380/2012, food additives bentonite (E558), calcium aluminosilicate (E556), aluminosilicate (kaolin) (E559) are excluded from the list of food additives approved for use in the European Union, and food additives E554 (Sodium aluminum silicate) and potassium aluminosilicate (E555) are used to a limited extent. In this regard, it seems appropriate to exclude food additives E 554, E 555, E556, E 558, and E 559 from the list of Appendix 2 TR CU 029/2012 "Safety requirements for food additives, flavors and processing aids". As a result, taking into account the data obtained, the above aluminum containing food additives are excluded from the list of permitted for use in the food industry of the Russian Federation [24, 28].

In our opinion, since the structure of montmorillonite is represented by a three-layer package of the (2:1) type: two layers of silicon-oxygen $[\text{SiO}_4]^{4-}$ tetrahedra facing each other with vertices on both sides, covering the layer of aluminum-hydroxyl octahedra $[\text{Al}(\text{O},\text{OH})_6]^{3-}$, it is quite stable and when

exposed to digestive enzymes in the gastrointestinal tract is not destroyed and aluminum ions do not enter the intestinal lumen.

Of the developed montmorillonite-containing preparation the "Sor bent" with prolonged use, namely the determination of its specific, local irritation, as well as toxicity and biocompatibility for experimental animals.

This experimental work is currently relevant due to the fact that the volume of consumption of various types of food micro-ingredients for technological purposes in the food industry is increasing (the standards for their use should be constantly reevaluated taking into account new scientific data on their effects on the body, the need for their application and possibilities changes in the conditions of their use) [29].

The object of study was the development of the "Sor bent" based on montmorillonite. The prototype enterosorbent is a powder from yellowish or grayish-white to grayish or brownish-yellow odorless. The proportion of montmorillonite in the preparation is 65-70 wt.%. The size of the most common particles in the suspension is 5-8 microns.

The experiments were carried out on white rats and guinea pigs, kept individually in separate cages on a standard diet in accordance with sanitary rules (No. 1045-73), approved by the Ministry of Health of the USSR on April 6, 73, by order of the Ministry of Health of the USSR No. 755 of 08/12/07 and GOST R 53434-2009. In the study, Wistar rats weighing 210 ± 20 g and non-linear Hartley guinea pigs with a body weight of 320 to 380 g were used. Animals were obtained from vivarium of Belgorod State University. The experiments were performed in accordance with the requirements of GOST ISO / IEC 17025-2009, GOST R ISO 5725-2002 and the "Laboratory Practice Rules", approved by order of the Ministry of Health and Social Development of the Russian Federation of 08.23.2010 No. 708n, in compliance with the "European Convention for the Protection of Vertebrate Animals Used for experiments or other scientific purposes Directive 2010/63/EU.

The locally irritating effect of the "Sor bent" preparation was evaluated by its possible effect on the gastric mucosa of animals with experimental ulcerative pathology. To identify the irritating effect, the drug was administered to animals in therapeutic doses of 200 mg/kg and three times the conditionally therapeutic dose - 600 mg/kg of body weight.

After exposure to forced substances, the animals were anesthetized with thiopental and decapitated with simultaneous opening of the chest. To evaluate ulcerative lesions, the stomach was removed, cut along a large curvature and spread on a glass plate. The resulting destructive changes were studied macroscopically. Ulcerogenic effect was evaluated by calculating the Pauls index [30].

The degree of ulceration was determined by the average number of ulcers per animal. In the calculations, along with the degree of ulceration, the area of ulceration in points according was also taken into account to A.A. Akimov (1968) [31], which more objectively reflects the degree of degenerative disorders. Ulcers with a size of 1-2 mm were evaluated at one point, 2-10 mm at 5 points, more than 10 mm at 10 points. The data obtained were processed by methods of computer variation statistics.

Ulcerative lesions of the gastric mucosa of rats were caused by the following methods: 1) neurogenic in nature (by immobilizing the animal); 2) reserpine; 3) butadiene. The last type of ulcerative lesions was also carried out on guinea pigs. Thus, the irritating effect of the drug was studied in two types of experimental animals.

The use of models with ulcers of neurogenic etiology included the identification of both the irritant effect, the developed enterosorbent, and the anti-ulcer effect. Two days before the experiment, the rats were deprived of food, animals received drinking water without restrictions. Experimental animals for 0.5-1.0 hours before immobilization were intragastrically injected with an isotonic sodium chloride solution suspension of the study drug. The rats of the control and experimental groups (16 animals each) for the legs were fixed abdomen down on the "machine" for 24 hours. After a given exposure, the animals were opened under thiopental anesthesia in order to detect ulceration of the gastric mucosa.

Butadione ulcerative lesions were reproduced on one-day, three-day and 12-day models. A day before the start of decapitation, experimental animals were stopped feeding and watering.

Ulcerative lesions in one-day rat models were caused by intraperitoneal administration of butadione at a dose of 200 mg/kg body weight. At the same time, 16 rats were involved in the control and experiment. At the same time, the animals of the experimental group were injected directly into the stomach once studied "Sorbent" at a dose of 600 mg/kg of body weight. After 24 hours, the animals of both groups were sacrificed, the stomach was removed, and the state of its mucous membrane was macroscopically evaluated.

In a three-day model, experimental animals (16 animals in the control and experimental groups) were injected intraperitoneally daily with a dose of 100 mg/kg body weight for three days. Experienced rats for three days were enterally prescribed the "Sorbent" developed by us. The dose of the drug was three times higher than the conditionally therapeutic. On the next day, animals were killed under thiopental anesthesia, and then the stomach was removed to examine for ulceration.

In the following experiment, laboratory animals of the control and experimental groups (30 rats each), a 4% solution of butadione were injected intramuscularly once a day for 12 days in a row at a dose of 120 mg/kg body weight. The butadiene was previously triturated with the Tween-80 emulsifier, then it was dissolved in distilled water. "Sorbent", as in previous studies, was administered intragastrically at a dose of 200 mg/kg body weight half an hour before the parenteral administration of butadione daily for 12 days.

In a series of experiments, pharmacological reserpine ulcers were caused in animals starving for two days. Reserpine was injected subcutaneously in rats in a 10% ascorbic acid solution at a rate of 10 mg/kg body weight.

Guided by the fact that hemorrhages and ulcers under experimental conditions occur 12-18 hours after administration of reserpine [32], studies to identify and evaluate destructive changes in the stomach wall of experimental animals (16 animals in the control, 10 in the

experiment) were evaluated after 18 hours from the moment of introduction of this alkaloid.

As in previous studies, the test drug "Sorbent" was administered intragastrically at a dose of 200 mg/kg body weight half an hour before parenteral administration of reserpine in experimental rats.

A study of the irritating effect of the "Sorbent" preparation, developed on the basis of dioctahedral smectite, was carried out in experiments on guinea pigs (12 individuals in the control group and 10 in the experimental group). The studied "Sorbent" was administered once directly into the stomach at a dose of 600 mg/kg body weight. The experimental conditions were identical to those for the study of ulcerative lesions from intraperitoneal administration of butadione to white rats.

The defeat was caused by intraperitoneal administration of butadione at a dose of 200 mg/kg body weight. Gastric ulcers occurred 24 hours after the administration of butadione.

III. RESULTS AND DISCUSSION

As a result of the experiment concerning the establishment of the irritating and anti-ulcer effect of the "Sorbent" preparation in models with ulcerative pathology caused by immobilization of white rats, it was revealed that the immobilization of control animals was accompanied by the formation of ulcerative lesions of the gastric mucosa in 81.25% (13 of 16 individuals) rats. The degree of ulceration (a quantitative indicator in points) in terms of one animal was 6.60 points, and the number of destruction - 5.81. As a result, the Pauls index was 5.36.

Preliminary single administration of test drug to the stomach before their immobilization was manifested by ulceration of the gastric mucosa in 50.00% of animals (in 8 out of 16 animals), the degree of ulceration and the number of destruction in terms of one rat, respectively, amounted to 4.13 points and 2.8. The Pauls index with a reliable degree of this indicator ($p < 0.05$) numerically decreased to 2.07 ± 0.43 .

From graphical indicators, it was found that a single administration of butadione causes, with this formulation of experience, pronounced changes in the morphology of the stomach in control rats. In a macroscopic assessment of the state of the gastric mucosa, the majority of visible ulcerative lesions in terms of one rat was evaluated at 5 points ($\bar{A} = 4.18 \pm 0.71$), there were fewer small ulcers, estimated at 1 point ($\bar{A} = 3.31 \pm 0.78$). Large ulcers with a score of 10 points were not registered in any animal in the control group.

In the experimental group of animals, the drug "Sorbent" was once introduced into the cavity of the stomach at a dose of 600 mg/kg body weight. According to the results, when "Sorbent" was administered in response to the subsequent administration of butadione, the number of small ulcers, estimated at 1 point, decreased 1.30 times, and the number of large ulcers, estimated at 5 points, decreased 1.80 times. Of particular interest are the results of the numerical expression of an integral indicator that reflects the area and degree of ulcerative lesions - the Pauls index. In the experimental group, its values were equal to 12.30 ± 2.17 , while in the control intact group of animals the introduction of the developed enterosorbent was 22.75 ± 4.03 . The decrease in

these indicators was justified by statistical reliability ($p < 0.05$) and amounted to 45.90%.

Three-day administration of butadione to the control group of animals at a dose of 100 mg per kg of body weight contributed to a more pronounced ulceration of the gastric mucosa than with a one-day intra-abdominal administration of butadione at a dose of 200 mg/kg of body weight. The relatively long-term administration of butadione contributed to the occurrence of large ulcers with a length of 10 or more mm in 6 rats (37.50%). These ulcers, given the large lesion area, were rated at 10 points. In addition, two very extensive ulcerative surfaces were revealed in 3 of 6 rats on the gastric mucosa.

A real reduction in the number of butadione ulcerative lesions was seen in the experimental group of white rats. Since their development was to some extent restrained by the enteral prescriptions of the studied "Sor bent". It should be noted that large ulcers developed in response to the introduction of butadion in only 4 individuals from the group of 16 animals, i.e. 25% of the total number of rats taken in the experiment. Compared with the results of ulceration from butadione in the control, the Pauls index in the experimental group decreased from 28.10 to 21.90 ($p = 0.05$).

In the intact group of animals, 12 rats survived out of 30 control individuals by the administration of the "Sor bent" preparation. All surviving animals in the glandular part of the stomach recorded characteristic ulcers of a rounded shape, the size of a pinhead and lip-shaped edges. After a 12-fold administration of butadione during the dissection of the stomach, its mucous membrane was characterized by the presence of a significant number of large ulcers, estimated at 5 points. The number of ulcers related to 10 points was detected in a much smaller volume. For this reason, the numerical indicator of the Pauls index reaches such a significant value - 44.70, and the number of destruction in terms of one animal in this group was 12.25.

Multiple dosed forced intragastric administration of the "Sor bent" preparation, first of all, lowered the mortality of experimental rats. So, if in the control group of 30, 18 (60%) died, then with a course administration of 30 rats, 14 (47%) died. Among surviving animals, the number and area of ulceration significantly decreased, and the Pauls index decreased to 13.70 ± 3.10 ($p < 0.001$).

Thus, on all models of ulcerous lesions caused by butadione, the enteral administration of the "Sor bent" preparation reduces the incidence of ulcers and reduces the area of ulcerative lesions in laboratory animals.

It was found that with the intragastric administration of a therapeutic dose of "Sor bent" dioctahedral smectite with subsequent injection of reserpine, the Pauls index significantly decreased. In confirmation of the above, the established Pauls index in the control (9.10 ± 0.07) exceeded the identical indicator in the experiment (5.30 ± 1.03) by 1.7 times ($p < 0.01$).

It was revealed that butadion in the control caused significant ulcerative lesions of the walls of the stomach of guinea pigs. The persuasiveness of the above is confirmed by the high level of the Pauls index, which reaches 22.75 ± 3.00 in numerical terms. In turn, this circumstance was caused by equal values of indicators of a large number of ulcers (in

terms of one animal), estimated at 1 and 5 points. Two animals also formed ulcerative surfaces, estimated at 10 points.

Forced intragastric administration of the "Sor bent" preparation in a therapeutic dose was accompanied by a decrease in qualitative and quantitative indicators reflecting the severity of ulcerative lesions. Its enteral administration reduced the number of ulcerative lesions, estimated at 5 points: from 3.60 to 0.90 in terms of one animal. The number of ulcerative lesions, estimated at 1 point, did not change significantly: from 3.60 in the control injection of butadiene to 3.30 with the administration of the drug "Sor bent" immediately before the injection of butadione. These indicators are reasonably confirmed by a decrease in the degree of the Pauls index to 7.80 ± 1.44 ($p < 0.01$).

Nevertheless, positive results were obtained experimentally on a different type of animal with the preliminary administration of "Sor bent" (dioctahedral smectitis): the severity of ulcerative lesions was reduced and there was no irritation of the gastric mucosa.

IV. CONCLUSION

In the experiment on white rats and guinea pigs, under conditions of simulated ulcerative lesions of various genesis, the developed dioctahedral smectite "Sor bent" not only did not have a locally irritating effect and did not enhance the synergistic effect of chemical compounds that cause experimental ulcerative pathology, but in the vast majority of cases it had a pronounced anti-ulcer effect, statistically significant when assessed by the integral anti-ulcer index - the Pauls index.

The information obtained as a result of the studies allows us to expand the indications for the use of the drug "Sor bent", made on the basis of bentonite-like clays. It can be indicated in patients with gastric ulcer, ulcerative colitis as a drug with pronounced anti-ulcer activity in the experiment.

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