5. R. A. Durinyan, The Central Structure of Afferent Systems [in Russian], Leningrad (1965).
6. V. V. Zakusov, Pharmacology [in Russian], Moscow (1960), pp. 83-84.
7. V. V. Zakusov, The Pharmacology of Central Synapses [in Russian], Moscow (1973), pp. 42-44.
8. V. K. Muratov, L. N. Sinitsyn, A. G. Rudakov, et al., Farmakol. Toksikol., No. 2, 191 (1973).
9. L. N. Sinitsyn, Farmakol. Toksikol., No. 3, 258 (1961).
10. L. N. Sinitsyn, Farmakol. Toksikol., No. 4, 387 (1962).
11. S. Fujita, M. Yasuhara, and K. Ogiu, Jap. J. Pharmacol., 3, 27 (1953).
12. H. H. Jasper and C. A. Ajmone-Marsan, A Stereotaxic Atlas of the Diencephalon of the Cat, Ottawa (1954).
13. J. S. MacKenzie and N. R. Beechey, Electroenceph. Clin. Neurophysiol., 14, 501 (1962).
14. R. Melzack and R. Wall, Science, 150, 971 (1965).
15. H. Takagi, M. Matsumura, A. Vanai, et al., Jap. J. Pharmacol., 4, 176 (1955).
16. L. G. Sharpe, J. E. Garnett, and T. J. Cicero, Behav. Biol., 11, 303 (1974).

ANTIARRHYTHMIC ACTIVITY OF THE β_2-ADRENOBLOCKER ALPRENOLOL

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Experiments on dogs, cats, and rats with various disturbances of the cardiac rhythm showed that the β_2-adrenoblocker alfeprol, the Soviet analog of alprenolol, has a marked antiarrhythmic action. The substance abolishes atrial arrhythmias induced by electrical stimulation of the atria or by application of aconitine, it controls ventricular arrhythmias arising as a result of occlusion of a branch of the coronary artery or of ouabain poisoning, and it prevents lethal ventricular fibrillation in rats after calcium chloride poisoning. The antiarrhythmic effect of alprenolol is ascribed not only to blocking of β-adrenoreceptors but also to the quinidine-like action of the compound.

KEY WORDS: cardiac arrhythmias; catecholamines; β-adrenoblockers; alfeprol (alprenolol).

β-Adrenoblockers differing from propranolol (Inderal, Anapriline) by their weaker cardiodepressive action have recently been obtained. They include alfeprol, the Soviet analog of alprenolol or aptin, synthezied by Simon [6]. The characteristic effects produced by this β-adrenoblocker have been explained by its adrenomimetic activity [8] or by its predominant action on β_2-adrenoreceptors [4].

Considering that the adrenoreceptors of the myocardium are of the β_1 type it was decided to study the degree of antiarrhythmic action shown by alprenolol in experimental arrhythmias.

EXPERIMENTAL METHOD

Experiments were carried out on 21 dogs (7-13 kg), 38 cats (1.9-3.1 kg), and 63 rats (150-200 g). Atrial arrhythmias in the acute experiments on dogs were induced by mechanical injury to the region of the opening of the venae cavae followed by stimulation of the right atrium with dc pulses, and in cats by application of a swab soaked in 0.05% aconitine nitrate solution to the auricle of the right atrium. Ventricular tachyarrhythmias were induced in dogs by ligation of the descending branch of the left coronary artery and in cats by poisoning

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TABLE 1. Antiarrhythmic Activity of Alprenolol

Effect of drug	No. of expts.		ED (in mg/kg)
	total	with positive result	
Abolishing atrial flutter in dogs	10	10	1.0 ± 0.15
Abolishing atrial fibrillation in cats	14	14	4.0 ± 0.2
Abolishing ventricular tachyarrhythmia in cats caused by ouabain poisoning	9	9	4.0 ± 0.14
Preventing ventricular fibrillation produced in rats by calcium chloride poisoning	63	-	7.0 ± 0.7 (ED_{50})

with ouabain (80 μg/kg). Ventricular fibrillation in rats anesthetized with urethane (1 g/kg) was produced by intravenous injection of calcium chloride (2 ml/kg of a 10% solution) [1].

The effect of alprenolol (0.5 and 5 mg/kg, intravenously) also was studied on the toxicity of ouabain for cats. By biological titration (ouabain solution in a concentration of $8 \cdot 10^{-6}$ g/ml was injected intravenously at the rate of 1 ml/min) the minimal dose of the glycoside causing the appearance of ectopic arrhythmias and the lethal dose leading to cardiac arrest were determined. The ECG was recorded in standard lead II.

EXPERIMENTAL RESULTS

Alprenolol was highly effective against disturbances of the atrial rhythm (Table 1). Intravenous injection of the compound at the rate of 0.5 mg/kg/min in all experiments abolished the tachyarrhythmic form of atrial flutter in dogs in all the experiments (the frequency of ventricular contractions reached 243 ± 9/min) and restored a stable and regular sinus rhythm with a rate of contraction of 155 ± 3 beats/min. The effective dose (ED) of alprenolol varied from 0.5 to 1.5 mg/kg, with a mean value of 1.0 ± 0.15 mg/kg.

Alprenolol abolished atrial fibrillation in cats also. Intravenous injection of the compound (1 mg/kg/min) in doses of 2 to 6 mg/kg (mean 4.0 ± 0.2 mg/kg) inhibited atrial fibrillation in all experiments and restored the sinus rhythm, at a frequency 26% below the initial level. The duration of the antiarrhythmic effect varied from 20 to 70 min.

Alprenolol also had an antiarrhythmic action against arrhythmias characterized by ectopic impulse formation in the ventricles. In dogs 24 h after occlusion of the branch of the coronary artery, ventricular tachyarrhythmia developed with a frequency of 190 ± 7 beats/min.

A single intravenous injection of alprenolol in a dose of 0.5 mg/kg into these animals had an antiarrhythmic action in 9 of 11 experiments. In three dogs the ectopic generation of impulses was completely suppressed and a regular sinus rhythm restored temporarily (for 20-40 min). In six animals the number of ectopic contractions was reduced by alprenolol by more than 50%. During repeated (at intervals of 15-30 min) injections of the compound in increasing doses (0.5-2 mg/kg), when the total dose given reached 4-6 mg/kg, ventricular tachyarrhythmia was completely abolished and the regular sinus rhythm restored temporarily (for 20-30 min). The duration of the antiarrhythmic effect, during which the number of ectopic beats was reduced by more than 50%, was 15-40 min.

Besides suppressing ectopic impulse generation, in every case alprenolol slowed (on the average by 30%) the tachycardia.

Ventricular fibrillation developed in the rats after calcium chloride poisoning in 70% of cases. Premedication with alprenolol in doses of 2-10 mg/kg 4-5 min before the injection of calcium chloride prevented the development of lethal ventricular fibrillation. In this model of arrhythmia, ED_{50} for alprenolol calculated by the method of Miller and Tainter was 7.0 ± 0.7 mg/kg.

TABLE 2. Effect of Alprenolol on Toxicity of Oubain for Cats

Dose of alprenolol (in mg/kg)	Number of experiments	Dose of ouabain (in μg/kg)	
		arrhythmogenic	lethal
—	9	87±4,3	125±4,7
0,5	8	98±4,5	144±6,0
5,0	7	115±5,0	153±5,0

Considering data indicating the role of catecholamines in the mechanism of the effect of cardiac glycosides [7] it was decided to study the antiarrhythmic activity of alprenolol in ouabain poisoning.

When injected intravenously (1 mg/kg/min) alprenolol abolished ventricular tachyarrhythmia induced in cats by poisoning with the cardiac glycoside. For alprenolol the ED was 4.0 ± 0.14 mg/kg. The regular sinus rhythm continued on the average for 10 ± 2 min, after which the ventricular arrhythmia was gradually restored; it could again be abolished by repeated injection of alprenolol in a dose of 4.0 ± 0.8 mg/kg. In that case the antiarrhythmic effect continued for 30-120 min.

As is clear from Table 2, alprenolol lowered the sensitivity of the heart to the bathotropic action of the cardiac glycoside, as the significant increase in the arrhythmogenic dose of ouabain demonstrates. The compound also increased the tolerance of the animals to ouabain and increased the lethal dose of the glycoside.

On the basis of its activity and the width of the spectrum of its antiarrhythmic action alprenolol is thus not inferior to antiarrhythmic agents with quinidine-like (of the membrane-stabilizing type) action, such as ajmalin [2].

Doses in which alprenolol had an antiarrhythmic action, it will be noted, were about 100-400 times smaller than doses which, according to data in the literature [6], completely block β-adrenergic structures. This fact, together with evidence of the predominantly β_2-adrenoblocking activity [4] of alprenolol, suggests that the antiarrhythmic effect of this compound is due not only to blocking of β-adrenoreceptors, but also to its quinidine-like action, as was shown previously for Inderal [3, 5, 9].

LITERATURE CITED

1. É. I. Gendenshtein, Cor Vasa (Prague), 8, 283 (1966).
2. E. I. Gendenshtein, Byull. Éksp. Biol. Med., No. 4, 60 (1969).
3. É. I. Gendenshtein, L. I. Igol'nikova, and R. E. Kiseleva, Kardiologiya, No. 10, 35 (1974).
4. I. V. Komissarov and I. I. Abramets, in: Pharmacology and Toxicology, No. 9 [in Russian], Kiev (1974), pp. 75-79.
5. L. V. Rozenshtraukh, Kardiologiya, No. 1, 98 (1968).
6. I. B. Simon, V. P. Vvedenskii, I. I. Levshina, et al., Khim.-Farm. Zh., No. 3, 7 (1974).
7. A. I. Cherkes and S. B. Frantsuzova, in: Proceedings of the Second Congress of Pharmacologists of the Ukrainian SSR [in Russian], Kiev (1973), pp. 264-265.
8. B. Ablad, M. Brogard, and L. Ek, Acta Pharmacol. Toxicol., 25, Suppl. 2, 9 (1967).
9. I. D. Fitzgerald, Int. J. Clin. Pharmacol., 11, 235 (1975).