INVESTIGATION OF THE SPECTRUM OF ANTIARRHYTHMIC ACTION OF N-PROPYL-AIMALINE BROMIDE

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UDC 615.22:547.944].015

In experiments on simulated atrial and ventricular arrhythmias produced in dogs and rats by various chemical (aconitine, acetylcholine, ouabaine) and physical agents and also by disturbance of the coronary circulation it was shown that an alkyl derivative of aimaline—N-propyl-aimaline bromide—possesses the same spectrum of antiarrhythmic action as aimaline itself, but its activity and toxicity are several times higher.

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Recent attempts to obtain aimaline derivatives with higher antiarrhythmic activity have led to synthesis [6] of N-propyl-aimaline bromide (NPAB), which is several times stronger than the natural alkaloid and influences the refractory period of the isolated guinea pig atrium [5].

It was decided to investigate this aimaline derivative* on experimental models of atrial and ventricular arrhythmias in order to determine the spectrum of its antiarrhythmic action.

EXPERIMENTAL METHOD

Experiments were carried out on dogs and rats. The methods of simulating experimental arrhythmias, described in earlier reports [1, 2], consisted of reproducing atrial arrhythmias either in the mechanically injured tissue of the right atrium followed by electrical stimulation (model of atria flutter), or application of a swab soaked in 0.05% aconitine nitrate or 5% acetylcholine solution to the right atrium (model of atrial fibrillation).

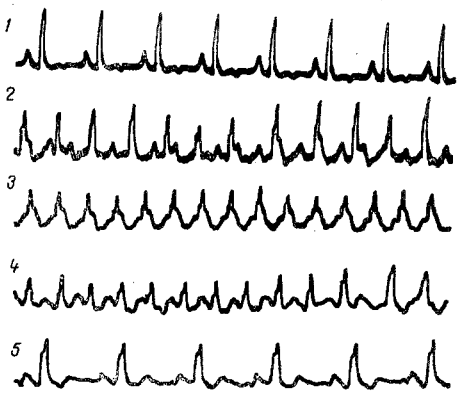

Fig. 1. Antiarrhythmic action of NPAB in auricular flutter in dogs (ECG, lead II). 1) Nembutal anesthesia; 2) 30 min after appearance of arrhythmia; 3, 4, and 5) 2 min, 3min, and 3 min 20 sec after beginning of intravenous infusion of NPAB (0.1 mg/kg/min).

Ventricular tachyarrhythmias were produced in dogs by two-stage ligation of the descending branch of the left coronary artery or by poisoning the animals with ouabaine (65-75 μg/kg), and in rats by aconitine poisoning (30 μg/kg). Ventricular fibrillation was produced in rats by intravenous injection of calcium chloride (10% solution, 3.5 ml/kg).

EXPERIMENTAL RESULTS AND DISCUSSION

In 29 tests on 19 dogs NPAB abolished atrial tachyarrhythmias of different forms and genesis.

In atrial flutter, characterized by dissociation of activity of the two divisions of the heart (the rate of atrial contraction was 561 ± 27/min, ventricular 297 ± 14/min), intravenous infusion of NPAB at the rate of 0.1 mg/kg/min restored the correct sinus rhythm in every case (Fig. 1). The effective dose (ED) of the compound varied from 0.2-0.7 mg/kg (mean 0.445 ± 0.05 mg/kg).

* The compound was supplied by I. F. Makarevich at the Khar'kov Pharmaceutical Chemical Research Institute.

Khar'kov Research Institute of Work Hygiene and Occupational Diseases (Presented by Academician V. V. Parin). Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 67, No. 4, pp. 60-63, April, 1968. Original article submitted May 12, 1968.

TABLE 1. Antiarrhythmic Activity and Toxicity of NPAB and Aimaline

Test	Dose	NPAB	Aimaline	Factor by which indices differ
		in mg/kg		
Atrial flutter in dogs	ED_{100}	0.44 ± 0.05	3.0 ± 0.24	6.8
Atrial fibrillation in dogs produced by aconitine	ED_{100}	0.32 ± 0.04	2.6 ± 0.18	8
Ventricular tachyarrhythmia in dogs:				
with experimental myocardial infarction	ED	2.1 ± 0.24	8.8 ± 1.2	4.2
poisoned with ouabaine	ED_{100}	0.58 ± 0.1	2.7 ± 0.35	4.5
Aconitine arrhythmia in rats:				
Protective action	ED	0.5*	15†	30
Curative action	ED	0.5	5	10
Toxicity for guinea pigs on intravenous injection	LD_{100}	7.05 ± 0.32	27.1 ± 3.7	3.8
Toxicity for mice on intraperitoneal injection	LD_{50}	19 ± 1.3	150 ± 5	7.9

* By intravenous injection.
† By intraperitoneal injection.

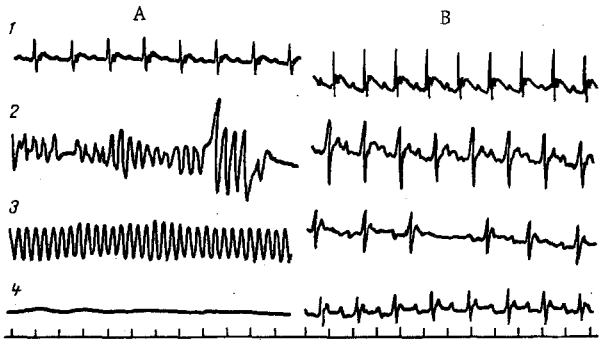

Fig. 2. Protective antiarrhythmic action of NPAB in rats with ventricular fibrillation produced by $CaCl_2$ (ECG, lead II). A) Control experiments; 1) nembutal anesthesia; 2, 3, 4) 1 min, 1 min 30 sec, and 2 min after injection of $CaCl_2$; B) effect of $CaCl_2$ against the background of NPAB action: 1) nembutal anesthesia, 2) 5 min after injection of NPAB (1 mg/kg); 3, 4) 1 and 5 min after injection of $CaCl_2$.

NPAB, if injected in the same way, abolished persistent atrial fibrillation produced by local application of aconitine. ED of the compound restoring sinus rhythm varied from 0.2-0.6 (0.325 ± 0.04) mg/kg.

In experiments on dogs in which atrial fibrillation was reproduced by a combination of the action of acetylcholine and mechanical stimulation of the right atrial wall, preliminary administration of NPAB in a dose of 0.3-0.5 mg/kg increased the resistance of the myocardium to the arrhythmogenic effect of acetylcholine (considered to be due to shortening of the repolarization phase of membranes of the myocardial fibers), and temporarily prevented the development of atrial fibrillation.

The compound thus was able to suppress ectopic impulse formation both at single and at multiple heterotopic pacemakers appearing in the atrial tissues and to restore the dominant role of the nomotopic pacemaker of the heart.

NPAB also proved to be highly effective in experimental cardiac arrhythmias characterized by ectopic impulse formation in the ventricles.

Tests on dogs with experimental myocardial infarction showed that repeated injection of NPAB in doses of 0.4-0.5 mg/kg significantly weakened ectopic impulse formation and reduced the heart rate slightly. After the mean concentration of the compound had reached 2.1 ± 0.24 mg/kg as a result of accumulation following repeated injections in the course of the experimental day, ventricular tachyarrhythmia was abolished completely in 6 of the 8 experimental animals and a regular sinus rhythm was restored for 46 ± 17 min. The duration of the partial antiarrhythmic effect (when the number of ectopic contractions was reduced by more than 50%) was 109 ± 19 min. In addition, NPAB slowed the cardiac activity of all the animals, on the average by 26%.

NPAB also abolished ventricular tachyarrhythmia produced in dogs by poisoning with the cardiac glycoside. After intravenous infusion at the rate of 0.1 mg/kg/min, the compound slowed the heart rate to normal for long periods in animals poisoned with ouabaine and prevented death. The ED of NPAB as established on this model of arrhythmia varied in 5 experiments from 0.4 to 0.7 (0.58 ± 0.1) mg/kg.

Experiments on 110 rats showed that NPAB has a protective and antiarrhythmic action in aconitine poisoning, abolishing the arrhythmia and significantly ($P < 0.05$) increasing the survival rate of the poisoned animals. ED_{50} of the compound, calculated by the method of Miller and Tainter, was 0.33 ± 0.07 mg/kg. NPAB also had a protective and defibrillating action, preventing the development of lethal ventricular fibrillation in rats poisoned with calcium chloride (Fig. 2). ED_{50} of the compound determined on this model of arrhythmia was 0.54 ± 0.22 mg/kg.

NPAB thus has a spectrum of antiarrhythmic action as broad as that of aimaline. However, according to our findings, this derivative of aimaline is 4.2-10 times stronger in its antiarrhythmic activity in various models of experimental arrhythmia, and is from 4 to 8 times more toxic for animals of different species (Table 1).

This conclusion regarding the similarity between the spectra of antiarrhythmic action of NPAB and aimaline is in agreement with the observations of Heistracher and Pillat [3, 4], made by means of a microelectrode technique, and showing that these compounds affect the dynamics of depolarization and repolarization of the Purkinje fibers in calves in a similar manner, and also with our own findings revealing analogous changes in function of the conducting system arising in guinea pigs after administration of NPAB and aimaline.

Consequently, the introduction of an alkyl group into the aimaline molecule leads to a marked increase in the antiarrhythmic activity and toxicity of the compound but does not affect the spectrum of its antiarrhythmic action.

LITERATURE CITED

1. É. I. Gendenshtein, Byull. Éksperim. Biol. i Med., No. 4, 71 (1961).
2. É. I. Gendenshtein, Cor et Vasa (Prague), 8, 283 (1966).
3. P. Heistracher and B. Pillat, Arch. Exp. Path. Pharmak., 245, 72 (1963).
4. P. Heistracher and B. Pillat, Arch. Kreisl-Forsch., 44, 300 (1964).
5. R. Kadats and N. Rossbach, Arch. Exp. Pharmak., 245, 71 (1963).
6. J. Keck, Z. Naturforsch., 18, 177 (1963).