THE EFFECT OF THE MAGNESIUM-DISODIUM SALT OF EDTA ON EXPERIMENTAL VENTRICULAR ARRHYTHMIAS IN DOGS

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Ethylenediamine-tetraacetic acid (EDTA) is one of the most active chelating agents widely used in experimental and clinical medicine [1, 2, 3]. Recently the disodium and dipotassium salts of EDTA have been suggested for use in the treatment of certain cardiovascular diseases [5, 9], especially for disturbances of the cardiac rhythm arising as a result of overdosage with preparations of cardiac glucosides [6, 15, 16].

The use of EDTA salts for the control of arrhythmias is based on their ability to lower the blood level of calcium, a synergist of the cardiac glucosides. Several workers have shown [11, 13, 14] that Na_2EDTA and K_2EDTA, by causing hypocalcemia when administered parenterally, normalize the cardiac activity in animals poisoned with strophanthin or digitoxin. Meanwhile clinical trials have also revealed that Na_2EDTA sometimes abolishes atrial and ventricular extrasystoles not due to treatment with digitalis preparations [9, 16].

The efficacy of EDTA salts in experimental ventricular arrhythmias has not been adequately explained. The object of the present research was to study the anti-arrhythmic action of the magnesium disodium salt of EDTA, synthesized at the Khar'kov Research Chemo-Pharmaceutical Institute by B. Yu. Yasnitskii and S. A. Sarkis'yants. The choice of this substance for the investigation was determined by the fact that it is a complex compound of Na_2EDTA and magnesium; the latter, firstly, is a calcium antagonist and, secondly, has been shown by experimental [8, 12] and clinical findings [4, 7] also to possess the property of depressing ectopic arrhythmias.

EXPERIMENTAL METHOD AND RESULTS

The investigation was conducted on two experimental models of ventricular arrhythmias reproduced in dogs by various methods: in one series of experiments by interfering with the coronary circulation, and in another by poisoning the animals with strophanthin G.

The first series of experiments was conducted on nine dogs in which a persistent polytopic ventricular tachysystole was produced 20-23 h after two-stage ligation of the descending branch of the left coronary artery. The frequency of the rhythm varied from 195 to 255 contractions per minute, and the ECG showed no impulses from the sinoatrial node. On the second day after the operation the rhythm was slightly slowed in the animals and isolated sinus contractions developed, although the overwhelming majority of the impulses kept their heterotopic origin (150-185/min, of which 105-150 were ectopic).

Twelve experiments were carried out on these animals: eight 24 h after ligation and four 48 h after ligation; a 5% solution of $MgNa_2EDTA$ was injected intravenously over a period of 5-15 min.

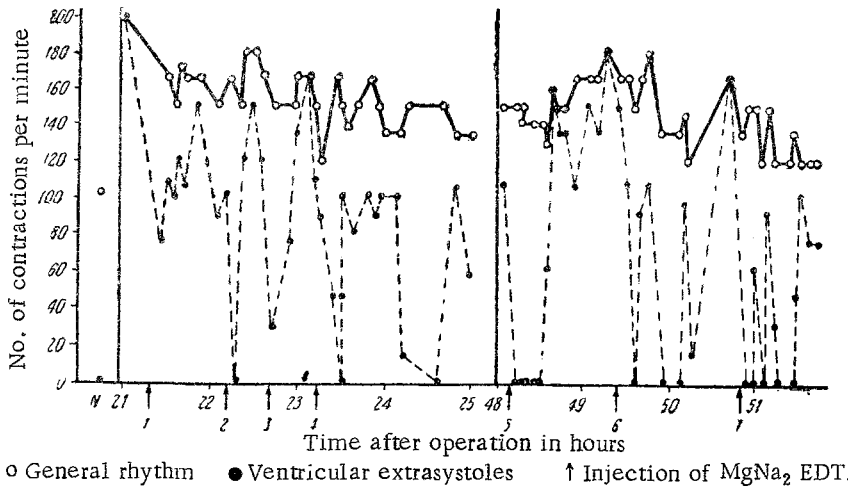
On the first day after the operation, when the arrhythmia was particularly pronounced, the repeated injection of $MgNa_2EDTA$ (50-100 mg/kg body weight) into two animals led to an appreciable decrease (by 25%) in the general frequency of the rhythm, and considerably weakened and at times completely suppressed the extrasystoles and restored the sinus rhythm (see figure). For instance, in one of these experiments the periodic (triple) injection of 50 mg/kg $MgNa_2EDTA$ abolished the arrhythmia and maintained the animal's normal sinus rhythm for 5 h. In one experiment, although the drug in a dose of 100 mg/kg did not alter the general frequency of the rhythm, it diminished the ectopic impulsation (from 220 to 100 extrasystoles per minute). This effect lasted only for 8 min.

In two dogs 6 or 7 injections of 50 mg/kg of $MgNa_2EDTA$ had no effect on the frequency of the rhythm and the intensity of the ectopic impulsation. These animals developed a particularly severe tachysystole (225-255 contractions per minute).

Three dogs died during the experiments from respiratory arrest after administration of $MgNa_2EDTA$ in a total dose of 200 mg/kg. The remaining five animals tolerated the drug well when given in a total dose of 200-350 mg/kg.

On the second day after application of the ligature, when the ventricular tachycardia was rather less pronounced, the injection of $MgNa_2EDTA$ hardly affected the heart rate but restored the sinus rhythm in all four dogs for a short time (10-30 min). Hence $MgNa_2EDTA$ weakened or suppressed the ventricular extrasystoles developing in dogs 24 h after artificial restriction of the coronary blood flow in some animals only. On the second day after the operation, the drug gave a more constant anti-arrhythmic effect, although even then its effect was transient.

The second series of experiments was carried out on unanesthetized dogs poisoned with strophanthin G. The animals received a subcutaneous injection of 1-2 ml of a 1% solution of morphine, followed after 30-40 min by an intravenous injection of a solution of the glucoside in a dose of 0.08 mg/kg body weight.



Anti-arrhythmic action of $MgNa_2EDTA$ in ventricular arrhythmia caused in a dog by ligation of the descending branch of the left coronary artery. Doses of solution: 1, 5-7) 100 mg/kg; 2-4) 50 mg/kg.

Control experiments on six dogs showed that strophanthin in this dose leads to a severe disturbance of the cardiac activity, causing ventricular tachysystoles with polymorphism of the ventricular complexes. At the same time the general condition of the animals worsened (transient excitation, giving way to depression, dyspnea, lying on their side). Four of the six animals died, three after 1-2 h and one after 5 h 30 min; two animals survived, but their sinus rhythm was restored only after 4-5 h.

The anti-arrhythmic action of $MgNa_2EDTA$ was investigated on 10 dogs in which, as in the control experiments, strophanthin had led to the development of a ventricular polymorphic tachysystole with a frequency of contractions ranging from 150 to 250 per minute. The intravenous infusion of a 5% solution of $MgNa_2EDTA$ began 20-30 min after the injection of strophanthin, i.e., 10-20 min after the development of the arrhythmia. Administration of the compound continued until stabilization of the normal cardiac rhythm was obtained.

The results of this series of experiments are shown in the table. When the injection of 25 mg/kg of $MgNa_2$-EDTA was repeated at intervals of 10 min, transient (for a few minutes) restoration of the sinus rhythm was observed after 4-5 injections, i.e., after an average total dose of 117 mg/kg. Permanent normalization of the rhythm was observed after a total dose of 217 mg/kg, 2 h 5 min after poisoning with strophanthin.

A second group of animals received repeated injections of $MgNa_2$ EDTA in a dose of 50 mg/kg at various intervals. Transient restoration of the sinus rhythm was observed after an average total dose of 112 mg/kg, and a permanent effect took place after an average total dose of 175 mg/kg, 1 h 20 min after strophanthin poisoning.

In a third group of experiments dogs received injections of the compound in doses ranging from 50 to 100 mg/kg. Transient periods of sinus rhythm appeared after a total dose of 100 mg/kg. The arrhythmia was suppressed by a mean total dose of 217 mg/kg of the compound 1 h 4 min after administration of strophanthin to the dogs.

Analysis of the ECGs (lead 2) taken throughout the experiment showed the following pattern of change in the cardiac rhythm: initially, a slight slowing of the very fast cardiac activity, a decrease in the number of ectopic contractions, and the appearance of isolated sinus impulses; the development of various allorhythmias (bi- and trigeminy);

Effect of $MgNa_2$ EDTA on Strophanthin Arrhythmia in Dogs

Expt. No.	Single dose of $MgNa_2$ EDTA (mg/kg)	Intervals between injections (in min)	Total dose of $MgNa_2$ EDTA (in mg/kg) causing normalization of rhythm				Time taken for normalization of rhythm after strophanthin (in min)	
			temporary		permanent			
21	25	10	100	117	225	217	135	125
22	25	10	125		150		90	
30	25	10	125		275		150	
17	50	15-20	100	112	150	175	55	81
19	50	30-45	150		250		135	
37	50	25	100		100		30	
38	50	20-30	100		200		105	
1	50-100	20-35	100	100	200	217	80	64
2	100-50	20-30	100		250		70	
5	100	25	100		200		43	

the appearance of signs of a disturbance of atrioventricular conduction (partial or complete block, in which the PP interval is longer than the RR interval), and sometimes alternation of nodal rhythm with sinus contractions (dissociation with interference); sudden restoration of the normal sinus rhythm. In some cases there was a transient lengthening and downward displacement of the S-T segment and an increase in the voltage of the negative T wave.

The injection of $MgNa_2$EDTA led not only to normalization of the cardiac activity, but also to an appreciable improvement in the general condition of the dogs poisoned with strophantin, and its tranquilizing effect was particularly marked.

Hence, by comparison with the controls, all the dogs receiving $MgNa_2$ EDTA survived and their normal cardiac activity was restored more rapidly than in the untreated animals (mean effective dose 200 ± 17 mg/kg). We also observed that the anti-arrhythmic action of the drug appeared sooner after large and moderate doses were given than after frequent injections of small doses (in the control experiments the intact dogs tolerated 400-575 mg/kg of $MgNa_2$EDTA, injected in doses of 25 mg/kg every 10 min).

The experimental findings demonstrate the value of $MgNa_2$EDTA in disturbances of the cardiac rhythm characterized by strong ectopic impulsation, mainly of ventricular origin. However, whereas $MgNa_2$EDTA abolished the arrhythmia caused by restriction of the coronary blood flow in only a proportion of cases, in poisoning with cardiac glucosides the compound gave excellent therapeutic results.

The strength of the complex of EDTA and a metal is known to be determined by the logarithm of the constant of its stability. For calcium this value is 10.6, and for magnesium only 8.7 (i.e., calcium is bound to EDTA approximately 100 times more firmly than is magnesium).

Human experiments have shown [10] that after administration of $MgNa_2$EDTA an exchange reaction takes place in the blood: Ca^{++} is incorporated into the complex in a quantity equivalent to the magnesium, and the magnesium passes into the plasma. We may therefore suppose that at least two components are present in the mechanism of the anti-arrhythmic action of $MgNa_2$ EDTA: hypocalcemia, arising as a result of complex formation with EDTA (of decisive importance in abolishing the strophanthin arrhythmia), and a decrease in the excitability of the myocardium by the action of magnesium ions (a calcium antagonist).

The weakening of the ectopic impulsation caused by a disturbance of the coronary circulation is evidently due principally to the pharmacological action of ionized magnesium, displaced from the complex by chelated calcium. This hypothesis is based on reports [8] showing that magnesium salts terminate the ventricular arrhythmia arising in dogs after ligation of the coronary artery.

We may conclude that $MgNa_2EDTA$ possesses definite advantages over the other EDTA salts used for the treatment of arrhythmias, because this complex, which possesses a wider and more comprehensive pharmacological action, acts simultaneously on several links of the pathogenetic mechanism of the arrhythmia.

SUMMARY

Experiments were staged on dogs with induced ventricular tachycardia. As shown, magnesium-disodium salt of EDTA had an antiarrhythmic effect. However, although in arrhythmia induced by ligature of the coronary artery this action was manifested only in some cases, in strophanthin intoxication $MgNa_2$ EDTA had a constant distinct therapeutic effect.

LITERATURE CITED

1. I. N. Bel'gova, Farmakol. i Toksikol., 2, 239 (1961).
2. D. I. Zakutinskii and L. N. Selivanova, Med. prom. SSSR, 10, 48 (1958).
3. D. I. Semenov, Priroda, 8, 25 (1959).
4. L. J. Boyd and D. Scherf, Am. J. med. Sci. 1943, v. 206, p. 43.
5. N. E. Clarke, N. E. Clarke, and R. E. Mosher, Am. J. med. Sci. 1960, v. 239, p. 732.
6. B. D. Cohen, N. Spritz, G. Lubash, et al., Circulation, 1959, v. 19, p. 918.
7. C. D. Enselberg, H G. Simmons, and A. A. Mintz, Am. Heart J. 1950, v. 39, p. 703.
8. A. S. Harris, et al., Am. J. Physiol. 1953, v. 172, p. 251.
9. J. R. Kitchell, L. E. Meltzer, and M. J. Seven, Progr. cardiovasc. Dis. 1961, v. 3, p. 338.
10. F. Mayr, A. Holasek, H. Flaschka, et al., Wien. med. Wschr. 1954, Bd. 104, S. 993.
11. E. Page and J. D. Real, Circulat. Res. 1955, v. 3, p. 501.
12. C. J. Rothberger and L. Zwillinger, Arch. exp. Path. Pharmak., 1936, Bd. 181, S. 301.
13. N Sapeika, Arch. inst. Pharmacodyn. 1954, v. 97, p. 373.
14. P. W. Smith and E. H. Grinnell, Fed. Proc. 1955, v. 14, p. 387.
15. A. Soffer, T. Toribara, D. Moore-Jones, et al., Arch. intern. Med. 1960, v. 106, p. 824.
16. B. Surawicz, M. G. MacDonald, et al., Am. Heart J., 1959, v. 58, p. 493.

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