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Safety assessment of the 4- (6-phenyl-7h - [1,2,4] triazolo [3,4-b] [1,3,4] thiadiazine-3- yl) -aniline compound and the effects of the substance on respiration and cardiac activity

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Abstract: 4-(6-phenyl-7H-[1,2,4]-triazolo-[3,4-b] - [1,3,4] - thiadiazine-3- yl) - aniline compound belongs to the group of triazole derivatives, belongs to class IV low-toxic compounds in acute toxicity, and sodium belongs to the compounds of this group, taking into account the presence of Due to its ability to block ion channels, it can be concluded that the 1.0 mg/kg dose studied during the experiment led to bradycardia in exchange for a decrease in the activity of the sinus node, which is considered the main regulator of the first-order heart rhythm.

Keywords: Acute toxicity, accumulation, number of breaths, blood pressure, cardiac activity, rhythm.

Introduction: Epilepsy is a chronic disease that is accompanied by a violation of the functioning of the neurons of the central nervous system, characterized by seizures and loss of ES Hus in exchange for a dysbalance of the activity of the excitatory and inhibitory mediators of the brain [1, 2]. Over the past few decades, more than 20 new antiepileptic drugs have been created, including escarbazepine acetate [3], perampanel [4] and ezogabin [5]. However, a large percentage of the population does not achieve a stable anticonvulsant effect with monotherapy [6], and about

30% of patients have refractory epilepsy and require a combination of treatment [7, 8]. In addition, many antiepileptic drug drugs have serious side effects [9, 10] and need lifelong treatment. Therefore, the search for more selective and safer anticonvulsant agents is of particular interest. In the same point of view, several antiepileptic drugs of different approaches were studied for the development of [11-13]. The GAMK-A receptor is a major target for a number of therapeutically important drugs such as barbiturates, steroids, anesthetics, and benzodiazepines [14,15]. 1,2,4-triazole derivatives have been found to exhibit many biological activities, including anticonvulsant [16, 17], anti-fungal [18-20], neurotrophic heterocyclic activity [21-24], anti-inflammatory [25-27], and antibacterial [28-31], based on experiments. The molecular structure and bioactivity of commercially available antiepileptic drugs are spatially long hydrophobic domains (typically phenyl rings), hydrogen-binding domains, and electron-donor fragments, elements required for high anticonvulsant activity. In addition, various other compounds with a 1,2,4-triazole moiety were found to have anticonvulsant properties in several animal models of epilepsy [32-35]. These findings prompted us to look for 1,2,4-triazole-based compounds with anticonvulsant activity and determine if the derived derivatives could act on the allosteric site of GABA-A receptors. The combination of 4-(6-phenyl-7h-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine-3-yl) - aniline conditionally (D-286) has been studied for its overall pharmacological activities and effects on vital organs.

METHODS

4-(6-phenyl-7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine-3- yl) is an aniline compound, with the substance twine-80 as a solvent, ethaminal-sodium as a narcosis agent, aconitin substance for arrhythmia calling purposes, mass 18-24 g white mice, 180-220 g white rats, cat with a mass of 2.2 kg, ZOOMED IM-10 cardiomonitor, a Schiller cardiovit at-1 electrocardiograph device was used. Experiments were carried out in a room with 30-60% air humidity, 400 Lux lighting at a temperature of 15-250C. The substance was observed for 14 days after one administration. The compound was evaluated for acute toxicity in oral white mice, venous white rats, cumulative properties, effects on vital organ function, and effects on heart rhythm. The results obtained were processed using statistical methods.

RESULTS AND DISCUSSIONS

1, Experiments on acute toxicity of the 2,4-triazole derivative D-286 were performed in white mice by oral administration of twin-80, administered at a dose of 500 mg/kg to a dose of 4,500 mg/kg to assess the resorbtive effect and the time of death.

In acute toxicity experimental animals, rates are assessed from a dose of up to 100% mortality with significant changes in the body. Each group receives at least 6 experimental animals. Acute toxicity of the compound 4-(6-phenyl-7H-(1,2,4)-triazolo(3,4-b)-(1,3,4)-thiadiazine-3-yl) - aniline (D-286) was studied in white mice by oral administration at a dose of 500 mg/kg to 4,500 mg/kg. At a dose of 500-1000 mg/kg, no significant changes were observed in experimental animals. From a dose of 1500 mg/kg, general powerlessness, motion attenuation began to be observed. With an increase in dose at doses of 2000-4500 mg/kg, tremor, tail reaction, sustained Tonico-clonic seizures, and death began to be observed at intervals of 3-7 hours. The average death dose was LD50 = 2150 mg/kg. The compound D-286 was studied intravenously at a dose of 100-500 mg/kg in white rats with a mass of 170-230 g. From a dose of 300 mg/kg, death began to be observed in experimental animals due to respiratory failure, tremor, seizures. The results obtained were LD50=351.25 mg/kg when the average death dose was administered intravenously after statistical processing.

Determination of cumulative property in the compound D-286, calculated from 1,2,4-triazole derivatives with high anti-seizure activity, in different proportions of the dose of LD50. It was carried out using the method proposed by R. K. Lim. No deaths were reported during the experiment and the 15-day follow-up period after the compounds were sent for 28 days. The results obtained are shown in Table 1.

Table 1.

Assessment of cumulative effects of compounds with activity higher than 1,2,4-triazole derivatives when administered orally in white mice

Experience days	1-4	5-8	9-12	13-16	17-20	21-24	25-28	cumulative coefficient Cc
LD_{50} share	0.1	0.15	0.22	0.34	0.5	0.75	1.12	

								Cc=27348/2150= 12.72

According to the results obtained, it turns out that the compound D-286 of the 1,2,4-triazole derivative does not have a cumulative property.

The effect of drug substance on breathing and heart function. Study of the effect of D–286 on arterial blood pressure in a research setting. Studies investigating the effects of D-286 on arterial blood pressure were conducted on a ZOOMED IM-10 cardiomonitor, in cats with a body weight of 2.2 kg, the substance studied was sent to the intra-abdominal introduction at a dose of 1.0 mg/kg. Prior to the experiments, preliminary indications demonstrated in cardiomonitor were recorded by calling narcosis using a cat's intra-abdominal introduction 40 mg/kg dose of ethaminal sodium. In studies, arterial blood pressure was monitored for 2 hours, starting from 10 minutes of the experiment, and the indicators on the cardiomonitor were recorded. In this experiment, in addition to arterial blood pressure, indicators such as the number of heart contractions, body temperature, saturation were also recorded. As a result of the study carried out, it was assessed by the differences that occurred in relation to the initial indicators demonstrated on the cardiomonitor. In studies carried out, arterial blood pressure under the influence of a dose of 1.0 mg/kg of the D-286 compound was observed almost no changes in the oxygen saturation of hemoglobin i.e. saturation indicators. A decrease in body temperature at 1-1.5℃, a decrease in the number of breaths, as well as a return to the initial state after 2 hours can be seen. In contrast, the number of cardiac contractions can be seen to have increased compensatorically after initial narcosis from 124 to 141 times, and later decreased experimentally from 135 to 94 times after administration of the studied substance, leading to bradycardia (Table 2).

Table 2.

The effect of D-286 on AQB, number of breaths and other indicators.

№		Substance D-286 at a dose of 1.0 mg / kg				
		Indicators studied in cardiomonitor				
	The time when the observation was carried out in minutes	Blood pressure in mmHg	heart rate number	Number of breaths	Body temperature at ℃	Saturation in %
1.	Initial condition	125/83	124	12	37.6	87
2.	D-286 1.0 mg/kg 10 minutes after administration	113/46	141	11	37.6	87
3.	20	114/57	135	9	36.9	85
4.	30	121/80	130	8	36.3	85
5.	40	126/71	121	8	36.8	85
6.	50	119/66	114	8	36.6	84
7.	60	119/66	113	8	36.5	86
8.	70	123/76	111	8	36.1	85
9.	80	118/76	105	7	36.8	86
10.	90	125/83	104	7	36.6	85
11.	100	135/79	100	7	36.7	85
12.	120	133/78	98	9	36.8	86

13.	130	129/82	94	12	37.3	86

Determination of the effect of the D-286 compound on cardiac electrophysiological indicators. The effect of the D-286 compound on the electrophysiological indicators of the heart scientific studies conducted in the study body weight 180-220 g. in laboratory white rats up to, SCHILLER CARDIOVIT was achieved by recording on the standard II connection of the AT-1 ECG hardware. For this purpose, the studied compound is evaluated for normal cardiac activity as well as antiarrhythmic activity in peripheral Genesis disorders of the heart rhythm through arrhythmia models called through a chemical compound of arrhythmic nature. Before the start of the experiment, an

electrocardiogram (ECG) analysis was carried out on the standard connection II in animals, and after that aconitin was sent to the tail vein in rats with a dose of 12-15 mcg/kg, which is called mixed in animals of all experimental groups-ventricular extrasystole. The formation of cardiac rhythm disturbances began in 1-2 minutes after the cessation of administration of aconitin, based on the rule. Writing in EKG was conducted in 1; 3; 5; 10; 15 and 20 minutes after administration of aconitin. The substance under study was administered 60 minutes before oral aconitin administration at doses of 1.0; 10.0; 30.0 and 60.0 mg/kg, and at doses of 1.0; 2.0 and 10.0 mg/kg after arrhythmia caused by aconitin. All the experiments carried out were carried out in accordance with the Control Research Scheme. The activity of the studied compound was assessed by its prevention of heart rhythm disturbances called aconitin.

Initially, the compound D-286 was used through the above-mentioned dosages and injection methods, the changes caused by its action on the normative electrophysiological indicators of the heart were recorded in the II standard connection of the ECG for 60-70 minutes after the introduction of the substance. When the D-286 compound was administered orally at doses of 1.0; 10.0; 30.0 and 60.0 mg/kg, it was observed that the number of heart contractions in 50-60 minutes of the study decreased by an average of 30-35 times compared to the original. No changes were observed in pqrst tooth voltage, with the intervals of PQ(R) and QRS (T) extending by 4-6% compared to the original. These results obtained indicate a decrease or slowdown in cardiac AV and Inter-ventricular conduction under the influence of the studied substance.

It was observed that the substance studied showed anti-arrhythmia activity called by aconitin, corresponding to each dose, when administered orally at the doses noted above. Heart rhythm disturbances in the form of polyphocals associated with cardiac conduction disorders occurred in the first minute after the introduction of aconitin at a dose of 1.0 mg/kg, and symptoms of recovery began to occur in these rhythm disturbances, which occurred from 11 minutes of the study, and a complete recovery of the rhythm was observed in 20-25 minutes. With aconitin exposure at doses of 10.0; 30.0 and 60.0 mg/kg, heart rhythm disturbances in the form of polyphocals occurred at 4.0; 2.0 and 1.5 minutes of the study, respectively, and from 10; 13 and 15 minutes began to develop signs of a begging of a disturbed rhythm. At a dose of 10 mg/kg, after 10 minutes of the study, the broken rhythm was completely restored according to all indicators, while at a dose of 30 mg/kg it was restored after 18 minutes, at a dose of 60 mg/kg, the rhythm recovery time was 5 minutes.Also, rhythm disturbances caused by aconitin exposure when the substance studied was injected intravenously for treatment purposes-from 3-4 minutes of the study under the action of a dose of 1.0 mg/kg-to the recovery of the disturbed rhythm-this rhythm recovery took up to 8-10 minutes. Signs of recovery of rhythm disturbances caused by aconitin exposure at doses of 2.0 and 10.0 mg/kg began to occur from 5 and 11 minutes of the study, and a complete recovery of rhythm occurred at 10 and 16 minutes.

CONCLUSION

Thus, the compound 4-(6-phenyl-7H-[1,2,4]-triazolo-[3,4-b]-[1,3,4]-thiadiazine-3-yl)-aniline belongs to the group of triazole derivatives, according to Stefanov on acute toxicity, class IV is among the less toxic compounds, and considering the presence of the sodium ion channel blocking property among these group compounds, the sinus, which was considered the first-order main controller of heart rhythm at a dose of 1.0 mg/kg studied during the experiment it can be concluded that nodini caused bradycardia in exchange for decreased activity. Although few signs of bradycardia occur under the influence of the substance, it does not negatively affect the normative electrophysiological indicators of the heart. In addition, in cardiac arrhythmias called by aconitin, its activity against arrhythmias can be associated with the siege of Na+ channels.

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