EURASIAN JOURNAL OF ACADEMIC RESEARCH
Innovative Academy Research Support Center
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TOXICOLOGICAL CHARACTERISTICS OF VINCANIN HYDROCHLORIDE AND ITS DERIVATIVES IN AN EXPERIMENTAL CONDITION

Yu.R. Mirzaev[1]
T.T. Khamraev[2]
E.M. Ruzimov[3]
Sh.M. Adizov[4]
B.B. Abduazimov[5]
B.N. Khandamov[6]
B.J. Elmurodov[7]
P.H. Yuldashev[8]
[1-2-3-4-5-6-7-8]Academy of Sciences RUz Institute of Chemistry of Plant Substances, Tashkent, Uzbekistan, e-mail: tolmas4th@mail.ru
https://doi.org/10.5281/zenodo.7244593

ARTICLE INFO

Received: 10th October 2022
Accepted: 15th October 2022
Online: 24th October 2022

KEY WORDS

Vinca erecta, Vincanin hydrochloride, pyrosaline hydrochloride, pyrosaline iodine methylate, acute toxicity, LD50, oral, subcutaneous, intravenous

ABSTRACT

This presented research paper presents the results of studying the acute toxicity of vincan and its derivatives using various methods of administration isolated from the Vinca erecta plant, As a result of experimental studies, it was determined that vincanin hydrochloride with oral administration is class III, that is highly toxic, according to the classification of acute toxicity of substances and with subcutaneous and intravenous administration II, that is substances that are highly toxic have been recognized as belonging to the class. While its derivatives with oral and subcutaneous administration belong to the IV, that islow-toxic class in accordance with the classification of acute toxicity of substances with intravenous administration, it was found that both substances belong to class II, that is substances that are highly toxic.

Introduction. The continued increase in the incidence of cancer among people of different ages from year to year around the world leads to serious social, physical, mental and financial consequences for individuals, families and the health system as a whole. According to official data from the World Health Organization, every year about 15 million people in the world are diagnosed with malignant neoplasms, most of whom live in low- and middle-income countries, and the number of deaths is less than the number of diseases such as HIV/AIDS, tuberculosis and malaria. In the Republic of Uzbekistan, this indicator is 65.7 for every 100 thousand inhabitants, of which mortality is about 38%. [1-3]. The frequency of occurrence of this disease and a large number of deaths from it are a global and urgent problem not only for medicine, but also for representatives of all branches involved in medicine. It should be noted that the achievement of growth in the treatment of oncological diseases is largely determined by the further improvement of methods of antitumor

treatment and measures. Currently, there is a large arsenal of chemotherapeutic drugs that are used to treat cancer, but most of them cause severe toxic reactions to normal human cells and tissues. In addition, during the treatment with these drugs, chemoresistance develops in tumors, which reduces the possibility of their use for cytostatic purposes. Despite certain successes in the chemotherapy of malignant tumor diseases, the task of finding new classes of compounds with antitumor activity remains relevant for scientists in the field of medical chemistry and oncobiology not only in our country, but also around the world. At the same time, it is considered one of the most promising areas of research in the field of biomedical chemistry, experimental and clinical oncology. Scientists are looking for new chemical compounds that make it possible to constantly improve existing methods and schemes of drug therapy for the therapeutic purposes of tumor diseases [4-8]. In this regard, currently in our country, including at the Institute of Chemistry of Plant Substances named after S.Yu. Yunusova AN RUz as well as all over the world, the effects of various substances on the cardiovascular system, the effect of diseases associated with metabolic disorders, adaptogenic properties, neuropsychological activity are studied as a result of studying the pharmacotoxicological properties of natural biologically active substances isolated from plant raw materials. As a direct continuation of this research work, a new chemical compound has been synthesized from the alkaloid norfluorocurarin isolated from Vinca erecta showing antitumor properties and their toxicological and biological activity is being studied [9-13].

The purpose of the study. Determination of acute toxicity of vincanin hydrochloride and its derivatives with different methods of administration in experimental animals.

Materials and methods. The indole alkaloids vincanin and 2 of its derivatives - pyrosaline hydrochloride and pyrosaline iodide, which exhibit cytostatic activity, were subjected to pharmacological research to determine acute toxicity. It was previously revealed that vincanin hydrochloride is a convulsive strychnine-like agent [9]. The studies were carried out on laboratory mongrel white mice weighing 18-22 g, by administration of substances per os - through the mouth, subcutaneous and intravenously, which is performed in accordance with the instructions given in the manuals [14, 15]. The ongoing research is necessary to assess the common and distinctive properties of the above three compounds. The studies were conducted on experimental animals that 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 [16]. Statistical processing of the obtained results was carried out by the tabular method proposed by R.B. Strelkov [17].

Results and their discussion. 1. Study of the general effect and toxicity of vincanin hydrochloride.

a) To determine the acute toxicity of vincanin hydrochloride, when administered orally, 42 mice were taken for experiments, which were divided into 7

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groups of 6 mice each. The dose of the injected substances is 20 mg/kg, 30 mg/kg, 40 mg/kg, 50 mg/kg, 60 mg/kg, 70 mg/kg, 80 mg/kg. When vincanin hydrochloride was administered orally at a dose of 20 mg / kg after 10 minutes, the animals showed slight muscle weakness. Weakness increased from a dose of 30 mg/kg, and at times convulsions were observed in mice, but no death of mice was observed from this dose. From a dose of 40 mg/kg of 6 mice, 1 mouse died on the background of clonic-tonic seizures. 2 mice out of 6 fell from a dose of 50 mg/kg, 3 out of 6 from a dose of 60, 4 from a dose of 70, and all 6 mice fell from 80 mg/kg. LD_{50} was 68 mg/kg orally (Table 1.)

Table 1.

Acute toxicity of vincanin hydrochloride in per os.

Dose of vincanin administered orally	The number of experimental mice	Mortality
20 mg/kg	6	0
30 mg/kg	6	0
40 mg/kg	6	1
50 mg/kg	6	2
60 mg/kg	6	3
70 mg/kg	6	4
80 mg/kg	6	6
LD_{50} = 68 (59.1÷78.2) mg/kg		

In the conducted studies, the substances of vincanin hydrochloride for acute toxicity were determined to belong to Class III in accordance with the classification of acute toxicity of substances, that is those that are moderately toxic.

b) To determine the acute toxicity of vincanin hydrochloride when administered subcutaneously, 30 mice were taken for experiments, divided into 5 groups of 6 mice. The dose of the injected substances is 5 mg /kg, 7 mg / kg, 10 mg/ kg, 12 mg / kg, 15 mg/kg.

With subcutaneous administration of vincanin hydrochloride, no death of mice was observed from a dose of 5 mg / kg, 2 mice fell from a dose of 7 mg / kg, 3 mice fell from a dose of 10 mg / kg, from a dose of 12 – 4, and from a dose of 15 mg/ kg, all 6 mice fell. LD_{50} was 11.7 mg / kg with subcutaneous administration of vincanin hydrochloride. Table 2.

Table 2.

Acute toxicity of vincanine hydrochloride during subcutaneous administration.

Dose of vincanin administered orally	The number of experimental mice	Mortality
5 mg/kg	6	0
7 mg/kg	6	2
10 mg/kg	6	3
12 mg/kg	6	4
15 mg/kg	6	6
LD_{50} = 11,7 (10.3÷13.2) mg/kg		

In the conducted studies, it was found that the substances of vincanin hydrochloride when injected under the skin, according to acute toxicity, belong to Class II in accordance with the classification of acute toxicity of substances, i.e., which are highly toxic.

c) To determine the acute toxicity of vincanin hydrochloride with intravenous administration, 36 mice were taken for experiments, divided into 6 groups of 6 mice in each group. The dose of the injected substances is 1 mg / kg, 3 mg /kg, 4 mg / kg, 5 mg /kg, 6 mg /kg, 7 mg/kg.

With intravenous administration of vincanin hydrochloride, no death of mice was observed from a dose of 1 mg / kg, 2 mice fell from a dose of 3 mg / kg, 2 mice fell from a dose of 4 mg / kg, 4 from a dose of 5 mg / kg, and 4.7 mg/ kg from a dose of 6 mg/kg– all 6 mice fell. LD_{50} was 5.5 (4.9 - 6.2) mg /kg with intravenous administration of vincanin hydrochloride. Table 3.

Table 3.

Acute toxicity of vincanine hydrochloride with intravenous administration.

Dose of vincanin administered orally	The number of experimental mice	Mortality
1 mg/kg	6	0
3 mg/kg	6	1
4 mg/kg	6	2
5 mg/kg	6	3
6 mg/kg	6	4
7 mg/kg	6	6
LD_{50} = 5,5 (4.9 ÷ 6.2) mg/kg		

In the conducted studies, it was found that the substances of vincanin hydrochloride when administered intravenously, according to acute toxicity, belong to Class II in accordance with the classification of acute toxicity of substances, that is which are highly toxic.

2. Study of the general effect and toxicity of pyrazoline chloride.

The studies were conducted on laboratory mice by administration of substances per os - through the mouth, under the skin and intramuscularly.

a) Experiments were carried out on white mice with the introduction of pyrosaline chloride per os. When pyrosaline **hydrochloride** per os was administered at a dose of 400 mg / kg 5 minutes after administration, weakness was noted, the animals were lying on their stomachs. After 7 minutes, sluggish clonic convulsions were observed without loss of consciousness. After 8 minutes – shaky gait, weakness, hopping gait, tail reaction. After 30 minutes - weakness lying on the stomach, gait hopping with tremor, tremor of the body and head.

Experiments were carried out on white mice with the introduction of pyrosaline **hydrochloride** per os. When pyrosaline chloride per os was administered to animals at a dose of 600.0 mg / kg 3 minutes after administration, muscle weakness, sluggish clonic convulsions without loss of consciousness, hopping gait, motor restlessness and death were noted. With oral administration of pyrosaline chloride LD_{50} = 550 (482.4 - 792) mg / kg.

b) Experiments were conducted on white mice when pyrosaline **hydrochloride** was injected under the skin. At a dose of 150 mg /kg, the mice showed weakness, sometimes verticalization, closed eyes, muscle weakness and grooming. The death of mice was not observed.

When a dose of 300 mg / kg was administered under the skin, pronounced weakness and depression were observed after 5 minutes, after 60 minutes – sharp weakness, sharp depression, pain sensitivity in animals remained.

When a dose of 500.0 mg / kg was administered after 10 minutes, weakness, disorientation, lateral position, slowing of respiratory movements to 100 per minute were observed. There is a hopping gait, clonic convulsions. The death of animals occurred for 3 days. With subcutaneous administration of pyrosoline **hydrochloride** LD_{50} = 320 mg / kg (283.1 - 361.6).

c) Acute toxicity of pyrosaline **hydrochloride** when administered intravenously in white mice.

The administration of pyrosaline **hydrochloride** at a dose of 8 mg / kg does not lead to the death of animals. When administered 10 mg / kg of 5 animals, 1 died, at a dose of 12 mg / kg of 5 animals, 2 died, at a dose of 14 mg / kg of 5 animals, 4 died and when administered 16 mg / kg, all 5 animals died. With intravenous administration of pyrosaline **hydrochloride** LD_{50} = 12.2 (10.1 - 14.8) mg / kg.

Study of the general effect and toxicity of pyrosaline **hydrochloride**. Experiments were conducted on white mice when administered orally. LD_{50} of pyrosaline chloride was 550 mg/kg orally, 320 mg/kg subcutaneously and 12.2 mg/kg intravenously.

The studies were carried out in the same way as in previous experiments and it was found that acute toxicity of pyrosaline **iodine methylate** when administered by oral administration LD_{50} = 1320 (1056-1650) mg / kg, intramuscular administration LD_{50} =656 (517-833) mg / kg, intravenous administration LD_{50}= 1.88 (1.53 - 2.3) mg/kg (Table 4)

Table 4.

Toxicity indicators of vincanine and its derivatives.

Name of the substance	Ways of introduction		
	Per os	subcutaneous	intravenous
Vincanine hydrochloride	68 (59.1÷78.2) mg/kg	11,7 (10.3÷13.2) mg/kg	5,5 (4.9 ÷ 6.2) mg/kg
Pyrosaline **hydrochloride**	550 (482.4÷792) mg/kg	320 (283.1÷361.6) mg/kg	12,2(10,1÷14,8) mg/kg
Pyrosaline **iodine methylate**	1320 (1056÷1650) mg/kg	656 (517÷833) mg/kg	1,88(1.53 ÷ 2.3) mg/kg

Note.*P≤0.05 comparison with the control group

Conclusions. Thus, studies on the acute toxicity of vincanin hydrochloride and its derivatives have shown that the levels of acute toxicity of the studied substances

increased in the order of vincanin hydrochloride, pyrosaline **hydrochloride** and pyrosaline **iodine methylate** in all the input channels used.

In this case, it is considered that vincanin hydrochloride, when administered orally, belongs to Class III according to the classification of acute toxicity of substances, that is moderately toxic, and with subcutaneous and intravenous administration, that is highly toxic II.

While pyrosaline **hydrochloride** and pyrosaline **iodine methylate**, when administered orally and subcutaneously, belong to the IV, that is low-toxic class in accordance with the classification of acute toxicity of substances, and when administered intravenously, both substances belong to the class.II, that is substances that are highly toxic.

References:

1. Каприн А.Д., Старинский В.В., Шахзадова А.О. (ред.). Злокачественные новообразования в России в 2019 году (заболеваемость и смертность). М.: МНИОИ им. Герцена — филиал ФГБУ «НМИЦ радиологии» Минздрава России; 2020. 252 с.

2. Умезава К., Ганцев Ш.Х., Кзыргалин Ш.Р., Ямиданов Р.С., Амиров Р.А., Жук Е.И. Противоопухолевая активность дегидроксиметилэпоксихиномицина (DHMEQ) (обзор литературы). Креативная хирургия и онкология. 2021;11(1):68-75. https://doi.org/10.24060/2076-3093-2021-11-1-68-75

3. Наврузов С. Н., Алиева Д.А. Онкология Узбекистана: достижения и перспективы. Российский онкологический журнал. 2016; 21 (1–2): 72–75. DOI: 10.18821/1028-9984-2015-21-1-72-75

4. Корман Д.Б. Основы противоопухолевой химиотерапии. М.: Практическая медицина, 2006. Бабин В.Н., Белоусов Ю.А., Борисов В.И., Гуменюк В.В., Некрасов Ю.С., Островская Л.А. и др. // Изв. АН. Сер. хим. 2014. № 11. С. 2405.

5. Wakabayashi H., Narita T., Suga A. Hormetic Response of Cultured Normal and Tumor Cells to 2-Aminotropone Derivatives. In vivo. 2010. V. 24. P. 39-44.

6. Shih Y.-H., Chang K.-W., Hsia S.-M. In vitro antimicrobial and anticancer potential of hinokitiol against oral pathogens and oral cancer cell lines. Microbiological Research. 2013. V. 168. P. 254–262.

7. Максимов А.Ю., Лукбанова Е.А., Саяпин Ю.А., Гусаков Е.А., Гончарова А.С., Лысенко И.Б., Протасова Т.П. Противоопухолевая активность алкалоидов трополонового ряда in vitro и in vivo // Современные проблемы науки и образования. – 2020.–№ 2.; URL: https://scienceeducation.ru/ru/article/view?id=29722

8. Островская Л. А., Корман Д. Б., Блюхтерова Н. В., Фомина М. М., Рыкова В. А., Грехова А. К., Абзаева К. А. Металлополиакрилаты – новый класс потенциальных противоопухолевых препаратов. Химическая физика, 2019, том 38, № 12, с. 64–73. DOI: 10.1134/S0207401X19120161

9. Изучение физико-химических и технологических свойств субстанции пирозалина гидрохлорида // Universum: технические науки : электрон. научн. журн. Рахимова О.Р. [и др.]. 2021. 9(90). URL: https://7universum.com/ru/tech/archive/item/12260
10. Rakhimova Nigina Furkat kizi, Sanoev Zafar Isomiddinovich PhD, & Mamatova Nodira Mukhtorovna. (2022). Study Of General Pharmacological Properties And Acute Toxicity Of Cistanche Mongolica Extract. Texas Journal of Medical Science, 13, 12–14. Retrieved from https://zienjournals.com/index.php/tjms/article/view/2425
11. Zakhidova L.T., Saidkhodjaeva D.M., Sanoev Z.I., Tukhtasheva V.F., Rakhmanova H.A.., Hamroyev T.T. Toxicological Characteristics Of N-Deacetyllappaconitine Under Chronic Administration In White Rats. The American Journal of Applied Sciences, 3(03), 34-41.
12. Mamatkulova N.M., Sanoev Z.I., Khamroev T.T., Khidyrova N.K., Maxmudova D.M. Изучение острой токсичности и биологическая активность сухого экстракта цветков gossypium hirsutum l. SOI:1.1/TAS DOI:10.15863/TAS International Scientific Journal Theoretical & Applied Science p-ISSN: 2308-4944 (print) e-ISSN: 2409-0085 (online) Year: 2021 Issue: 10 Volume: 102 Published:30.10.2021http://T Science.org.
13. Sanoev Z.I., Abdinazarov I.T., Sanoev A.I., Khamroev T.T., Rakhimboev S.D., & Rashidov S.Z.. (2022). Study of antihypoxic activity of dry grape seed extract under normal conditions. Oriental Journal of Medicine and Pharmacology, 2 (03), 6-13. https://doi.org/10.37547/supsci-ojmp-02-03-02
14. Миронов А.Н. Руководство по проведению доклинических исследований лекарственных средств. Част первая. — М.: Гриф и К, 2012. — 944 с.
15. Хабриев Р.У.(Ред.). Руководство по экспериментальному (доклиническому) изучению новых фармакологических веществ. Москва. 2005, с.832.
16. European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes, ETS №123, Strasbourg (1986).
17. Стрелков Р.Б. Статистические таблице для ускоренной количественной оценки фармакологического эффекта. Фармакология и токсикология 1986. №4 с.100-104.