The American Journal of Medical Sciences and Pharmaceutical Research (ISSN – 2689-1026)
Published: March 30, 2021 | **Pages:** 60-64
Doi: https://doi.org/10.37547/TAJMSPR/Volume03Issue03-08

IMPACT FACTOR 2021: 5. 64
OCLC - 1121105510

Study Of The General Pharmacological Properties Of A New Antiarrhythmic N-Deacetyllappaconitine With Oral Administration

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ABSTRACT

The aim of the present study was to study a new antiarrhythmic effect of N-deacetyllappaconitine on the general pharmacological irritant effect on the skin, when applied to the conjunctival sac of the eye, mucosal hyperemia and lacrimation, cumulative, allergenic and diuretic effects. At the same time, it does not cause changes, which makes it more secure.

KEYWORDS

N-deacetyllappaconitine, local irritant, cumulative, allergenic, diuretic effect.

INTRODUCTION

Cardiovascular diseases are in the first place in terms of prevalence among the population of economically developed countries. They also remain the main cause of death, only in the Russian Federation it is more than 50% of the total mortality of the population. At the same

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time, one of the main pathophysiological mechanisms of mortality is cardiac arrhythmia [1]. It is known that arrhythmias can be caused by various etiological factors, including arterial hypertension, which is especially common in the elderly. With arterial hypertension, the heart muscle works with an increased load, since it has to pump blood through the vessels that are in a state of spasm. With a prolonged course of the disease, hypertrophy of the left ventricle develops, which can lead to heart rhythm disorders [2]. Timely diagnosis and adequate treatment of hypertension and arrhythmias remain an important problem in clinical medicine, and therefore the search for compounds that have both antihypertensive and antiarrhythmic effects is relevant. In addition, you need to remember that antiarrhythmic drugs often show side effects. Requirements for new antiarrhythmic agents it is safe for the organ and body systems, highly selective, highly effective, and must also have a long-lasting effect. Some scientists have studied the protonation of N-deacetyllappaconitine in methanol solutions [3]. As well as the antiarrhythmic activity of [4] N-deacetyllappaconitine in different models of oral arrhythmia. In this regard, the studied substance N-deacetyllappaconitine was selected, which meets many of the above requirements, and the local irritant, cumulative, allergenic and diuretic effects were investigated.

THE PURPOSE OF THE STUDY

Improvement of the system of drug therapy of cardiac arrhythmias based on the search for new antiarrhythmic agents that are highly effective and safe for the organ and body systems when used.

MATERIALS AND METHODS OF RESEARCH

Experiments were conducted in rabbits, albino guinea pigs and white rats weighing 200-220 g. All procedures with animals were carried out in accordance with the requirements of the international recommendations of the European Convention for the Protection of Vertebrates Used for Experiments or Other Scientific Purposes [5]. To study the local irritant effect of the dosage form of the drug, it was carried out in experiments on rabbits by applying it to a pre-burned area of the skin of the back (4x5cm). N-deacetyllappaconitine was applied daily as a solution of 4 drops for 20 days [6]. A solvent was applied to the control group of animals under similar conditions.

The study of the irritant effect on the mucous membrane of the eye of the drug was evaluated when applied to the conjunctival sac of the eye of rabbits.

The cumulative effect of the drug was studied in experiments on white rats when used internally. N-deacetyllappaconitine was administered in doses of 0.1-0.5 and 1.0 mg / kg daily for 20 days. The control group of animals under similar conditions was injected with a saline solution. During the experiment, the general condition, weight, behavior, condition of the hair cover of the skin, mucous membranes, food and water consumption were observed.

The study of the possible allergenic effect of the drug was carried out in experiments on albino guinea pigs. The anaphylactic activity of the drug was evaluated on the model of anaphylactic shock (1gr), active skin anaphylaxis (2gr). Guinea pigs of group 1 were administered the drug according to the following scheme: three sensitizing injections

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were made, the first subcutaneously, the next two intramuscularly every other day.

The permissive dose of the drug was administered intraperitoneally on 21 days from the beginning of the experiment. Control animals were administered a saline solution and a permissive dose of the drug for 21 days according to a similar scheme.

In the study of cutaneous anaphylaxis, animals of group 2 were immunized as well as animals of group 1. On the 21st day of the experiment, guinea pigs were injected intradermally with 0.05 ml of the drug solution on the shorn area of the back. Active cutaneous anaphylaxis was assessed by intravenous administration of 0.5 ml of 1% Evans blue solution. In control non-immunized animals, the permissive dose of the drug and the blue Evans solution was administered according to a similar scheme. After 30 minutes, the animals were slaughtered (under ether anesthesia) and the size of the blue spot on the inside of the skin at the injection site was determined.

Experiments on kidney function were carried out by the method of water loading of 5 groups on 30 white rats weighing 175-215 g of both sexes. The studied drug was administered orally at a dose of 0.05; 0.1; 0.5 and 1.0 mg/kg.

RESULTS AND DISCUSSION

The experiments conducted to study the irritant effect showed that the drug does not irritate the skin with repeated subcutaneous application (20 times). When applied to the conjunctival sac of the eye, there was no hyperemia of the mucous membranes and lacrimation.

The results of the cumulative effect studies have shown that the drug does not cause noticeable changes in the general condition and behavior during the experiment. On the part of the skin (injection site), no visible changes were noted. All the animals ate food well, gained weight. No animal deaths were reported.

Consequently, N-deacetyllappaconitine does not cause material accumulation in the body of animals.

The results of the studies of the possible allergenic effect of the drug showed that after the administration of the permissive dose of the drug in group 1 of guinea pigs, there were no signs of anaphylactic shock. The general condition and behavior of all animals were unchanged, the condition of the hair, skin, and visible mucous membranes did not differ from the intact animals. In group 2 animals, the size of the spot on the back of the skin did not exceed 5 mm. Therefore, N-deacetyllappaconitine does not have an allergenic effect.

Preclinical toxicological studies have established that the drug N-deacetyllappaconitin with a single and repeated use does not have an irritating effect on the skin and mucous membrane of the eyes of experimental animals.

N-deacetyllappaconitine, when reused, does not have a cumulative and allergenic effect. With its long-term use, it does not have a toxic effect on the animal body and does not have an irritant effect at the injection site.

The effect on the diuresis of the drug was carried out in experiments on white rats when used internally in therapeutic doses. The effect of N-deacetyllappaconitine on diuresis was studied in comparison with the control group. The results obtained are shown in Table 1.

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Table 1.

Effect of N-deacetyllappoconitine on diuresis in rats

№	Drugs under study	Number of animals, pcs	Drug doses, ml / kg	Number of urine excreted per day, in ml	Diuretic effect, in %
1	Control of diss. water	10	5	7,2±1,2	100
2	N-deacetyllappaconitine	10	0,05	8,6±1,7	119
		10	0,1	8,7± 1,5	120
		10	0,5	9,0±1,05	125
		10	1	9,6±1,7	133

Note: the differences with respect to the control group data are insignificant (P>0.05)

As can be seen from this table, N-deacetyllappaconitine in the studied doses in rats imperceptibly increased urination compared to control animals. So, if in the control group of animals, the amount of urine excreted per day averaged 7.2 ml, then when administered 0.05; 0.1; 0.5 and 1.0 mg / kg of the drug, the amount of urine excreted was 8.6; 8.7; 9.0 ml and 9.6 ml, respectively.

CONCLUSION

Thus, it was established that the drug N-deacetyllappaconitine in the studied doses does not have an irritating effect on the skin. When applied to the conjunctival sac of the eye, there was no hyperemia of the mucous membranes and lacrimation. It does not have a cumulative and allergenic effect. As can be seen, the test drug increases urination within the physiological norm, that is, from 119% to 133%.

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