ANTIARRHYTHMIC ACTION OF SERPENTINE IN SOME EXPERIMENTAL DISTURBANCES OF THE AURICULAR AND VENTRICULAR RHYTHM

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Among the alkaloids of Rauwolfia discovered in recent years are two substances, ajmaline and serpentine, which can normalize arrhythmia [2, 4, 5, 10]. Ajmaline has already gained recognition in the clinic as an effective antiarrhythmic agent [7, 11]. The question of the pharmacodynamics and antiarrhythmic activity of serpentine is elucidated appreciably less in the literature.

The purpose of the present work was to study the effect of the hydrochloride of serpentine * on experimental auricular and ventricular arrhythmia in dogs.

EXPERIMENTAL METHOD

Disturbances of the auricular rhythm were evoked by the experimental methods described in the literature which can reproduce either auricular flutter [8] or auricular fibrillation [9]. In the former case the dogs, which were under morphine-nembutal anesthesia and on controlled respiration, underwent dextral thoracotomy, pericardiostomy, and mechanical damage (crushing) of the tissue of the right atrium between the superior and inferior vena cava. Then the atrium was stimulated for 2 min by square pulses with a current duration of 15 msec, frequency of 20 cps, and voltage of 15-20 V.

The tachycardia that occurred immediately after the start of stimulation was characterized by dissociation of the activity of the auricles and ventricles. The auricular contraction rate averaged 447±17 per min and that of the ventricles, 256±23 per min. On the EKG recorded at the II standard lead, the atrial P waves followed one another at equal intervals, frequently being superposed on the ventricular QRST complex and deforming it. Testing of the preparation on this model of arrhythmia began at least 30 min after the onset of fluttering.

In the other experimental variant, small cotton tampon impregnated with a 0.05% solution of aconitine nitrate was applied to the right auricular appendage to reproduce auricular arrhythmia, and after 3-7 min this caused in all animals a persistant fibrillation of the auricle. The rhythm of the ventricles became frequent, averaging 246 ±11 per min, and irregular. In place of distinct P waves on the EKG, numerous (more than 500 per min) uneven oscillations with a very low amplitude, so-called f-waves, were seen. Testing of the preparation in this series of experiments began 5 min after fibrillation began.

In both cases serpentine was injected intravenously at a rate of 1 mg/kg/min; in atrial flutter it was injected before the appearance of the sinus rhythm and in atrial fibrillation, also before the restoration of the sinus rhythm or slowing of the heart rate below an arbitrarily selected level, 200 contractions per min; one ventricular contraction should have corresponded to one atrial contraction (rhythm 1:1). The EKG was recorded every 30 sec and a constant visual observation was simultaneously made by means of a vectorcardioscope.

* Serpentine was obtained in our institute by D. G. Kolesnikov, A. P. Prokopenko and V. A. Dadali from Rauwolfia serpentina root.

EXPERIMENTAL RESULTS

Infusion of serpentine in all 6 experiments eliminated atrial flutter and rapidly (in 1 min 55 sec on the average) restored the normal sinus rhythm. Fluttering ended instantaneously after having completed a pause that was drawn out in comparison with the subsequent normal heart cycle.

After transition of the heart to a sinus rhythm, the activity of the heart in 5 of the 6 experiments was slow (by 20% on the average) in comparison with the rate before the occurrence of arrhythmia. The effective dose of serpentine that eliminated atrial flutter was 1.55 ± 0.16 mg/kg.

Eight experiments were set up on the aconitine model of fibrillation. In three of them the preparation did not have a defibrillatory effect even though the administered doses were 5.2-7.1 mg/kg. In 5 dogs the infusion of serpentine eliminated auricular arrhythmia. In 4 cases the normal sinus rhythm was restored with a contraction frequency between 140 and 188 per min. In one experiment the cardiac activity slowed to 200 contractions per min with the establishment of a 1:1 rhythm. The effective dose of serpentine that suppressed aconitine-induced fibrillation was 2.96±0.67 mg/kg.

The data obtained indicate an antiarrhythmic activity of serpentine in the basic disturbances of the auricular rhythm – flutter and fibrillation of the atrium reproduced by various experimental methods. Serpentine was more effective in atrial flutter than in fibrillation. We need note that the serpentine dose suppressing atrial flutter is almost half the ajmaline dose established by us [1] and by other authors [4] on an analogous model of arrhythmia. This fact is all the more interesting since both alkaloids have approximately the same toxicity [4].

To study the effect of serpentine on ventricular arrhythmia, we used two experimental models reproduced by various methods. The first series of investigations was carried out on dogs, in which a two-stage ligation of the descending branch of the left coronary artery (the procedure was described in previous reports [1, 3]) caused myocardial infarction which, as is known, is attended by disturbances of cardiac activity.

Between 19 and 23 h after ligation of the artery, marked ventricular tachycardia developed in all experimental dogs. The heart rate averaged 204 beats per min (from 165 to 225 per min), and in five experiments it exceeded 200 beats per min. The complexes on the EKG were a continuous stream of ventricular extrasystoles of varying configuration, which indicated their polytopic origin.

Thirteen experiments were set up on 8 dogs: 8 experiments on the day after ligation and 5 on the second day. In 2 dogs on the day after the operation, the intravenous injection of serpentine (1 mg/kg) caused a slowing of the rhythm by 32% on the average: in one case arrhythmia was completely suppressed for 35 min and in the other case the number of ectopic contractions was reduced by 41%. After injection of serpentine in a dose of 3 mg/kg an attenuation of tachycardia (by 30% on the average) and a restoration of the normal sinus rhythm for 10-60 min was observed in 3 dogs. The preparation in a dose of 4-5 mg/kg in three experiments caused an analogous slowing of the rhythm and completely eliminated arrhythmia for 30-120 min.

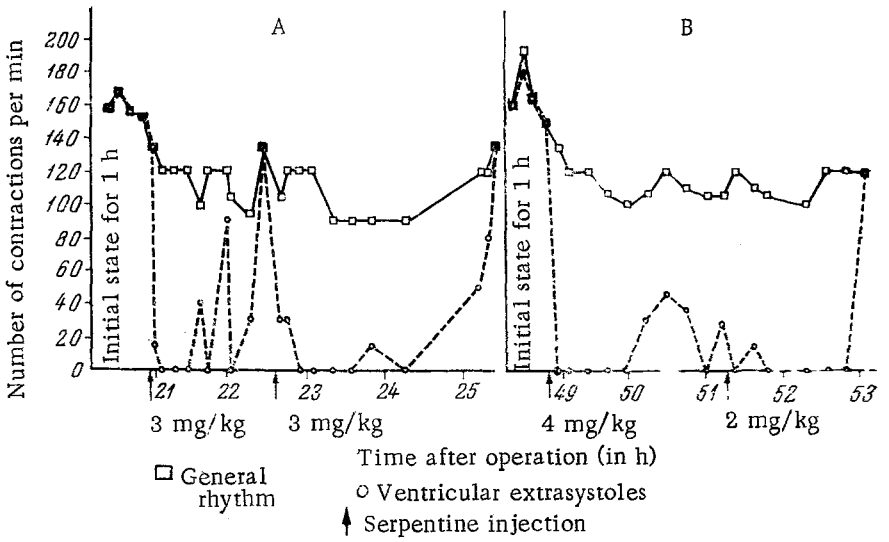
In 6 dogs serprentine was readministered in a dose of 2-3 mg/kg at various time intervals depending on the duration of the effect of the first dose. The interval between the 1st and 2nd injection averaged 85 min (with variations from 30 to 125 min). The total dose injected into these dogs was 6-7 mg/kg.

After reinjection of serpentine, arrhythmia in five experiments was completely eliminated for 10-170 min (averaged 53±25 min). In one dog the number of ectopic contractions was reduced 87% (35 min).

On the second day after ligation, when the rhythm frequency averaged 179 contractions per min (from 150 to 220 per min), serpentine in a dose of 3-4 mg/kg evoked in five experiments a slowing of the rhythm, averaging 34%, wherein in 3 dogs the arrhythmia was completely suppressed for 25-210 min (averaging 123 min) and in two cases the number of ectopic contractions was reduced by 65% for 15-60 min. After reinjection of the preparation in a dose of 2-4 mg/kg, the sinus rhythm was again restored and maintained for 60-90 min (see figure).

Serpentine in the indicated doses did not cause any side effects, in particular it did not change the atrioventricular and intraventricular conductivity. The general condition of the experimental dogs under the effect of the preparation improved considerably.

The results of these experiments indicate an evident antiarrhythmic action of serpentine in ventricular tachycardia in dogs caused by experimental myocardial infarction. The test preparation noticeably slowed the markedly accelerated cardiac activity of these dogs, which in itself favorably affects the work of the heart and general hemo-



Antiarrhythmic action of serpentine in ventricular arrhythmia in dogs caused by experimental myocardial infarction. A) Dog No. 11 (1st day after ligation of left coronary artery); B) dog No. 35 (2nd day after ligation).

dynamics. An even more important property of serpentine is its ability to suppress the activity of foci of heterotopic excitation and to restore temporarily the normal sinus rhythm.

Testing of the phylatic effect of serpentine was carried out on a model of ventricular arrhythmia induced by epinephrine. On the 3-5th day after ligation of the coronary artery, when the sinus rhythm recovered spontaneously, the dogs were injected subcutaneously with 2 ml of 1% morphine solution and after 30-40 min epinephrine was injected intravenously in a dose of 5-10 μg/kg, which evoked an attack of paroxysmal ventricular tachycardia lasting 3-6 min.

Serpentine, preliminarily injected intravenously in a dose of 2-3 mg/kg, temporarily blocked this reaction, protecting the animals from the occurrence of an attack of ventricular extrasystole after the injection of epinephrine. This effect is possibly associated to some extent with the established [12] adrenolytic action of serpentine.

The results of our investigations, as well as the observations of other authors, indicate an appreciable antiarrhythmic activity of serpentine, thus making this alkaloid, along with ajmaline, of interest for the cardiological clinic.

SUMMARY

In experiments on dogs the authors, depict the high antiarrhythmic activity of serpentine, one of the alkaloids of Rhauwolfia – in auricular tremor and fibrillation, caused by mechanical and electric stimulation of the latter or by aconitine applications, as well as in ventricular tachycardia, occurring as a result of experimental myocardial infarction. Besides, serpentine blocked the reaction to adrenalin, preventing an attack of paroxysmal tachycardia.

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