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THERAPEUTIC EFFICIENCY OF SORBENTS MODIFIED BY HYDROXIC ACIDS DURING ANIMAL EXPERIMENTAL POISONING WITH IVERMECTIN

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Abstract

The development of modified sorbents combining the adsorption properties of the initial porous material and the biological activity of the modifiers is a current issue of sorption therapy. The purpose of the study was to develop a method for modifying carbon sorbents with hydroxyacids and to conduct a comparative assessment of their effectiveness upon poisoning animals with ivermectin. A granular carbon enterosorbent with a specific surface area of 300-400 m^2/g was the matrix for the preparation of biospecific sorbents, glycolic acid (50 wt.%, manufactured by Merk Schuchardt OHG, Germany) and lactic acid (80 wt.%, produced by MOSREACTIVE, Russia) and a copolymer thereof were used as modifiers. To study the morphology and surface topography of the obtained samples, scanning electron microscopy (JSM 6460LV, JEOL Ltd, Japan) was used. The therapeutic efficacy of the modified sorbents was measured in 5 groups (10 animals each) of outbred adult white rats weighing 180-200 g. During 5 days animals of different groups received one of the modified sorbents in doses of 0.3 g/kg upon acute intoxication with Baymec® (1 % solution of ivermectin, Bayer Animal Health GmbH, Germany; manufactured by Federal Centre for Animal Health, Russia). The controls were intact and intoxicated animals. At the end of the experiment, blood was taken from all animals for biochemical studies, as well as histological examination of organs and tissues was performed post mortem. Electron microscopic examination showed that upon modification, the size and shape of the granules of the initial sorbent are preserved, but surface topography and morphology change. The results of in vivo experiments showed varying degrees of efficiency of enterosorption in rats when modified sorbents were applied to the animals intoxicated with ivermectin-containing Baymec® preparation. Creatinine varied from 40.86±0.66 μmol/l ($p < 0.0001$) for the sorbent with lactic acid to 82.32±2.74 μmol/l ($p = 0.4698$) for the sorbent with glycolic acid; in intoxicated animals, the creatinine level reached 87.00±5.52 μmol/l, $p < 0.0001$). Intoxication was accompanied by an increase in the total protein content in blood of rats (73.08±0.96 g/l, $p = 0.0001$), mainly due to globulins. At the same time, the concentration of urea decreased (2.44±0.05 mmol/l, $p = 0.0001$) but the content of total bilirubin increased (1.80±0.07 μmol/l, $p = 0.0379$), while the level of creatinine increased 2.3 times compared to intact animals. Post-mortem analysis indicated the polytropic nature of the drug. In animals, acute congestive hyperemia of the internal organs and the brain was found. Under the epicardium, petechial hemorrhages were noticeable. There were also marked the heart dilatation, granular dystrophy of cardiomyocytes, protein-fatty degeneration of the liver, emphysematous changes in the lungs, congestive hyperemia and hemorrhages in the kidneys. In the gastrointestinal tract signs of acute catarrh were prevailing. The most distinct corrective effect of enterosorption was noted when using a sorbent

modified with lactic acid oligomer. The research results confirm the prospects for the development of bifunctional sorbents as well as expand the possibilities of sorption therapy.

Keywords: ivermectin, Baymec®, modified enterosorbents, hydroxyacids, lactic acid, glycolic acid, clinical pathology, blood biochemistry, histopathology, intoxication, sorbent therapy

Sorption therapy is a promising area of detoxification measures. A distinctive feature of biospecific sorbents is a combination of the adsorption properties of the initial porous material and the biological activity of the modifiers. Chemical modification of the surface of sorbents can increase the selectivity of sorption. Known methods of chemical modification include immobilization of enzymes, polyenzyme complexes, cell organelles [1-4], incorporation of heteroatoms (Si, N), functional groups (−NH2, −COOH, −C = O, phosphonic acid residues) or carriers of functional groups followed by treatment of the modified sorbents with various reagents and protein solutions. Currently, interest in polymer compounds is growing [5-9]. Oligo- and polymers of hydroxy acids (glycolic and lactic) can be used as modifiers of carbon sorbents. They are approved for use in medicine, since they do not have pronounced toxicity, are compatible with body tissues and biodegradable [10-14]. An important advantage of immobilizing acids on a carbon matrix is the preservation of the antimicrobial properties of immobilized compounds and the high adsorption capacity of the carbon material [15-19]. Upon exogenous poisoning, a change in the pH in the gastrointestinal tract during acid desorption is of great importance, since this significantly affects the rate of absorption and elimination of toxicants.

In this work, the feasibility of a new carbon sorbent modified with lactic acid for enterosorption upon acute poisoning with ivermectin has been proved for the first time using a rat model (outbred white rats). Our findings prove the advantages of the proposed modifier, as compared to glycolic acid and a copolymer of these hydroxy acids.

Our subjective was to develop a method for modifying the carbon sorbents with hydroxy acids and to compare their therapeutic efficacy upon ivermectin poisoning.

Materials and methods. Novel carbon sorbents were synthetized at the Institute of Hydrocarbon Processing SB RAS (Omsk) via modification of granular carbon enterosorbent (300-400 m^2/g) glycolic acid (GA, 50 wt.%, Merk Schuchardt OHG, Germany), lactic acid (MK , 80 wt.%, MOSREACTIVE, Russia), and their copolymer according to an original methodology.

The morphology and surface topography of the obtained sorbents were investigated by scanning electron microscopy (JSM 6460LV, JEOL Ltd, Japan) with vacuum coating of specimens with a gold film 10-15 nm thick (voltage 15-20 kV, current 10-30 mA to ensure contrasting). Five to ten granules of sorbents with different modifiers were examined.

Therapeutic efficacy of the modified sorbents was evaluated using 50 outbred mature white rats with a body weight of 180-200 g. Animals were analogues in age, gender and body weight. For simulation of acute poisoning with ivermectin the Baymec® preparation (Federal Center for Animal Health, Vladimir) containing 1% ivermectin was applied. Prior to the experiment, the rats were clinically supervised during a 2-week quarantine in order to exclude infectious diseases. Throughout the entire period, the animals were fed a full-grain cereal mixture according to common laboratory standards.

The rats were assigned into five groups of 10 animals each. In the control (group I), intact rats were not subjected to any manipulations. The rest animals were injected subcutaneously with Baymec® at a dose 10 times higher than the therapeutic dose. In group II, no sorbents were administered, rats of group III, IV and

V received sorbents modified with glycolic acid, lactic acid, and with a copolymer of glycolic and lactic acids, respectively. All enterosorbents were administered as bread boluses (0.3 g/kg body weight) 2 times a day for 5 days, starting from 1 day after the date of experimental poisoning.

The rats were weighed before and after the experiment. At the end of the experiment, blood was sampled from all animals for biochemical analysis, and then they were euthanized. Fragments of internal organs, mesenteric lymph nodes and the brain were collected for histological examination.

Pathological material was fixed in 4% neutral formaldehyde and Carnoy's solution, and paraffin-embedded to make sections (Rotational Microtome Labo-Cut 4055, Slee, Germany). To investigate histomorphological features, the specimens were stained with Hansen hematoxylin and eosin, and also as per Van Gieson [20]. Glycogen and neutral glycosaminoglycans (neutral GAGs) were detected by Schiff (PAS) reaction according to Shabadash method [21]. Specimens were studied using light microscopy (Altami Bio, Altami Russia, zoom Ч300, Ч600).

The principles set forth in the European Convention for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes (Strasbourg, March 1986) and the Declaration of Helsinki (Helsinki, June 1964) were observed.

Statistical processing was done using Statistica 6.0 software (StatSoft, Inc., USA). The data were checked using the Shapiro-Wilk normality *W*-test, after which the Student *t*-test was used for independent samples. Differences were deemed statistically significant at $p < 0.05$. The results were presented as arithmetic mean and standard error of the mean ($M \pm SEM$).

Results. The matrix for the preparation of biospecific sorbents was a granular carbon enterosorbent (CE) with a mesoporous structure, high chemical purity, biocompatibility, and specific surface area of 300-400 m^2/g. The modifiers should be safe, soluble, having reactive groups, capable of fixing on the sorbent surface and biodegradable [22]. Glycolic and lactic acids fully possess these properties [23] and, therefore, were used as surface modifiers of the carbon sorbent.

A two-step matrix modification with a glycolic acid oligomer includes i) the carbon sorbent impregnation with an aqueous solution of glycolic acid (50 wt%) for 8 hours in air at 20-25 °C (sorbent:modifier as 1:2), and ii) heat treatment in a sand bath at 105±5 °C and 195±5 °C for 1 h followed by heating at 225±5 °C for 5 h. The CE-GA modified carbon sorbent contains 12-15 wt% GA oligomer, has a specific surface area of 180-210 m^2/g, and provides a low pH of saline solution (pH 4.3-4.6) after a 1-day contact with a specimen.

Modification of the carbon sorbent with lactic acid oligomer also was a two-step procedure which includes i) impregnation with an aqueous solution of lactic acid (50 wt%) for 24 h in air at 20-25 °C (sorbent:modifier as 1:2), and ii) heat treatment in a sand bath at 130±5 °C for 2 h and at 150±5 °C for 4 h, than at 170±5 °C for 18 h in a tube furnace with a desiccant in an argon stream. The CE-LA modified carbon sorbent contains 25-30 wt% LA oligomer, has a specific surface area of 30-60 m^2/g, and provides a low pH of saline solution (2.3-2.6) after a 1-day contact with a specimen.

CE modification with GA-LA copolymer was a tree-step and includes i) the sorbent impregnation with aqueous solution of hydroxy acids (GA:LA 70:30 wt%) for 24 h at room temperature (sorbent:hydroxy acids as 1:2), ii) drying in a sand bath for 1 h at 103-107 °C, and iii) a 14-h heat treatment at 160-170 °C in a sand bath with a molded NaA-U zeolite (Ishimbay Specialized Chemical Catalyst Plant LLC, Republic of Bashkortostan) as a desiccant, followed by 7-h

heating in tube furnace with zeolite at 170-180 °C in an argon stream.

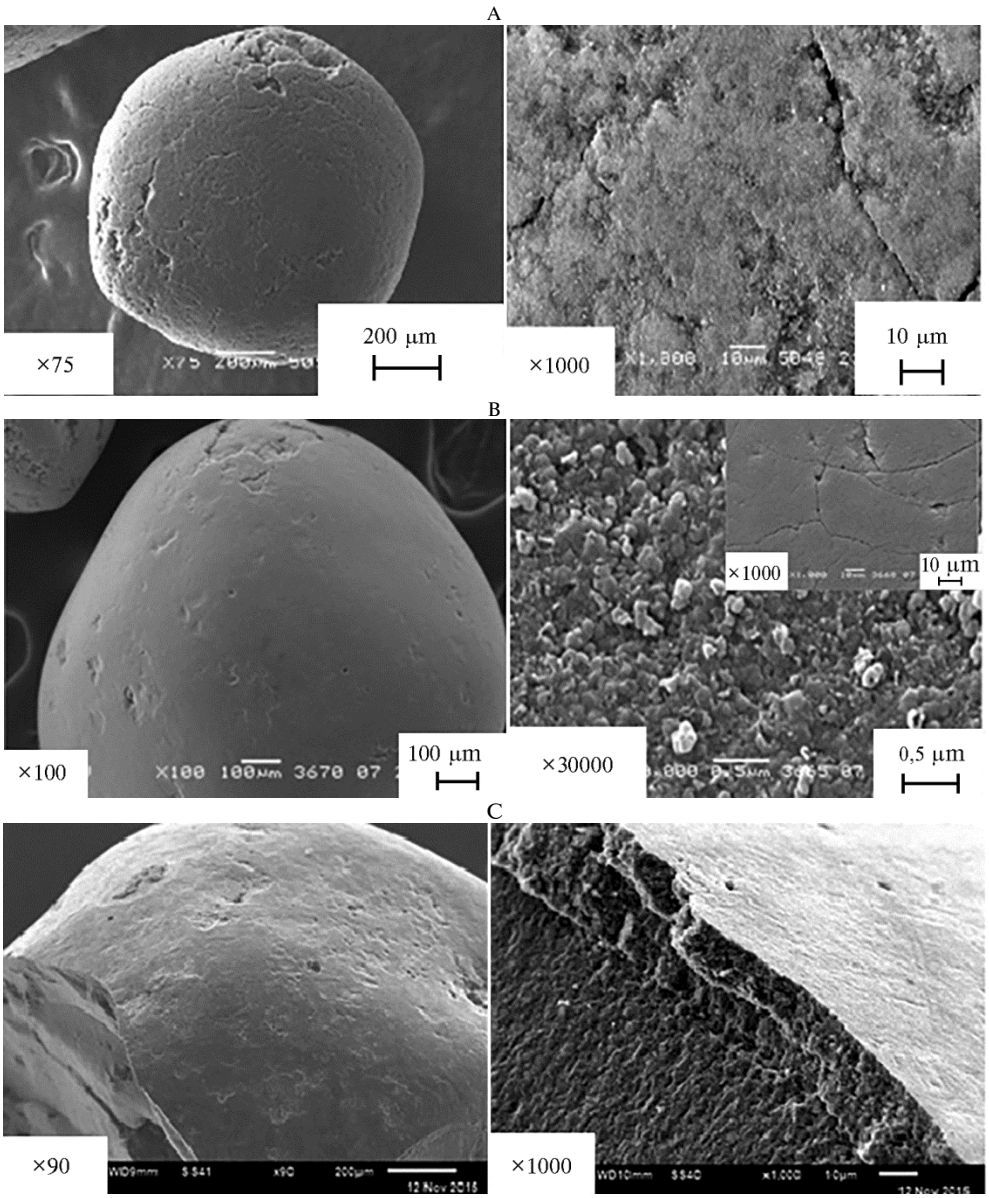

Fig. 1. Granules (left) **and chips** (right) **of sorbents:** A — carbon sorbent, B — carbon sorbent modified with glycolic acid, C — carbon sorbent sample modified with lactic acid (scanning electron microscopy with gold coating, JSM 6460LV, JEOL Ltd, Japan).

Several papers describe methods for generation of polyglycolic, polylactic acids and their copolymer by heating with compounds based on antimony, zinc, tin, etc., as catalysts [24, 25]. All these methods of the synthesis of polymers and copolymers of hydroxy acids are not safe when producing materials for medical and veterinary purposes, since they involve the use of organic solvents and heavy metal-based catalysts that are toxic to the human and animals. Our methods for producing modified sorbents does not use such chemical compounds.

Electron microscopy showed that upon modification, the size and shape of the granules of the initial sorbent are retained. However, the relief and surface morphology of the modified samples noticeably change. In contrast to the initial

sorbent (Fig. 1, A), small polymer particles of various shapes smaller than 1 μm in size are observed on the carbon surface of the samples modified with the glycolic acid oligomer (see Fig. 1, B). They are distributed locally, mainly in cracks, pores, and other surface defects. The LA modifier formed an uneven polymer film screening the carbon surface (see Fig. 1, B).

In vivo tests showed varying efficiency of modified sorbents in enterosorption upon acute intoxication of rats with the ivermectin-containing Baymek® drug. Clinical symptoms of acute intoxication developed in rats within 2 hours after poisoning simulation. Tousled fur and hypersalivation indicated worsening of the rats. Over time, the response to sound and tactile stimuli intensified. Periods of anxiety gave way to oppression, a decrease in motor activity. These signs are due to the mechanism of action of the drug. The injected ivermectin interacts with glutamate GABA-ergic receptors of the Cl^- channels and receptors of glycine-activated channels, which leads to hyperpolarization of postsynaptic membranes and impaired interneuron transmission of impulses [26-28].

A day after the start of the experiment, intoxicated animals remained sedentary, with dull hair and, slight hypersalivation and reduced appetite. Rats of test groups (III-V) receiving sorbents began to show interest in food faster and performed grooming. In 48 h after the start of the experiment and until its end, there were no significant differences in the behavior and clinical signs in animals upon enterosorption.

The behavior of intact animals (control) remained unchanged throughout the observation period. Comparing the data of control weighings did not reveal statistically significant differences at the beginning and at the end of the experiment.

The blood tests (Table) showed that rat intoxication by Baymec® led to an 11.9% ($p = 0.0001$) increase in the total blood protein in and a significant increase in the globulin index (by 17.86%, $p = 0{,}0002$). The urea concentration decreased (by 29.89%, $p = 0.0001$), while the total bilirubin level increased (by 26.76%, $p = 0.0379$), indicating the hepatotoxic effect of Baymec® [29]. However, an increase in creatinine concentration was more significant (a 2.3-fold). These changes indicate a decrease in protein catabolism and impaired renal filtration. At the same time, the activity of alanine aminotransferase in intoxicated rats decreased. The LA-enterosorbent contributed to a 7.5% ($p = 0.0014$) increase in the protein concentration compared to this indicator in the rats intoxicated without correction. The sorbents modified with hydroxy acids affected the total blood protein content in rats ambiguously.

The sorbent modified with LA-GA, on the contrary, reduced the blood protein concentration by 17.8% compared to rats intoxicated with Baymec®. Moreover, the first of the sorbents offered (with lactic acid) equally increased the concentration of albumin and globulins, the second one (with glycolic acid) predominantly decreased the globulin fractions, but did not decrease the creatinine concentration as much as the LA-sorbent. The GA-sorbent did not cause statistically significant changes in creatinine level compared to that in the intoxicated animals which were not treated.

All sorbents declined the activity of aspartate aminotransferase (AST) and alanine aminotransferase (ALT). However, for making clinical decisions, it is of fundamental importance that the ALT activity in intoxicated rats was lower than in intact rats, although the increase in blood alanine aminotransferase levels more often indicates hepatotoxic effects [30, 31].

Blood biochemical parameters of outbred white rats intoxicated with Baymec® when corrected with modified carbon sorbents (M±SEM, lab tests)

Total protein, g/l	Albumins, g/l	Globulins, g/l	Urea, mmol/l	TB, rmol/l	Creatinine, rmol/l	Glucose, mmol/l	AP, U/l	AST, U/l	ALT, U/l	Ca, mmol/l	P, mmol/l	Fe, rmol/l	Ca, mmol/l
Control (n = 10)													
65.3±0.36	27.58±0.69	37.72±0.86	3.48±0.13	1.42±0.13	38.22±2.03	5.60±0.28	433.22±46.07	148.88±2.49	79.64±5.23	3.08±0.03	2.82±0.11	40.56±2.88	8.64±0.37
Rats intoxicated with Baymec® without correction													
73.08±0.96	28.62±0.44	44.46±0.52	2.44±0.05	1.80±0.07	87.00±5.52	5.52±0.10	394.56±6.26	155.76±1.70	58.62±0.16	2.84±0.02	2.40±0.20	37.34±0.55	8.82±0.12
$p_к$ = 0.0001	$p_к$ = 0.2424	$p_к$ = 0.0002	$p_к$ = 0.0001	$p_к$ = 0.0379	$p_к$ < 0.0001	$p_к$ = 0.7979	$p_к$ = 0.4298	$p_к$ = 0.0745	$p_к$ = 0.0039	$p_к$ = 0.0007	$p_к$ = 0.1094	$p_к$ = 0.3046	$p_к$ = 0.6576
Rats intoxicated with Baymec®:													
upon correction with sorbent modified with glycolic acids (n = 10)													
73.32±0.94	29.42±0.47	43.90±0.88	3.74±0.10	2.04±0.22	82.32±2.74	7.58±0.37	339.88±23.01	122.84±0.83	49.30±2.52	2.94±0.05	2.28±0.10	52.86±0.86	9.98±0.42
$p_б$ = 0.8635	$p_б$ = 0.2504	$p_б$ = 0.6023	$p_б$ < 0.0001	$p_б$ = 0.3344	$p_б$ = 0.4698	$p_б$ = 0.0007	$p_б$ = 0.0510	$p_б$ < 0.0001	$p_б$ = 0.0062	$p_б$ = 0.1151	$p_б$ = 0.6143	$p_б$ < 0.0001	$p_б$ = 0.0315
upon correction with sorbent modified with lactic acid (n = 10)													
78.56±0.63	31.20±0.46	47.36±0.88	4.16±0.09	0.89±0.01	40.86±0.66	8.06±0.10	194.88±2.89	120.38±0.76	53.02±1.20	3.16±0.05	2.12±0.03	54.22±0.43	9.06±0.16
$p_б$ = 0.0014	$p_б$ = 0.0039	$p_б$ = 0.0228	$p_б$ < 0.0001	$p_б$ < 0.0001	$p_б$ < 0.0001	$p_б$ < 0.0001	$p_б$ < 0.0001	$p_б$ < 0.0001	$p_б$ = 0.0017	$p_б$ = 0.0005	$p_б$ = 0.2109	$p_б$ < 0.0001	$p_б$ = 0.2805
upon correction with sorbent modified with copolymer of glycolic and lactic acids (n = 10)													
60.10±0.38	26.48±0.43	33.62±0.32	3.76±0.12	0.81±0.01	66.82±2.81	2.80±0.23	466.80±46.51	66.02±17.41	57.60±4.73	2.76±0.04	3.08±0.23	37.68±1.13	10.62±0.46
$p_б$ < 0.0001	$p_б$ = 0.0085	$p_б$ < 0.0001	$p_б$ < 0.0001	$p_б$ < 0.0001	$p_б$ = 0.0116	$p_б$ < 0.0001	$p_б$ = 0.1624	$p_б$ = 0.0008	$p_б$ = 0.8350	$p_б$ = 0.1265	$p_б$ = 0.0599	$p_б$ = 0.7941	$p_б$ = 0.0058

Note. The t-test is applied for independent samples. $p_к$ — significance level compared to the control group, p_b — significance level compared to the group intoxicated with Baymec®; TB — total bilirubin, AP — alkaline phosphatasea, AST — aspartate aminotransferase, ALT — alanine aminotransferase.

LA-sorbent caused a maximum increase in the blood iron (by 45.2% at $p < 0.0001$) and calcium (by 11.26% at $p = 0.0005$) levels in rats but did not significantly affect the phosphorus concentration. The bilirubin concentration was the lowest while the glucose concentration was the highest.

Analysis of post-mortem changes in rats subjected to Baymec® acute intoxication indicated the polytropic nature of the drug action, noted by other authors in their study of adverse systemic effects of ivermectin [32].

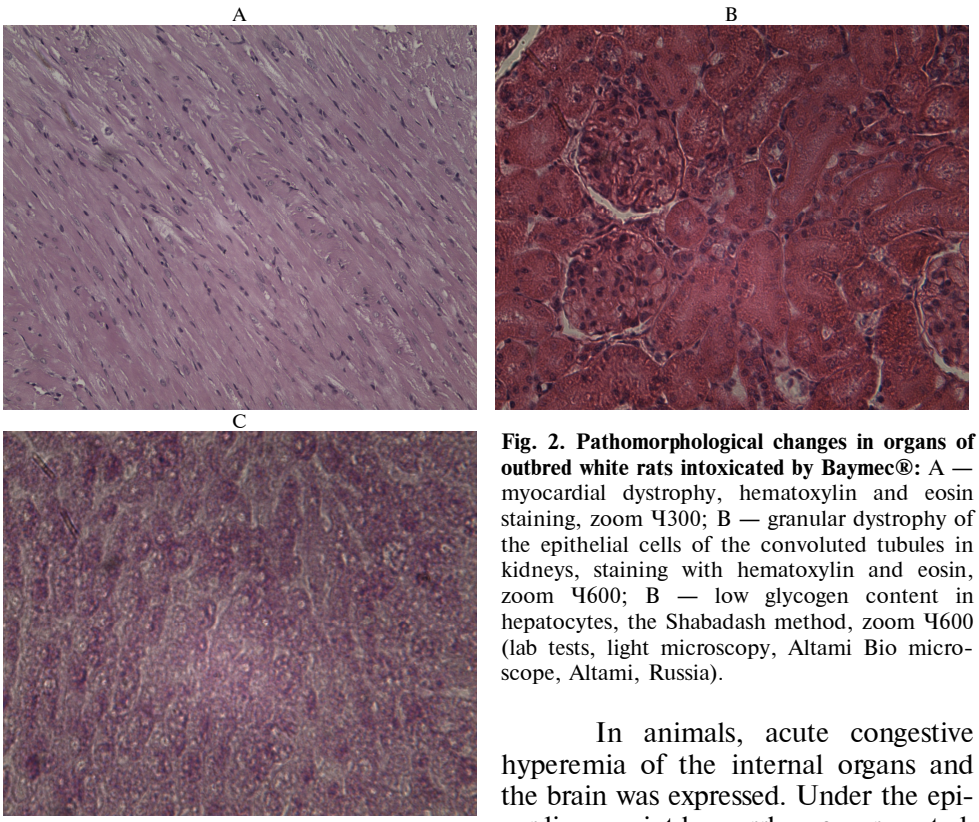

Fig. 2. Pathomorphological changes in organs of outbred white rats intoxicated by Baymec®: A — myocardial dystrophy, hematoxylin and eosin staining, zoom Ч300; B — granular dystrophy of the epithelial cells of the convoluted tubules in kidneys, staining with hematoxylin and eosin, zoom Ч600; B — low glycogen content in hepatocytes, the Shabadash method, zoom Ч600 (lab tests, light microscopy, Altami Bio microscope, Altami, Russia).

In animals, acute congestive hyperemia of the internal organs and the brain was expressed. Under the epicardium, point hemorrhages were noted. The heart was enlarged, its cavities were filled with blood. Myocardium had a grayish tint. Histological examination showed pronounced swelling of muscle fibers with a loss of transverse striation of cardiomyocytes (Fig. 2, A). Glycogen content in cardiomyocytes decreased.

The kidneys had a red-brown color with light gray patches. Their capsule was easily removable. Microscopic examination revealed hyperemia of the kidneys, and hemorrhages in the medulla. The gaps of the convoluted tubules were narrowed and contained an oxyphilic colored mass. The cytoplasm of the proximal nephron epithelial cells had a granular structure, part of the nuclei in the epithelial cells were in a state of pycnosis or lysis (see Fig. 2, B). The liver was unevenly colored. Microscopy showed a sharp decrease in the glycogen content in hepatocytes (see Fig. 2, B), pronounced blood-filled vessels with expanded intralobular sinusoidal capillaries, hepatocytes were in a state of protein-fatty degeneration. The nuclei of many hepatocytes were pyknotic or lysed (Fig. 3, A).

The lungs of the rats were unevenly colored, with patches of red and pale pink. A histological examination revealed focal hemorrhages, overflow of blood vessels with the blood. In areas of emphysema, stretching of the alveoli, thinning and rupture of their walls were observed. In some animals, infiltrates, mainly consisting of lymphoid cells, were noted around the bronchi. The surface of the

bronchial epithelium was covered with a significant amount of mucus.

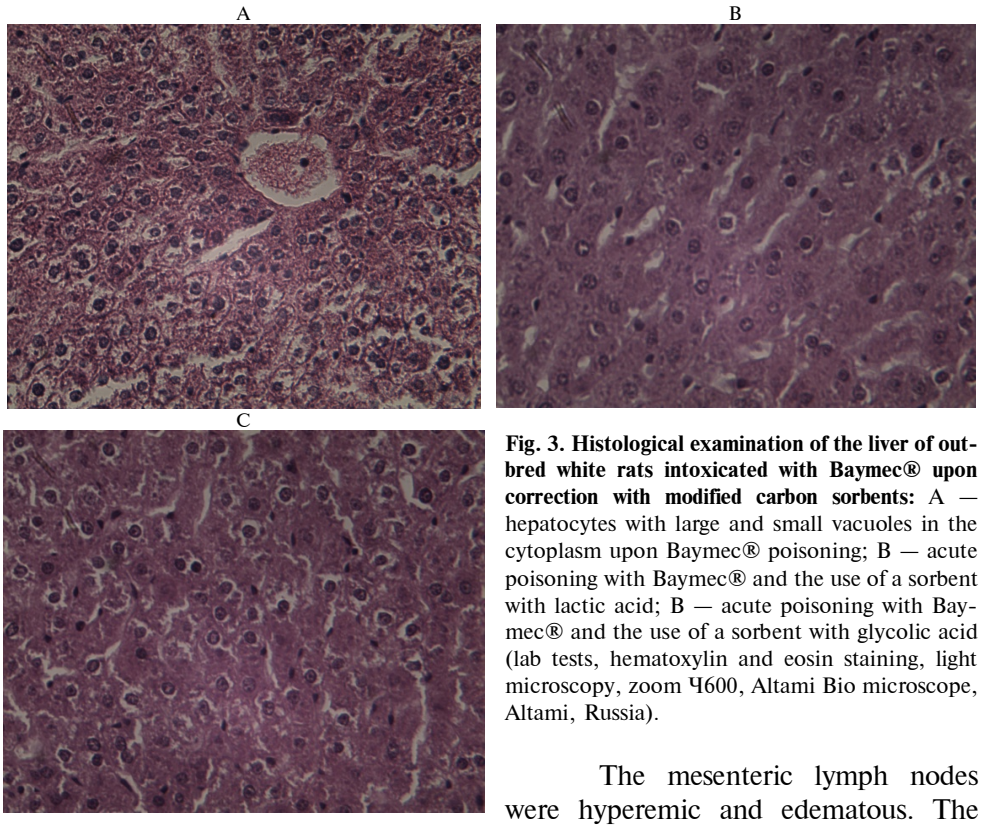

Fig. 3. Histological examination of the liver of outbred white rats intoxicated with Baymec® upon correction with modified carbon sorbents: A — hepatocytes with large and small vacuoles in the cytoplasm upon Baymec® poisoning; B — acute poisoning with Baymec® and the use of a sorbent with lactic acid; B — acute poisoning with Baymec® and the use of a sorbent with glycolic acid (lab tests, hematoxylin and eosin staining, light microscopy, zoom Ч600, Altami Bio microscope, Altami, Russia).

The mesenteric lymph nodes were hyperemic and edematous. The mucous membrane of the stomach and intestines was swollen, reddened, with hemorrhages. On the surface of the mucous membrane, mucus is detected containing a significant amount of desquamated epithelial cells.

Application of GA-, LA- and GA-LA-modified enterosorbents decreased the intensity of pathological processes in animals. A comparative pathomorphological study of rats subjected to Baymec® intoxication and pharmacocorrection allowed us to conclude that the LA-modified sorbent has a more pronounced detoxifying effect. Histological examination of the liver when using this sorbent showed only signs of granular dystrophy (see Fig. 3, B). Enterosorbents with glycolic acid and a hydroxy acid copolymer did not completely eliminate necrobiotic changes in hepatocytes (see Fig. 3, C), as well as signs of congestive hyperemia of organs, which explained the revealed changes in the metabolic profile of animals.

The noted differences in the action of sorbents modified with hydroxy acids are probably due to a lower pH of the LA-sorbent. Ivermectin undergoes biotransformation in the liver with the participation of cytochrome P450, mainly its isoenzyme CYP3A4, the oxidative activity of which increases significantly in an acidic environment [33].

Thus, for the first time, methods have been developed for modifying the surface of a carbon sorbent with glycolic and lactic acid oligomers, as well as their copolymer. The technology is based on sorbent impregnation with aqueous solutions of hydroxy acids or their mixture and prolonged heat treatment (polycondensation) without the use of toxic catalysts and organic solvents. This made it possible to obtain bifunctional sorbents combining the adsorption properties of the matrix and the biological activity of the modifiers. Our findings confirm the

therapeutic efficacy of sorbents modified with hydroxy acids for the intoxication of animals with ivermectin containing Baymec® drug. The sorbent modified with lactic acid expresses the most pronounced detoxifying effect. With its use, the concentration of blood globulins maximally increases, the total bilirubin is halved, and mineral metabolism is activated. Histological investigation revealed only slight dystrophic changes in parenchymal organs after enterosorption. The use of the modified sorbents significantly increases the effectiveness of detoxification and provides new possibilities for sorption therapy.

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