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# PRECLINICAL INVESTIGATION OF THE ALLERGENIC EFFECT OF THE DRUG BASED ON THE PHENOLIC COMPOUND KUD975

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**Abstract**

***Introduction:*** *Vascular endothelium is a cellular monolayer that covers the internal lumen of all blood vessels, thus separating blood from the vessel wall and tissues. The study of the role of endothelium in the pathogenesis of cardiovascular diseases led to an understanding of the concept of it as a target for the prevention and treatment of these pathologies.*

***Research tasks:*** *The purpose of this study was preclinical study of the allergic effect of the drug KUD975, based on a phenolic compound, which is a selective inhibitor of arginase 2.*

***Methods:*** *Experiments on the allergic properties of the phenolic compound KUD975, which is a selective inhibitor of arginase II, were carried out on albino sexually mature guinea pigs weighing 300 ± 20 g. The preparation was administered intragastrically as a suspension in a 1% starch paste using a specially prepared atraumatic probe at 0, 1 ml of suspension per 10 g of body weight of animals. As a control, we used data obtained in animals with intragastric administration of the corresponding volume of placebo-1% starch paste.*

***Results:*** *In the course of the study of the allergic properties of KUD975, when the reaction of active cutaneous anaphylaxis was formulated, it was found that the studied preparation in two and eight times daily therapeutic dosages did not possess allergic properties*

*In the course of the study of the allergic properties of KUD975 in the formulation of a delayed-type hypersensitivity reaction, it was found that the study drug in two and eight times daily therapeutic dosages had no allergenic properties. Erythema, or, especially, infiltration and the appearance of ulcers at the site of administration as a resolving dose of the drug, as well as in the control of reactivity, were not observed in any animal participating in the experiment.*

***Conclusion:*** *When investigating the allergenic properties of the phenolic compound KUD975, which is a selective inhibitor of arginase II in the reaction of active cutaneous anaphylaxis, it was found that the study preparation in two and eight times daily therapeutic dosages does not have allergic properties. In the reaction of active cutaneous anaphylaxis in guinea pigs, the allergic properties of KUD975 in two and eight times daily therapeutic dosages were not detected*

**Key words***: compounds of phenolic nature, allergic action, endothelium, inhibitors of arginase II*

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## INTRODUCTION:

The vascular endothelium is a cellular monolayer that covers the internal lumen of all blood vessels, thus separating blood from the vessel wall and tissues. The study of the role of endothelium in the pathogenesis of cardiovascular diseases led to an understanding of the concept of it as a target for the prevention and treatment of these pathologies

Using the concept of privileged structures and methods of computer modeling, project participants assume the presence of endothelioprotective activity in phenolic compounds containing directly bound heteroatomic and / or heterocyclic structural fragments. The design of molecular structures of these low-molecular compounds was carried out using modern medical-chemical approaches and assumes a high probability of advancing the compounds being developed to preclinical and clinical trials.

The purpose of this study was preclinical study of the allergic effect of the drug KUD975, based on a phenolic compound, which is a selective inhibitor of arginase 2.

The search for innovative molecules [1, 2] is an important task of pharmacology. In addition, their study should be carried out on pharmacological targets [3, 4], in vivo models [5, 6], pharmacokinetic parameters [7, 8] and clinical studies [9, 10].

## MATERIALS AND METHODS:

Experiments to study the allergenic properties of KUD975 were carried out on albino sexually mature guinea pigs with a mass of 300 ± 20 g [11, 12].

In the course of the study of allergic properties, the drug KUD975 was used in two and eight times daily therapeutic doses. The twice daily therapeutic dose of the study drug for guinea pigs was 5.3 mg / kg / day, eight times - 21.2 mg / kg / day.

The drug was administered intragastrically as a suspension in a 1% starch paste using a specially prepared atraumatic probe at the rate of 0.1 ml of suspension per 10 g of body weight of the animals. As a control, we used data obtained in animals with intragastric administration of the corresponding volume of placebo-1% starch paste.

The animals were kept 5 in the cage, the males separately from the females. For the maintenance of animals, a system of individually ventilated cells Tecniplast, Italy with temperature control function was used. The distribution of animals in groups was carried out after a 10-day period of quarantine in accordance with gender and body weight. Identification - applying individual labels to the body. Forage throughout the study was used granulated. The water in the fillets is filtered, disinfected with ultraviolet irradiation. Layer - sterilized by UV-irradiation sawdust. Photoperiod - 12 hours a night / 12 hours a day with artificial daylight fluorescent lighting.

During the research, the study of allergic properties of KUD975 was carried out by setting up two reactions: active cutaneous anaphylaxis and delayed type hypersensitivity.

Reaction of active cutaneous anaphylaxis. [11, 13]

The animals were divided into the following groups (10 in the group, 5 females and 5 males): I - control; II - KUD975 in a dose of 5.3 mg / kg / day; III - KUD975 in a dose of 21.2 mg / kg / day.

Sensitization of guinea pigs with the test drug was carried out by intragastric administration for 30 days. The next day after the last administration, anaphylactogenic activity was evaluated in the reaction of active cutaneous anaphylaxis by intradermal (in the back region) administration of the resolving dose of the test preparation in a volume of 0.05 ml, and 0.05 ml of a sterile isotonic solution sodium chloride.

The resolving dose was selected by the experimental method in such a way that it does not cause irritant effect at the site of administration. 5 males and 5 female albino guinea-pigs were used to determine the resolving dose. Each guinea pig was injected intradermally with 0.05 ml of an aqueous solution of KUD975, film-coated tablets, 10 mg in the following concentrations: 20%, 10%, 5%, 2%, 1%. Then, for three hours, the places of administration were observed to determine the possible local irritant effect. It was found that after intradermal administration of 20% and 10% of KUD975 solutions, there were signs of local irritating effect, consisting of local reddening of the skin. Intracutaneous administration of 5%, 2%, and 1% of aqueous solutions of KUD975 in this volume did not lead to signs of local irritant effect. Thus, in further experiments, the maximum concentration of the drug was used, which did not have a local irritant effect with intradermal administration, 5%.

After 20-25 minutes, animals under light anesthesia were injected intravenously with 0.5 ml of a 1% solution of blue Evans. Thirty minutes later, the animals were euthanized and a blue spot on the inside of the skin at the injection site was determined by means of a caliper.

Hypersensitivity reaction of delayed type

The animals were divided into the following groups (10 in the group, 5 females and 5 males): IV - control; V - KUD975 in a dose of 5.3 mg / kg / day; VI - KUD975 in a dose of 21.2 mg / kg / day.

Sensitization of guinea pigs with the test drug was carried out by intragastric administration for 30 days. Anaphylactogenic activity was assessed in a delayed-

type hypersensitivity reaction through 10 and 30 injections by intradermal (in the back) administration of the resolving dose of the test preparation-5% aqueous solution of the preparation in a volume of 0.05 ml, and 0, 05 ml of sterile isotonic sodium chloride solution. The reaction was assessed visually after 1 hour, 24 hours and 48 hours on the outer surface of the skin and expressed in points according to the SV scale. Suvorov:

0 points - no visible reaction;

1 point - pale pink erythema throughout the site or along its periphery;

2 points - bright pink erythema throughout the site or its periphery;

3 points - red erythema throughout the site;

4 points - infiltration and swelling of the skin (thickening of the skin fold) with or without erythema;

5 points - erythema, marked infiltration, focal ulcerations (necrosis), hemorrhages are possible, crust formation.

## RESULTS AND DISCUSSION:

In the course of the study of the allergenic properties of the study drug KUD975, the reaction of active cutaneous anaphylaxis was found to show that the study preparation in two and eight times daily therapeutic dosages does not have allergic properties (Table 1). The results of the study are presented in Table 1.

**Table 1: Results of the study of the allergic properties of KUD975 preparation in the formulation of the reaction of active cutaneous anaphylaxis**

| № | Group / Ingredient / Spot size, mm | | | | | |
|---|---|---|---|---|---|---|
| | Control | | KUD975 2,65 mg/kg | | KUD975 21,2 mg/kg | |
| | resolving dose | reactivity control | resolving dose | reactivity control | resolving dose | reactivity control |
| 1 | 3.3 | 2.5 | 3.1 | 3 | 3.1 | 2.7 |
| 2 | 2.8 | 2.7 | 2.6 | 3.3 | 3.2 | 2.5 |
| 3 | 2.8 | 3.4 | 3.1 | 3.3 | 2.6 | 2.9 |
| 4 | 2.9 | 3.4 | 2.9 | 2.9 | 3.3 | 3.4 |
| 5 | 3.5 | 3.3 | 2.7 | 2.5 | 3.5 | 3.1 |
| 6 | 3.4 | 3.1 | 3.5 | 3.4 | 3.4 | 2.9 |
| 7 | 3.5 | 2.6 | 3. | 2.9 | 3.1 | 3.2 |
| 8 | 2.8 | 2.8 | 3.4 | 2.7 | 3.2 | 3.4 |
| 9 | 2.8 | 3.3 | 3.3 | 3 | 2.8 | 3.1 |
| 10 | 3.5 | 2.8 | 3 | 2.8 | 2.9 | 3.3 |
| Mean, M±m | 3.1±0.1 | 3.0±0.1 | 3.1±0.1 | 3.0±0.1 | 3.1±0.1 | 3.1±0.1 |

It was found that in the guinea pigs sensitized by the test preparation, the size of the spots of exudate formed at the points of administration of the resolving doses reached a diameter of 3.5 mm and, on average, did not statistically significantly exceed the size of the exudate spots at the control points and in the control animals.

Thus, in the reaction of active cutaneous anaphylaxis in guinea pigs, the allergic properties of KUD975 preparation in two and eight times daily therapeutic dosages were not revealed.

In the course of the study of the allergenic properties of the KUD975 preparation in the formulation of a delayed-type hypersensitivity reaction, it was found that the study preparation in two and eight times daily therapeutic dosages had no allergic properties (Table 2).

**Table 2: Record of reaction results hypersensitivity delayed type**

| № п/п | | Group / Input / Evaluation of response in points after 1/24/48 hours after administration | | | | | |
|---|---|---|---|---|---|---|---|
| | | Control | | KUD975 2,65 mg/kg | | KUD975 21,2 mg/kg | |
| | | resolving dose | reactivity control | resolving dose | reactivity control | resolving dose | reactivity control |
| Through 10 introductions of the preparation | 1 | 0/0/0 | 0/0/0 | 0/0/0 | 0/0/0 | 0/0/0 | 0/0/0 |
| | 2 | 0/0/0 | 0/0/0 | 0/0/0 | 0/0/0 | 0/0/0 | 0/0/0 |
| | 3 | 0/0/0 | 0/0/0 | 0/0/0 | 0/0/0 | 0/0/0 | 0/0/0 |
| | 4 | 0/0/0 | 0/0/0 | 0/0/0 | 0/0/0 | 0/0/0 | 0/0/0 |
| | 5 | 0/0/0 | 0/0/0 | 0/0/0 | 0/0/0 | 0/0/0 | 0/0/0 |
| | 6 | 0/0/0 | 0/0/0 | 0/0/0 | 0/0/0 | 0/0/0 | 0/0/0 |
| | 7 | 0/0/0 | 0/0/0 | 0/0/0 | 0/0/0 | 0/0/0 | 0/0/0 |
| | 8 | 0/0/0 | 0/0/0 | 0/0/0 | 0/0/0 | 0/0/0 | 0/0/0 |
| | 9 | 0/0/0 | 0/0/0 | 0/0/0 | 0/0/0 | 0/0/0 | 0/0/0 |
| | 10 | 0/0/0 | 0/0/0 | 0/0/0 | 0/0/0 | 0/0/0 | 0/0/0 |
| After 30 introductions of the preparation | 1 | 0/0/0 | 0/0/0 | 0/0/0 | 0/0/0 | 0/0/0 | 0/0/0 |
| | 2 | 0/0/0 | 0/0/0 | 0/0/0 | 0/0/0 | 0/0/0 | 0/0/0 |
| | 3 | 0/0/0 | 0/0/0 | 0/0/0 | 0/0/0 | 0/0/0 | 0/0/0 |
| | 4 | 0/0/0 | 0/0/0 | 0/0/0 | 0/0/0 | 0/0/0 | 0/0/0 |
| | 5 | 0/0/0 | 0/0/0 | 0/0/0 | 0/0/0 | 0/0/0 | 0/0/0 |
| | 6 | 0/0/0 | 0/0/0 | 0/0/0 | 0/0/0 | 0/0/0 | 0/0/0 |
| | 7 | 0/0/0 | 0/0/0 | 0/0/0 | 0/0/0 | 0/0/0 | 0/0/0 |
| | 8 | 0/0/0 | 0/0/0 | 0/0/0 | 0/0/0 | 0/0/0 | 0/0/0 |
| | 9 | 0/0/0 | 0/0/0 | 0/0/0 | 0/0/0 | 0/0/0 | 0/0/0 |
| | 10 | 0/0/0 | 0/0/0 | 0/0/0 | 0/0/0 | 0/0/0 | 0/0/0 |

Erythema, or, especially, infiltration and the appearance of ulcers at the site of administration as a resolving dose of the drug, as well as in the control of reactivity, were not observed in any animal participating in the experiment.

## CONCLUSION:

Experiments to study the allergenic properties of KUD975 were carried out on albino sexually mature guinea pigs with a mass of 300 ± 20 g [11, 12]. In the course of the study of allergic properties, the drug KUD975 was used in two and eight times daily therapeutic doses. The twice daily therapeutic dose of the study drug for guinea pigs was 5.3 mg / kg / day, eight times - 21.2 mg / kg / day When investigating the allergenic properties of the phenolic compound KUD975, which is a selective inhibitor of arginase II in the reaction of active cutaneous anaphylaxis, it was found that the study preparation in two and eight times daily therapeutic dosages does not have allergic properties. In the reaction of active cutaneous anaphylaxis in guinea pigs, the allergic properties of KUD975 in two and eight times daily therapeutic dosages were not detected.

Thus, in the delayed-type hypersensitivity reaction in guinea pigs, the allergic properties of KUD975 preparation in two and eight times daily therapeutic dosages were also not revealed.

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