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The study of the analgesic properties of combined aerosols with the propolis phenolic hydrophobic drug in the experiment

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Abstract

The article presents the results of the experimental study of the analgesic properties of model samples of combined aerosol drugs with the cooling action, which contain the propolis phenolic hydrophobic drug (PPHD) and topical anaesthetics as the main active ingredients. The samples studied are intended for external use in order to remove the pain syndrome in traumas occurring mainly in sports medicine and extreme conditions.

The results of the study have demonstrated the essential role of halocarbons in the final analgesic activity of the drugs under research. Thus, the optimal content of topical anaesthetic is 3.0% because the aerosols containing 3.0 g of lidocaine hydrochloride or articaine hydrochloride show the analgesic activity at the level of the experimental sample containing 5.0 g of articaine hydrochloride.

According to the results of the researches conducted, as well as for reasons of stability of the dosage forms of the samples studied it has been found that the sample containing 10% solution of PPHD in propylene glycol and 3.0% of lidocaine hydrochloride is the most appropriate for further development of the aerosol drug.

Keywords: aerosol, propolis phenolic hydrophobic drug, topical anaesthetics, analgesic effect, sports medicine.

1. Introduction

Currently the problem of providing a stable professional performance and improving the level of functional reserves of the human body under the conditions of physical extreme loads is of great medical and social importance [1]. Along with it, as well as in connection with early specialization in sport, an exceptionally high level of traumatic injuries in competitive athletes is observed; it, in turn, leads to the loss of competition form [2-5]. Long-term study of localization of injury in athletes promotes to identify the dynamics of the most vulnerable elements of the locomotor apparatus.

Under modern conditions in professional sport the most common injuries are injuries of knee and ankle joints accompanied with bruises, dislocations, tensions, ruptures of ligaments and tendons, ruptured muscles, broken bones, etc. [6]. When they occur, in most cases there are rupture of capillaries and microbleeding, which quickly spreads to adjacent tissues increasing the injured area. Inflammation in damaged tissues can be manifested as formation of oedema, local increase of temperature, redness, acute pain and dysfunction [7-8]. In this regard, there is a serious problem of discontinuation of sporting competition, as well as increase of duration of the period of rehabilitation and restoration of the health of athletes.

An alternative method of exposure to damaged areas in organs of the locomotor apparatus with the purpose of instant pain relief and reduction of inflammation is the use of effective drugs in the form of cooling aerosols with the topical anesthetic and anti-inflammatory action [9].

Previously in the experimental researches we studied anti-inflammatory properties of model samples of the combined aerosol containing the propolis phenolic hydrophobic drug (PPHD), topical anesthetics and coolants (a mixture of freons) [10] with the purpose of development of the rational composition of the drug for use in sports medicine and extreme conditions.

The aim of the present work is further studying analgesic properties of various pharmaceutical compositions in order to substantiate the most rational formulation and to develop the technology of the present aerosol drug possessing a multivalent spectrum of the pharmacological activity and a low toxicity.

2. Materials and Methods

A comparative study of analgesic properties of the compositions under research were conducted in 70 white outbred rats of both genders with the body weight of 180.0–200.0 g. According to the standard health and safety regulations [11] the experimental animals were kept on the appropriate food diet in the vivarium at the Central Research Laboratory (CRL) of the National University of Pharmacy certified by the State Enterprise «The State Expert Centre of the Ministry of Public Health of Ukraine» as a base for research in experimental pharmacology. The studies were conducted in accordance with EC Directive 86/609 EEC dated November, 24, 1986 on compliance of laws, acts and regulations of the EU countries as to protection of animals rights used for experimental and other scientific purposes [12, 13].

As the study subjects the experimental samples of combined drugs in aerosol dosage forms (aerosols 1, 2, 3 and 4) were used; they contained various substances with the analgesic, anti-inflammatory and cooling action, including 10% solution of PPHD in propylene glycol, topical anaesthetics (lidocaine hydrochloride or articaine hydrochloride), as well as a mixture of halocarbons (freons) as coolants. The formulations of all drugs studied are presented in Table.

As reference drugs the medicine «Proposol» manufactured by «Zdorovya» Pharmaceutical company», Ltd. (Ukraine) (registration certificate UA/8215/02/01), as well as the aerosol containing a mixture of freons without other active pharmaceutical ingredients were used.

In the course of the experiment all experimental animals were divided into 7 groups, there were 10 rats in each group. The groups were as follows:

- group 1 – control pathology;
- group 2 – rats with hyperalgesia receiving aerosol 1 as skin application;
- group 3 – rats with hyperalgesia receiving aerosol 2 as skin application;
- group 4 – rats with hyperalgesia receiving aerosol 3 as skin application;
- group 5 – rats with hyperalgesia receiving aerosol 4 as skin application;
- group 6 – rats with hyperalgesia receiving the reference drug «Proposol» as skin application;
- group 7 – rats with hyperalgesia receiving the mixture of freons as skin application.

Previously the initial values of the pain threshold (PT) [14] were determined for all rats using an analgesiometer 37215 (Ugo Basile, Italy) in the way of stimulating the pain reaction on the rear right paw [15–16].

After that in not less than 30 minutes the inflammatory hyperalgesia was modelled in all animals by subplantar introduction of 0.1 ml of 1% solution of λ -carrageenan (Fluka, Switzerland) in the rear right paw [15].

In 2 h after pathology modelling the samples of aerosols studied were applied on the skin of all animals as a single dose on the rear right paw on the area of a limb from the beginning of the hair-covering, including the ankle, and below in conventionally therapeutic dose of 20 mg. Aerosols were applied with a tampon, preliminary placing the content of the vial in a glass container under conditions of thorough rubbing-in and prevention of their licking by the animals from the surface of the skin at least for 15 min.

In 3 h after pathology modelling (in an hour after application

of the aerosols studied) determination of PT was conducted for all animals. Then the analgesic activity (AA) was calculated by the level of reduction hyperalgesia degree compared to the control animals and expressed in percent [17]:

$$AA = \frac{\Delta PT_k - \Delta PT_0}{\Delta PT_k} \cdot 100\%,$$

Where, ΔPT_k – is the average percentage of changes in the level of the pain sensitivity in the control pathology group before and after simulation of inflammatory hyperalgesia; ΔPT_0 – is the percentage of changes in the level of the pain sensitivity for each animal in the experimental group before and after simulation of inflammatory hyperalgesia and application of the aerosol studied.

The obtained values of the anti-inflammatory and analgesic activity were subjected to statistical processing by standard methods of variation statistics with the computer programs, as well as using the Student–Fischer test [18–19]; they were presented in the form of comparative table with the results of different groups.

3. Results and Discussion

During the study of analgesic properties of model samples of pharmaceutical compositions in aerosol dosage forms the results presented in Table were obtained.

Unlike the results of the study of anti-inflammatory properties [10] in the present studies the following regularity is observed: the mixture of freons has no less significant contribution to the final level of the analgesic activity in addition to the main active ingredients exhibiting analgesic properties, i.e. topical anaesthetics and menthol. This can be argued by a relatively small decrease in the level of PT in the group receiving the mixture of freons – only by 40.6%. In the control group pathology this parameter was reduced by 60.6%. This fact complicates a comparative study of the analgesic activity and eliminates differences in activity levels of different components to some extent not only depending on their concentration, but also on the type. However, there is no doubt that the contribution of PPHD to the final analgesic activity of the samples studied compared to the components mentioned above is minimal.

The results obtained showed that aerosol 3 exhibited the highest level of AA (60.9%) in the course of the conducted researches. Thus, it significantly exceeded the activity of the mixture of freons, aerosol 4 and the reference drug «Proposol».

In contrast, aerosols 1 and 2 exhibited a slightly lower level of AA, but without significant differences from aerosol 3, at the same time aerosol 2 took a second place by level of AA. AA of both samples was significantly higher than the activity level of the mixture of freons and «Proposol».

At the same time aerosol 4 exhibited AA at the level 53.0% that corresponded the levels of aerosols 1 and 2 without reliable differences, as well as significantly exceeded the level of AA of the mixture of freons and «Proposol», but it was inferior to the activity of aerosol 3.

It should also be noted that the reference drug «Proposol» showed the lowest level of AA in the present study – 38.0% that had not any differences from the group of the animals receiving the mixture of freons. Therefore, it can be explained not so much by the presence of weakly expressed analgesic properties of this drug, but initially high AA of the mixture of

freons as a base for all dosage forms presented.

Table: A comparative analgesic activity of pharmaceutical compositions in aerosol dosage forms

Name	Object The content of active pharmaceutical ingredients, %							PT, conventional units		Δ PT, %	AA, %
	PPHD solution	articaïne	lidocaine	menthol	rosemary oil	sea-buckthorn oil	allantoin	initial data	1 hour after drug application		
Control pathology	–	–	–	–	–	–	–	225.0±18.2	89.0±9.9	60.6±2.3	–
Aerosol 1	10.0	3.0	–	1.0	1.0	5.0	–	204.0±9.6	152.0±8.7	25.7±1.5 _{1,2,4}	57.6±2.4 _{2,4}
Aerosol 2	10.0	–	3.0	1.0	1.0	5.0	–	200.0±13.1	148.0±7.7	25.4±1.5 _{1,2,4}	58.2±2.4 _{2,4}
Aerosol 3	10.0	5.0	–	2.0	2.0	–	1.0	239.0±13.5	183.0±11.6	23.7±1.0 _{1,2,3,4}	60.9±1.6 _{2,3,4}
Aerosol 4	–	–	3.0	1.0	1.0	–	–	213.5±14.4	151.5±8.7	28.5±1.5 _{1,2,4}	53.0±2.5 _{2,4}
«Proposol»	10.0	–	–	–	–	–	–	236.0±15.9	147.0±10.0	37.6±1.3 _{1,3}	38.0±2.1 ₃
Mixture of freons	–	–	–	–	–	–	–	229.5±15.9	135.5±8.9	40.6±1.5 _{1,3}	33.0±2.4 _{3,4}

Notes: 1 – differences were significant compared to the control pathology group ($p \leq 0.05$);
 2 – differences were significant compared to the animals receiving the mixture of freons ($p \leq 0.05$);
 3 – differences were significant compared to the animals receiving aerosol 4 ($p \leq 0.05$);
 4 – differences were significant compared to the animals receiving the reference drug «Proposol» ($p \leq 0.05$).

4. Conclusions

- The results of the study of the analgesic properties of the aerosols under research are the evidence of a more significant contribution of halocarbons to the final analgesic activity than the main active components.
- The aerosol of formulation 3 has exhibited the highest level of the analgesic activity among all other aerosols in the given research; it is due to the highest content of topical anaesthetic articaïne hydrochloride – 5%, as well as menthol – 2%.
- The results obtained show that the most optimal content of a topical anaesthetic in aerosols is 3% since the aerosols of formulation 1 and 2 have activity at the level of the aerosol of formulation 3 without significant differences.
- According to the results of the research conducted, as well as for reasons of stability of the dosage forms of the samples studied it has been found that further development of the drug based on the aerosol of formulation 2 containing 10% solution of PPHD in propylene glycol and 3.0 g of lidocaine hydrochloride is the most appropriate since it is exactly this sample has exhibited 58.2% of the level of the analgesic activity without significant differences from the aerosol of formulation 3 containing 5.0% articaïne hydrochloride.

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