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Research Article

COMPARATIVE ASSESSMENT OF ACUTE TOXICITY OF VINCANIN HYDROCHLORIDE DERIVATIVES IN RESEARCH CONDITIONS

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ABSTRACT

This research paper presents the isolation of norfluorocurarine alkaloids from the Vinca erecta plant, substances with different chemical structures and the study of toxicological properties in various types of animals. Experiments have shown that mice are more resistant to the effects of pyrazoline chloride and pyrazoline iodide than rats. From the conducted studies, it can be concluded that it is advisable to carry out the biological activity of the studied substances to rats that are relatively immune to the action of these substances and this will allow further use of dosages that are relatively harmless to humans in various pathologies.

KEYWORDS

Acute toxicity, pyrazoline chloride, pyrazoline iodine methylate, intraperitoneal, Average lethal dose (LD50)

INTRODUCTION

In medical practice, the synthesis of new biologically active substances to create new medicines with valuable properties for the treatment and prevention of various diseases is one of the most important tasks of modern organic, bioorganic and medical chemistry, as well as pharmacology. At the present stage of intensive development of the pharmaceutical industry, there are a number of successes in the chemical synthesis of new compounds that are the basis for the production of new drugs with high pharmacological activity. Despite these successes, well-known drugs used for the prevention and treatment of a number of pathological conditions have low activity or lack of effectiveness, as well as the presence of adverse reactions that cause unpleasant sensations in patients during treatment. The problem of finding new substances with high pharmacological efficiency has not lost its importance and relevance to this day [1-3]. In this regard, at the Institute of Chemistry of Plant Substances named after S.Yu Yunusova Academy of Sciences of the Republic of Uzbekistan has been conducting large-scale research work on the isolation and study of various biological activity of plant and synthetic substances for many years. Currently, scientific and practical work is underway on the widespread use of these extracted substances not only for pharmaceutical and medical applications, but also as chemical and bioreactive substances for experimental research. In the course of these works, the outstanding scientist Professor P.X. Yuldashev, senior researcher B.B. Abduazimov and other scientists are conducting extensive work on the isolation of norflorocurarine alkaloids from the Vinca erecta plant, substances with different chemical structures. Currently, a number of scientific studies are being conducted on the pharmacotoxicological properties of these alkaloids in relation to their acute toxicity and antitumor activity [4-11].

The purpose of the study. Evaluation and comparison of species sensitivity of vincanine hydrochloride derivatives in various experimental animals

Materials and methods of research. The studies were carried out on mongrel laboratory white mice weighing

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18-22 g and white rats weighing 150-180 g, kept in standard vivarium conditions for 14 days and the studied ones were carried out in accordance with the methods set out in methodological, training manuals and manuals [12-15]. In studies conducted on acute toxicity, the studied substances were administered to experimental animals by various methods of administration and 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 [16]. The studied substances were administered by various routes of administration, from low doses to doses causing death, in all animals in the experimental group. At the same time, all signs that occurred before death in experimental animals exposed to substances were recorded within 14 days. To determine the parameters of "acute" toxicity, the Litchfield and Wilcoxon method was used, and statistical processing of the results obtained was carried out by the tabular method proposed by R.B. Strelkov [17-18].

Results and their discussion. 1. Evaluation study of acute toxicity of the substance pyrosaline chloride and pyrosaline iodide when administered orally. The general effect and "acute" toxicity of the substance of the preparations pyrosaline chloride and pyrosaline iodide were determined in mice and rats with a single oral administration in various doses. Each dose of the substance was studied on 6 animals. The observation was conducted for 14 days.

To determine the parameters of "acute" toxicity, the Litchfield and Wilcoxon method was used [17]. When the substance pyrosaline chloride was administered orally to mice and rats in small doses, the general condition and behavior of the animals did not differ from intact animals. Grooming was observed in the studied large doses of pyrosaline chloride, after 5 to 10 minutes, depending on the doses, muscle weakness appeared, manifested in the form of periodic lying on the stomach and rare movements on the table surface. During the study, after 30 minutes, the animals react to external stimuli, but pain sensitivity to gentle pinching of the tail root is preserved, weakness is visible, and after 60 minutes, disorientation in space is sometimes noticeable, repeated 2 – 3 times repeated sluggish clonic convulsions, lateral position, slowing down and stopping breathing. In the conducted studies, the acute toxicity of pyrosaline chloride was LD50 = 550 (482.4-792) mg/kg in mice and LD50 = 420 (381.3-471.4) mg/kg in rats (Table - 1).

Table – 1. Comparison of acute toxicity of pyrosaline chloride when administered orally in mice and rats.

Name of the substance	With oral administration		Attitude to the toxicity of the substances under study
	Types of animals		
	mice	rats	
Pyrazoline Chloride	550 (482.4÷792) mg/kg	420 (381.3÷471.4) mg/kg	1,31

Note.P≤0.05 comparison with the control group

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Symptoms of poisoning caused by pyrazolone chloride were similar in mice and rats, and only mice showed resistance up to 1.31 times compared to rats.

In the conducted studies, when the substance pyrosaline chloride was administered orally to mice and rats in doses in small doses, the general condition and behavior of animals did not differ from intact animals as if it were pyrazoline iodine methylate. The symptoms of poisoning caused by a substance that was also studied in high doses are similar to the symptoms of pyrazoline chloride poisoning, but death from exposure to pyrazoline iodine methylate occurred in a very short period of time, that is, within 30-35 minutes after the administration of the substances under study. The data obtained as a result of the studies are presented in table 2 below.

Table – 2. Comparison of acute toxicity of pyrazoline iodine methylate when administered orally in mice and rats.

Name of the substance	With oral administration		Attitude to the toxicity of the substances under study
	Types of animals		
	mice	mice	
Pyrazoline iodine methylate	1320 (1056÷1650) mg/kg	813 (765.2÷911.5) mg/kg	1,62

Note.P≤0.05 comparison with the control group

The results of the studies showed that the symptoms of poisoning caused by pyrazoline iodine methylate were similar in mice and rats, and only mice showed resistance up to 1.62 times compared to rats.

2. Evaluation study of acute toxicity of the substance pyrazoline chloride and pyrosaline iodide when administered intraperitoneally.

With oral administration of the substance pyrazoline chloride and pyrazoline iodide to mice and rats in small doses, the general condition and behavior of animals did not differ from intact animals. An increase in the dose caused inactivity, increased breathing, "bunching". This condition lasted for 30-40 minutes, according to the doses. When the drugs were administered in these doses, the animals retracted their stomachs. These phenomena disappeared after 10-15 minutes. The death of mice occurred during the day in a dose of large doses. The average lethal dose (LD50) with a single intraperitoneal administration of the substance of the preparations pyrosaline chloride and pyrosaline iodide in mice was 350 (270-490) mg/kg and 128.4 (105.1-131.5) mg/kg, respectively, in rats 129 (115.2-171.5) mg/kg and 98.2 (87.6-106.2) mg/kg.

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Table – 3. Comparison of acute toxicity of pyrosaline chloride and pyrazoline iodine methylate when administered orally in mice and rats.

Name of the substance	With intraperitoneal administration		Attitude to the toxicity of the substances under study
	Types of animals		
	mice	mice	
Pyrosaline chloride	350 (270÷490) мг/кг	129 (115.2÷171.5) мг/кг	2,71
Pyrazoline iodine methylate	128,4 (105,1÷131,5) мг/кг	98,2 (87,6÷106,2) мг/кг	1,31

Note.P≤0.05 comparison with the control group

As can be seen, pyrosaline chloride and pyrosaline iodide belong to low-toxic substances (class IV toxicity, in which, with intraperitoneal administration, LD50 ranges from 350 (270-490) mg/kg to 128.4 (105.1-131.5) mg /kg mg/kg in mice [12], however, pyrosaline chloride and pyrosaline iodide are less toxic in rats as compared to rats. Mice can withstand higher doses of pyrazoline chloride and pyrazoline iodide than rats. Natural alkaloids, due to their high toxic effect on the entire body, in doses possible for use, cannot cause a high biological effect.

CONCLUSIONS

Preclinical study of general toxicology, general pharmacology, as well as specific toxicology allowed us to draw the following conclusions.

As a result of the work carried out to determine the acute toxicity of pyrazoline chloride and pyrosaline iodide in various experimental animals, it was found that when administered orally, it belongs to class IV of low-toxic substances, the studied substances when administered intraperitoneally belong to class III of medium toxic according to the toxicity classification of substances.

However, mice were found to be more resistant to pyrazoline chloride and pyrazoline iodide than rats.

From the conducted studies, it can be concluded that it is advisable to carry out the biological activity of the studied substances to rats that are relatively immune to the action of these substances and this will allow further use of dosages that are relatively harmless to humans in various pathologies.

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