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PHARMACOLOGICAL CORRECTION OF THE EXUDATION PROCESS WITH CELAGRIP IN PREPUBERTAL RATS

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Abstract: In order to develop a new anti-inflammatory drug for the treatment of inflammatory diseases in pediatric practice, the pharmacological activity of CelAgrip and Ibuprofen on the development of exudation induced by histamine and carrageenan was studied in prepubertal animals. It was found that both drugs exhibited almost the same degree of anti-exudative effect, which was confirmed in an additional series of experiments using a model of aseptic peritonitis induced by acetic acid. It is believed that the action of the drugs does not show a pronounced dose dependence. Considering its low toxicity and absence of side effects, the use of CelAgrip in pediatric practice is recommended for the treatment of diseases in which inflammation plays a central role in the pathogenesis.

Keywords: prepubertal period, phlogogens, histamine, carrageenan, aseptic peritonitis, exudation

Introduction

One of the important phases of inflammation is the development of exudation, which is a clinical manifestation of this pathology. The development of the exudative process is largely due to increased vascular permeability and the release of the liquid part of the blood into the surrounding tissue. Suppression of this phase of inflammation helps to relieve pain caused by mechanical pressure on nociceptors, as well as to eliminate functional disturbances in the affected area.

Well-known anti-inflammatory agents, both steroidal and non-steroidal in structure, generally suppress exudation processes, since by inhibiting phospholipase A or cyclooxygenase activity, they reduce the generation of prostaglandins—the main mediator of inflammation—as well as the degranulation of mast cells containing large amounts of histamine. In adult subjects, these processes have been studied in sufficient detail, which has made it possible to develop effective anti-inflammatory agents. However, this problem has not been adequately studied in children, which hinders the development of effective treatments.

In recent years, an important role has been established for polyphenolic compounds with antioxidant properties, which therefore suppress lipid peroxidation processes that lead to the release of arachidonic acid—the main source of pro-inflammatory prostaglandin synthesis. It has been shown that the polymeric complex of the polyphenolic compound gossypol has a

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pronounced antioxidant property, leading to the suppression of inflammation in adult subjects [1,2].

The inflammatory process often develops during the prepubertal period due to the low activity of compensatory-adaptive processes. Anti-inflammatory agents used in adults are administered to children in doses adjusted according to the patient's age. However, as literature data show, the number of drugs specifically developed for pediatric use is extremely small [3,4]. This situation necessitates the development of experimentally justified doses and administration regimens of non-steroidal anti-inflammatory drugs, or the creation of new medicinal compounds with a different mechanism of anti-inflammatory action [5].

The above considerations indicate the need for experimental studies to determine the effectiveness of known or novel anti-inflammatory drugs during the prepubertal period.

The aim of this work was a comparative study of the effects of CelAgrip and Ibuprofen on the course of the exudative process induced by phlogogens with different mechanisms of action.

Materials and Methods

The experiments were conducted on two-month-old white rats weighing 70–85 g, obtained from the vivarium of the Sanitary-Epidemiological Station of the Medical-Sanitary Association under the Ministry of Health of the Republic of Uzbekistan. Prior to the start of the experiment, after a two-week quarantine period, all animals were examined and weighed, with age, sex, motor activity, and skin condition taken into account. Each experimental and control group consisted of six animals. The air temperature in the facility was maintained at +22.0–24.0 °C, with humidity at 50–60%. The light cycle was set to 12 hours and regulated by artificial lighting. Animals were kept on a standard diet with free access to drinking water.

All work with laboratory animals was carried out in strict compliance with the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes (ETS No. 123, Strasbourg, 18 March 1986), within the framework of the research project: "Study of the Anti-phlogogenic Activity of CelAgrip in Animals during the Prepubertal Period." The experimental studies on laboratory animals were approved by the Ethics Committee of the Tashkent Medical Academy under the Ministry of Health of the Republic of Uzbekistan (protocol No. 6 of April 25, 2025).

The study drug was CelAgrip tablets (manufacturer: Radiks, Scientific Production Enterprise, Uzbekistan). As a reference drug, Ibuprofen tablets were used, which are considered the "gold standard" among nonsteroidal anti-inflammatory drugs (NSAIDs) and are widely recognized as the reference standard for evaluating the therapeutic potential and safety of medicines in this pharmacotherapeutic group in pediatrics [6] (manufacturer: Borisov Medical Preparations Plant, Belarus).

To study the anti-exudative activity of CelAgrip and Ibuprofen, classical models of experimental aseptic arthritis were used, induced by solutions of various phlogogenic agents at the following concentrations: histamine (0.1%), carrageenan (1%), and acetic acid (1%)

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[7,8,9]. Histamine and carrageenan solutions (0.1 ml per animal) were administered subplantarly (under the plantar aponeurosis) into the right hind paw of rats on the dorsal side of the foot. The paw volume before the introduction of the phlogogen was taken as the baseline (100%).

Intragastrically, using a metal probe, one day and one hour before the induction of aseptic arthritis, rats in the control group were given an equivalent volume of water, while experimental groups received CelAgrip or Ibuprofen at doses of 10, 25, and 50 mg/kg. The volume of the right hind paw was measured using an oncometric method with a digital plethysmometer (Ugo Basile Srl, Italy) before and 30, 60, 90, and 120 minutes after histamine administration, and before and 1, 2, 3, and 4 hours after carrageenan administration.

The criteria for evaluating the anti-phlogogenic effect of the drugs included the paw volume increase, inhibition index, and calculated anti-inflammatory activity.

- **Edema Increase (EI)** was calculated by the formula [8,11]:

$$EI = (O - I) / I \times 100 = \%$$

where:
EI – edema increase,
O – paw volume after the introduction of the inflammation inducer,
I – paw volume before the introduction of the inflammation inducer.

- **Inhibition Degree (ID)** was calculated by the formula:

$$DI = 100\% - [(O - I) / I\,(E) : (O - I) / I\,(C)] \times 100 = \%$$

where:
E – experimental group (treated animals),
C – control group (untreated).

- **Anti-inflammatory Activity (AIA)** was calculated by the formula:

$$\mathbf{AIA = (V\_control - V\_exp) / V\_control \times 100 = \%}$$

Where:

- **V_control** – mean increase in limb volume in the control group, cm^3;
- **V_exp** – mean increase in limb volume in the experimental group, cm^3.

Aseptic peritonitis in rats was induced by intraperitoneal administration of a 1% acetic acid solution (1 ml per 100 g body weight) [10]. CelAgrip and Ibuprofen at a dose of 25 mg/kg were administered intragastrically one hour before inflammation induction. Rats in the control group received physiological saline one hour before acetic acid injection. Three hours after the administration of acetic acid or saline, the rats were decapitated under light ether anesthesia, after which a gentle massage of the abdominal wall was performed, and peritoneal fluid was collected.

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The results of the experimental studies were processed using generally accepted methods of variational statistics with the standard software package StatPlus 2009, with evaluation of the significance of indicators (M ± m) and differences between the studied samples by Student's t-test. Differences were considered statistically significant at a probability level of 95% or higher ($P < 0.05$).

Research Results

Previously, we established the high anti-exudative activity of CelAgrip in prepubertal rats with dextran-induced inflammation [12]. In the phlogogenic mechanism of dextran, histamine plays an important role [13,14]. In the present study, to clarify this point, we investigated the effect of CelAgrip on the course of aseptic inflammation induced by histamine.

The results of the study showed that during the first hours of observation, histamine doubled the volume of the rats' paws, which subsequently slightly decreased (1.8–1.9 times). These data confirm the significant role of histamine in the development of the exudative process.

In contrast, the tested drugs clearly inhibited the development of exudation, demonstrating anti-inflammatory activity. The magnitude of this parameter when using CelAgrip at doses of 10, 25, and 50 mg/kg was 13.9%, 19.0%, and 21.5%, respectively, 30 minutes after histamine administration.

Prolongation of the observation time led to a slight increase in the observed effect, with a clear dose dependence of CelAgrip. At a dose of 50 mg/kg, its anti-inflammatory activity reached 23.4% and 24.1% after 90 and 120 minutes of the experiment, respectively.

As shown in Table 1, Ibuprofen exhibited the same trend of action, and the values of its anti-inflammatory activity did not differ statistically significantly from those of CelAgrip.

Table 1

Anti-inflammatory activity of CelAgrip and Ibuprofen in a model of acute exudative inflammation induced by histamine in prepubertal rats

Groups	Doses, mg/kg	Volume of paws, cm3		Increase in edema,%	PVA, in%
		Original volume	30 minutes after histamine administration		
Control	-	0,72 ± 0,03	1,51 ± 0,11*	109,7	-
CelAgrip	10	0,66 ± 0,02	1,34 ± 0,09*	103,0	13,9
CelAgrip	25	0,76 ± 0,04	1,40 ± 0,11*	84,2	19,0
CelAgrip	50	0,73 ± 0,03	1,35 ± 0,07*	84,9	21,5
Ibuprofen	10	0,77 ± 0,03	1,43 ± 0,10*	85,7	16,4
Ibuprofen	25	0,70 ± 0,02	1,33 ± 0,09*	90,0	20,2
Ibuprofen	50	0,73 ± 0,03	1,34 ± 0,10*	83,5	22,8

Note: * - reliable difference in relation to the original corresponding groups

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Therefore, the pharmacological agents under study inhibit the development of exudation induced by histamine in prepubertal animals. In the case of CelAgrip, a dose-dependent effect is observed, which is not seen with Ibuprofen.

According to the requirements for preclinical studies of new anti-inflammatory agents—particularly their anti-exudative activity—carrageenan is commonly used [7,15]. Based on this, in a separate series of experiments, we studied the characteristics of the exudation process induced by carrageenan in prepubertal rats with the preventive administration of CelAgrip and Ibuprofen. As in the previous series of experiments, the drugs were used in three different doses, which was necessary to determine the effective dose of the agent.

The carrageenan-induced inflammation model is used not only to study new potential anti-inflammatory agents but also to investigate the mechanisms of inflammatory processes, since the action of this phlogogen has two phases: the initial kinin phase and the later prostaglandin edema phase [17,18; Okpo O.S., Irivboje O.J., Maduekwe C.Ch., Idemudia O.J. Evaluation of the anti-inflammatory properties of the aqueous extract of Albizia zygia stem bark. Journal of PHARMACY AND BIORESOURCES, Vol. 13, no. 2, pp. 83-91 (September 2016). Notably, the cardinal sign of inflammation—edema—develops immediately after subplantar injection of the phlogogen without tissue damage, which is a significant distinguishing feature of carrageenan's phlogogenic action [17,18].

The results of this series of experiments showed that subplantar injection of carrageenan in prepubertal rats led to an increase in paw volume of 30.7%, 38.7%, 49.3%, and 58.7% at 1, 2, 3, and 4 hours from the start of the experiment, respectively. In previous studies on adult rats, carrageenan injection caused a more pronounced exudative reaction (2–3 times greater) than in immature animals [16]. This fact indicates the insufficient development of physiological processes in immature rats responsible for responding to the phlogogen. It should be noted that in both mature and immature prepubertal animals, carrageenan shows a biphasic effect, with a more pronounced response in the prostaglandin phase of inflammation.

Preventive administration of CelAgrip, as shown in Table 2, clearly inhibited the development of exudation, especially at a dose of 25 mg/kg, where the anti-inflammatory activity of the drug was 21.7% and 27.6% at 1 and 2 hours, and 35.1% and 38.6% at 3 and 4 hours, respectively. From the data in Table 2, it is evident that doubling the dose did not lead to an increase in the pharmacological effect of the drug. Almost the same effect was observed in the group of rats that received preventive Ibuprofen, especially at the high dose (50 mg/kg).

Table 2

Anti-inflammatory activity of CelAgrip and Ibuprofen in a model of acute exudative inflammation induced by carrageenan in prepubertal rats

Gruppy	Dose, mg/kg	Volume of paws, cm3		
		Initial volume	2 hours after administration of carrageenan	4 hours after administration of carrageenan

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Control	-	0,75 ± 0,03	1,04 ± 0,05*	1,19 ± 0,06*
CellAgrip	10	0,73 ± 0,02	0,97 ± 0,08*	1,04 ± 0,07*
CellAgrip	25	0,71 ± 0,03	0,92 ± 0,06*	0,98 ± 0,06*
CellAgrip	50	0,72 ± 0,02	0,94 ± 0,08*	1,00 ± 0,07*
Ibuprofen	10	0,74 ± 0,04	0,97 ± 0,09	1,02 ± 0,09*
Ibuprofen	25	0,77 ± 0,03	0,98 ± 0,08	1,04 ± 0,07*
Ibuprofen	50	0,76 ± 0,04	0,96 ± 0,08	1,02 ± 0,09*

Note: * - reliable difference in relation to the original corresponding groups

Thus, similar to Ibuprofen, CelAgrip in prepubertal animals exhibits a pronounced anti-inflammatory effect, manifested in the suppression of the exudation process. It is considered that if the anti-inflammatory activity of a drug reaches 30% or more, it is regarded as promising [19,20].

The results of the present series of experiments confirm the validity of the previous study's findings regarding the high anti-inflammatory activity of CelAgrip, similar to Ibuprofen, in prepubertal animals.

In many studies, the method of aseptic peritonitis induced by intraperitoneal injection of acetic acid is used as an objective test to evaluate the anti-exudative effect of new compounds [10,21]. Based on this, we conducted studies to examine the effect of CelAgrip, in comparison with Ibuprofen, on the course of exudation in a model of aseptic peritonitis.

The results of the experimental studies in prepubertal animals showed that three hours after the intraperitoneal injection of acetic acid, 1.95 ± 0.04 ml of exudate was detected in the abdominal cavity. Pretreatment with CelAgrip at doses of 10, 25, and 50 mg/kg led to a decrease in exudate volume by 15.4%, 39.5%, and 41.5%, respectively. In animals pretreated with Ibuprofen at the same doses, the exudate volume was also reduced by 22.6%, 36.4%, and 44.6%, respectively.

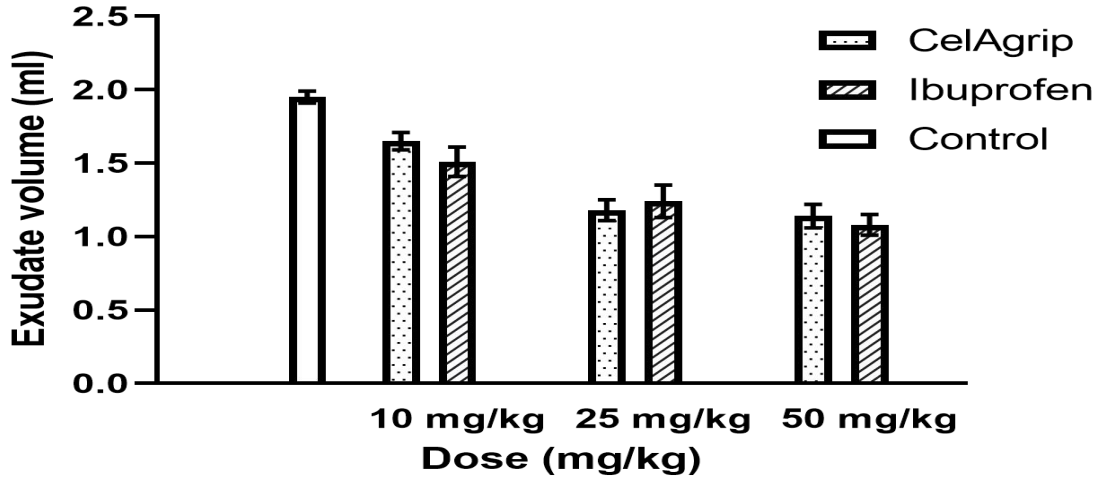

Figure 1. Anti-inflammatory activity of CelAgrip and Ibuprofen in a model of aseptic peritonitis in prepubertal rats

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It can be seen that both drugs significantly reduce the volume of exudate compared to the control, especially at higher doses. At the same time, no significant difference in the pharmacological activity of the studied drugs was noted. It should be noted that the results of the last series confirm the conclusions drawn from the results of previous series of experiments conducted with various phlogogens.

Summarizing the results of the experimental studies, it can be stated that the polymer complex of gossypol – CelAgrip – has a significant inhibitory effect on the development of aseptic inflammation induced by various phlogogens, which indicates its anti-inflammatory activity previously established in sexually mature animals [16, 22]. We consider it possible to use CelAgrip in pediatric practice as a treatment for pathological conditions in which inflammation plays an important role in the pathogenesis. CelAgrip is a low-toxicity compound, both with single and repeated administration, and does not have local irritating, embryotoxic, cumulative, or allergenic effects [23, 24]. All this is an advantage of CelAgrip over Ibuprofen, since the drug also has a stimulating effect on the production of antiviral proteins – interferons [1, 25].

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