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ACUTE TOXICITY OF 3-METHYL- (1,3-DIMETHYL) -7-β-HYDROXY-γ-ARYLOXYPROPYLXANTHINYL-8-THIOACETIC ACID DERIVATIVES IN EXPERIMENT

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Abstract

Recently, the urgency of the problem of atherosclerosis is only increasing, which is why the state of hyperlipidemia is called the «epidemic of the XXI century». Despite its high hypolipidemic effect, the statin group has a number of disadvantages associated with both economic feasibility for patients and significant side effects. A promising direction in this regard is the search for effective and low-toxic hypolipidemic agents, in particular on the basis of xanthine derivatives. In the study of future medicines, one of the key places is to study the complex of their toxicometric parameters, characterizing the degree of their toxicity and safety.

The aim of the study *was to study the acute toxicity of 3-methyl-(1,3-dimethyl)-7-β-hydroxy-γ-aryloxypropylxanthinyl-8-thioacetic acid derivatives in rats.*

Object and methods of research. *The subjects of the study were 9 derivatives of 3-methyl-(1,3-dimethyl)-7-β-hydroxy-γ-aryloxypropylxanthinyl-8-thioacetic acid, synthesized at the Department of Biological Chemistry of Zaporizhzhya State Medical University, which are promising for the creation of medicines.*

When studying acute toxicity, we chose the tabular express method according to V.B. Prozorovsky. The experiments were performed on white laboratory rats of the Wistar line weighing 180-220 g. Animals were kept on a standard diet under «natural day-night light mode». The compounds were administered to laboratory animals following the aseptic and antiseptic rules in the form of a fine aqueous suspension, which was stabilized with

tween-80 at the rate of 0.2 ml tween-80 per 50 mg of the substance. The analysis of the studies was performed according to the classification of K.K. Sidorov.

Results and Discussion. *Acute toxicity (LD_{50}) of the new compounds obtained is in the range of 357 - 624 mg/kg. According to the Sidorov classification, all synthesized 3-methyl-(1,3-dimethyl)-7-β-hydroxy-γ-aryloxypropylxanthinyl-8-thioacetic acid derivatives were of low toxicity and moderately toxic with intragastric administration. It should be noted that the least toxic compounds are 7-(3-ethylphenoxy)-propyl-theophylline-8-yl-thioacetic acid (compound 2), its LD50 - 624 ± 83 mg / kg and 2,4-dichlorophenoxypropyl derivative (compound 5), LD50 of which is 566 ± 68 mg / kg.*

Conclusions. *Acute intragastric toxicity studies of 3-methyl- (1,3-dimethyl) -7-β-hydroxy-γ-aryloxypropylxanthinyl-8-thioacetic acid derivatives showed that they all belong to low-toxic and moderately toxic substances III-IV toxicity class according to the classification of K. Sidorov (9 substances). The most toxic was compound 6 (357 ± 43 mg/kg). The least toxic compound is 7-(3-ethylphenoxy)-propyl-theophylline-8-yl-thioacetic acid (compound 2), its LD_{50} being 624 ± 83 mg/kg.*

Keywords: *xanthines, acute toxicity, hyperlipidemia.*

Introduction. Recently, the urgency of the problem of atherosclerosis is only increasing, which is why the state of hyperlipidemia is called the «epidemic of the XXI century» [1]. The most severe forms of atherosclerosis include such serious cardiovascular diseases as coronary heart disease, transient cerebral ischemic attacks, obliterating atherosclerosis of the lower extremities, which in the course of further leading to such life-threatening infections.

To date, in the treatment of hyperlipidemia, in accordance with the recommendations of the 2019 European Association of Atherosclerosis, the following groups of drugs are used: statins, fibrates, nicotinic acid, bile acid sequestrants, ω-3 fatty acids, inhibitors of cholesterol absorption, inhibitors of the protease convertase subtilisin of kexin type 9, selective inhibitors of microsomal triglyceride-carrying protein, antisense oligonucleotides, cholesterol ether transporter protein inhibitors [2]. Statins are the most effective and sought-after lipid-lowering agents since the 1990s. During this time, a number of clinical studies were conducted to study statins. The main ones are ALLHAT, PROSPER, WOSCOPS, PROVE-IT, CARE for the study of pravastatin, HPS, IDEAL, A to Z, 4S – simvastatin, ASCOT LLA, CARDS – atorvastatin, AF-CAPS – lovastatin, LIPS – fluvastatin, CORONA, JUPITER – rosuvastatin.

Despite the high hypolipidemic effect, the statin group has a number of disadvantages associated with both economic feasibility for patients and significant side effects (hepatotoxicity, development of myodystrophy, etc.) [3].

The creation of new high-efficiency and low-toxicity drugs and their introduction into clinical practice is an important task of pharmacological science. A promising direction in this regard is the search for effective and low-toxic hypolipidemic agents, in particular on the basis of xanthine derivatives [4]. In the study of future medicines, one of the key places is to study the complex of their toxicometric parameters, characterizing the degree of their toxicity and safety. One such parameter is acute toxicity [5].

The aim of the investigation was to investigate the acute toxicity of 3-methyl- (1,3-dimethyl)-7-β-hydroxy-γ-aryloxypropylxanthinyl-8-thioacetic acid derivatives in rats.

Object and methods of research. The objects of the study were 3-methyl- (1,3-dimethyl)-7-β-hydroxy-γ-aryloxypropylxanthinyl-8-thioacetic acid derivatives synthesized at the Department of Biological Chemistry of Zaporizhzhya State Medical University under the guidance of Professor M.I. Romanenko that are promising for the creation of medicines. In our studies, they were studied as hypolipidemic agents. The structure of compounds is confirmed by a complex of modern physicochemical methods of analysis: IR, PMR spectroscopy, mass spectrometry.

When studying acute toxicity, we chose the tabular express method according to V.B. Prozorovsky. The method is based on the proposal to use the test substances at doses placed on a logarithmic scale at intervals of 0.1, and all possible reliable results of LD_{50} and their errors were calculated in advance by the program of probit-analysis. The experiments were performed on white laboratory rats of the Wistar line weighing 180-220 g. The rats were obtained from the rat farm of the State Institution «Institute of Pharmacology and Toxicology of the Academy of Medical Sciences of Ukraine». Animals were kept on a standard diet with natural day-night light. For the study of acute toxicity, 4 groups of animals were used, with 2 observations each with the additional use of one previous and subsequent dose. The compounds were administered to laboratory animals following the aseptic and antiseptic rules in the form of a fine aqueous suspension, which was stabilized with tween-80 at the rate of 0.2 ml tween-80 per 50 mg of the substance. Observations were made after 24 hours [6].

In our studies, the acute toxicity of 9 compounds of 3-methyl-(1,3-dimethyl)-7-β-hydroxy-γ-aryloxypropylxanthinyl-8-thioacetic acid derivatives was studied (Table 1). The analysis of the studies was performed according to the classification of K.K. Sidorov [7].

In carrying out the experiment, the rules and regulations of the European Convention for the Protection of Vertebrate Animals Used for Experiments or for Other Scientific Purposes (Strasbourg, 1986) and the European Union Directive on Animal Experiments 2010/10/63 were approved and approved by bioethics commission.

Results and Discussion. Because toxicity is a concept and a relative value, the question arises of the need to classify the degree of toxicity depending on the pathway of the introduction the pharmacological substance into the body of experimental animals. In this regard, we conducted acute toxicity studies on novel synthetic 3-methyl-(1,3-dimethyl)-7-β-hydroxy-γ-aryloxypropylxanthinyl-8-thioacetic acid derivatives.

The analysis of the obtained data shows that among the test substances the most toxic was compound 6 and the least toxic is compound 2. The acute toxicity (LD_{50}) of the new compounds obtained is in the range 357 - 624 mg/kg (Table 1). According to the Sidorov classification, all synthesized 3-methyl-(1,3-dimethyl)-7-β-hydroxy-γ-aryloxypropylxanthinyl-8-thioacetic acid derivatives were of low toxicity and moderately toxic with intragastric administration.

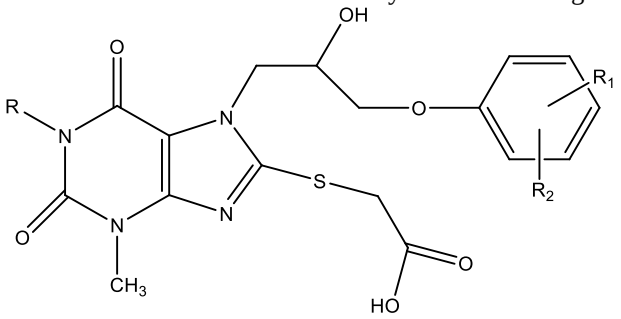

Table 1 Acute toxicity of 3-methyl-(1,3-dimethyl)-7-β-hydroxy-γ-aryloxypropylxanthinyl-8-thioacetic acid derivatives

№	Number of substance	R	R_1	R_2	$M \pm S_{LD50}$, mg/kg
1	9223	H	H	C_2H_5-3	490 ± 46
2	9224	CH_3	H	C_2H_5-3	624 ± 83
3	9225	H	CH_3-3	CH_3-5	382 ± 82
4	9226	CH_3	CH_3-3	CH_3-5	482 ± 104
5	9228	H	Cl – 2	Cl – 4	566 ± 68
6	9229	H	CH_3-3	CH_3-4	357 ± 43
7	9230	CH_3	CH_3-3	CH_3-4	395 ± 69
8	9250	H	$CH(CH_3)_2$-2	CH_3-5	525 ± 51
9	9251	CH_3	$CH_3(CH_3)_2$-2	CH_3-5	421 ± 72

As can be seen from the above data, the 7-substituted theophylline-8-yl-thioacetic acid derivatives (2,4,7) are less toxic than the similar 3-methylxanthines derivatives (1,3,6). An exception is the 2-isopropyl-5-methyl 3-methylxanthine derivative, which exhibits less toxicity than the analogous 3-methylxanthine derivative (8) and theophylline (9). It should also be noted that 3,5-dimethyl-phenoxypropylxanthine (3,4) exhibits less toxicity than 3,4-disubstituted analogues (6,7). It should be noted that the least toxic compounds are 7-(3-ethylphenoxy)-propyl-theophylline-8-yl-thioacetic acid (compound 2), its LD_{50} – 624 ± 83 mg/kg and 2,4-dichlorophenoxypropyl derivative (compound 5), LD_{50} of which is 566 ± 68 mg/kg.

Conclusions

1. Conducting acute toxicity studies on intragastric administration of 9 derivatives of 3-methyl-(1,3-dimethyl)-7-β-hydroxy-γ-aryloxypropylxanthinyl-8-thioacetic acid showed that they all belong to low-toxic and moderately toxic substances and belong to the III-IV class of toxicity according to the classification of K. Sidorov.

2. The most toxic was 7-((3,4-dimethylphenoxy)-2-hydroxypropyl)-3-methyl-xanthine-8-ylthioacetic acid compound 6 (357 ± 43 mg/kg).

3. The least toxic compound is 7-(3-ethylphenoxy)-propyl-theophylline-8-yl-thioacetic acid (compound 2), its LD_{50} being 624 ± 83 mg/kg.

Prospects for further research. This experiment reflects the safety of this class of chemicals and the prospect of their further pharmacological studies. In the process of analyzing future results of preclinical research, it is necessary to evaluate the hypolipidemic efficacy of the compounds being tested and the feasibility of using them in practical medicine.

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