Journal Healthcare Treatment Development
ISSN: 2799-1148
Vol. 1 No. 02 (2021): Oct-Nov 2021
http://journal.hmjournals.com/index.php/JHTD
DOI: https://doi.org/10.55529/jhtd.12.12.19

Evaluation of Anticonvulsant Activity of Allapinine and N-Deacetylappaconitine in Experimental Animals

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Received: 03 August 2021 **Accepted:** 20 October 2021 **Published:** 22 November 2021

***Abstract**: The present article presents a research paper on the evaluation of anticonvulsant activity of allapinine and N-debacetylappaconitine with high antiarrhythmic activity caused at different doses and with different analyzers. The results of the conducted studies showed that allapinine and N-debacetylappaconitine are not inferior and even slightly superior to carbamazepine in anticonvulsant activity. In this regard, based on the conducted studies, it can be concluded that allapinin affects not only cardiomyocytes, but also ion exchange in nerve cells.*

***Keywords:** Allapinine, N-Deacetylappaconitine, Corazole, Strychnine, Isoniazid, Antiarrhythmic, Kidling, Lappaconitine*

1. INTRODUCTION

It is known that the treatment of complex cardiac arrhythmias with an antiarrhythmic drug is one of the most important sections of clinical cardiology. To date, arrhythmology has made significant progress in prescribing antiarrhythmic drugs, has allowed to deepen therapeutic measures and predict the effectiveness in patients with complex or severe cardiac arrhythmias [1]. Among the drugs with high antiarrhythmic activity, a widely used drug is Allapinin, it is a highly effective treatment for patients with paroxysmal atrial fibrillation, ventricular extrasystole and tachysystolic arrhythmias [2, 3]. Allapinine is a hydrobromic salt of the alkaloid lappaconitine, contained in the roots and aboveground part of the plants of Aconitum leucostomum and Aconitum septentrionale. The drug was developed in the late 70s at the Institute of Plant Chemistry of the Academy of Sciences of Uzbekistan, received for clinical trials in the early 80s and approved for clinical use in 1986 - 1989 [4-7]. During this time, great scientific progress has been made in studying the mechanisms of action,

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pharmacokinetic and pharmacodynamic parameters of allapinin using a number of preclinical and clinical biochemical, as well as physical methods. Allapinin has a membrane stabilizing effect and its antiarrhythmic mechanism of action is due to the depressing effect on the fast incoming sodium current through the membrane of the cardiomyocyte [8-10]. For many years, local anesthetics, anticonvulsants with the property of blocking sodium channels have been widely used in medical practice. Scientific research on the study of ion channels of cell membranes of various organs and systems has shown that it is providing intermembrane movement of sodium ion that several subunits of channels have been identified and it can be concluded that the specificity of the sensitivity of each subunit to substances with a certain biological activity. The composition of allapinin consists of several metabolites that react as follows: lappaconitin, N-Deacetylappaconitin (N-DAL), ranaconitin, N - acetylapaconitin, leuconin. A study of the pharmacokinetics of the drug showed that, after ingestion of lappaconitine, it turns into the main metabolite N-Deacetyllappaconitine and exhibits antiarrhythmic activity [11-14]. A number of scientists of our country, such as Sh.Sh. Sagdullaev, A.Z. Sadikov, F.N. Jahangirov, J. Rejepov, etc., conducted large-scale studies on the individual isolation of the substance N-Deacetylappaconitine and the study of its pharmacotoxicological properties and achieved scientific and practical success. Conducted preclinical experiments have shown that N-DAL in its individual form is low-toxic, several times superior in the breadth of therapeutic action, antiarrhythmic index compared to allapinin [15-21]. Despite the long-term use of allapinin in clinical practice and N-Deacetylappaconitin in preclinical research, information about the results of its study to date is few and often contradictory. In this regard, anticonvulsant activity was carried out on various models of allapinine and N-Deacetylappaconitine in an experimental condition.

The Purpose of the Study

Evaluation of anticonvulsant activity of allapinin and N-Deacetylappaconitin in animals under experimental conditions.

2. MATERIALS AND METHODS

A study on the anticonvulsant activity of allapinin and N-deacetylappaconitin was conducted on mongrel white mice weighing 18-22 g and white rats weighing 180-220 g, which were quarantined for 14 days under standard vivarium conditions. All experiments with animals were carried out in accordance with the requirements of the international recommendations of the European Convention for the Protection of Vertebrates [22]. The studied substances allapinin and N-DAL were used for experiments in various doses that have antiarrhythmic activity and administered orally as well, the comparative drug carbamazepine (200 mg No. 20, JSC "Synthesis" (Russia)) it was administered in doses of 10, 20 and 50 mg / kg orally an hour before the introduction of pro-convulsive analyzers. When performing experiments to cause convulsive seizures [23] of pro-convulsive analyzers, including, isoniazid was administered at a dose of 300 mg / kg and corazole (pentylentetrazole) (Sigma, AKSH) at a dose of 80 mg/ kg intraperitoneally, and strychnine was administered at a dose of 1.2 mg/ kg subcutaneously. Anticonvulsant activity was assessed by the following indicators: the latent period of seizures, the number of clonic-tonic paroxysms per 1 animal, the severity of paroxysms in points, the duration of convulsive

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seizures, the time of death as well, lethality. Statistical processing of the obtained results was carried out using statistical analysis methods [24], the reliability of changes was calculated by the indicator P≤0,05.

3. RESULTS AND THEIR DISCUSSION

Determination of anticonvulsant activity of allapinin and N–DAL in different doses in white mice caused by isoniazid. Experiments were carried out on white mice. Isoniazid inhibits GABA biosynthesis by blocking the enzyme glutamate decarboxylase and, consequently, reducing its inhibitory activity [25, 26]. As a result of inhibition of gabaergic mediators, seizures with increased excitability of neurons occur. For experiments, doses of allapinin in the amount of 0.01; 0.05; 0.1 and 0.5 mg/kg and N-DAL in the amount of 0.1; 0.5 and 1.0 mg/kg were used. In this case, allapinin in the studied doses demonstrated a slight advantage over N-DAL and the control group in terms of such indicators as the time of onset of seizures, the number of seizures and the survival of animals caused by the action of isoniazid. But carbamazepine showed high activity compared to allapinine and T-Dal in that model. The results obtained are presented in Table 1.

Table 1. Evaluation of anticonvulsant activity of allapinin and N-Dal by comparison with carbamazepine in white mice.

№	Groups and substances	Doses per мг/кг	The onset of seizures in min.	Number of seizures	Survival rate per min.
1.	Control +300 mg/kg isoniazid i/p	Dis.water	31±2,9	17±2,1	10,8±1,2
2.	Allapinine + 300 mg/kg isoniazid i/p	0,01	34±2,4	3,75±0,72	9,25±1,2
		0,05	30,5±4,2	3,25±0,48	11±1,44
		0,1	26,25±3,89	2,5±0,96	6,25±1,44
		0,5	29±2,89	3,25±0,72	3,75±0,96
3.	N-DAL + 300 mg/kg isoniazid i/p	0,1	25,6±4,6	18±1,8	25,2±5,8*
		0,5	38,4±7,8*	16±2,4	8±0,9
		1,0	31±5,6	41±7,6*	15,6±1,7*
4.	Carbamazepine +300 mg/kg isoniazid i/p	20	56±12,1*	9±0,9	1,3±0,1*
		50	67,2±11,8*	25±3,1*	0

Note.*P≤0.05 comparison with the control group.

Despite the positive trend of changes in the convulsive activity of Allapinin and N-DAL in the studied doses, this did not have a statistically significant effect on the latency period of clonic seizures associated with isoniazid and the survival of animals. This can be explained by the involvement of other nervous structures in epileptogenesis, unlike other models of seizures caused by GABA receptor blockers [27]. Based on the results obtained, allapinin and N-DAL showed higher activity compared to the control group and carbamazepine of low activity.

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Evaluation of anticonvulsant activity of allapinin and N–DAL in different doses in white mice caused by strychnine. This test allows you to visualize the clinical signs of epilepsy, as it reveals conditions similar to primary disseminated seizures in humans [28]. Anticonvulsant activity of compounds in this model may be associated with direct activation of glycine-sensitive receptors and a combined increase in glycine and gabaergic activity [27]. For the experiments, doses of allapinin in the amount of 0.1; 0.5 and 1.0 mg/kg and N-dal in the amount of 0.01; 0.05; 0.1 and 0.5 mg/ kg of Allapinin in the studied doses increased the latent period of convulsive seizures, respectively, to 1.17; 1.21 and 1.42 times, the number of seizures decreased to 5.33; 3.2 and 2.67 times and the survival rate of animals increased to 1.25; 1.37 and 1.87 times compared to the control group. Under the action of N-DAL at doses of 0.1 and 0.5 mg / kg, the latent period of convulsive seizures began 1 minute, at other doses, respectively, 2 and 3 minutes later, the number of convulsive seizures was observed, respectively, 5.33; 10; 10 and 2.85 times less, the survival rate of zhyvot 1.25; 2; 2 and 1.5 times compared with the control group. The results obtained are presented in Table 2.

Table 2. Evaluation of anticonvulsant activity of allapinin and N-Dal by comparison with carbamazepine in white mice.

№	Groups and substances	Doses per мг/кг	The onset of seizures in min.	Number of seizures	Survival rate per %.
1.	Control +1,2 mg/kg strychnine s/c	Dis.water	6±0,86	4	40
2.	Allapinine +1,2 mg/kg strychnine s/c	0,1	7±1,2*	0,75	50
		0,5	7,25±0,96*	1,25	55
		1,0	8,5±0,72*	1,5	75
3.	N-DAL +1,2 mg/kg strychnine s/c	0,05	7±0,43*	0,75	50
		0,1	7±0,8*	0,4	80
		0,5	8±0,56*	0,4	80
		1,0	9±2,15*	1,4	60
4.	Carbamazepine +1,2 mg/kg strychnine s/c	20	8±0,24*	1	60
		50	7±0,43*	1,3	40

Note.*P≤0.05 comparison with the control group.

Thus, Allapinin showed significant anticonvulsant activity in relation to the indicators of seizures: the onset and number of seizures, as well as survival by comparison of control and carbamazepine. In animals treated with N-DAL, a statistically significant change in these indicators of seizures caused by subcutaneous administration of strychnine indicates that the studied compound has a significant effect on the glycinergic system compared to allapinine.

Determination of anticonvulsant activity of allapinin and N–DAL in different doses in white mice caused by corazole. According to the evaluation of anticonvulsant activity through the corazole kidling test, it was carried out on mongrel white rats weighing 180-220 g. During this test, doses of 0.1; 0.5 and 1.0 mg/kg of allapinin and slightly larger-scale doses were used, that is, in the amount of 0.01; 0.05; 0.1; 0.5; 1.0 and 2 mg/kg of N-DAL and carbamazepine. In this model, the anticonvulsant properties of the studied substances were

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evaluated in points. Allapinin showed high activity in relation to N-DAL and carbamazepine in the occurrence of seizures and the degree of seizures. The results obtained are presented in Table 3.

Table 3. Evaluation of anticonvulsant activity of allapinin and N-Dal by comparison with carbamazepine in white mice.

№	Groups and substances	Doses per мг/кг	Convulsions in points	Effects per %
1.	Control + 30 mg/kg corasole i/p	Dis.water	17,23±1,89*	
2.	Allapinine + 30 mg/kg corasole i/p	0,1	8,75±1,2*	49,2
		0,5	2,25±0,72*	86,9
		1,0	11,75±0,96*	31,8
3.	N-DAL + 30 mg/kg corasole i/p	0,01	10,75±2,4	37,6
		0,05	5,25±1,2*	69,5
		0,1	6±0,73*	65,2
		0,5	6,92±1,1*	59,8
		1,0	10,5±1,44*	39
		2,0	6,5±0,48*	62,3
4.	Carbamazepine + 30 mg/kg corasole i/p	0,1	12±1,44*	30,3
		1	16,5±31,2	4,2
		5	7±1,2*	59,4
		10	4,75±0,24*	72,4
		25	13,5±0,12*	21,6
		50	6,75±0,96	61

Note.*P≤0.05 comparison with the control group.

It is known that the anticonvulsant activity of compounds in this model may be directly related to the activation of gabaergic receptors [29]. Thus, the presented data indicate that Allapinin is superior to N-DAL and carbamazepine in the corazole kidling model and it can be concluded that in this respect it is more sensitive to gabaergic receptors.

4. CONCLUSIONS

Thus, allapinin prolongs the latent period of seizures and reduces the duration of seizures. In addition, it has a positive effect on survival compared to groups receiving different doses of carbamazepine, which is widely used in practice. The studies show that allapinin showed significant anticonvulsant activity compared to carbamazepine.

Based on the conducted studies, it can be concluded that allapinin affects not only cardiomyocytes, but also ion exchange in nerve cells.

N-DAL is not only superior to allapinin with low toxicity, onset of antiarrhythmic effects, duration and breadth of antiarrhythmic action, but also is not inferior to allapinin in anticonvulsant activity and exceeds it in sensitivity to glycine receptors.

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DOI: https://doi.org/10.55529/jhtd.12.12.19

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ISSN: 2799-1148
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