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Excitability of the myocardium of white rats on the models of arrhythmia when introducing compounds of bromonicotinic acid

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Abstract.

The aim of the research is to study the excitability of the myocardium of white rats on the models of arrhythmia when introducing compounds of bromonicotinic acid. Simulation of the heart rhythm disorder was reproduced on laboratory white sexually mature non-pedigree rats. Before the experiment, they were anesthetized with diethyl ether; then a catheter for intravenous introduction of preparations was implanted into the tail vein. The antiarhythmic activity of the substances was studied by the frequency of fibrillation in the experimental and control groups. The effectiveness of the antiarrhythmic effect of the studied compounds was evaluated by the duration of the latent period, arrhythmia or by its prevention. 2 minutes prior to provoking arrhythmia, the selected studied compounds and comparator preparations were injected intravenously. The effectiveness of the antiarhythmic influence of the studied substances was evaluated by the duration of arrhythmia and the percentage of animals in which the sinus rhythm was restored, i.e. upon return of the ECG to the original rate. Thus, the preliminary introduction of the compounds at a dose of 20 mg / kg of a 1% aqueous solution helps to restore the heart rhythm on the 5th–15th minute of the ECG. It was found that the following compounds were the most effective for further study in the chloride-calcium model of arrhythmia in rats during the initial evaluation of the antiarhythmic properties of the studied chemical compounds: 2,4,6 – trimethylpyridine-3-amide-5-bromonicotinic acid, hydroxylamide-5-bromonicotinic acid, 4-methoxy-6-methyltriazine-2-amide-5-bromonicotinic acid and monoethanolamide nitrate of 5-bromicotinic acid. The compounds 2,4,6-trimethylpyridine-3-amide-5-bromonicotinic acid and hydroxylamide-5-bromonicotinic acid help to prevent ventricular extrasystole on the adrenaline model of heart rhythm disorder. The compounds 4-methoxy-6-methyltriazine-2-amide-5-bromonicotinic acid and 2,4,6 – trimethylpyridine-3-amide-5-bromonicotinic acid influence the restoration of the myocardium excitability on the chloride-barium model of the heart rhythm disorder.

Key words: Excitability, myocardium, heart, rats, bromonicotinic acid, cardiac arrhythmia, arrhythmia.

INTRODUCTION.

Changes in the electrophysiological parameters of the heart muscle [1,2,3] are directly related to the heart rhythm disorder. Despite the existence of the large group of medicinal preparations used in case of pathology of the cardiac muscle, the frequency of myocardial damage remains high [4,5,6].

Therefore, it is necessary to find and study new medicinal preparations that combine high efficiency and use safety [4,8]. In addition, the existing antiarrhythmic praparations have many side effects [9,10] which leads to the search of new antiarrhythmic compounds. As a result, new compounds - derivatives of bromonicotinic acid - were synthesized [11,12]. The aim was to study the changes in the excitability of the myocardium of white rats on the arrhythmia models when introducing the studied compounds.

MATERIAL AND METHODS.

11 compounds of derevatives of bromonicotinic acid were the object of the research. They were synthesized at the Department "Chemical Technology of Organic Compounds of Nitrogen" of Kazan National Research Technological University by E. Petrov, Candidate of Agricultural Sciences, under the supervision of R. Karimova and R. Gilmanov.

The research of the antiarrhythmic properties of the studied compounds was carried out in accordance with the guidelines on the experimental (preclinical) study of preparations suggested for clinical trials as means of preventing and treating heart rhythm disorders.

Methods of simulation of arrhythmias were used on laboratory white sexually mature non-pedigree rats (males and females, body weight 180-240 g). Before the experiment, the rats were anesthetized with diethyl ether to provoke the arrhythmia model; then a catheter for intravenous introduction of preparations was implanted into the tail vein.

Cardiac abnormalities and evaluation of antiarrhythmic activity of the studied substances were registered with the help of the ECG. The recording was carried out in the II standard lead with the help of the electrocardiograph «Medinova ECG 9801» (China); the recording speed was 50 mm/s and the calibration was 20 mm/mV at the 1st, 2nd, 3rd, 5th, 10th, 15th, 20th, 25th, 30th minute after intravenous injection of the compounds and arrhythmogen. The studied compounds were injected intravenously at the doses of 20 mg/kg of a 1% aqueous solution 2-3 minutes prior to the introduction of the arrhythmogen.

The effectiveness of the antiarrhythmic influence of the studied compounds was evaluated by the duration of the latent period, arrhythmia or its prevention. The study of myocardial excitability on the calcium-chloride arrhythmia model was carried out by intravenous introduction of calcium chloride at a dose of 250 mg/kg. The antiarrhythmic activity of the studied substances was evaluated by the frequency of fibrillation appearance in the experimental and control groups.

Subsequently, the antiarrhythmic properties of the most active compounds were studied on the models of heart rhythm disorders caused by barium chloride at a dose of 25 mg/kg and adrenaline hydrochloride at a dose of 0.3 mg/kg. 2 minutes prior to provoking arrhythmia, the selected studied compounds and comparator preparations were injected intravenously. The effectiveness of the antiarhythmic influence of the studied substances was evaluated by the duration of arrhythmia and the percentage of animals in which the sinus rhythm was restored, i.e. upon return of the ECG to the original rate.

Statistical processing of all obtained results was carried out with the help of the statistical software package (MS Office® «Excel 2007»).

RESULTS AND DISCUSSION.

It was established that the test animals had ventricular extrasystole occurred in 0.5-1.0 minutes after the introduction of arrhythmogen of calcium chloride in combination with sinus bradycardia and block of atrioventricular conduction. The normal sinus rhythm was restored only by the 30th minute.

Preload with the studied compounds of derivatives of bromonicotinic acid under the codes 2465, ГАМ, 4265, ОЭТАН, 5421, БНК, 1245, РОДАН, ТБК, ББК promote reducing excitability of arrhythmia (table 2).

Table 1 – Compounds of derevatives of bromonicotinic acid.

Compounds of derevatives of bromonicotinic acid	Code of the compounds of derevatives of bromonicotinic acid
2,4,6-tribromanilide 5-bromonicotinic acid	ТБК
Diethylamide 5- bromonicotinate acid	ДЭА
1,2,4-triazolamide-5- bromonicotinic acid	5421
Hydroxylamide -5- bromonicotinic acid	ГАМ
Nitrate monoethanolamide 5- bromonicotinic acid	ОЭТАН
4-methoxy-6-methyltriazine-2-amide-5- bromonicotinic acid	4265
2,4,6– trimethylpyridine-3-amide-5- bromonicotinic acid	2465
5- bromonicotinic acid	БНК
1,2,4-triazole-4-amide 5- bromonicotinic acid	1245
Thiocyanate 5- bromonicotinic acid	РОДАН
4-bromanilide 5- bromonicotinic acid	ББК

Table 2 – Arrhythmia excitability in case of chloride calcium model of arrhythmia, % (n=5)

Time after introduction of calcium chloride with preliminary introduction of the studied compounds, minute	Control	Compounds										
		ГАМ	ОЭТАН	4265	2465	ТБК	ДЭА	5421	БНК	1245	РОДАН	ББК
3	447,6 ±42,17	58,6 ±1,57*	66,34 ±1,61*	66,31 ±1,61*	35,18 ±1,54*	114,8 ±0,98	87,6 ±1,57*	108,61 ±1,51	87,63 ±1,52	104,8 ±0,82	106,3 ±1,6	96,34 ±1,67
5	544,33 ±57,12	26,83 ±1,43*	114,8 ±0,98*	5,32 ±0,47*	42,58 ±1,33*	157,3 ±1,95	114,8 ±0,98	86,22 ±1,51*	57 ±1,55*	66,3 ±1,6*	95,1 ±1,75*	66,1 ±1,5*
15	8,35 ±0,57*	3,16 ±0,45*	1,53 ±0,23*	25,14 ±1,5*	6,65 ±0,57	26,65 ±0,57*	15,39 ±0,44*	33,23 ±3,45	8,35 ±0,57	5,3 ±0,45	18,45 ±0,51	8,35 ±0,57
30	32,41 ±3,47	11,13 ±1,19*	6,65 ±0,57*	5,39 ±0,45*	23,21 ±0,95*	38,45 ±0,51*	15,37 ±0,45*	13,13 ±1,45	8,35 ±0,57	6,65 ±0,57	8,35 ±0,57	8,35 ±0,57

Note: * - accurately in comparison with the control group (p<0,05)

Table 3 – Change of the heart rate in case of chloride calcium model of arrhythmia, bpm. (n=5)

Time, minute (after introduction of calcium chloride)	Control	Compounds										
		ГАМ	ОЭТАН	4265	2465	ТБК	ДЭА	5421	БНК	1245	РОДАН	ББК
Before introduction	366,2 ±6,02	361,±6,02	362 ±6,22	375 ±0,71	357,8 ±4,12	348 ±0,88	352 ±6,07	355 ±1,41	368,9 ±5,82	345 ±0,77	366 ±5,28	365 ±1,61
3	225,2 ±25,76*	204,4 ±31,82*	185,6 ±33,96*	266,8 ±4,22*	219 ±24,05*	208 ±24,81*	285,6 ±3,16	216,4 ±19,4*	239,6 ±5,27*	234,4 ±13,82	285,6 ±10,06*	286,8 ±4,49*
5	317,2 ±12,3*	268,4 ±33,13*	299,8 ±22,73*	295,2 ±4,93*	308,2 ±17,3*	288,5 ±13,3*	279,8 ±12,4	195,2 ±14,3*	317,2 ±12,3*	268,4 ±33,13	269,6 ±12,73*	295,2 ±4,93*
15	355 ±5,09	327,2 ±19,1	323,8 ±17,25*	369 ±2,87*	345 ±5,91	237, ±1,82	323,8 ±17,25*	269 ±12,7*	355 ±5,09	327, ±19,12	333,8 ±17,5*	356,2 ±1,56*
30	348 ±7,13*	318,2 ±15,25*	314,2 ±12,87*	361,4 ±2,95*	308 ±3,15*	218,2 ±1,25*	314,2 ±12,8	347,6 ±6,56*	347,6 ±6,59*	317,6 ±8,51*	319,4 ±9,6*	364,4 ±4,6*

Note: * - accurate in cpmparison with the control group (p<0,05)

Table 4 – Excitability of arrhythmia in case of adrenaline model of arrhythmia, % (n=5)

Time, minute (after introducing adrenaline, with preliminary introduction of the studied compounds)	Compounds				
	Control	ГАМ	ОЭТАН	4265	2465
3rd minute	92,4±5,26	7,2±2,27*	70,6±4,47*	63,6±2,14*	4,6±2,86 *
5th minute	76±0	6,2±1,85*	43±19,64	7,34±1,94*	3,2±1,56*
15th minute	12±0	4,8±2.27*	4,2±1,34*	3,63±1,54*	2,2±1,14*
30th minute	18±0	4,8±2.27*	6,4±0,57*	5,94±0,63*	2,2±1,14*

Note: * - accurate in comparison with the control group (p<0,05)

Table 5 – Changes in the heart rate in case of adrenaline model of arrhythmia, bpm. (n=5)

Time, minute (after introducing adrenaline, with preliminary introduction of the studied compounds)	Compounds			
	ГАМ	ОЭТАН	4265	2465
Before the introduction of the compound	375,6±8,32	407,4±14,79	392,4±17,35	407,4±14,79
3rd minute	358,4±12,41*	223,2±25,5	336,2±19,05*	386,6±13,81*
5th minute	354,4±13,69*	268,4±33,13	353,4±10,26*	386,6±13,81*
15th minute	361,8±11,42*	347±9,6*	360,8±13,08*	387,6±13,55*
30th minute	374,2±8,5*	368,2±16,86	354,4±15,41	383,2±15,3*

Note: [1] – accurate in comparison with the benchmark data (p<0,05)

Introduction of the compounds under the codes 4265 and ОЭТАН accurately reduce excitability of arrhythmia beginning with the 3rd minute by 6,75 times (p<0,05) and on the 30th minute by 6,11 times (p<0,05), and by 4,87 times (p<0,05) correspondingly, in comparison with the control (table 2).

The compounds under the codes ГАМ and 2465 also accurately reduce excitability of arrhythmia on the 3rd minute by 7,64 times (p<0,05), and by 12,77 times (p<0,05), and on the 30th minute by 2,95 times (p<0,05), and by 1,4 times (p<0,05) correspondingly, in comparison with the benchmark data (table 2).

The compounds under the codes 5421, БНК, 1245, РОДАН, ТБК, ББК and ДЭА have a tendency to reducing arrhythmia in comparison with the benchmark data. At the beginning of the experiment before the introduction of the studied compounds and calcium chloride the basic values of the heart rate were from 366,2±6,02 to 375±0,71 bpm (table 3).

Introduction of the studied compounds of derivatives of bromonicotinic acid under the codes 4265 and 2465 with the aim to prevent heart rhythm disorder led to accurate reduction of the basic values of heart rate to 345±5,48 bpm (on the 2nd minute when introducing 4-methoxy-6-methyltriazine-2-amide-5-bromonicotinic acid) (p<0,05) and to 358,2±5,27 bpm (on the 2nd minute when introducing the compound under the code 4265) (p<0,05). The load with the toxic dose of calcium chloride (250 mg/kg) was revealed in the accurate negative chronotropic effect up to 139.6±5.27 (on the 4th minute of the ECG). By the end of the observation (after the 10th minute), all groups of animals had accurate recovery of the heart rate (p <0.05) (table 3).

By the 30th minute the heart rate was 348±7,13 bpm (when introducing the compound under the code ГАМ, and before the introduction of the studied substance the heart rate was 366,2±6,02 bpm); 318,2±15,25 bpm (when introducing ОЭТАН, before the introduction - 361,8±6,02 bpm); 314,2±12,87 bpm (when introducing the compound 4265, basic value of the heart rate - 362±6,22 bpm.); 361,4±2,95 bpm (when introducing ТБК, before the introduction - 375±0,71) (table 3).

When comparing the obtained analyses with the results of the research, it was found that the derivatives of bromonicotinic acid have antiarrhythmic effect without side proarrhythmic effect. The studied compounds of the derivatives of bromonicotinic acid, namely 2465, ГАМ, 4265 and ОЭТАН, show the greatest antiarrhythmic effect, and can not only significantly reduce the severity of cardiac arrhythmia, but also lead to more rapid recovery of heart rhythm when introducing these substances for preventive and therapeutic purposes.

Thus, the preliminary introduction of the studied compounds at a dose of 20 mg/kg of a 1% aqueous solution helps to restore the heart rhythm on the 5th–15th minute of the ECG. The compounds under the codes 2465 and ГАМ, introduced intravenously two minutes before provoking arrhythmia, prevent ventricular extrasystole.

In case of preliminary introduction of the compounds of bromonicotinic acid derivatives under the codes ОЭТАН and 4265, adrenaline arrhythmia occurs but by the 5th minute the severity of arrhythmia decreases, and parameters of the electrocardiogram are restored.

At the beginning of the experiment before the introduction of the studied compounds and adrenaline hydrochloride, the basic values of the heart rate were from 375,6±8,32 to 407,4±14,79 bpm. The introduction of the studied compounds was carried out with the aim to prevent heart rhythm disorders and led to accurate reduction of the basic values of the heart rate up to 383,2±15,3 bpm (during the whole period of analysis when introducing the compound under the code 2465) (p<0,05). By the end of the observation (after the 10th minute) all groups of the animals had the accurate restoration of the heart rate (p<0,05).

By the 30th minute the heart rate was 374,2±8,5 bpm when introducing the compound ГАМ (before the introduction the heart rate was 375,6±8,32 bpm); 368,2±16,86 bpm when introducing ОЭТАН, (before the introduction - 407,4±14,79 bpm); 354,4±15,41 bpm (when introducing 4265, the basic value of the heart rate - 392,4±17,35 bpm); 383,2±15 bpm (when introducing 2465, before the introduction - 407,4±14,79).

Barium chloride is able to inhibit potassium conductance. Usually after the introduction of barium chloride at a dose of 25 mg/kg, arrhythmia develops and animals die. The ECG of the normal heart rhythm before the introduction of barium chloride.

Compounds of the derivatives of bromonicotinic acid during the prophylactic course introduction at a dose of 20 mg/kg of a 1% aqueous solution significantly increase the survival of animals. At the same time, the studied compounds are the most active and significantly increase the lifetime by more than 90% before the complete cardiac arrest in animals.

CONCLUSION.

The compounds of the derivatives of bromonicotinic acid under the codes 2465, ГАМ, 4265 and ОЭТАН promote restoration of the excitability of the myocardium on the chloride calcium model of arrhythmia, prevention of ventricular extrasystole on the adrenaline model of the heart rhythm disorder and restoration of the excitability of the myocardium on the chloride barium model of arrhythmia.

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