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Comparative assessment of the osmotic and anti-inflammatory activity of soft dosage forms of pyrimidine drugs on hydrophilic bases in an experiment

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ABSTRACT

BACKGROUND: Despite the constant search for new medications for local prevention of surgical infection, the problem of purulent-inflammatory complications from postoperative soft tissue wounds remains relevant to this day.

AIM: To experimentally study the osmotic activity and anti-inflammatory properties of the developed xymedone-containing ointment composition levoxycol in comparison with the well-known ointment dioxomethyltetrahydropyrimidine + chloramphenicol (levomekol).

MATERIAL AND METHODS: The anti-inflammatory properties of the ointments were studied *in vivo* on 60 outbred male Wistar rats, which were divided into three groups, 20 animals each. The first group served as control. In the second group of animals, levomekol ointment was used, in the third group — levoxycol. An assessment of the osmotic activity of the experimental ointment composition levoxycol in comparison with a known drug was carried out in an *in vitro* experiment. To evaluate the anti-inflammatory activity of ointments, a model of carrageenan-induced edema of rat paws was used. To analyze differences in the frequency of the studied outcomes in groups of animals, the Mann–Whitney U test was used.

RESULTS: Osmotic activity showed that wipes soaked in ointment forms absorbed the following amount of contrast (Me [Q_1; Q_3]): levomekol — 28.2 (26.4; 31.3) ml; levoxycol — 41.8 (39.5; 43.4) ml (p=0.001). The anti-inflammatory activity of the ointment forms manifested itself in the form of suppression of swelling of the rats' paws at 3 and 5 hours after the injection of carrageenan. When using the ointment form of levomekol, the volume of displaced liquid with the introduction of carrageenan, starting from 3 hours, was 1.8±0.19 ml. When using the ointment form of levoxicol, the amount of displaced liquid when carrageenan was administered, starting from 3 hours, was 1.57±0.16 ml (p=0.013).

CONCLUSION: *In vitro* experiments have shown that the ointment form of levoxicol has a longer osmotic activity; experimental data in vivo indicated that the use of the developed ointment form of levoxicol, in contrast to the ointment form of levomekol, has a positive effect on the course of inflammatory processes in soft tissues in the first 2–3 hours by reducing the volume of displaced fluid.

Keywords: inflammation; osmotic activity; ointment form; carrageenan; edema.

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Сравнительная оценка осмотической и противовоспалительной активности мягких лекарственных форм препаратов пиримидинового ряда на гидрофильных основах в эксперименте

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АННОТАЦИЯ

Актуальность. Несмотря на постоянный поиск новых медикаментозных средств для местной профилактики хирургической инфекции, проблема гнойно-воспалительных осложнений со стороны послеоперационных ран мягких тканей остаётся актуальной до настоящего времени.

Цель. Изучить в эксперименте осмотическую активность и противовоспалительные свойства разработанной ксимедон-содержащей мазевой композиции левоксиколь в сравнении с известной мазью диоксометилтетрагидропиримидин + хлорамфеникол (левомеколь).

Материал и методы. Изучение противовоспалительных свойств мазей проводили *in vivo* на 60 беспородных крысах-самцах линии Wistar, которые были распределены на три группы, по 20 животных в каждой. Первая группа служила контролем. Во второй группе животных применяли мазь левомеколь, в третьей группе — левоксиколь. Оценку осмотической активности экспериментальной мазевой композиции левоксиколь в сравнении с известным лекарственным средством выполняли в эксперименте *in vitro*. Для оценки противовоспалительной активности мазей использовали модель каррагенин-индуцированного отёка лап крыс. Для анализа различий частоты изучаемых исходов в группах животных использовали U-критерий Манна–Уитни.

Результаты. Осмотическая активность показала, что салфетки, пропитанные мазевыми формами, впитали следующее количество контраста (Me [Q_1; Q_3]): левомеколь — 28,2 (26,4; 31,3) мл; левоксиколь — 41,8 (39,5; 43,4) мл (p=0,001). Противовоспалительная активность мазевых форм проявлялась в виде подавления отёка лапок крыс на сроках 3 и 5 ч после инъекции каррагенина. При использовании мазевой формы левомеколь объём вытесненной жидкости при введении каррагенина, начиная с 3 ч, составил 1,8±0,19 мл. При применении мазевой формы левоксиколь количество вытесненной жидкости при введении каррагенина, начиная с 3 ч, составило 1,57±0,16 мл (p=0,013).

Вывод. Эксперименты *in vitro* показали, что мазевая форма левоксиколь обладает более длительной осмотической активностью; экспериментальные данные *in vivo* свидетельствуют о том, что применение разработанной мазевой формы левоксиколь, в отличие от мазевой формы левомеколь, положительно влияет на течение воспалительных процессов в мягких тканях в первые 2–3 ч за счёт уменьшения объёма вытесненной жидкости.

Ключевые слова: воспаление; осмотическая активность; мазевая форма; каррагенин; отёк.

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BACKGROUND

Despite ongoing efforts to develop new drugs for the local prophylaxis of surgical infections, purulent inflammatory complications in postoperative soft tissue wounds remain a significant concern [1, 2].

Various methods and drugs have been developed to stimulate healing, promote rapid and optimal scar formation, facilitate early cleansing of the wound from purulent necrotic tissue, and accelerate reparative regeneration processes [3–6]. Among the most commonly used agents for stimulating wound healing are those of the pyrimidine series, such as dioxomethyltetrahydropyrimidine (methyluracil) and pentoxyl.

Methyluracil, one of these drugs, is included in a water-soluble ointment base, specifically in combination with dioxomethyltetrahydropyrimidine and chloramphenicol (Levomecol). This combination, categorized as a universal ointment, is designed to target multiple aspects of the wound healing process. However, the topical application of methyluracil within Levomecol ointment is ineffective due to its weak (equal to placebo) regenerative and anti-inflammatory effects and lack of antibacterial properties [7].

A key requirement for pharmacological agents used in local wound treatment is their good solubility, which enables a high therapeutic concentration of the drug and thus ensures an optimal therapeutic effect [8, 9].

In the course of developing this approach, scientists V.S. Reznik and N.G. Pashkurov at the A.E. Arbuzov Institute of Organic and Physical Chemistry of the Kazan Scientific Center of the Russian Academy of Sciences in 1964 created a more effective drug of the pyrimidine series, namely, hydroxyethyldimethyldihydropyrimidine (Ximedon) [10]. The pharmacological effects of Ximedon have generated significant interest in its use, and the lack of toxicity, therapeutic breadth, and extremely narrow contraindications allow the drug to be used in various areas of medicine. Ximedon also holds potential for further studies and local use in various medicinal forms.

Different local forms, as compositions, are developed by Prof. S.G. Izmailov et al. [11–14]. All this was the subject of our experimental research.

The aim of the study was to experimentally investigate the osmotic activity and anti-inflammatory properties of the developed Ximedon-containing ointment composition, Levoxycol, and the known ointment, Levomecol.

MATERIALS AND METHODS

The first material studied was the well-known Levomecol ointment, an officially approved preparation for clinical use in the Russian Federation. Its composition includes the following ingredients by weight percentage: levomycetin (0.75%), methyluracil (4.0%), polyethylene oxide 1,500 (19.05%), and polyethylene oxide 400 (76.2%). The second ointment, Levoxycol, was developed by our research team. This name is an abbreviation derived from the initial letters of its main active ingredients [14]. The therapeutic composition has the following components, expressed in weight percentage: levomycetin (0.75), Ximedon (4.0), polyethylene oxide 1,500 (19.05), and polyethylene oxide 400 (76.2) [13].

The osmotic activity of the experimental ointment composition, Levoxycol, in comparison with the known drug, was evaluated in an *in vitro* experiment using the method described by Y.K. Abaev (2005) [11]. The tested ointment composition in the amount of 40 g was heated in a thermostat to a liquid consistency, maintaining an ointment temperature of 35°C–36°C. A gauze strip, 35 mm wide and 700 mm long, was placed into the studied liquid ointment and soaked for 30 min.

Following exposure, the materials under investigation were affixed to the laboratory rack at an equal height from the base using surgical thread (Fig. 1).

A contrast agent, specifically a 0.3% $K_2Cr_2O_7$ solution, was used as the liquid absorbed by the ointment forms. This solution was placed in laboratory dishes in 60 mL quantities corresponding to the number of series under study, which has a distinct yellow color and dissolves well in water. The $K_2Cr_2O_7$ solution does not interact with the components of ointment compositions. Upon dissolution, $K_2Cr_2O_7$ dissociates into cations ($2K^+$ and $Cr_2O7_2^-$), which polarizes the solution and enhances the penetration of the contrast into the gauze dressing impregnated with the ointment composition (Fig. 1, *b*).

The free edge of the ointment strips was submerged 0.5 cm into the contrast medium. The osmotic activity of the studied ointment compositions was assessed by measuring the rate and intensity of staining of the ointment strips, as well as the amount of liquid absorbed during 24 hours.

The study of the anti-inflammatory properties of the ointments was conducted *in vivo* on 60 male Wistar strain mongrel rats. The animals were selected based on the following criteria: males with a body weight of 250–300 g, aged 8–12 months, no visible injuries, clear eyes, clean skin, active, and a good appetite.

Animals were divided into groups based on their ability to solve the tasks given.

A model of carrageenin-induced edema of the rat paws was used to assess the anti-inflammatory activity of the ointments. Inflammation was induced by injecting a 1% aqueous solution of carrageenin in a volume of 0.1 mL under the plantar aponeurosis of the right hind paw. The rats in the experimental groups were bandaged on the hind limb with the studied ointments 30 min after carrageenin administration, and measurements were taken every hour. The bandage was only removed to take measurements.

In the control group, animals were treated with an aseptic bandage without ointment. A group in which the ointment forms were not applied served as controls.

In the experiment, the animals were divided into three groups of 20: Group 1 served as a control, Group 2 received Levomecol, and Group 3 was treated with Levoxycol [8].

We tested the hypothesis that Levoxycol would have a positive effect on the inflammatory process in soft tissues

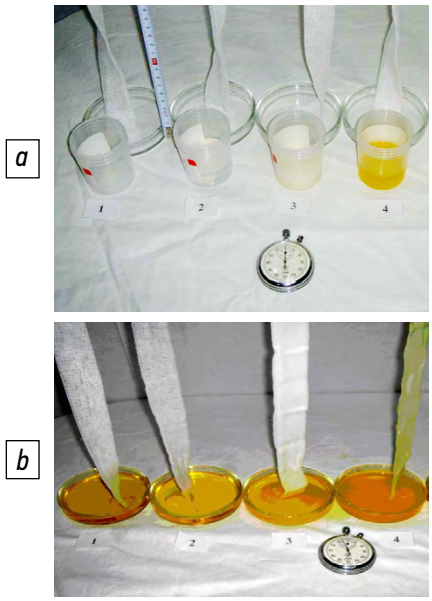

Fig. 1. *a*. General view of laboratory materials used in the experiment to assess the osmotic activity of ointment compositions. Gauze strips are fixed to the tripod at an equal height. Explanations in the text. *b.* Experiment to evaluate the osmotic activity of ointment compositions. The edge of the gauze strip is immersed in a contrast agent of 0.3% $K_2Cr_2O_7$; 1 — dry cloth; 2 — hypertonic NaCl solution; 3 — levosmekol ointment; 4 — levoxycol ointment. Explanations in the text

within the first hours of application and reduce the duration of inflammation.

The severity of edema was assessed using a plethysmometer from Ugo Basile (Italy). A plethysmometer with a standard water container (1.8 cm diameter) and a rat foot container (1.3 cm diameter) was used. Edema was measured to the nearest 0.01 mL of displaced liquid volume. In this experiment, inflammation was modeled using carrageenin.

During the experimental studies to investigate the effect of Levoxycol and Levomecol ointments on the inflammatory process in soft tissues, the volume of displaced water (mL) was calculated. A greater volume of displaced water indicated greater swelling of tissues. The inflammatory response was assessed by measuring paw swelling at 2, 3, 4, and 5 hours after carrageenin injection.

The anti-inflammatory effect of the studied substances was evaluated by measuring the degree of edema suppression compared to the control group. Throughout the experiment, the general condition, body weight changes, and survival rate of the animals were closely monitored. The anti-inflammatory activity of the ointment forms was evaluated by calculating the reduction in the volume of displaced water, expressed as a percentage of the initial volume, in comparison to the control group.

During the experiment, blood samples were collected from the rats' tail tips before modeling inflammation and at 2, 3, 4, 5, and 24 hours after modeling inflammation. In each experimental group, five series were conducted to obtain reliable data on key indicators, including erythrocyte sedimentation rate (ESR), C-reactive protein, white blood cell count, and the ratio of leukocyte subpopulations (lymphocytes, monocytes, and granulocytes). ESR, leukocyte count, and the ratio of their subpopulations were determined in whole blood collected by the traditional method.

The study was approved by the local ethics committee of the Kazan State Medical University of the Ministry of Health of Russia for conducting scientific research involving human and animal research subjects (protocol No. 4, dated 24.04.2018).

The data analysis was conducted in the R 3.4.4 environment for statistical computing. The Mann–Whitney U criterion was used to analyze the differences in the frequency of the studied outcomes in the animal groups. Differences were considered statistically significant at $p < 0.05$. All data are presented as the mean value ± standard deviation.

RESULTS AND DISCUSSION

The experiment revealed that dry tissue (1) and tissue soaked in hypertonic NaCl solution (2) exhibited a high saturation rate of staining immediately upon immersion, indicating the early activation of the drainage function. In contrast, the area of staining in the dry tissue after one hour of immersion was (Me [Q_1; Q_3]) 12.7 (12.2; 13.1) cm^2, while that of the tissue soaked in a hypertonic solution was 18.5 (17.9; 19.1) cm^2.

During the first 3 hours of observation, the staining area of the indicated gauze wipes increased significantly to 41.4 (40.8; 42.1) cm^2 and 77.2 (76.7; 77.7) cm^2, respectively ($p = 0.001$).

It was observed that the dry gauze wipe, when saturated with contrast, lost its osmotic properties by the fourth hour of the experiment, leading to a cessation of the observed increase in the staining area. Similarly, the high rate of contrast saturation of the hypertonic solution-impregnated tissue rapidly decreased and ceased after 6 hours from the start of the experiment. After 6 hours, the staining area of the dry wipe was (Me [Q_1; Q_3]) 68.7 (68.1; 69.5) cm^2, while that of the hypertonic solution-impregnated wipe was 91.1 (90.6; 91.7) cm^2 ($p = 0.001$). No further increase in the staining area was observed for either the dry or hypertonic solution-impregnated wipes during the subsequent observation time.

When studying gauze wipes impregnated with ointment compositions, the following results were obtained: During the first 3 hours of observation, the staining area of the tested materials remained relatively unchanged, and the rate of contrast agent uptake by the wipes was low compared to that of dry and hypertonic solution-impregnated wipes.

Thus, 1 hour from the beginning of the experiment, the area of contrast staining for Levomecol (3) was (Me [Q_1; Q_3]) 3.2 (3.1; 3.3) cm^2, while that for Levoxycol (4) was 3.1 (2.9; 3.4) cm^2. At 3 hours from the start of the experiment, there was a significant difference in the area of impregnation of the ointment wipes with Levomecol at 5.4 (5.2; 5.8) cm^2 and Levoxycol at 5.7 (5.6; 5.9) cm^2 ($p = 0.0039$). Subsequently, the difference in the area of impregnation of the ointment wipes increased over time. Thus, after 6 hours

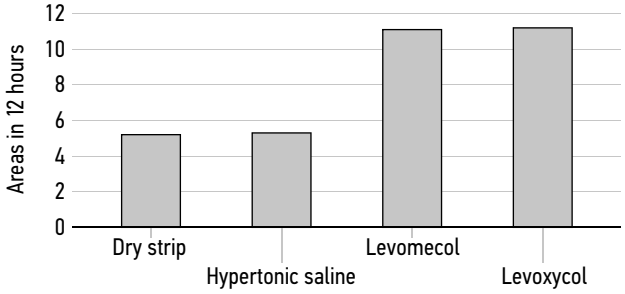

Fig. 2. General view of the experiment to evaluate the osmotic activity of ointment compositions, a diagram of the saturation degree of gauze napkins with contrast 12 hours from the start of the experiment. Impregnation of strips with ointments with contrast continues, but the rate of staining of strips with levomekol ointment has noticeably decreased. Explanations in the text

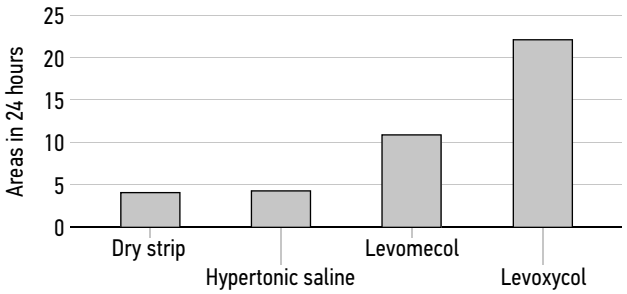

Fig. 3. General view of the experiment to evaluate the osmotic activity of ointment compositions, a diagram of the saturation degree of gauze napkins with contrast 24 hours from the start of the experiment. End of the experiment. Explanations in the text

of the experiment, the area of wipe impregnation was 11.9 (11.7; 12.2) cm^2 for Levomecol and 13.6 (13.5; 13.8) cm^2 for Levoxycol (p_{1-2} = 0.001).

At 12 hours from the beginning of the experiment, the osmotic activity of the wipe with Levomecol ointment decreased, and the staining rate became noticeably lower. After 16 hours from the beginning of the experiment, the staining of the wipe with contrast stopped. The area of contrast staining of the gauze with Levomecol ointment was 15.5 (14.3; 16.2) cm^2. At the subsequent observation period, the area of impregnation of this dressing did not change.

In contrast, the contrast staining area of the smudge-shaped Levoxycol wipes increased throughout the experiment. After 12 hours from the beginning of the experiment (Fig. 2), the area of impregnation of the gauze with the ointment was 19.9 (19.8; 20.0) cm^2 (p = 0.001).

By 18 hours, there was a decrease in osmotic activity of the Levoxycol ointment tissue, but the area of contrast staining continued to increase and after 24 hours (Fig. 3) was 28.4 (28.1; 29.2) cm^2 (p = 0.001).

At the end of the study, the amount of contrast absorbed by each material was analyzed. The dry tissue was found to absorb 55 mL of contrast, while the tissue soaked in hypertonic solution absorbed all of the contrast. The ointment-impregnated wipes demonstrated the following absorptive capacities for the contrast agent: (Me [Q_1; Q_3]) Levomecol absorbed 28.2 (26.4; 31.3) mL, while Levoxycol absorbed 41.8 (39.5; 43.4) mL.

These results suggest that the Levoxycol composition, which contains Ximedon and is developed on a polypropylene oxide base, exhibits both longer temporal (up to 24 hours) and quantitative draining properties in comparison with Levomecol (up to 16 hours).

In the control group, the increase in the volume of displaced water relative to the intact group averaged 1.61 ± 0.04 mL, which was taken as 100%. The volume of displaced water before the carrageenin injection was considered initial and was taken as 100%. Maximum edema development was observed in the control group animals 3 hours after the carrageenin injection.

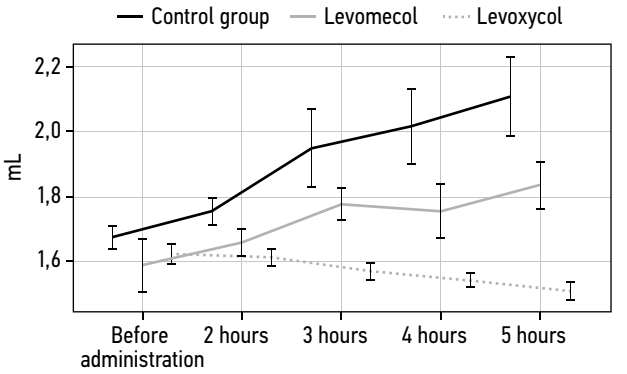

Fig. 4. Volume of displaced fluid at different stages of inflammation (%)

The inflammatory reaction was evidenced by redness, tenderness upon palpation, and swelling. The conducted research showed that when measuring the paw in animals of the control group after 2 hours without the application of ointment forms, the volume of displaced liquid was up to 2.1 mL compared to the baseline values (1.58 ± 0.13 mL). The result indicates the development of the exudative phase of inflammation, with edema as the primary sign.

The liquid displacement volume at different stages of the experiment is shown in Fig. 4. In the control group, which did not receive any ointment, as well as in the groups treated with Levomecol and Levoxycol, there was an increase in the volume of displaced liquid 2 to 3 hours after the onset of inflammation. Subsequently, the volume of displaced fluid varied depending on the ointment form applied.

The anti-inflammatory activity of the ointment forms was manifested as a suppression of rat paw edema at 3 and 5 hours after carrageenin injection.

In all experimental groups, the liquid displacement volume was the same before carrageenin injection. When Levomecol was used before carrageenin injection, the displaced liquid indices were 1.65 ± 0.14 mL, whereas when carrageenin was administered starting from 3 hours, the amount was 1.8 ± 0.19 mL. When Levoxycol was applied before carrageenin injection, the displaced liquid values were 1.62 ± 0.13 mL, while when carrageenin was administered starting at 3 hours, they were 1.57 ± 0.16 mL (p = 0.013).

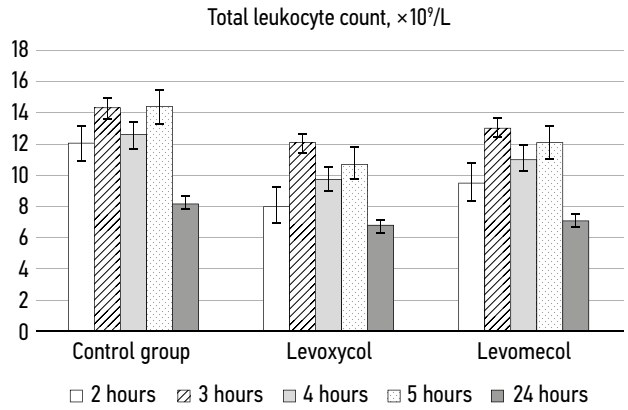

Fig. 5. Changes in the number of leukocytes in the blood of rats under the influence of inflammation and the studied ointment forms

In a rat foot edema model, preapplication of Levoxycol significantly reduced limb swelling induced by carrageenin injection. The conducted research demonstrated that the volume of displaced liquid was significantly reduced in both Levoxycol and Levomecol ointments, showing a 30% and 18% decrease, respectively, compared with the control. This finding suggests that the developed ointment forms possess antiedematous and anti-inflammatory properties.

It was demonstrated that in the control group, in the absence of ointment application, a peak in the changes observed in the parameters of ESR and C-reactive protein was evident at 2 and 3 hours following the modeling of inflammation. While the ESR was 0 mm/hour and the C-reactive protein was (–) in all intact animals at the beginning of the experiment, the ESR was increased to 2 ± 2.2 mm/hour, and the C-reactive protein content to (+) and (++) at 2 and 3 hours, respectively. Both indices did not return to baseline values within 4 hours of observation.

In both experimental groups, the administration of Levomecol and Levoxycol led to a notable restoration of ESR and C-reactive protein levels to reference values. At the 2-hour period, the ESR values were approximately equivalent for both experimental groups, averaging 0.8–1.5 and 0.5–1 mm/hour for Levomecol and Levoxycol, respectively. In the group where Levoxycol was administered, the ESR was 0 mm/hour at 3 hours and remained consistent with baseline values. In the Levomecol group, ESR was lower than in the control group throughout the observation period but did not reach baseline values (0 mm/hour) until after 5 hours.

C-reactive protein in the Levoxycol group was already at the second hour (+) in only one animal out of five; the other four were negative. When using Levomecol, the C-reactive protein was (+) in three out of five animals and (–) in two out of five animals ($p = 0.5238$).

As a result of modeling inflammation, an increase in the white blood count by three times was registered in the control group after just 2 hours, with the peak ($15 \pm 1.3 \times 10^9$/L) occurring at 5 hours (Fig. 5). In the group where Levomecol was used, a significant increase in the white blood cell count occurred with a delay compared to the control group, approximately by 1 hour, and started at 3 hours. In the fourth hour, the indicators were higher than in the control, and from the fifth hour, there were no differences from the control group. In the group where Levoxycol was used, the white blood count did not rise above $10 – 12 \times 10^9$/L throughout the observation period.

Analysis of the leukocyte subpopulation ratios (leukocyte formula) revealed that 2 hours after modeling inflammation, the number of granulocytes and monocytes increased in the control group, whereas the number of lymphocytes remained unchanged. The peak levels of granulocytes and monocytes were recorded at 5 hours after modeling inflammation. Within 24 hours, the number of granulocytes completely returned to normal, although the number of monocytes decreased but remained above the baseline values. In contrast, the number of monocytes in the control group reached maximum values after 24 hours, three times higher than the baseline values.

CONCLUSIONS

1. *In vitro* experiments showed that Levoxycol has a more pronounced osmotic activity (for 24 hours vs. 12 hours in the control group).

2. *In vivo* experimental data indicate that the use of Levoxycol, in contrast to Levomecol, has a positive effect on the course of inflammatory processes in soft tissues during the initial 2–3 hours.

ADDITIONAL INFORMATION

Authors' contribution. A.G.I. — investigation, writing — original draft, visualization; S.V.D. — supervision, project administration, validation, formal analysis; S.G.I. — conceptualization, methodology, writing — original draft; E.E.L. — software, investigation, data curation; A.Yu.Zh. — methodology, resources, data curation.

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Competing interests. The authors declare that there is no conflict of interest in the presented article.

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Вклад авторов. А.Г.И. — исследование, создание черновика, визуализация; С.В.Д. — общее руководство, администрирование проекта, проверка, анализ; С.Г.И. — концептуализация, методология, создание черновика; Е.Е.Л. — программное обеспечение, исследование, обработка и управление результатами; А.Ю.Ж. — методология, ресурсы, обработка и управление результатами.

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