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Study of Antiexudative Effect of Gel Containing Extract of Convolvulus Arvensis

Z. Z. Khakimov[1], A. Kh. Rakhmanov[1,*], U. B. Yakubova[2], K. Sh. Shukurlaev[2]

[1]Pharmacology and Toxicology Department, Tashkent Medical Academy, Tashkent, Uzbekistan
[2]Urgench Branch of the Tashkent Medical Academy, Uzbekistan

Abstract The antiexudative effect of a gel containing *Convolvulus arvensis* extract was studied in an experiment on male white rats. The mechanism of the antiflogogenic action of this compound is associated with its antihistamine and antiseratonin action. It is concluded that the pharmacological activity of the gel containing *Convolvulus arvensis* extract practically does not differ from the ibuprofen gel.

Keywords Inflammation, Local action, Exudation

1. Introduction

The development and implementation of effective import-substituting anti-inflammatory drugs from local raw materials is one of the important areas of modern pharmacology, because they are widely used in the treatment of diseases in the pathogenesis of which inflammation takes the leading place. Non-steroidal anti-inflammatory drugs (NSADs) are widely used in daily life. However, the regular use of the latter does not always provide the necessary therapeutic effect, moreover, they quite often cause side effects (gastro-, nephro-, cardio-, hemato-, hepatotoxicity), which is associated with their ability to penetrate the histohematogenous barriers and the manifestation of systemic action [1,2,3]. Therefore, in recent years, great importance has been attached to the local use of anti-inflammatory drugs in soft drug forms [4,5,6,7]. It is known that aqueous extract of the aerial part of *Convolvulus arvensis* has a distinct anti-inflammatory effect in experimental animals at oral administration, which is associated with its antagonism in relation to inflammatory mediators, a decrease of vascular permeability and suppression of hyaluronidase activity [8]. One of the effective ways to prevent the development of adverse drug reactions is their local application in the form of a gel, cream, ointment, etc. Moreover, their action is limited to the place of their application and does not allow the development of systemic action. Gels, due to the special composition of excipients, promotes the fast onset of the local anti-inflammatory effect [9,10]. Therefore, gels are currently the most common "modification" of NSAIDs for external use.

The above circumstance served as the basis for the development of a new drug form - a gel containing an extract of *Convolvulus arvensis* and the study of its antiexudative activity at local application.

2. Material and Methods

Experimental studies were carried out on sexually mature white male rats with an initial weight of 155-180 g. Before the experiment, the animals were quarantined for 12-14 days. All animals were kept in vivarium conditions (with natural lighting, at a temperature 22-24℃; relative humidity 40-50%) using a standard diet. Each experimental group consisted 6 individuals. The antiexudative effect of the drugs was studied on models of acute inflammatory edema of the paws of animals by subcutaneous injection of 6% dextran solution, 0.2% histamine solution and 0.01% serotonin solutions (0.1 ml per animal) into the paw of the hind right limb of the rats. These models of inflammatory edema are widely used to assess the anti-inflammatory activity of new potential drugs [11,12,13]. Measurement of the volume of the paws of animals was carried out by the oncometric method using a plethysmometer [14] before and hourly for four hours after the injection of the flogogens. The value of anti-inflammatory activity (VAA) of drugs was calculated according to the formula VAA = Vcontrol-Vexperiment / Vcontrol x 100 =% [11]. A gel containing *Convolvulus arvensis* extract and ibuprofen gel was applied to the surface of the right hind paw of the animals one hour before flogogen injection and after each measurement. Experimental studies were carried out in accordance with the rules of good laboratory practice (GLP) in conducting preclinical studies in the Republic of Uzbekistan.

* Corresponding author:
dr.ali.fl@mail.ru (A. Kh. Rakhmanov)
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The approval of the Ethic Committee of Uzbekistan were taken before carrying out the experiments on animals. All experiments were performed in compliance with the requirements of the European Convention "On Protection of vertebrate animals used for experimental and other scientific purposes" (Strasbourg 1986).

2.1. Statistical Analysis

The received results were subjected to the statistic processing with the using of standard software package Biostat 2009 on well-known method of variation statistics, all results were considered as mean ± SEM. Differences between groups were analyzed using the Student's t-test. $P<0.05$ was considered significant.

3. Results and Discussion

The results of the studies showed that the subplantar injection of the dextran solution leads to increase of the volume of paws an almost two times during the first two hours from the beginning of the experiment, which remained without significant changes in the next four hours of the experiment. This result once again convincingly proves the high activity of dextran as a flogogen. The use of 5% ibuprofen gel led to a distinct decrease of the level of paw's edema of rats developing under the influence of dextran.

So, after 1 hour the paw of animals increased by 61.0%, after 2 hours - 63.0%, and after 3 and 4 hours - 52.6% and 44.2% in comparison with the initial volume. During the indicated study periods, the VAA of the drug was 34.8; 36.2; 38.3 and 40.0%, respectively. It can be seen that the ibuprofen gel, when applied locally, exhibits a distinct anti-inflammatory activity. Further studies have shown that the gel containing *Convolvulus arvensis* extract also has anti-exudative activity. It can be seen in table 1 that during the application of 1% gel of the *Convolvulus arvensis* extract, VAA was 10.1 and 9.6% at the first two hours of the experiment. The increase of the concentration of the gel to 3% led to rise degree of antiexudative effect of *Convolvulus arvensis* extract. So, after 1 hour from the onset of dextran action, the volume of the paws increased by 67.0%, and after 2 hours - 68.1%. This effect persisted with slight fluctuations in subsequent periods of observation. The calculation of the VAA during the using of 3% gel showed that VAA was equal to 31.4; 34.0; 35.8 and 37.1%, respectively in the indicated periods of the experiment.

The presented data allow us to state that the pharmacological activity of 3% *Convolvulus arvensis* extract gel is not inferior to 5% ibuprofen gel. There was a great interest to establish the antiexudative effect of the gels in the same concentrations. The results of carried out experiments showed that the application of 5% gel of extract led to the inhibition of the exudation process greater than the 3% gel of the *Convolvulus arvensis* extract and 5% ibuprofen gel.

Thus, the *Convolvulus arvensis* extract gel and ibuprofen gel exhibit a distinct antiexudative effect on the dextran model of aseptic inflammation in experimental animals. However, the differences between the results were statistically insignificant, which makes possible to assert the used drug concentrations have the same VAA.

Poryadina G.V. [15] considered that the development of aseptic inflammation induced by dextran is due to the release of histamine and serotonin from mast cells, which are one of the important mediators of inflammation. Based on this, in a separate series of experiments, we investigated the effect of *Convolvulus arvensis* extract gels and ibuprofen gels on the course of histamine and serotonin inflammation.

Based on this, in the subsequent series of experiments, we conducted studies to establish the antiexudative effect of the *Convolvulus arvensis* extract gel in comparison with the ibuprofen gel on histamine- and serotonin-induced aseptic arthritis models. The results of these series of experiments showed that the subplantar injection of histamine led to an increase of rats paw volume by 72.3% compared to the initial paw volume, then it increased by 44.5% in *Convolvulus arvensis* extract gel treated rats, and by 53.6% in ibuprofen gel treated rats. It can be seen that the used gels clearly suppress the exudation process induced by histamine. We noted the same effect, but more expressed, after 2-4 hours of the experiment. It is noteworthy that the pharmacological activity of the *Convolvulus arvensis* extract containing gel was superior to the ibuprofen gel, which was clearly demonstrated by the results of the VAA values of the preparations (see Fig. 1).

Table 1. Study of the effect of the gel containing the extract of *Convolvulus arvensis* and ibuprofen on the course of dextran inflammation

Groups	Volume of paw,cm^3				
	Initial	1 hour	2 hours	3 hours	4 hours
Control	0,96±0,04	1,85±0,08*	1,90±0,09*	1,77±0,08*	1,66±0,06*
Convolvulus arvensis, (1 % gel)	0,90±0,04	1,70±0,09*	1,75±0,08*	1,67±0,08*	1,58±0,08*
Convolvulus arvensis, (3% gel)	0,91±0,03	1,52±0,07*	1,53±0,08*	1,43±0,07*	1,35±0,09*
Convolvulus arvensis, (5% gel)	0,95±0,05	1,49±0,07*	1,51±0,05*	1,41±0,04*	1,30±0,05*
Ibuprofen, (5% gel)	0,95±0,05	1,53±0,08*	1,55±0,09*	1,45±0,10*	1,37±0,10*

Note: * - statistically significant compared to the control ($P<0.05$).

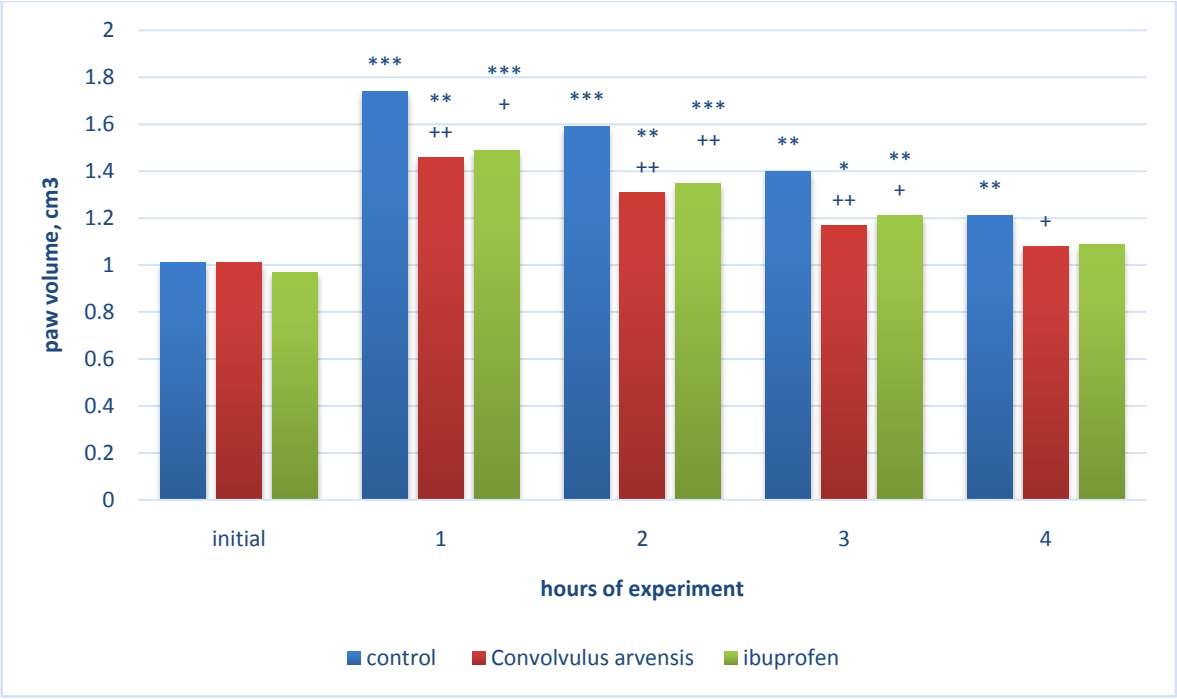

Figure 1. Comparative antiexudative activity of the gel containing the extract of *Convolvulus arvensis* and ibuprofen on the course of histamine inflammation (significance comparing initial indexes: *** - P<0.001, ** - P<0.01, *- P<0.05, significance comparing to control group: $^{+++}$ - P<0.001, $^{++}$ - P<0.01, $^{+}$- P<0.05)

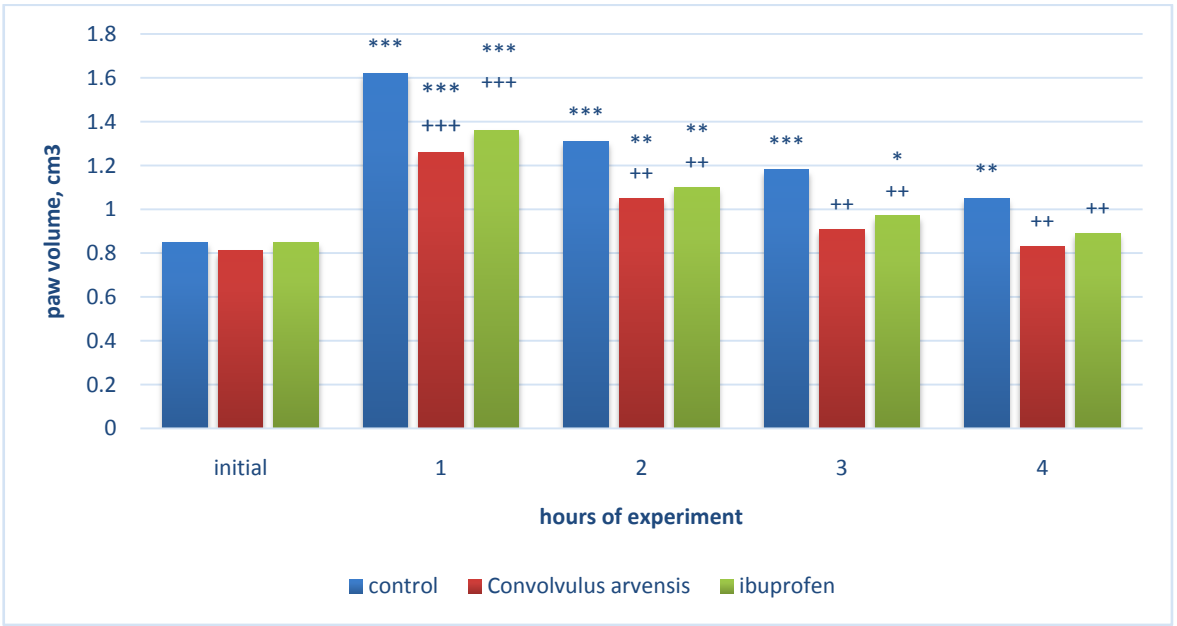

Figure 2. Comparative antiexudative activity of the gel containing the extract of *Convolvulus arvensis* and ibuprofen on the course of serotonin inflammation (significance comparing to initial indexes: *** - P<0.001, ** - P<0.01, *- P<0.05, significance comparing to control group: $^{+++}$ - P<0.001, $^{++}$ - P<0.01, $^{+}$- P<0.05)

Histamine stimulating H1-receptors located in the vessels, bronchi and stomach, has a multifaceted effect on the human body, in particular, causes an increase of vascular permeability, bronchial spasm, a decrease of blood pressure and it increases secretion of gastric juice [15,16]. This mediator is determined in the site of inflammation simultaneously with the onset of damage. It causes vasodilatation of the microvascular vessel, increases their permeability, stimulates the endings of pain nerves. Thus, histamine "triggers" an acute inflammatory response. The appearance of histamine in the focus of inflammation is closely related to the degranulation of mast cells, in which the synthesis of new mediators from the lipids of the membranes of activated mast cells and basophils is stimulated, such as proteases, proteglycans, eosinophil chemotaxis factors, kinins, complements, ecazonoids,

leukotrienes (platelet activation factor) and others [15].

The results of the study of the antiexudative effect of the gel containing extract of *Convolvulus arvensis* on the model of serotonin inflammation do not significantly differ from the data obtained on the histamine -induced aseptic arthritis model. So, after 1 hour from the beginning of the application of the gels in animals with histamine-induced inflammation, the VAA value was 38.3% in *Convolvulus arvensis* extract treated group, and 28.8% in ibuprofen treated group, so this value was 39.37% and 28.6%, respectively in animals serotonin-induced aseptic arthritis model. In the subsequent hours of the experiment, the degree of the noted effect tended to grow (Fig. 2).

Biogenic amines, hormones and cytokines are active compounds that under physiological conditions provide homeostasis of body tissues, under conditions of overproduction and local increasing of them to the critical concentration, they turn from physiological regulators into their opposite - mediators of early inflammation. They cause to the disturbances of the permeability of lysosomal membranes following by the release of tissue lysosomal hydrolases, which have a cytotoxic effect. Acting as a factor of the initiating cell destruction, the influence of lysosomal enzymes aggravates the damage process that has begun deeply in the tissues and they are considered an additional factor in the development and maintenance of tissue destruction.

These shifts are accompanied by certain changes in the content of acetylcholine, serotonin and cytokines in the blood serum. Due to this the destabilization of homeostasis occurs with a local disturbance of microcirculation, disturbances of the permeability of cell membranes and membranes of cell organelles, which leads to the release of enzymes beyond the "permitted" limits under normal conditions, that is, into the cytosol and further into the intercellular medium, thus, a typical inflammatory process develops [17].

Thus, the results of the last two series of experiments has shown that, on the one hand, the effects of histamine and serotonin play an important role in the mechanism of the flogogenic action of dextran, and on other hand, VAA value of the studied gels are largely expressed due to their antagonism with the investigated inflammatory mediators.

4. Conclusions

1. The gel containing *Convolvulus arvensis* extract exhibits a distinct anti-exudative effect on the model of dextran-induced aseptic arthritis.
2. The anti-exudative effect of the gel containing the extract of *Convolvulus arvensis* is largely due to the antagonistic effect on the histamine and serotonin systems.
3. In terms of its pharmacological activity, the gel containing *Convolvulus arvensis* extract practically does not differ from the activity of ibuprofen gel.

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