EFFECT OF CHLORACIZINE* ON EXPERIMENTAL AURICULAR ARRHYTHMIAS

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Previous investigations have shown that chloracizine abolishes experimental ventricular arrhythmias caused by ligation of the descending branch of the left coronary artery in dogs, and also increases the refractory period of the isolated auricle of the rabbit [1, 2]. The object of the present investigation was to study the effect of chloracizine on auricular arrhythmias.

EXPERIMENTAL METHOD

Auricular arrhythmias were produced by the method suggested by Rosenblueth and Garcia Ramos [3]. In 19 dogs, anesthetized with morphine and urethane, the intervenous tubercle between the orifices of the venae cavae was injured, and the auricle was stimulated with rectangular pulses with a duration of 1 msec, voltage 10-20 V, and frequency 15-20 cps. Animals with spontaneous auricular arrhythmias arising without injury to the atria were also used in the experiments. The contractions of the atria were recorded by means of the electrogram of the right atrium, and those of the ventricles by the ECG taken with standard lead II. The compounds for testing were injected 30 min after the onset of the arrhythmias. Their activity was estimated by "biological titration" (by injecting them intravenously at constant rate) until the sinus rhythm was fully restored. In some experiments the substances were injected intravenously at the rate of 1 mg (in 1 ml)/min. Additionally, in order to create more adequate conditions for comparison of the activity of the compounds to be tested with those described in the literature, the method of titration suggested by Winbury and Hemmer [5] was used. In this case the substances were injected intravenously at the rate of 1 mg/kg (in 1 ml)/min until complete restoration of the sinus rhythm. Besides chloracizine, quinidine (sulfate) was used as a standard.

EXPERIMENTAL RESULTS

The disturbance of cardiac activity after mechanical injury and electrical stimulation of the right atrium usually took the form of auricular flutter. The rate of the auricular contractions rose by 2-7 times over their initial value. The frequency of the ventricular contractions also rose: in some experiments by a few beats, in others by 2-3 times. Dissociation between the ventricular and auricular contractions in different experiments occurred in ratios of between 1 :2 and 1 :6. Control experiments confirned reports [3] of a persistent and prolonged (for 2 h or more) disturbance of the auricular contractions after a 30 min control period with no tendency towards spontaneous restoration of the normal rhythm.

Like quinidine, chloracizine abolished the dissociation between the auricular and ventricular contractions and subsequently restored the sinus rhythm. The action of chloracizine and quinidine on the process of restoration of the sinus contractions of the heart was similar in character. A regular sinus rhythm was restored at a frequency of contractions below 200 beats per minute (Fig. 1). Intravenous injection of chloracizine at the rate of 1 mg/kg

*2-chloro-10-(3-dimethylaminopropionyl)phenothiazine (Publisher's note).

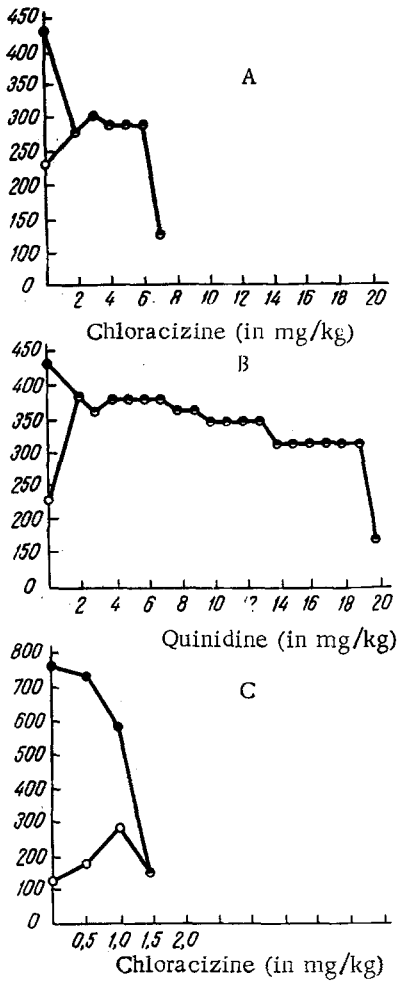

Fig. 1. Restoration of sinus rhythm under the influence of chloracizine and quinidine in dogs with experimental (A, B) and spontaneous (C) arrhythmias. Along axis of abscissas—doses of drugs (in mg/kg), along axis of ordinates—number of contractions of auricles (●——●) and ventricles (o——o) per minute.

(in 1 ml)/min brought about restoration of the sinus rhythm in a total dose of 9.6 ± 1.78 mg/kg, or 9.6 min after the beginning of the injection. Initially the action of the drug was to lower the rate of auricular contractions (Fig. 1). The changes in the rate of the ventricular contractions were not similar in type. As a rule their rate rose while the rate of the auricular contractions fell, with restoration of the 1 :1 ratio. With the continuing injection of the drug the rate of the auricular and ventricular contractions fell together until the sinus rhythm was clearly restored.

The general pattern of the action of chloracizine on the auricular arrhythmias is illustrated in Fig. 2, A. After the initial contractions of the heart (I) had been recorded, auricular arrhythmias were reproduced (II). The electrogram of the right atrium and the ECG both showed the presence of considerable dissociation between the rhythms of auricular and ventricular contractions (3 :1). Intravenous injection of chloracizine in a dose of 1 mg/kg/min (III) lowered the atrial contraction rate to 300 beats per minute, and at the same time the ventricular contraction rate rose to 300. Further injection of chloracizine (7 mg/kg) led to restoration of the normal sinus rhythm with a heart rate of 120 per min (IV). In similar experiments on three dogs quinidine also abolished the auricular flutter in an average dose of 23 ± 3.5 mg/kg. The results of one of the experiments illustrating the effect of quinidine on auricular flutter are shown in Fig. 2, B. Comparison of the experimental results with chloracizine and quinidine clearly revealed the similar effects of the preparations on the auricular arrhythmias by abolishing the dissociation between the atrial and ventricular contractions and restoring the normal sinus rhythm.

In a series of experiments on three dogs using a different rate of injection [1 mg (in 1 ml)/min] chloracizine brought about restoration of the sinus rhythm in a much smaller dose (mean 1.4 ± 0.61 mg). As the drug was injected in these conditions the rate of auricular contraction fell, but the sinus rhythm was restored without any preliminary removal of the dissociation between the auricular and ventricular contractions. It was observed that the time of restoration of the sinus rhythm was approximately the same (after 12 min) as in the earlier series of experiments (9.6 min).

In the dogs with spontaneous arrhythmias a considerable increase in the frequency of the auricular contractions to 700-1000 per min was observed, which could be regarded as auricular fibrillation. Administration of chloracizine (1 mg/kg/min) in experiments on four dogs abolished the spontaneous auricular arrhythmias in a mean dose of 3.1 ± 1.8 mg/kg and restored the sinus rhythm. The initial action of the drug was shown by a decrease in the rate of auricular contraction, and this decrease grew progressively more marked. At the same time the rate of ventricular contraction increased, but not by more than two-fold. The sinus rhythm was restored without the preliminary abolition of the dissociation between the auricular and ventricular contractions. The results of one of the experiments illustrating the general principles governing the action of chloracizine on spontaneous auricular arrhythmias are shown in Fig. 2, C.

The experimental results described above show that chloracizine possesses a marked antiarrhythmic activity, similar in its general features to the action of quinidine. Like quinidine, chloracizine abolishes auricular arrhythmias, and its activity in this type of arrhythmia is twice as strong as that of quinidine. It may be concluded from analysis of the results of the experimental study of chloracizine and quinidine that chloracizine in experimental conditions possesses a more marked activity than quinidine, as regards the abolition of not only auricular, but also ventricular arrhythmias [2].

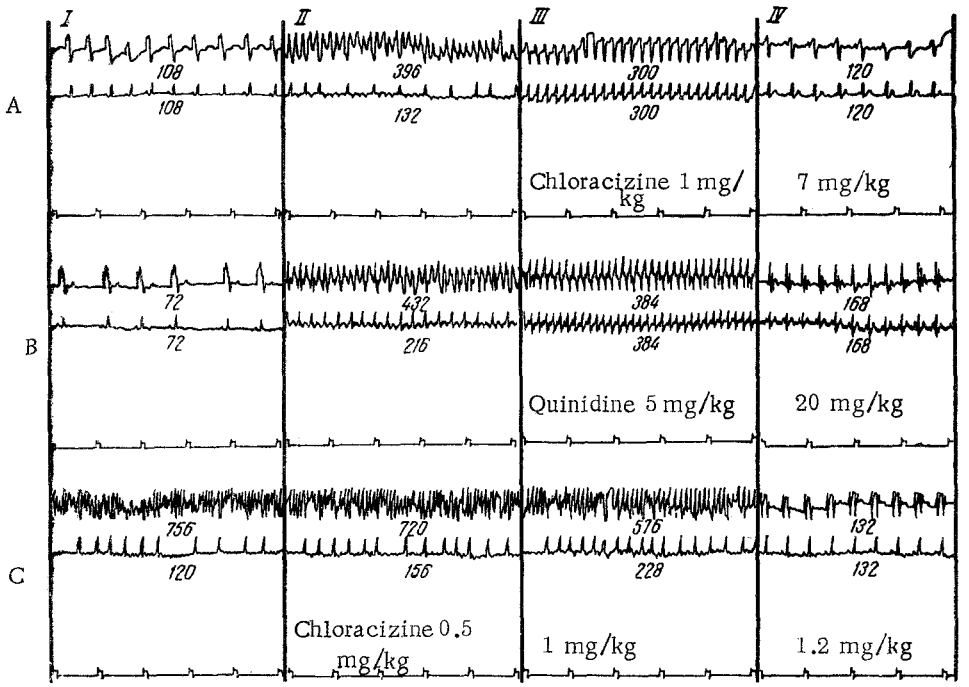

Fig. 2. Effect of chloracizine and quinidine on experimental (A and B) and spontaneous (C) auricular arrhythmias. Significance of curves (from top to bottom): elecrogram of right atrium, ECG in standard lead II, time marked (1 sec). 1) Normal cardiac contractions; II) auricular flutter; III) changes after administration of drugs; IV) restoration of regular sinus rhythm. Injections of the drugs chloracizine and quinidine began between II and III (A and B) and between I and II (C).

Studies of the antiarrhythmic properties of chlorpromazine and its analogues have established [4] that these substances can restore the normal cardiac activity of animals with experimental arrhythmias. Their activity was found to be 1.5-7 times greater than that of quinidine in this test. However, in respect to their ability to restore the normal cardiac activity in cases of ventricular tachycardia with an ectopic rhythm, they were much inferior (only 1.3-2.5 times more active than quinidine), and only five compounds showed this activity: diethazine, ethopropazine, promethazine, promazine, and chlorpromazine. Comparison of the experimental data obtained during the study of chloracizine and the chlorpromazine analogues reveals that chloracizine is somewhat less effective in abolishing auricular arrhythmias: it is twice as active as quinidine. However, chloracizine is much more active in ventricular arrhythmias: it is 7.5 times more active than quinidine [2], whereas the chlorpromazine analogues are only 2.0-2.5 times more active than quinidine. Analysis of the results of an experimental study of the antiarrhythmic action of a large series of substances (85) belonging to different classes of chemical compounds [6] revealed a definite relationship between their ability to abolish experimental auricular and ventricular arrhythmias and their efficacy in clinical conditions. Compounds which exhibited inconstant activity in experimental auricular arrhythmias as a rule were inactive in ventricular tachycardia. Substances with inconstant activity in ventricular arrhythmias possessed marked activity in auricular disturbances. Furthermore, substances abolishing ventricular arrhythmias in small doses as a rule also were effective in auricular arrhythmias. Compounds active against experimental auricular arrhythmias were found to be less effective in clinical practice than substances active in experimental ventricular arrhythmias.

The results of this experimental investigation of the antiarrhythmic properties of chloracizine suggest that the drug may be used in clinical practice for the treatment of certain forms of cardiac arrhythmia.

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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 this issue.**