PROLONGING THE ANTIARRHYTHMIC ACTION OF AIMALIN

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The possibility of prolonged maintenance of an effective concentration of a preparation in the blood is of fundamental importance for the antiarrhythmic drugs [1,4,5,10]. Several authors have tested, in particular, long-acting preparations of quinidine and have demonstrated their obvious advantages [6,7,11].

In the light of these findings it was interesting to attempt to obtain a long-acting preparation of aimalin. Aimalin leaves the blood stream comparatively quickly [8] and to maintain an effective concentration of this preparation in the blood it must be given in large doses and at short intervals, which introduces the risk of side effects [9].

In this paper the results of an experimental study of the antiarrhythmic activity of a long-acting aimalin preparation, consisting of two-layered tablets, are described. The results of the authors' experiments in vitro showed that the outer cover of the tablet breaks up within a few minutes in the gastric juice, liberating the initial dose of the preparation; the core of the tablet breaks up only in the intestinal juice, and in this way the maintenance dose of the preparation is liberated steadily in the course of 8 h.

EXPERIMENTAL METHOD

The investigation of the antiarrhythmic activity of the long-acting aimalin preparation and of the ordinary aimalin tablets was carried out on dogs with experimental myocardial infarction, which developed ventricular tachysystole 24 h after ligation of the descending branch of the left coronary artery (the technique is described in previous communications [2,3]). Experiments were carried out on unanesthetized animals in which, after administration of the tablet, periodic recordings were made of the electrocardiogram (ECG) in lead II, and observations were made on the general condition and for the appearance of side effects. In most animals the changes in the concentration of aimalin in the blood were determined [8].

EXPERIMENTAL RESULTS

The antiarrhythmic activity of the ordinary aimalin tablets was tested in seven dogs. In all the animals the rhythm before administration of the preparation was very fast (212 ± 16 per minute) and continuous polytopic extrasystoles were present.

After a single dose of the ordinary tablets of aimalin (35-40 mg/kg) in two experiments the heart rate was slowed after 75-150 min by 36-40%, and the rhythm was partly restored to normal; 50% of the contractions were of sinus origin. However, the effect was of short duration (20-60 min) and it was accompanied by toxic manifestations (vomiting, generalized excitation, tremor, clinical convulsions) and it terminated in death of the animals.

In 5 experiments, the dogs received the ordinary aimalin tablets in a dose of 10 mg/kg twice or three times (at intervals of 2 h). In all the animals, 1 h 48 ± 10 min after receiving the first dose of the preparation, slowing of the heart rate was observed (by 35 ± 6%) and was accompanied by partial restoration of the normal rhythm. This partial effect lasted for 2 h 36 ± 32 min. In 4 experiments, 2 h 37 ± 10 min after the first dose of the preparation, the regular sinus rhythm was fully restored in the animals. However, the effect was brief (from a few minutes to half an hour) after which the extrasystoles reappeared. In all the animals the antiarrhythmic effect was accompanied by side effects. Of the 5 dogs of this group, 3 died after 4-5 h, and the rest survived.

Hence, two or three administrations of aimalin by mouth in a dose of 10 mg/kg, at intervals of 2 h, gave essentially only a partial antiarrhythmic effect, but in these circumstances severe side effects developed and caused death of most of the animals.

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It is interesting that these observations agreed with those made by other authors [12] who studied the efficacy of quinidine on an analogous model of arrhythmia, when administered by various methods.

To investigate the possibility of prolonging the pharmacological effect of aimalin and of determining the optimal initial and maintenance doses of the long-acting preparation, four series of experiments were carried out on 12 dogs (12 experiments on the 1st day after the operation and 2 experiments on the 2nd day).

Before the trials of the preparation, the ECG of 12 dogs revealed continuous extrasystoles, and in 2 dogs extrasystoles accounted for 60-80% of the total number of contractions. In all the dogs, the rhythm was fast (213 ± 5/min).

Four animals each received one tablet of long-acting aimalin containing an initial dose of 10 mg/kg and a maintenance dose of 24 mg/kg, liberated in the course of 8 h at the rate of 3 mg/kg/h. In three experiments, a regular sinus rhythm was restored 60-90 min after administration of the preparation and the heart rate was slowed by 43 ± 3%. The effect persisted for 2-5 h, after which the ventricular tachysystole returned. The antiarrhythmic effect was accompanied by severe toxic manifestations; the animals died 5-7 h later. In one experiment, the preparation caused only partial restoration of the normal rhythm, which continued for the period of observation (12 h). The dog survived, although toxic manifestations were observed with this dog also. The aimalin concentration in the blood serum of these animals was 546 ± 106 μg%, rising to 612 ± 53 μg% after 4 h. This concentration of the preparation in the blood is evidently toxic.

Two animals each received one aimalin tablet containing an initial dose of 10 mg/kg and a maintenance dose of 16 mg/kg, which was liberated at the rate of 2 mg/kg/h. In both cases, a regular sinus rhythm was restored after 45 min and persisted for 4 h. The sinus contractions then began to alternate with extrasystoles. This partial effect was observed for 7-11 h. The side effects were of slight severity. Both dogs survived. The serum aimalin concentration was 417 ± 64 μg% 2 h after administration of the preparation, 412 ± 61 μg% 4 h after, 378 ± 106 μg% 6 h after and 272 μg% (in 1 animal) 12 h after administration. It may be concluded from the relatively rapid change from the complete effect to the partial, together with the ill-defined side effects, that in these cases also the initial and the maintenance doses were rather too high.

Accordingly, in the third series of experiments, 5 dogs each received one aimalin tablet containing an initial dose of 6-8 mg/kg and a maintenance dose of 12-14 mg/kg, which was liberated at the rate of 1.5-1.7 mg/kg/h. In 4 dogs, a partial effect (a decrease in the number of extrasystoles by 50%) appeared 1 h 23 ± 25 min after administration of the drug, and complete restoration of the regular sinus rhythm was observed after 2 h 8 ± 33 min. The maximal slowing of the rhythm in relation to the initial rate was 37 ± 9%. A regular sinus rhythm in these animals was observed for 7 h ± 1 h 5 min without any side effects. All the animals survived, and next day the ECG showed mainly a sinus rhythm, sometimes mingled with bursts of extrasystoles. In one experiment of this series, only a partial effect was observed, which persisted throughout the period of observation (12 h).

The blood aimalin concentration in these animals after 1 h of the experiment was 184 ± 80 μg%, after which it remained fairly constant: after 2 h it was 308 ± 62 μg%, after 4 h 404 ± 96 μg%, after 6 h 374 ± 24 μg%, after 8 h 350 ± 64 μg%, and not until after 12 h (results of one experiment) had it fallen to 30 μg%.

The development of the complete effect in these experiments coincided with the period when the concentration of the preparation in the blood exceeded 300 μg%, and the effect continued for the next 6-8 h, while this concentration was maintained in the blood. Consequently, the therapeutic concentration of aimalin in the blood giving rise to a complete and stable antiarrhythmic effect, and not causing side effects in these experimental conditions, was 300-350 μg%.

In the sixth series of experiments, three dogs each received one tablet of aimalin in which the initial dose was reduced to 4 mg/kg and the maintenance dose of 8 mg/kg (rate of liberation of the preparation from the core of the tablet 1 mg/kg/h). In two experiments, a complete effect developed after 1 h 30 min-2 h, and lasted for 5-11 h. In one animal only partial restoration of the normal rhythm was observed for a period of 9 h. In all the dogs the heart rate was slowed by 34 ± 3% and no side effects were noted. The concentration of aimalin in the blood, which was measured in only one experiment, was 180 μg% after 1 h, 344 μg% after 2 h, 332 μg after 4 h, and 318 μg% after 8 h.

The results obtained show that, unlike ordinary aimalin tablets, the long-acting preparation of aimalin when given by mouth has a prolonged antiarrhythmic effect, abolishing a ventricular tachyarrhythmia and completely restoring the regular sinus rhythm in dogs with experimental myocardial infarction. The optimal initial and maintenance doses established experimentally enable a therapeutic concentration of the preparation to be maintained

in the blood for a long time (for 8 h), and this provides a steady antiarrhythmic effect free from side effects. In similar experimental conditions, the intravenous injection of aimalin, repeated 2-3 times, in a dose of 3 mg/kg, restored the normal rhythm for only 2 h [2].

Hence, the use of the principle of prolonging the pharmacological effect based on the gradual and uniform liberation of a maintenance dose of the preparation administered by mouth provides a means of greatly strengthening and prolonging the antiarrhythmic effect of aimalin.

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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 the first issue of this year.
