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Pharmacological studies of the veterinary medicinal product “Dibutalastin Ointment”

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Abstract

The study of pharmacological studies of the veterinary medicinal product for external use in the form of ointment – “Dibutalastin Ointment” is a mandatory stage of preclinical research of the drug, which is a new development of PP “Biopharm” and LLC “DEVIE”. In a scientific experiment on laboratory animals, it is possible to assess the drug's safety for different terms of use to determine the zone of toxic action and doses that do not cause harmful effects on health. Therefore, the work aimed to carry out pharmacological studies of the drug with methyl salicylate and dimethyl sulfoxide in the form of an ointment for treating European fallow deer, deer, dogs, and cats with mastitis, arthritis, myositis, and injuries of various origins. The toxicological characteristics of the studied ointment “Dibutalastin” based on methyl salicylate and dimethyl sulfoxide were studied in an "acute" study on warm-blooded animals. The average lethal dose (LD_{50}) for intragastric administration could not be established, as the volume exceeded the permissible level. It was established that according to the “average lethal dose when entering the stomach” indicator, the veterinary medicinal product belongs to relatively non-toxic substances (toxicity class IV). The results of pharmacological studies indicate the absence of resorptive-toxic effects, sensitizing properties, and irritating effects on the mucous membranes of the eyes and skin. Pathomorphological studies of animal organs when studying the acute toxicity of the drug showed that the developed ointment with methyl salicylate and dimethyl sulfoxide does not cause pathological changes in internal organs. From the point of view of veterinary toxicology, this drug is safe. Further studies will be the next stage of pre-registration tests aimed at studying the embryotoxic effect of “Dibutalastin Ointment”, which is mandatory material of the “Safety and residue studies” section of the dossier for this medicinal product.

Keywords: methyl salicylate, dimethyl sulfoxide, toxicity, white rats, internal organs.

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1. Introduction

One of the most critical stages of the preclinical evaluation of veterinary medicinal products is the study of their specific activity and harmlessness (Sachuk et al., 2019; Zazharskyi et al., 2020; Martyshuk et al., 2022; Karpenko et al., 2022; Varkholiak et al., 2022). To carry out this stage of pharmaceutical development, models and methods are used taking into account the requirements of the Law of Ukraine “On Veterinary Medicine” and the Directive of the Commission of July 23, 1991, on the principles and working instructions of good manufacturing practice for veterinary drugs (91/412/EEC). They make it possible to objectively assess the degree of safety of pharmacotherapeutic agents, justify the frequency, method, and dosage of application, and predict the possibility of adverse reactions in the body (Gutyj et al., 2016; 2018; Todoriuk et al., 2018; Vasylyev et al., 2021).

Despite the comprehensive discussion of the need for proper pharmacological quality control of combined ointments for external use and the study of their toxicological studies, the number of scientific publications on this issue is quite limited, which indicates the relevance of conducting such studies.

Analysis of recent research and publications. Among all traditional preparation forms of veterinary medicines, oint-

ments for external use occupy one of the first places in treating dermatological diseases and are also often used in gynecology, obstetrics, surgery, and other fields of clinical veterinary medicine.

For the pharmacotherapy of dermatological diseases, dermatological medicines based on methyl salicylate and dimethyl sulfoxide are often used, as well as drugs of non-specific action, which have a combined antimicrobial and anti-inflammatory effect (Borda et al., 2019; Hoi, 2020; Kıpçak et al., 2022).

Taking into account his experimental studies and literary data of Pertsev et al., 2010 on the treatment of European doe, deer, dogs, and cats with mastitis, arthritis, myositis, and injuries of various origins. We included the following active ingredients in the soft dosage form: methyl salicylate for external use as a distraction agent for temporary relief of deep pain; dimethyl sulfoxide (10 %) as an anti-inflammatory and transport component.

Dimethylsulfoxide (DMSO) has an anti-inflammatory, local analgesic, and anti-edematous effect (Demir et al., 2020; Gkiatas & Gelalis, 2021; Sanli et al., 2021; Anzelc & Burkhart, 2021). The anti-inflammatory effect is based on several pharmacological effects, mainly the inactivation of hydroxyl radicals, which are formed in large quantities during inflammation and lead to tissue destruction. DMSO has a local anesthetic effect, reducing the speed of conduction of excitatory impulses in peripheral neurons. The anti-edema effect is explained by the inactivation of hydroxyl radicals and the consequent improvement of metabolic processes in the center of inflammation. The hygroscopic properties of DMSO are also partly responsible for this.

It is also important to note the known pathogenetic effect of dimethyl sulfoxide as an immunomodulatory agent, which explicitly affects the vital activity of cells of macro- and microorganisms (Kravchenko et al., 2017; Huang et al., 2020).

Methylsalicylate (Methylis salicylas) (DFU, 2nd ed.) is a colorless or slightly yellowish liquid with a characteristic aromatic smell (Gilleron et al., 2020; Wu et al., 2021; Yeoh & Goh, 2022). It dissolves very little in water P, miscible with 96 % ethanol P and ether, fatty and essential oils. The relative density is from 1.180 to 1.186.

Methyl salicylate non-selectively inhibits cyclooxygenase, reduces PG synthesis, normalizes increased permeability of capillaries, improves microcirculation processes, and reduces swelling and infiltration of inflamed tissues. With the local application, it quickly penetrates the deep layers of the skin, is absorbed, hydrolyzed, and turns into an anion of salicylic acid (Pertsev et al., 2010).

The classic application of methyl salicylate as an analgesic and anti-inflammatory agent is joint and muscle rheumatism, arthritis, osteochondrosis, and exudative pleurisy. In different periods, dosage forms containing methyl salicylate were manufactured. Liniment (balsam) (Linimentum (Balsamum) contains 24 g of methyl salicylate, 1.2 g of eucalyptus oil, 3.2 g of purified turpentine oil, 5 g of camphor, 33.3 g each of lard and petroleum jelly; Baum-Benge ointment (Unguentum Boum-Benge) – contains menthol 3.9 g (or peppermint oil 7.8 g), methyl salicylate 20.2 g, medical petroleum jelly 68.9 g, medical paraffin 7.0 g (per 100 g); liniment (Linimentum) – contains methyl salicylate, analgin and naphthalene oil 2.5 parts each, a mixture of fatty alcohols of sperm whale fat – 3 parts, emulsifier – 13 parts, water – up to 100 parts; capsin (Capsinum) - liniment containing methyl salicylate 1 part, oils blekota and tincture of capsicum 2 parts each; methyl salicylate complex liniment (Linimentum methylii salicylatis compositum) – contains methyl salicylate and chloroform 33.3 g each, oil of blekota (or dope) 33.4 g (per 100 g); salinimentum (Salinimentum) – contains 20.0 g of methyl salicylate and chloroform, 60.0 g of evening primrose oil (per 100 g). It has long been available in pharmacies that produce medicinal preparations with methyl salicylate for rubbing (the ratio of methyl salicylate and chloroform is 50.0; 10 % methyl salicylate ointment; liniment methyl salicylate complex). In the pharmaceutical market of Ukraine, methyl salicylate is included in medicines used locally for joint and muscle pain. These are “Flamidez gel” and “Dicloran® plus” gel, which contain diclofenac diethylamine in their composition and belong to the pharmacotherapeutic Group according to the ATS classification M01A – Nonsteroidal anti-inflammatory drugs for local use. Ointments “Bom-benge”, “Doloxen fast”, and cream “Dip hit” as auxiliary substances contain paraffin, several fatty oils; that is, they are fatty and do not penetrate deeply.

All the listed drugs contain information about their effectiveness and indications for medical use in the instructions for use. Therefore, the development of domestic dermatological medicines for use in veterinary medicine based on methyl salicylate and dimethyl sulfoxide remains relevant.

In connection with the above, a prospective study of the possibility of creating dosage forms for external use based on methyl salicylate and dimethyl sulfoxide with available domestic technologies, which make it possible to make them available for the treatment of European fallow deer, deer, dogs, and cats with mastitis, arthritis, myositis, and injuries of various types, is predicted origin. After the positive results of preclinical tests, such drugs are admitted to clinical trials.

The purpose of the work is pharmacological studies of a medicinal preparation with methyl salicylate and dimethyl sulfoxide in the form of an ointment for treating European fallow deer, deer, dogs, and cats with mastitis, arthritis, myositis, and injuries of various origins.

2. Materials and methods

Preclinical study of ointment with methyl salicylate and dimethyl sulfoxide for therapy and prevention of mastitis, arthritis, myositis, and injuries of various origins in European fallow deer, deer, dogs, and cats, conducted based on the laboratory for quality control, safety, and registration of veterinary medicinal products and fed additives LLC “DEVIE”. Pharmacological studies were conducted in the volume determined by the standard test method (Kotsiumbas et al., 2006).

The animals were injected intragastrically with the developed ointment in doses of 5000, 10000, 15000, 20000, and 25000 mg/kg. Animals were observed for 14 days. To determine the criteria for assessing the acute toxicity of the drug, when used intragastrically, the number of animals that died, their general condition, functional condition, and skin condition were noted**.**

Determination of the toxicity of the ointment in a subchronic experiment. The chronic toxicity of the ointment was studied with long-term use.

The study of the skin resorptive effect of the ointment was conducted on 24 outbred white rats: 12 males and 12

females. Four groups (6 animals each) were formed for the experiment: two – control and two – received the studied drug. Ointment in the amount of 0.5 g/animal was applied to a cut area of skin 2×2 cm, which is 5 % of the area of the skin of the animals. The dose of the drug is sufficient for the specified area, and, in addition, it is minimal, which does not cause a toxic effect. In the same way, the control animals were treated with ointment based on the treated area of the skin. The study duration was one month, which is due to the Federal State University of Applied Sciences requirements for the study of new L3s. The drug was applied to the animals every day during the entire period of research.

During the experiment, the animals of all groups were kept in the same conditions on a complete diet following the established norms. A comparative analysis of the appearance, behavior, and attitude to the food of the experimental animals did not differ from the given indicators of the control group of animals. No changes in animal behavior were noted. There were no signs of inflammation, cracks, or seborrhea.

The selection of indicators for evaluating the overall toxic effect of the ointment on the body in a chronic experiment was carried out according to the following indicators: the degree of the harmful effect of the drug, with its long-term entry into the body of animals, with the subsequent identification of organs and systems sensitive to the drug.

The resorptive effect of the drug was evaluated by indicators of peripheral blood, the functional state of the liver and kidneys, the mass coefficients of internal organs, and the state of the central nervous and cardiovascular systems. All indicators were analyzed in dynamics: the beginning and the end of the experiment (after one month from the start of the drug application).

Study of the local anesthetic effect of the drug. The study of the local anesthetic effect was carried out on the rabbit eye anesthesia model. The experiment was conducted on ten male rabbits. As a comparison drug, Kapsikam ointment produced by JSC "Tallinn Pharmaceutical Plant" was used with the following composition: 1 g of ointment contains 50 mg of dimethyl sulfoxide, 30 mg of racemic camphor, 30 mg of turpentine essential oil, 20 mg of benzyl nicotinate and 2 mg of nonivamide.

The animals were divided into two groups, five rabbits in each Group. Animals of the 1st Group were injected with 0.1 g of the drug under the lower eyelid. Animals of the 2nd Group were injected with the same amount of the ointment base preparation. After 30 seconds after the start of the experiment, they were irritated by the conjunctiva (horsehair was passed over the eye's surface from the outer corner in the direction of the pupil). Stimulation was repeated every 10 seconds. The speed of appearance of local anesthesia was determined by the time from the placement of the test sample to the disappearance of the reaction to eye irritation. The duration of the action of the anesthetic substance was determined by the recovery time of the irritation reaction.

3. Results and discussion

It was established that after intragastric administration of the drug in doses: 5000, 10000, 15000, 20000, and 25000 mg/kg, no death of animals was observed. The general condition of the experimental groups did not differ from that of the animals in the control group. All animals had an average appetite; the skin was normal in color. No change in body temperature and tissue turgor was observed. All animals maintained reflex excitability, and no changes in urination and defecation were observed. The wool coat is smooth. The general behavior of the animals in the experimental groups did not differ from that of the animals in the control group. The obtained research results are shown in the table 1.

Table 1

Study of acute toxicity (LD_{50}) of the drug under conditions of single intragastric administration for rats

№ Group	Animals	Dose, mg/kg	Dead animals / surviving animals
Control	Males	The drug was not injected	0/5
	Females		0/5
1	Males	5000	0/5
	Females	5000	0/5
2	Males	10000	0/5
	Females	10000	0/5
3	Males	15000	0/5
	Females	15000	0/5
4	Males	20000	0/5
	Females	20000	0/5
5	Males	25000	0/5
	Females	25000	0/5

Thus, the obtained research results indicate that the developed drug, when administered intragastrically, does not show toxic effects on animals.

LD_{50} during intragastric administration of the drug could not be established because the volume of the drug exceeded the permissible level. Accordingly, according to the classification of substances, toxicity, and danger (according to the requirements of SOU 85.2-37-736:2011 and GOST 12.1.007-76), the drug "Dibutalastin Ointment" belongs to toxicity class IV – low-toxic substances and danger class IV – low-hazard substances.

The analysis of the obtained data shows that the drug does not cause changes in the studied indicators (tables 2 and 3).

The indicators of the morphological state of the blood of white rats after 14 days of applying the ointment to the skin are given in the table 4.

Table 2
Dynamics of changes in body weight during 14-day application of ointment on the skin of white rats (M ± m, n = 5)

Group	Initial body weight of animals, g	Research period	
		Seven days	14 days
Control	198.2 ± 5.13	202.5 ± 1.09	211.0 ± 3.01
Experiment	193.9 ± 3.14	199.7 ± 1.70	221.3 ± 2.23

Table 3
Weight coefficients of internal organs of white rats after a single intragastric administration of the drug (M ± m, n = 5)

Organ mass coefficients	Group of animals	
	Control	Experiment
Liver	3.61 ± 1.13	3.65 ± 1.21
Lungs	0.459 ± 0.71	0.434 ± 0.11
Spleen	0.436 ± 0.21	0.425 ± 0.19
Heart	0.354 ± 0.32	0.358 ± 0.13
Gonads	0.797 ± 0.16	0.795 ± 0.17
Adrenal glands	0.031 ± 0.01	0.032 ± 0.01
Kidneys	0.390 ± 0.02	0.386 ± 0.03
Thymus	0.149 ± 0.02	0.144 ± 0.01

Table 4
Indicators of the morphological state of the blood of white rats after 14-day application of the ointment on the skin (M ± m, n = 5)

The name of the indicators	Ointment	
	Control	Experiment
Total hemoglobin, g/L	142.1 ± 0.14	141.8 ± 1.17
Erythrocytes, T/L	7.6 ± 0.32	7.8 ± 0.37
Leukocytes, g/L	12.1 ± 2.03	13.1 ± 2.51
Hematocrit, %	38.1 ± 1.17	38.4 ± 3.14

The study of the irritating properties of the drug after a single application of the drug to the skin was carried out on animals: white rats (weighing 198–220 g) and rabbits (weighing 2.0–2.5 kg).

As a result of the experiment, it was established that when the drug is applied once to the skin of animals (white shuri, rabbits), no symptoms of irritation are observed. Also, when repeatedly applied to the skin of animals, no irritating effect of the drug was detected.

Thus, it has been proven that a single application of the drug to the skin of animals does not cause a local irritant effect.

The experiment to determine the irritating effect of the drug on the mucous membrane of the eyes was carried out on rabbits (except albinos).

In its native form, the drug was applied to the mucous membrane of the eye of a rabbit (50 mg in the form of a working 20.0 % solution). The absence of symptoms of irritation of the eye's mucous membrane during the entire experiment period was proved. That is, the drug does not have irritating properties of the ointment when in contact with the mucous membranes of the eye.

In this way, it was established that the drug has no resorptive-toxic effect even with epicutaneous (application to the skin) entry into the body.

Table 5
The effect of the ointment on the anesthesia of the rabbit eye (M ± m, n = 5)

Object of study	The speed of appearance of local anesthesia, sec.	Duration of anesthesia, sec.
"Dibutalastin" ointment	160 ± 11	311 ± 19
Ointment "Kapsicam"	154 ± 19	273 ± 17

Analysis of the data is given in the table. Five showed the advantage of the developed drug (immediate and long-lasting local anesthetic effect) over the comparison drug.

Summarizing the results of the conducted research, we can conclude: according to toxicological properties, "Dibutalastin" ointment belongs to toxicity class IV – low-toxic substances and danger class IV – low-hazard substances, exhibits a resorptive-toxic and non-irritating effect on the body of animals. There are no sensitizing properties.

4. Conclusions

1. The toxicological characteristics of the studied ointment "Dibutalastin" based on methyl salicylate and dimethyl sulfoxide were studied in an "acute" study on warm-blooded animals. The average lethal dose (LD_{50}) for intragastric administration could not be established, as the volume exceeded the permissible level.

2. It was established that according to the "average lethal dose when entering the stomach" indicator, the veterinary medicinal product belongs to relatively non-toxic substances (toxicity class IV).

3. The results of the conducted pharmacological studies indicate the absence of resorptive-toxic effects, sensitizing properties, and irritating effects on the mucous membranes of the eyes and skin.

4. Pathomorphological studies of animal organs when studying the acute toxicity of the medicinal product showed that the developed ointment with methyl salicylate and dimethyl sulfoxide does not cause pathological changes in internal organs. From the point of view of veterinary toxicology, this drug is safe.

Prospects for further research. Further studies will be the next stage of pre-registration tests aimed at studying the embryotoxic effect of "Dibutalastin Ointment", which is mandatory material of the "Safety and residue studies" section of the dossier for this medicinal product.

Conflict of interest

The authors declare that there is no conflict of interest.

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