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STUDY OF SAFETY AND SPECIFIC ACTIVITY OF THE COMPOSITION OF THE GEL "BENZPAI-S"

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Abstract:
Studies have been conducted to study the toxicological effects: safety and specific anti-inflammatory action (on the stomatitis model) and wound-healing activity (skin wounds) of a new combined dosage form in the form of a gel based on benzketozone and papaya extract. Experiments were conducted on oral wounds and cutaneous wounds in an experiment on rats. The results obtained in studying the effect of the new composition of the Benzpay gel indicated that the gel under study has a wound-healing effect, which reduces the time of cleansing and healing of wounds by 4-8 days. A comparative analysis of the wound-healing effect of the new composition of the Benzpay gel was carried out with the comparison drugs Asepta and Salcoseryl gels, the advantage of the former was revealed. The developed gel can become an alternative means in the treatment and prevention of dental diseases with a minimal risk of side effects.

Keywords: Dental diseases, nonsteroidal anti-inflammatory drugs, phenylglycinic acid, benzketozone, papaya, genivitis, stomatitis.

Introduction

Dental diseases, including inflammatory processes in the oral cavity, such as stomatitis and genigivitis, remain a pressing problem among the population of Uzbekistan. According to WHO, about 60% of the adult population of the country suffers from oral diseases (1,2,3). One of the promising areas is the use of domestically developed drugs and biologically active substances based on natural and synthetic components.

A derivative of phenylglyoxylic acid, a domestic non-steroidal anti-inflammatory drug Benzketozone, was approved for use in the form of tablets (0.1 g of active substance) VFS 42 Uz - 0663-2003 and ointments (0.5% and 3%) FSP 42 Uz-0186-2007 by the Main Directorate for Quality Control of Medicines and Medical Equipment of the Ministry of Health of the Republic of Uzbekistan. 3% Benzketazole ointment in accordance with the order of the Ministry of Health of the Republic of Uzbekistan is approved for the treatment of inflammatory viral diseases (conjunctivitis, colpitis, as part of complex therapy (FSP 42 Uz - 0186-2007) (4.5). The effectiveness of the drug Benzketazole in clinical studies was evaluated in comparison with the steroid anti-

inflammatory drug 0.5%.Experiments on various animals have shown that benzketozone has high anti-inflammatory activity and low toxicity. It should also be noted the importance of using enzyme preparations for combination with non-steroidal anti-inflammatory drugs. Their enhancing effect is noted (6). The purpose of this study is to study the toxicological effects: acute toxicity as well as specific action: anti-inflammatory (on the model of stomatitis) and wound-healing activity (skin wounds) of a new combined dosage form in the form of a gel based on benzketozone and papaya extract.

Materials and methods of research

Dental gel - "Benzpay-S", aluminum tubes of 20 g, containing benzketozone 0.1 g, papaya extract 10 g ser. 10 09 24, developed and experimental laboratory samples were obtained at the Department of Organization of Pharmaceutical Production and Quality Management of the Tashkent Pharmaceutical Institute.

Combined gel "Asepta" containing propolis (comparative drug), ser. 12.01.21. manufactured by the pharmaceutical company JSC VERTEX, Russia. And gel "Salcoseryl" medicinal product manufactured by LEGACY PHARMACEUTICALS SWIZERLAND, GmbH (Switzerland).

The tests were conducted in the laboratory of the Institute of Bioorganic Chemistry of Pharmacology named after academician A.S. Sadykov.

General action and acute toxicity

The new composition of the combined gel "Benzpay-S" was carried out according to the Sanotsky method. To determine the parameters of acute toxicity, the Lichfield and Wilcoxon method was used (7). The study of acute toxicity of the drug was carried out on white outbred mice, males, weighing 20 ± 2.0 g, 5 animals in each group, a total of 25 mice were used. The dental gel was administered into the oral cavity, in doses of 2000, 2500, 3000, 4000 and 5000 mg / kg. The last two doses were fractionally after 1 hour.

All pharmacological studies were conducted on healthy adult animals (mice) that had been quarantined for at least 10-14 days. The general condition, behavior, and death of the animals were taken into account. The animals were observed hourly during the first day of the experiment in the laboratory, with survival during the experiment, general condition, possible convulsions, and death used as indicators of the functional state of the animals. Then, daily, for 2 weeks in vivarium conditions, the general condition and activity, behavioral features, frequency and depth of respiratory movements, condition of the hair and skin, tail position, changes in body weight, and other indicators were observed in animals of all groups. All experimental animals were kept in normal vivarium conditions at a temperature of 23-260C, on a common diet with free access to water and food. At the end of the experiment, the average lethal dose (LD50) was calculated and the toxicity class was determined (8.9).Statistical processing of the

obtained data was carried out using the computer programs Microsoft Office Excel and Staticrica 6.0.

In the second series of experiments, the specific anti-inflammatory activity of the new composition of the "Benzpai-S" gel was studied on the model of experimental stomatitis, corresponding to stomatitis, and the reparative activity on the model of alterative inflammation of skin wounds

Model of experimental stomatitis

The anti-inflammatory study was conducted on 25 guinea pigs weighing 300-350 g, 5 males in each experimental group. The model of inflammation of experimental stomatitis in animals was induced by introducing formalin at 0.15 ml of 25% formalin into the oral cavity of the pigs.

Treatment was carried out 2 hours after inducing the experimental model of the disease, by introducing Benzpay-S gel to the guinea pigs at a dose of 150 mg / kg. The dose was calculated according to the methodological recommendations for the development of drugs and biologically active substances [2]: 1600 mg per person: 70 kg = (mg / kg) x 39 (human coefficient): 6 (guinea pig coefficient) mg / kg. 1. The comparison drug was the combined gel "Asepta" containing propolis, and "Salcoseryl" a medicinal product, deproteizeddialezate from the blood of healthy dairy calves (in terms of dry matter) 4.15 mg, 20 g each. - anti-inflammatory and regenerating agent.

Systematically, under the conditions of the experimental study, on the 3rd, 7th, 14th and 21st days after oral administration of formalin, changes in the skin and oral mucosa were observed. The severity of the developing disease was judged by the general condition (general appearance, condition of the coat, discharge from the oral cavity, weight dynamics) and behavior (motor activity, aggressiveness, appetite). At the same time, the temperature of the guinea pigs was recorded using an electronic thermometer. In addition, peripheral blood was examined: hemoglobin content, g / l, the number of erythrocytes, 1012 / l and leukocytes 109 / l. on the hematology analyzer Diatron Ltd, 2002 (Hungary).

Model of alterative inflammation (model of skin wounds)

The skin wound model was performed on 25 rats (males) weighing 200-215 g, 5 animals in each experimental group. In rats anesthetized with sodium ethaminal (dose 50 mg/kg, i/p), under aseptic conditions, a skin wound of standard diameter and depth measuring 1.0 x 1.0 cm and 0.5 mm deep was applied to the previously depilated surface of the back skin. The wounds were left open [2,3].

Treatment was started immediately after reproduction of the experimentally induced pathology. The studied gels were administered until complete recovery (21 days). The control group of animals did not receive anything. The wounds remained open. The observation periods were 1, 3, 7, 14 and 21 days after the start of the experiment. The rate of wound healing was assessed:

1. by the presence of wound exudate and its cellular composition;
2. by the state of the adjacent tissues;
3. by the change in its area, mm^2.

Research results

Studies of the general action and acute toxicity of the Benzpay-S gel were conducted on healthy laboratory animals, white outbred male mice weighing 18-22 g. Before the experiment, the animals were kept in quarantine for 10 days. As indicated above, Fenzin-ob was administered in doses of 2000, 2500, 3000, 4000 and 5000 mg / kg. Studying higher doses is practically impossible.

Monitoring the condition of the animals after the administration of the drug was carried out for 2 days in laboratory conditions and 14 days in vivarium conditions.

During the observation of the animals, the main attention was paid to the general condition, relaxation of the tone of skeletal muscles and legs, the condition of the pupil of the eye, the reaction to external stimuli, as well as the consistency of the feces.

Experimental studies have shown that when the new composition of the Benzpai-S gels is introduced into the oral cavity at a dose of 2000-5000 mg/kg, no negative reactions or pathological changes are observed in animals. Analysis of the general condition of the animals showed that there were no significant differences in weight in mice that received the new composition of the Benzpai-S gels. All animals had a satisfactory appetite. No deaths were observed during the observation period (Table 1).

Table 1 Results of acute toxicity indices upon oral administration of the new composition of the "Benzpai-S" gel to mice

Drug, animal species, route of administration	floor	Doses mg/kg	Number of animals in a group / number of deaths	Th.D_{16} -m+m mg/kg		Th.D_{50} -m+m mg/kg	Th.D_{84} -m+m mg/kg	Generalaction
mice orally into the oral cavity	males	2000	6/0	-		≥5000		The drug does not cause any negative reactions or pathological changes in animals.
		2500	6/0					
		3000	6/0					
		4000	6/0					
		5000	6/0					

Consequently, the results of the study of acute toxicity of the new composition of the gel "Benzpai-S" showed that they belong to class V I of relatively harmless substances. LD50 in mice when administered into the oral cavity was more than ≥5000 mg / kg.

In the second series of experiments, the specific anti-inflammatory activity of the studied drugs and their effect on the treatment of experimental stomatitis were studied. Against the background of the model of experimental stomatitis induced by a 25% formalin solution, treatment was carried out in five groups: in the first group of animals,

placebo suppositories were administered, this group was the control, the second group of animals was administered the gel "Benzpai-S" at a dose of 150 mg / kg, the third and fourth groups treated experimental stomatitis with comparison drugs combined gel "Asepta" containing propolis, and dental gel "Salcoseryl". At the moment of formalin introduction into the oral cavity, all animals showed excitation, expressed in increased motor activity and increased respiratory rate. After 3-4 hours, the animals showed sharp aggression, which remained towards the control group until the end of the experiment. In the experimental animals of the control group, a day after the reproduction of the pathology, both the local inflammatory reaction and its general manifestations increased. The most striking symptoms during this period include gaping of the mouth, the mucous membrane of which is hyperemic and edematous. In the following days, local inflammatory reactions appeared, blood with mucus, mucous discharge and swelling were observed. On the 3rd-7th day of the study, bloody and purulent aphthae were observed. At the same time, the guinea pigs become pasty. On the 3rd day, diarrhea joined these symptoms in 70% of the animals, which was observed for 9-10 days. On the 14th-21st day of the experiment, the general condition of the animals was restored to the original. The duration of the experimental stomatitis process was observed up to 14-21 days in the experiment.

The treated animals tolerated the damaging effect of formalin on the oral mucosa better. The first clinical signs of the disease, as in the control group, appeared a day after the reproduction of the pathology.

In the experimental group, when using the new composition of the Benzpay-S gel and comparison drugs, the indicated changes were mild. Symptoms of local inflammation on the 3rd day of the experiment were more pronounced, but blood with mucus, swelling and discharge from the mouth, compared with animals in the control group, on average decreased by 1.5-2 times, bleeding was not noted and manifested in 50% of animals. However, after 5-7 days of treatment, the general condition of the treated animals improved. Guinea pigs showed their usual activity. On the 7th day of the study, the experimental animals showed a decrease in body weight, in the control group by 26%, and in the experimental groups with the introduction of the dental gel composition by 10% and the comparison drug for Asept and Solcoseryl 22.3% and 24.4%, respectively. On the 21st day, we observed in the control group and the group treated with the comparison drug the return of the body weight of animals to the initial values, and in the group treated with the composition of the Benzpay-S gel - on the 14th day. It should be noted that 2 out of 5 control animals died on the 6th-7th day, which was accompanied by a sharp drop in body weight. There were no deaths in the experimental groups (Table 2, Fig. 1).

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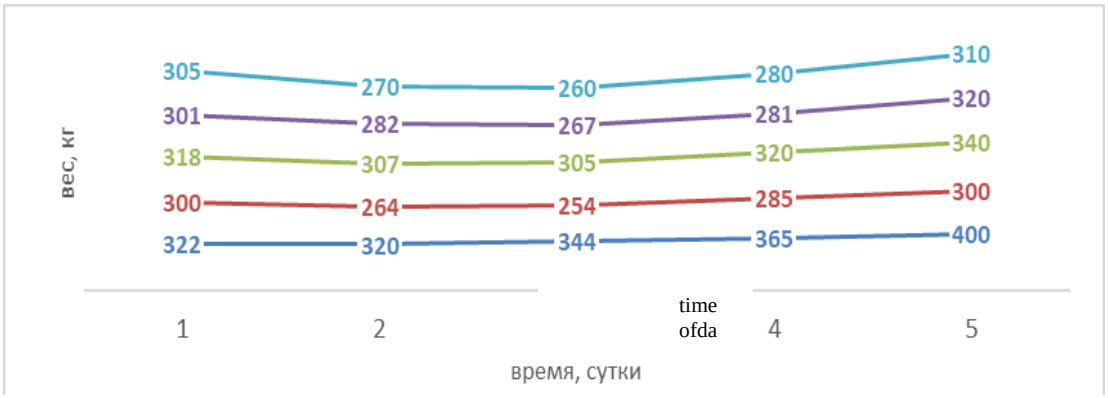
Table 2 The effect of the new composition of the gel "Benzpai-S" on the weight of guinea pigs with experimental stomatitis (M±m; n=5)

Experimental conditions, dose, mg/kg					
	Exodus	3	7	14	21
Intactanimals	322±16,3	330±12,4	344±12,5	365±14,5	400±15,0
Control (untreatedanimals)	300±16,3	264±12,4	254±12,5	285±14,5	300±15,0
New composition of the gel "Benzpai-S"	318±13,5	307±13,0	310±13,8	320±13,9	340±14,8
AseptaGel	301±13,5	282±13,0	267±3,8	281±13,9	320±14,8
Salcoseryl gel	305±13,0	270±11,0	260±3,1	280±13,4	310±13,0

*P≤ 0,05 in relation to the control group.



- Intact animals
- Control
- New composition of the gel "Benzpai-S"
- Gel Asepta
- Gel Salcoseryl

Fig. 1 Effect of the new composition of the gel "Benzpai-S" on the weight of guinea pigs with experimental stomatitis

Manifestations of the severity of local inflammation and general intoxication were an increase in rectal temperature by 0.6-0.80C on days 3-7. In groups of animals treated with the new composition of the Benzpai-S gel and the comparison drug, Asepta gel and Solcoseryl gel, the temperature reaction was smoothed out and short-lived. Its maximum peak did not exceed 0.30C (Table 3).

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Table 3. The effect of the new composition of the gel "Benzpai-S" on the rectal temperature of guinea pigs (M±m; n=5)

Experimental conditions, dose, mg/kg	Rectal temperature, 0C/days of study				
	Exodus	3	7	14	21
Control (untreatedanimals)	38,7±3,2	39,3±3,2*	39,5±3,2*	38,9±3,2*	38,5±3,2*
New composition of the gel "Benzpai-S"	39,0±3,2	39,1±3,2	39,3±3,2	38,9±3,2	39,0±3,2
Aseptagel	39,0±3,2	39,2±3,2	39,3±3,2	38,8±3,2	39,0±3,2

time of daytime of day*P≤ 0,05 in relation to the outcome

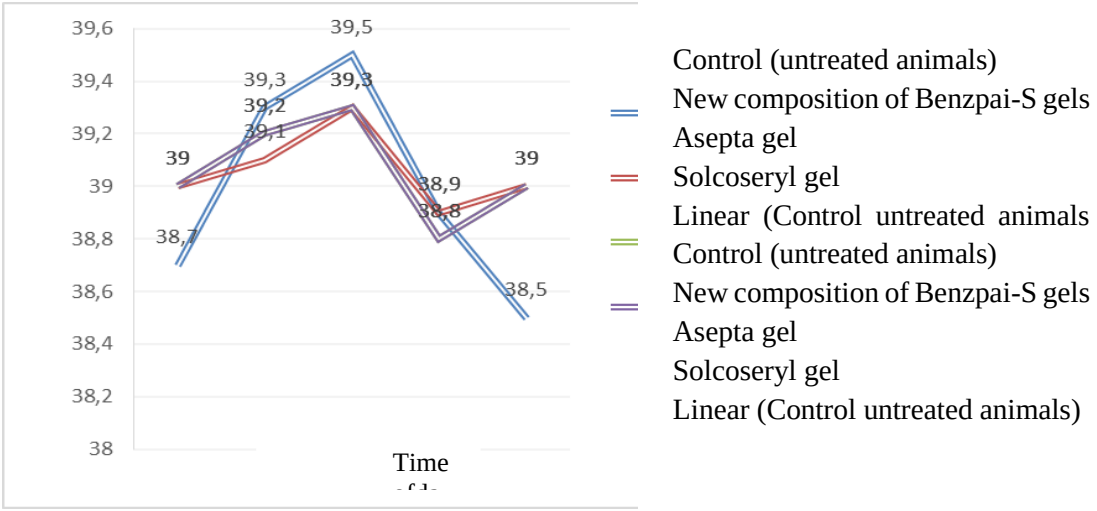

Fig. 2. The effect of the new composition of the Benzpai-S gel on the rectal temperature of guinea pigs with experimental stomatitis

Significant changes were observed in peripheral blood parameters. In the first three days after the pathology was reproduced, the number of leukocytes increased by 30%, the maximum leukocytosis was noted on the 7-14th day (65-100%).

As the inflammatory process increased, signs of erythropoiesis disorders were noted in all animals. In the control, after 7-14 days of the experiment, the hemoglobin level decreased by 21-10%, and the concentration of erythrocytes by 30-31%, and returned to normal on the 21st day.

Changes in the peripheral blood of the treated animals had some peculiarities, leukocytosis, as a rule, was less pronounced.

The hemoglobin level decreased to a lesser extent than in the control group of animals, and by the 7th day it reached the initial values. The concentration of erythrocytes did not decrease significantly (Table 4).

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Table 4. The influence of the new composition of the gel "Benzpai-S" on the morphological composition of the peripheral blood of guinea pigs with experimental stomatitis (M±m; n=5)

Indicators	Studydays				
	Intact	Control	Composition of gels "Benzpaya-S"	Aseptagel	Salcoserilgel
After 3 days					
Hemoglobin, g/l	10,5±0,4	8,8±0,3	10,6±0,2	9,3±0,2	8,9±0,5
Erythrocytes, 10 ^{12}/l	5,9±0,5	4,6±0,2	5,8±0,3	4,3±0,3	4,0±0,4
Leukocytes, 109/l	9,2±1,0	13,5±1,1	10,0±1,2	9,8±1,1	11,2±1,5
After 7 days					
Hemoglobin, g/l	11,0±0,4	8,2±0,3	11,3±0,2	9,3±0,2	9,0±0,1
Erythrocytes, 10 ^{12}/l	6,0±0,5	4,0±0,2	7,0±0,3	4,8±0,3	4,8±0,3
Leukocytes, 109/l	9,0±1,0	19,2±1,1	9,25±1,2	8,2±1,1	8,0±1,1
After 14 days					
Hemoglobin, g/l	11,0±0,4	8,8±0,3	12,0±0,2	10,1±0,2	9,5±0,2
Erythrocytes, 10 ^{12}/l	6,0±0,5	4,3±0,2	7,4±0,3	5,2±0,3	5,0±0,3
Leukocytes, 109/l	10,0±1,0	15,25±1,1	11,0±1,2	10,0±1,1	9,0±0,8
After 21 days					
Hemoglobin, g/l	10,5±0,4	9,6±0,3	11,0±0,2	10,3±0,2	10,0±0,1
Erythrocytes, 10 ^{12}/l	5,8±0,5	5,0±0,2	6,8±0,3	5,7±0,3	5,3±0,2
Leukocytes, 109/l	10,5±1,0	12,25±1,1	9,0±1,2	10,8±1,1	10,8±1,1

*P<0,05 in relation to control

Based on the results of the pharmacological study, it can be concluded that the new gel "Benzpai-S" has an anti-inflammatory and reparative effect, characteristic of its components, having a beneficial effect on the course of experimental stomatitis.

In the second series of experimental studies, the alternative effect of the new composition of the gel "Benzpai-S" on a skin wound model was also studied. As can be seen from the data in Table 5, in the control animals, one day after the injury, the wound area exceeded the operating area by 1.4 times. In the control rats, the edges and bottom of the wound were edematous during this period, and there was exudate on the surface. On the 3rd-7th day of observation, the wound characteristics remained the same. A thin brown-purple crust formed on the wound surface, quite tightly adhering to the bottom of the wound. It should be noted that epithelialization of the defect in the control rats was slow. The wound area corresponded to the area of the initially inflicted defect. Subsequently, the surface of the wounds gradually tightened, complete healing occurred on the 20-21st day. A full-fledgedregenerate with a woollycoveringformedatthesiteoftheskindefect.

In the cytological study of the imprints from the experimental wounds on the 1st day according to M. P. Pokrovskaya, a decrease in the protective cellular reaction and a degenerative nature of the changes were found in the control group of animals. In 40% of the animals, wound suppuration was observed. This was expressed in significant

destruction and degeneration of neutrophils, the presence of pronounced microflora without signs of active phagocytosis. Cytograms on the 7th day showed a neutrophilic reaction, but at the same time there was a tendency for an increase in the number of macrophages and polyblasts, which confirms the intensification of the reparative process.

In animals, the new composition of Benzpay-S gels at a dose of 150 mg / kg and Asepta gels and Salcoseryl gels at a dose of 150 mg / kg during the first 4-6 days in 40% of animals also observed suppuration in the rest of the animal wounds remained dry, did not bleed, did not suppurate. In no case was an edematous reaction observed. The formed crust was dense and dark. After 6-7 days, juicy, granular granulations were visible under it. On the 7-8th day, the crusts fell off. The epithelial wedge formed on the 3rd-7th day, growing, led to early and complete epithelialization of the skin defect, completed on the 10-12th day. Subsequently, by the 14-18th day, complete restoration of the epidermis with the formation of dereates (hair follicles and glandular elements) occurred. In the cytogram on the 1-3 day of the experiment, signs of regeneration and increased protective cellular reactions were noted: neutrophils became more intact, macrophages, profibroblasts, polyblasts appeared. Later, the regeneration process became even more pronounced: maturation of profibroblasts and fibroblasts was observed. The onset of epithelization was expressed in the formation of layers of young cells of the squamous epithelium. Microflora decreased or disappeared completely.

Thus, under the influence of Benzpay-S gel at a dose of 150 mg / kg and Asepta gels and Salcoseryl gels at a similar dose, reparative processes in skin defects in rats occur faster than in untreated animals, although the percentage of infected wounds did not differ from the control.

During the treatment, dynamic observation of the course of the wound process was carried out with control of the timing of cleansing and healing of wounds. On the 3rd day, the animals of the experimental groups showed a decrease in skin hyperemia and edema around the wounds. On the 7th day, the perifocal inflammatory changes around the wound subsided in the animals of these groups. The wound surface was cleared of purulent-necrotic masses, granulations appeared. By this time, the area of the wound surface in relation to the outcome decreased in the control by 38% under the influence of the new composition of the Benzpay-S gels at a dose of 150 mg / kg by 64%, and under the influence of the comparison drug, Asepta gels and Salcoseryl gels - by 60% (Table 5, Fig. 3).

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Table 5 Change in the area of the wound surface of rats treated with the new composition of the gel "Benzpai-S" in comparison with the gels Asepta and Salcoseryl gels(M±m; n=5)

Drugs Dose, mg/kg	Wound area, mm2/ follow-up period, day					
	1	3	7	10	14	21
Control	13,8±2	11±1,0	10±1,0	6,2±0,3	4,0±0,3	2±0,1
Composition of gel "Benzpaya-S" -150	16±1,0	8,2±0,4	5,8±0,2*	4,4±0,04*	2,3±0,2*	0
HeliumAsepta -100	14±1,0	6,5±0,4	5,2±0,2*	3,8±0,1*	1,1±0,1*	0
Salcoserilgel	14,5±1,0	6,4±0,4	5,0±0,2*	3,6±0,1*	1,0±0,1*	0

*P<0,01 in relation to control

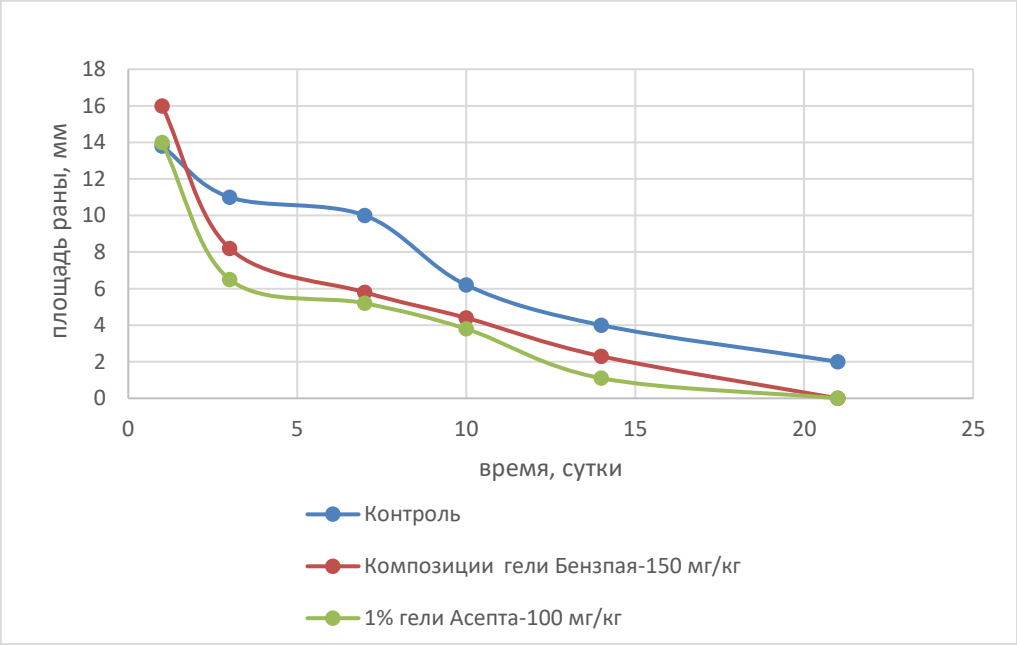

Fig. 3. Change in the area of the wound surface of rats treated with the new composition of the Benzpai gel in comparison with the Asepta gel.

The results of treatment: the terms of wound cleansing and healing, as well as the rate of wound healing are shown in Table 7. Thus, wound cleansing in the control group of animals took place on day 14. When using the new composition**,** Benzpaya gelsat a dose of 150 mg/kg - on day 9, and when using Aseptagels- on day 10. during the treatment of a new composition of gels **"Benzpay"** for day 21. Comparing the drugs by increasing the healing rate on the 7th day of treatment, they can be arranged in the following order: control – 24%, **Asepta gels** – 37%,**Salcoseril gels** – 37%, new **gels "Benzpay"** – 46% (Table 6).

Table 6 Results of Treatment of Experimental Skin Wounds of the New Composition of Benzpaya Gel in Comparison with 1% of Asepta and Salcoseril Gels (M±m; n=5)

PreparationDose, mg/kg	Terms, days		**Speed woundhealingonday 7, %
	Woundcleansing	Woundhealing	
Control	14±1,2	29±2,0	24
Compositionofgel "Benzpay"	9±1,0*	21±2,0*	46
Aseptagels	10±1,0*	21±2,0*	37
Salcoserilgel	10±1,0*	21±2,0*	37

*P<0,01 in relation to control
**in relation to the initial area of the wound surface.

The results obtained to study the effect of the new composition of the dental gel "Benzpay" on skin wounds in an experiment on rats made it possible to draw the following conclusions:
Based on the results of pharmacological study, it can be concluded that the drug of the new composition of the gel "Benzpaya-S" has an anti-inflammatory and reparative effect characteristic of its components, having a beneficial effect on the course of experimental stomatitis.
The new composition of Benzpaya gel at a dose of 150 mg/kg has a wound-healing effect, which reduces the time of cleansing and healing of wounds by 4-8 days. Comparative analysis with the comparator gels Aseptaand Salcoserilrevealed the advantage of the former.
The results of the study of the acute toxicity of the new composition ofthe gel"Benzpaya-S" showed that they belong to the V I class of relatively harmless substances. LD50 in mice when injected into the oral cavity was greater than ≥5000 mg/kg.

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