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 interventricular tubercle between the orifices of the vena 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 confirmed 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).
(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 con-
tractions 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 chlor-
acizine 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 experi-
mental 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 con-
tractions 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 con-
tractions fell, but the sinus rhythm was restored without any preliminary
removal of the dissociation between the auricular and ventricular con-
tractions. 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. Adminis-
tration 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].