

Toxicity And Anti-Arrhythmic Activity 1-(4-Dimethylaminophenyl Dimethylaminophenyl) -6, 7-Dimethoxy-1, 2, 3, 4 Tetrahydroisoquinoline

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Abstract

The effect of 1 - (- 4-dimethylaminophenyl) -6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoloin hydrochloride (conditionally -F-24) on antiarrhythmic activity in simulating calcium chloride arrhythmia, as well as acute toxicity in experiments, was studied on white out bred rats with the intravenous route of administration. It was found that the drug F-24 has a pronounced ant arrhythmic effect. The average effective (ED50) ant arrhythmic dose is 4.8 mg/kg, the ant arrhythmic index is 20.3, which is significantly more than the comparison drugs verapamil and lidocaine.

Keywords: alkaloid, ant arrhythmic activity, isoquinoline alkaloids, cardio arrhythmic action.

Introduction

The disease cardiovascular system wide prevalence and occupies first place among disability and mortality of population in the world. In particular, among the population of Uzbekistan, mortality from cardiovascular disease is 56%, and disability is 25%. According to the statistics in the Republic, more than 26% of people over the age of 40 suffer from hypertension, which causes cerebral stroke, acute myocardial infarction, heart and kidney

failure, about 11% suffer from various forms of coronary heart disease. About 8 thousand cases of acute myocardial infarction are registered annually in the Republic, of which 60% of patients die at the hospital stage [3]. The most common and life-threatening complications of these diseases are cardiac arrhythmias come to the fore of the underlying disease and its prognosis is determined. Currently, in practical medicine, such ant arrhythmic drugs as amlodipine, flecainide, etatsizin, allapinin, verapamil, etc. are widely used. Despite the presence of a large number of ant arrhythmic drugs, the research a new highly effective and safe ant arrhythmic drugs is one of the most actual tasks of modern pharmacology. This is due to the fact that antiarrhythmics used in medical practice have serious side effects and, in particular, cardio arrhythmogenic action

Intensive research in this direction is carried out by scientists of many large scientific centers around the world. In particular, isoquinoline alkaloids and their synthetic derivatives are of great interest in the research for the development and creation of new ant arrhythmic.

In this connection, 1- (4-dimethylaminophenyl) -6,7-dimethoxy-1,2,3,4 tetrahydroisoquinoline, which we conventionally called F-24, was synthesized in the laboratory of alkaloids of the Institute of Plant Chemistry of the Academy of Sciences of the Republic of Uzbekistan.

The aim of this study was to study the parameters of acute toxicity and ant arrhythmic activity of the drug F-24.

Research Methods

The study was performed on 210 white outbred male rats (190-220 g) contained in standard vivarium conditions with free access to water and food. All procedures with animals were carried out in accordance with the requirements of the International Recommendations of the European Convention for the protection of vertebrate animals used for experiments or other scientific purposes. The determination of acute toxicity of compound F-24 was carried out on white out bred male rats using the intravenous route of administration.

Each dose of the drug was tested in 6 animals. The average lethal dose (LD₅₀) was determined by the Litchfield-Wilnerson method. Ant arrhythmic activity was studied on white out bred male rats anesthetized with sodium ethamine (50 mg/kg ip) compared with verapamil and lidoxin. Heart rhythm disturbance was modeled by intravenous administration of a 10% solution of calcium chloride at a dose of 250 mg / kg [8].

The test drug F-24 and the reference drug were administered in 2 minutes before arrhythmia was reproduced; the effectiveness was assessed by the ability of the heart rhythm. The ratio of LD₅₀ / ED₅₀, which was designated as the ant arrhythmic index, was taken as a criterion for the breadth of ant arrhythmic index.

All experiments were conducted in comparison with verapamil and lidocaine.

Results and discussion

The results of studies to determine acute toxicity are presented in table 1.

Table 1

Comparative acute toxicity of F-24, verapamil and lidocaine preparations.

Nº	Name of drugs	Injection method	Types of animals	LD ₅₀ mg / kg
1	F-24	intravenously	Rates	97,5 (84,8± 119,1)
2	Verapamil	intravenously	Rates	15,8 (13,7± 18,1)
3	Lidocaine	intravenously	Rates	39,0 (34,2 ±44,4)

As can be seen, from the data presented in table 1, in experiments on rats, the drug F-24 in terms of acute toxicity parameters when administered intravenously 6.1 times and 2.5 times respectively less toxic than verapamil and lidocaine used in medical practice.

The results of the experiments showed that in control anesthetized animals, intravenous administration of a 10% solution of calcium chloride at a dose of 250 mg / kg after 10-20 seconds led to the development of a rhythm disturbance that rolling into flutter and fibrillation of the heart and the death of 100% of the animals within 1.5 -3 minutes.

Preliminary intravenous injection of the drug F-24 in doses of 3-5-8 mg / kg, verapamil in doses of 1-2,5-5 mg / kg prevented the development of ventricular fibrillation of the heart in 30, 60, 100% of animals. When using lidocaine, the maximum ant arrhythmic effect (50%) was noted with a dose of 9.8 mg / kg. the average effective ant arrhythmic dose (ED₅₀) was 4.8 mg / kg for F-24, 2.1 mg / kg of verapamil and 9.8 mg / kg of lidocaine. The drug F-24 in terms of breadth of therapeutic effect (LD 50 / ED₅₀) exceeds verapamil and lidocaine, respectively, 2.7 and 5.2 times (table 2)

Table 2

Comparative ant arrhythmic activity in the model of calcium chloride heart rhythm disturbances.

Nº	Name of drugs	LD ₅₀ mg/kg intravenously	ED ₅₀ mg/kg intravenously	Antiarrhythmic index LD ₅₀ /ED ₅₀
	F-24	97,5 (84,8± 112,1)	4,8(4,1± 5,5)	20,3 (17,8± 23,1)
	Verapamil	15,8 (13,7± 18,1)	2,1 (1,8 ±2,4)	7,5 (6,5± 8,6)

	Lidocaine	39,0 (34,2 ±44,2)	9,8 (8,5± 11,2)	3,9 (3,4 ±4,5)
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Therefore, the F-24 preparation, being less toxic compared to verapamil and lidocaine, surpasses them in ant arrhythmic activity in the model of cardiac arrhythmia caused by calcium chloride.

1. The drug F-24 in terms of acute toxicity compared with verapamil 6.1 times and with lidocaine 2.5 times less toxic.
2. F-24 in ant arrhythmic activity is significantly superior to verapamil and lidocaine.
3. A higher anti-arrhythmic index of the drug F-24 indicates its greater cardio selectivity and safety compared with the compared drugs.

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