THE EFFECT OF AIMALINE ON AURICULAR AND VENTRICULAR ARRHYTHMIA IN DOGS

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The very limited selection of anti-arrhythmia agents available to the clinic creates considerable difficulties in the treatment and prevention of various disturbances of the heart rhythm [2, 3]. Intensive research carried out to find new anti-arrhythmia preparations has disclosed several synthetic compounds and natural substances possessing an effect similar to that of quinidine. Among the latter is aimaline, a Rauwolfia alkaloid which, according to the data of several authors, has an anti-arrhythmia effect under conditions of both experimental [4, 5, 7] and clinical [9] pathology.

The investigations we conducted in collaboration with Ya. I. Khadzhai [1] showed that aimaline* has a prophylactic and arresting effect on aconite arrhythmia in rats; this drug was found to prevent ventricular fibrillation in rats given a toxic dose of calcium chloride and to shorten the period of ectopic impulsation in guinea pigs poisoned with G-strophanthin. The ECG changes in intact animals (dogs, cats, rats, guinea pigs) induced by different doses of aimaline indicate that the preparation clearly lowers the conductivity of the myocardium and somewhat retards the heart rate.

A wide variety of experimental models of arrhythmia have been created to study anti-arrhythmia agents. Many of these, however, are essentially different from the clinical pathology. In recent years, certain researchers [6, 11, 12] have given preference to the model of auricular arrhythmia proposed by Rosenblueth and Ramos [10] and the ventricular arrhythmia model described by Harris [8].

We employed these models in this work to test the effect of aimaline on auricular and ventricular arrhythmia in dogs.

METHODS AND RESULTS

Auricular arrhythmia was induced in dogs under morphine-Nembutal anesthesia and conditions of artificial respiration. The right side of the animal's chest was dissected open and the 4th and 5th ribs partially removed to provide free access to the right atrium. Hemostatic forceps were used to compress a section of the auricular tissue between the two venae cavae. Then the auricular appendage was stimulated with square-wave pulses of current, 20 cps in frequency, with each pulse lasting 15 msec. The development of auricular flutter was clearly evident on the ECG. The preparation was not tested until 25-30 min after the flutter developed in order that the arrhythmia induced might become stably established. The aimaline solution was introduced through a cannula into the femoral vein at a rate of 1 mg/kg per min. In all the experiments, the ECG was recorded in the

* The aimaline we studied was isolated from Rauwolfia serpentina roots by D. G. Kolesnikov, A. P. Prokopenko and V. T. Chernobai at the Khar'kov Institute for Scientific Research in Pharmaceutical Chemistry.

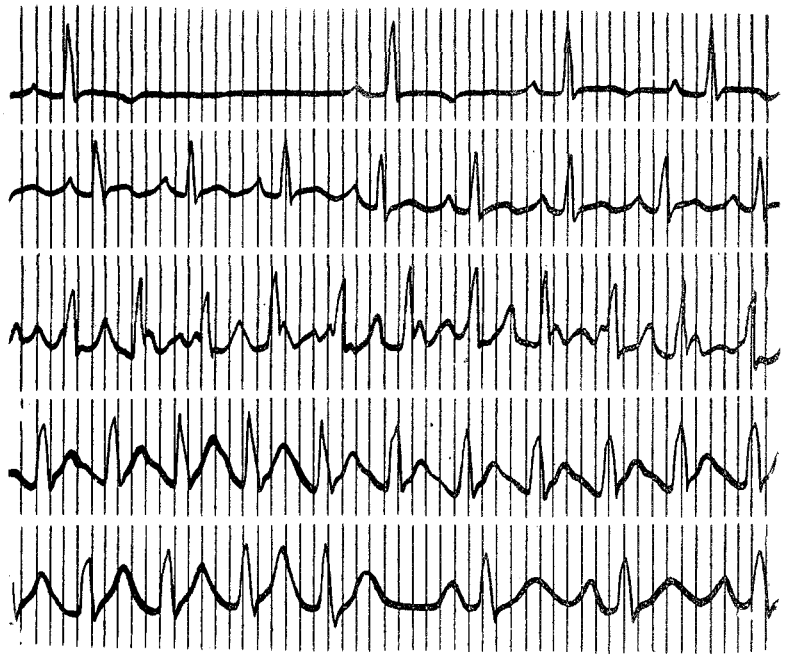

Fig. 1. Restoration of sinus rhythm effected by aimaline under conditions of auricular flutter. ECG of a dog in lead II. 1) After morphine injection (2 mg/kg); 2) 20 min after intraperitoneal injection of Nembutal (20 mg/kg); 3) 25 min after development of auricular flutter; 4) and 5) 2 min, 30 sec and 3 min, 10 sec after start of aimalin infusion (1 mg/kg per min).

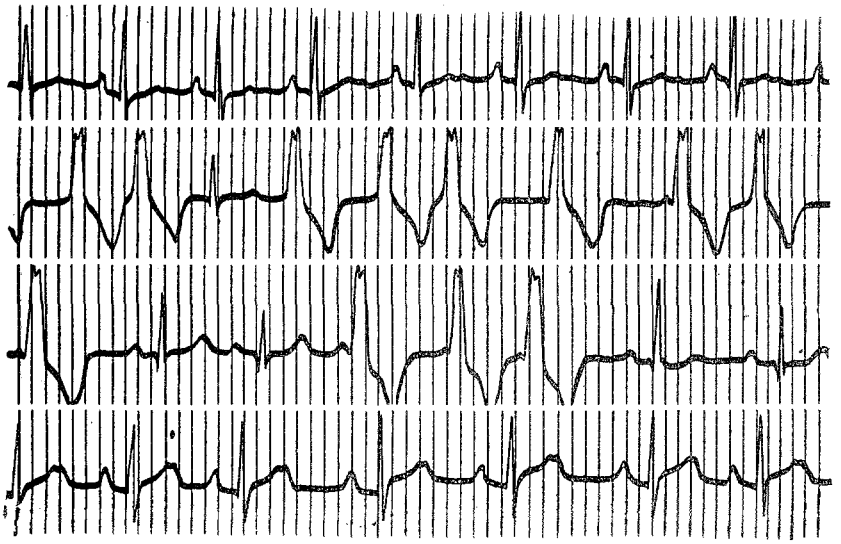

Fig. 2. Aimaline suppression of ectopic ventricular rhythm developing after ligation of descending branch of left coronary artery. ECG of a dog in lead II. 1) Before operation and after administration of Nembutal; 2) 22 hr after application of ligature; 3) 3 min after administration of aimaline (3 mg/kg); 4) 40 min after third administration of aimaline (in doses of 3 mg/kg).

three standard leads, and constant visual observation was maintained with the aid of a vector electrocardioscope.

The auricular flutter induced in the five experimental dogs resulted in total dissociation of auricular and ventricular activity. The rate of the auricular contractions ranged from 360 to 428 per min, while the number of ventricular contractions varied from 246 to 272 per min.

Rapidly developing retardation of the rate of the auricular contraction was the first result observed of the aimaline infusion. The rate of the ventricular contractions also decreased, but to a considerably lesser degree. Then a rapid rhythm (about 240 contractions per min) developed, lasting 0.5-1.5 min, during which period each ventricular contraction was matched with an auricular. Conspicuous during this period was a sharp expansion of the P wave and an increase in its voltage. When the dose of the preparation was further increased, the normal sinus rhythm, 120-140 contractions per min in frequency, was suddenly established. Suppression of the auricular flutter and restoration of the normal heart rhythm was observed in all the experiments. The median effective dose of aimaline was found to be 3.2 mg/kg, the dose varying from 1.5 to 5 mg/kg in individual cases.

Comparison of these results with the literature data on other anti-arrhythmia agents obtained on the same arrhythmia model [12] shows that the effective dose of aimaline is considerably smaller than that of quinidine (23 mg/kg) and procaine amide (36 mg/kg).

Figure 1 shows the arresting effect of aimaline on the ECG changes observed with auricular flutter.

The model of ventricular arrhythmia resulting from acute myocardial infarction which we used makes it possible to test the preparation on a nonanesthetized animal.

Under sterile conditions, two-stage (first, partial, and then, after 30 min, total) ligation of the descending branch of the left coronary artery at the level of the lower edge of the left auricular appendage was performed on dogs under morphine-Nembutal anesthesia. The experiments were performed on six dogs weighing 11-18 kg each. Stable ventricular tachycardia lasting three hours or longer developed in all the animals 16-25 hours after the operation.

The heart rhythm fluctuated between 140-240 contractions per min; in three dogs, the majority of the contractions (120-230 per min) were polytopic ventricular extrasystoles. In the other three animals, all the contractions were solely of ectopic origin, and the configuration of the ventricular complex was variable. The P wave was usually lacking (Fig. 2).

Nine experiments were performed on these animals—six on the first postoperative day and three on the second. Aimaline, dissolved in 5-10 ml of a physiological solution, was administered intravenously for 3-5 min. In two experiments, the preparation was tested in different doses (1-5 mg/kg), and in the others, the same dose (3 mg/kg) was administered several times.

In five of the experiments performed the day after ligation of the coronary artery, aimaline caused some retardation of heart activity and considerable reduction of ectopic pulsation up to complete elimination of arrhythmia and temporary restoration of the normal sinus rhythm. Only in one experiment, in which the animal died on the second day from hemothorax, was total disappearance of the ectopic contractions not observed, although the latter were reduced by more than 50%.

The results of one of these experiments are shown in Fig. 3; in this dog, the over-all frequency of the rhythm 22 hr after the operation was equal to 210 contractions per min, 195 of which were ectopic. After the administration of aimaline in a dose of 3 mg/kg, the general rhythm slowed to 150 contractions per min, and the number of ventricular extrasystoles decreased to 60. This effect did not last long; after a few minutes, the rhythm again began to speed up, and the number of ectopic contractions increased to 150. After the second (40 min later) administration of aimaline in the same dose, the general rhythm stayed at a level of 150 contractions per min for 1.5 hr, the number of extrasystoles varying between 100 and 120. The third dose of the preparation (3 mg/kg), administered 1.5 hr after the second, decreased the frequency of the ventricular extrasystoles to 40 per min, and after the fourth dose (bringing the total dose of the preparation up to 12 mg/kg), ectopic impulsation disappeared entirely for a 10-min period. The extrasystoles which appeared subsequently comprised 20% of the total number of contractions.

On the second postoperative day (45 hr after the operation), the over-all frequency of the rhythm was 150 contractions per min, 60 of which were ectopic. A single administration of 3 mg/kg aimaline sufficed to totally suppress ectopic impulsation and to restore the sinus rhythm of 100-120 contractions per min.

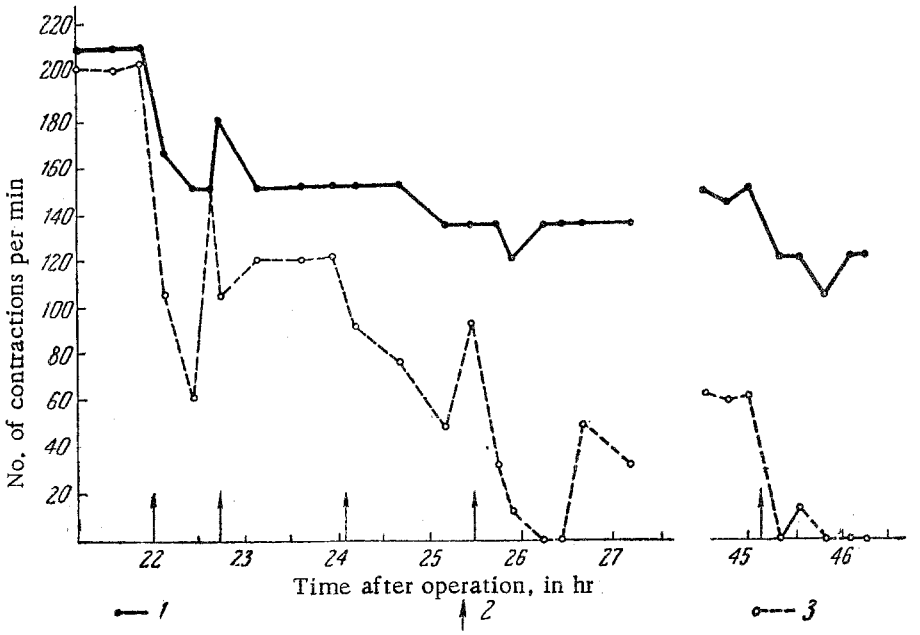

Fig. 3. Anti-arrhythmia effect of aimaline on ventricular arrhythmia induced in a dog by ligation of the descending branch of the left coronary artery. 1) General rhythm; 2) administration of aimaline (3 mg/kg); 3) ectopic rhythm.

In another experiment, acute ventricular tachycardia (230 contractions per min) developed in the dog 16 hr after the operation. There were no impulses from the sinus node at all. The animal was given three infusions of aimaline (each in a dose of 3 mg/kg) at 30 min intervals, which led to considerable inhibition of ectopic impulsation and partial restoration of the sinus rhythm. For 1.5 hr following the administration of the preparation, the ventricular extrasystoles did not exceed 30-40 per min in frequency, the general frequency of the rhythm being 160 contractions per min, and were sometimes totally absent. The sinus rhythm was maintained without extrasystoles for a period of one hour following the fourth dose of aimaline (3 mg/kg), administered every 2.5 hr; then ectopic contractions began to appear again.

Tachycardia was less pronounced in the other animals after the operation; the rhythm ranged from 140 to 180 contractions per min in frequency, and the ventricular contractions comprised 60-100% of the total number of contractions. The arrhythmia in these dogs yielded better to the therapeutic action of aimaline. In one of the animals, for example (120 ectopic out of a total 140 contractions), two influsion of aimaline (1 mg/kg first dose, 4 mg/kg second dose) restored the normal sinus rhythm for a period of 1 hr and 45 min. The ectopic contractions which developed at the end of this period were again eliminated by the administration of the preparation in a dose of 2 mg/kg.

It should be noted that no side effect usually attended the two- and threefold administrations of 3 mg/kg aimaline to the dogs. General excitation and salivation were observed in the animals in only one experiment after the third administration (total dose, 9 mg/kg). Control experiments on healthy dogs showed the toxic dose of aimaline to be 5-6 mg/kg in the case of its intravenous administration. In this dosage, the preparation causes general excitation, salivation, tremor, clonic convulsions, defecation and urination.

These investigations, therefore, have established that aimaline arrests ventricular extrasystole developing in dogs after acute myocardial infarction induced by ligation of the descending branch of the left coronary artery. When used in a total dosage of 5-12 mg/kg administered in several doses, aimaline either sharply reduces the frequency of ventricular extrasystoles or totally eliminates them and temporarily (for 1-2 hr) restores the normal sinus rhythm. Aimaline not only suppresses ectopic impulsation, but clearly retards the cardiac activity.

This effect of aimaline is of real interest, it being known that under clinical conditions ventricular extrasystole and tachycardia, which aggravate the course of myocardial infaction, can lead to the development of cardiovascular insufficiency or ventricular fibrillation [3].

One can conclude from the data presented that aimaline exerts an anti-arrhythmia effect on ectopic forms of auricular and ventricular arrhythmia under conditions of experimental pathology in dogs.

SUMMARY

The anti-arrhythmic action of aimaline was studied on two models of arrhythmia in dogs. Auricular fibrillation was provoked by mechanical injury and subsequent stimulation of the auricles with induced current; ventricular arrhythmia was caused by ligating the descending branch of the left coronary artery. It was established that aimaline arrests auricular arrhythmia and either sharply reduces the frequency of ventricular extrasystoles or completely eliminates them and decelerates the cardiac activity.

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