THE ANTI-ARRHYTHMIC ACTIVITY OF THE TETRABUTYLAMIDE OF EDTA

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According to reports in the literature [4, 5, 6] the disodium salt of ethylenediaminetetraacetic acid (Na_2EDTA) in experimental and clinical conditions abolishes disturbances of the cardiac rhythm arising as a result of poisoning by cardiac glycosides. Some clinicians [8, 9] assert that Na_2EDTA also exerts an anti-arrhythmic effect in ventricular arrhythmias not associated with the administration of preparations of the digitalis group. It has been claimed [7, 9] that in these cases the anti-arrhythmic action of Na_2EDTA is due not only to the chelation of the ionized calcium of the blood serum, but also to the direct effect of EDTA on the excitability of the myocardium and, in particular, to the lengthening of the refractory phase of the heart.

In face of these facts, it was interesting to study the anti-arrhythmic activity of one of the substituted amides of EDTA, namely the tetrabutylamide of EDTA (TBAEDTA), synthesized at the Khar'kov Research Chemo-Pharmaceutic Institute by S. A. Sarkisyants and Yu. E. Aronov. This compound is unable to form complexes with the cations of polyvalent metals [3], and consequently, its pharmacological effect is not the result of changes in the electrolyte balance of the organism.

EXPERIMENTAL METHOD AND RESULTS

The investigations were conducted on dogs and rats in which disturbances of the cardiac rhythm were produced by various experimental procedures. The disturbances were characterized by a mainly ventricular ectopic pacemaking activity.

As a result of 14 experiments on eight dogs with ventricular tachycardia arising as a result of ligation of the descending branch of the left coronary artery (the technique was described in previous communications [1, 2]) it was found that TBAEDTA, in a dose of 5-10 mg/kg, when given by repeated intravenous injection, temporarily (for 20-60 min) depressed the ectopic pacemaker, restored the normal sinus rhythm, and slowed the cardiac activity by 15-20% (Fig. 1). The partial effect, i.e., the period when the sinus and heterotopic impulses alternated, lasted for 2 h. The electrocardiogram (ECG) of the animals during normalization of the cardiac rhythm and before ligation of the coronary artery showed no essential difference.

The next series of experiments was carried out on 12 unanesthetized dogs receiving an intravenous injection of ouabain in a dose of 80 μg/kg, causing disturbances of the cardiac rhythm characterized by a severe ventricular polymorphic tachyarrhythmia (190-230 contractions/min). The injection of TBAEDTA in a dose of 10-20 mg/kg completely abolished the arrhythmia and restored the normal cardiac rhythm (Fig. 2). In addition, a slowing of the heart rate was observed – in some cases the rate regained its initial value (before poisoning) – and the initial durations of the intervals of the cardiac cycle (PQ and QT) were restored. This effect lasted 10-30 min and, in individual cases, 90 min. The repeated injection of the preparation lengthened the period of normal rhythm to 1.0-1.5 h. The animals poisoned with the cardiac glycoside tolerated repeated injections of TBAEDTA in a dose of 10-20 mg/kg well.

When administration of TBAEDTA was combined with that of ouabain, the toxicity of the latter was appreciably lowered. The lethal dose of the cardiac glycoside for guinea pigs receiving a preliminary injection of 20 mg/kg TBAEDTA was raised by 30% ($P < 0.05$).

In experiments on 34 rats anesthetized with Nembutal, it was found that TBAEDTA, in a dose of 10 mg/kg, gave an antifibrillatory effect. The preparation prevented the onset of a lethal ventricular fibrillation in 73% of

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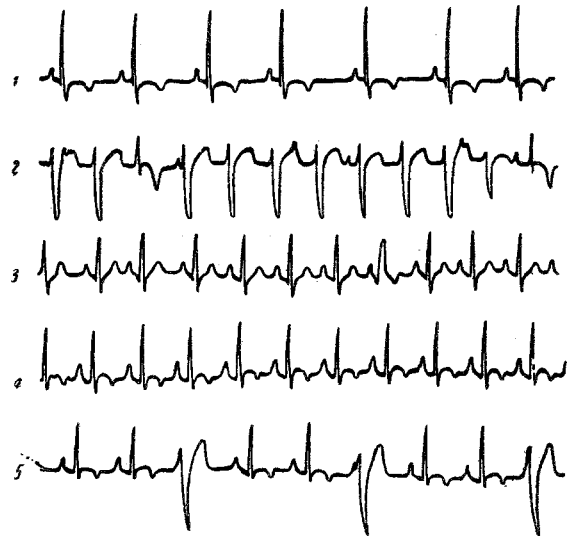

Fig. 1. Effect of TBAEDTA on ventricular arrhythmia in a dog arising after ligation of the descending branch of the left coronary artery. ECG in lead 2. 1) Before operation and after injection of Nembutal; 2) 22 h after ligation; 3-5) 1, 20, and 50 min after injection of TBAEDTA in a dose of 10 mg/kg.

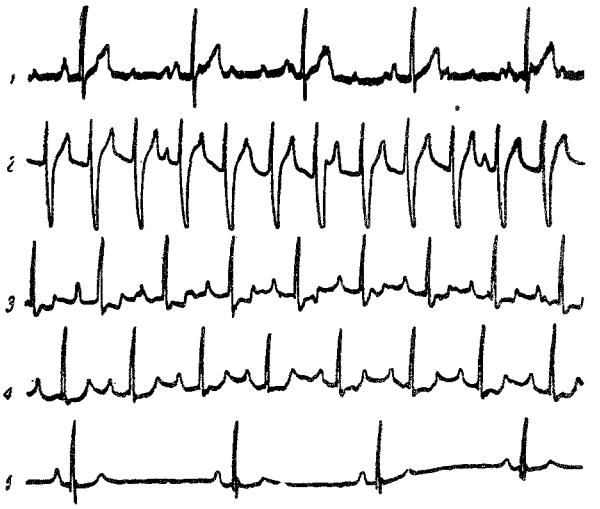

Fig. 2. Effect of TBAEDTA on ventricular arrhythmia in a dog caused by ouabain poisoning. ECG in lead 2. 1) Initial; 2) after poisoning with ouabain (80 μg/kg); 3-5) 3, 20, and 90 min after injection of TBAEDTA in a dose of 10 mg/kg.

rats receiving a toxic dose (0.2 ml of a 10% solution per 100 g body weight) of calcium chloride intravenously. In the control series 92% of the animals died from this dose.

When TBAEDTA was given by intravenous infusion (at a rate of 4 mg/kg/min) to intact guinea pigs, its lethal dose was 113 ± 11 mg/kg. In a dose equal to 30% of lethal, the preparation produced sinus bradycardia, a slowing of atrioventricular conduction, and a lengthening of electrical ventricular systole – the QT interval. Hence TBAEDTA had a marked influence on the functional state of the myocardium, depressing the functions of automatism and conduction.

The results obtained demonstrate this anti-arrhythmic activity of TBAEDTA, which was found to have a wider spectrum of anti-arrhythmic action than $MgNa_2EDTA$, investigated by the author previously [1, 2]. TBAEDTA was effective not only in arrhythmias caused by poisoning with a cardiac glycoside, but also in ventricular tachycardia arising as a result of experimental myocardial infarction.

Taking account of the property of TBAEDTA mentioned above (its lack of complex-forming ability), it must be postulated that the anti-arrhythmic effect of this substance is evidently due to its direct effect on the functional state of the myocardium. The EDTA molecule may evidently be used for the synthesis of active anti-arrhythmic substances by introducing appropriate radicals and functional groups into it, even if the resulting compound loses its complex-forming power.

SUMMARY

Experimental models of cardiac fibrillation induced in dogs and rats were used to study the antifibrillatory activity of tetrabutylamide of ethylendiaminetetraacetic acid (TBAEDTA) – a compound devoid of the capacity for complex formation. TBAEDTA in a dose of 5-20 mg/kg repeatedly injected into a vein somewhat decelerated intensified cardiac activity, suppressed the ectopic impulse formation and temporarily restored the correct sinusal rhythm in dogs with experimental myocardial infarction and in dogs intoxicated with oubain. TBAEDTA produced an antifibrillatory effect preventing lethal ventricular fibrillation in rats given a toxic dose of calcium chloride intravenously. The EDTA molecule can apparently be used for the synthesis of substances capable of antifibrillatory activity after the introduction into it of corresponding functional groups, even if this results in the loss of the capacity of the compound for complex formation.

LITERATURE CITED

1. É. I. Gendenshtein and L. A. Karskaya, Byull. Éksp. Biol., No. 11 (1962), p. 72.

2. É. I. Gendenshtein, Kardiologiya, No. 5 (1964), p. 87.
3. A. Badinand et al., Bull. Soc. Chim., No. 2, France (1960), p. 382.
4. R. S. Eliot et al., Am. Heart. J., Vol. 62 (1961), p. 7.
5. J. Kitchell et al., Progr. Cardiovasc. Dis., Vol. 3 (1961), p. 338.
6. E. Page et al., Circulat. Res., Vo. 3 (1955), p. 501.
7. E. Rothlin, Cited by E. Rothlin and M. Taeschler, In: Advances in Cardiology [Russian translation], Moscow (1959), p. 185.
8. A. Soffer et al., Arch. Intern. Med., Vol. 106 (1960), p. 824.
9. B. Surawicz et al., Am. Heart. J., Vol. 58 (1959), p. 493.

All abbreviations of periodicals in the above bibliography are letter-by-letter transliterations of the abbreviations as given in the original Russian journal. *Some or all of this periodical literature may well be available in English translation.* A complete list of the cover-to-cover English translations appears at the back of the first issue of this year.
