COMPARATIVE STUDIES ON THE PHARMACOLOGICAL ACTIONS OF ANTI-ARRHYTHMICS IN ISOLATED GUINEA-PIG ATRIA

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Ajmaline, cocaine, diphenylhydantoin, lidocaine, procainamide, propranolol, quinidine, and trimetazidine were comparatively examined as to their actions in isolated guinea-pig atria on the beat rate of their spontaneous contractions and on their contractile tension and their functional refractory period. All the drugs except diphenylhydantoin could increase the functional refractory period. When the influence of each drug on beat rate or contractile tension was compared at the concentrations in which each could prolong the refractory period to twice that of the controls, lidocaine, procainamide, propranolol, and quinidine were found to decrease the tension by more than 60% but the beat rate by less than 60% of those of the respective controls. Ajmaline, however, was found to reduce the beat rate by 20% of that of the control already at a concentration by which the refractory period of atrial muscle would begin to be increased by this drug. Cocaine and trimetazidine were found to have a relatively stronger effect on the refractory period than they did on the beat rate or the contractile tension.

To prevent ectopic beats, the drug which can prolong the heart muscle's functional refractory period, would prove a useful anti-arrhythmic. However, if the effective doses of such a drug decreases either beat rate or contractile tension, it would have a narrow safety margin, and its clinical use would require much skill. In the present experiment, the currently used anti-arrhythmics, ajmaline, lidocaine, procainamide, propranolol, quinidine, and their related drugs, cocaine, diphenylhydantoin, and trimetazidine were examined in isolated guinea-pig atria from the above standpoint, although the individual properties of these drugs have already been independently reported by many investigators. As the causes of arrhythmia are many and various, a thorough investigation of a drug would not only require an examination of its action on atrium but also on sino-atrial node, on the ventricular conduction system, and on the ventricular muscle, but the present study and discussion have been confined to drug action on the atrium. This being so, these results can hardly do more than point out some of the relative anti-arrhythmic merits and characteristics of the drugs examined. Comparative studies on the effects of these same drugs on the other parts of the heart will be reported in the succeeding paper.

METHODS

Male adult guinea-pigs weighing 300 to 400 g were used. After lethal cranial clubbing, the heart was immediately removed. Then, the right and left atria were prepared and independently suspended in a Magnus’ apparatus in a Locke’s solution saturated with oxygen at 30°C.

The right atrium was used to examine the drug effect on spontaneous beat rate, and the left atrium was used to examine the drug effects on
Fig.1. The relations between the concentrations of tested drugs applied to the Locke’s solution and the changes of beat rate of spontaneous contractions in isolated guinea-pig right atrium at 30 minutes after their applications.

contractile tension and functional refractory period. In the experiment in which the left atrium was used, the atrium was driven by electrical stimulation at supramaximal intensity, at durations of 5 msec., and at 120 cycles per minute. The drug applied was added to the medium in which the preparation was contracting, and was expected to act easily on the atrial tissue. When the functional refractory period of the left atrial muscle was examined, Govier’s method was used: basal stimulation was given to the muscle at a supramaximal intensity, at durations of 5 msec., and at 60 cycles per minute; and test stimulation, whose conditions were the same as those of the basal stimulation, were given at 60 to 480 msec. after each corresponding basal stimulation. If the time interval between the two kinds of stimuli was shorter than the functional refractory period proper to the tested muscle, a muscle contraction corresponding to the test stimulation could hardly be expected. Then, when the muscle response corresponding to the test stimulation made its appearance during the gradual increasing of the time intervals between the basal and the test stimuli from 60 to 480 msec., the estimated time interval represented the functional refractory period of the tested muscle.

Electronic stimulators (Nihon-kohden MSE-3R and JM) were used, and stimulated

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muscle contraction was recorded by means of a strain gauge and an electrical recorder (Shinkotsushin AS-3A).

The Locke's solution used consisted of NaCl 9.0 g, KCl 0.42 g, CaCl₂ 0.24 g, NaHCO₃ 0.7 g, and glucose 1.0 g per litre of distilled water. The drugs used were ajmaline (Gilurymal, Giulini), cocaine-HCl (Cocaine, Dainihon), diphenylhydantoin (Aleviatin, Dainihon), lidocaine-HCl (Xylocaine, Fujisawa), procaainamide-HCl (Amisalin, Daiichi), propranolol-HCl (Inderal, Sumitomo), quinidine sulfate (Merck), and trimetazidine-2HCl (Vastarel, Inabata), which were applied by addition to a medium containing the atria, the drug concentrations in the media being expressed in terms of g/ml.

This experiment was carried out in spring and early summer.

RESULTS

1. Drug influences on the beat rate of spontaneous contractions in isolated guinea-pig atria

At high concentrations, each drug tested reduced the beat rate of the atrial spontaneous contractions. The drugs which, at concentrations lower than 10⁻⁵, could reduce the beat rate by 50% or more of the control rate were ajmaline, cocaine, diphenylhydantoin, propranolol, and
quinidine; the other drugs needed the concentrations higher than $10^{-5}$ to reduce the beat rate to the same degree (Fig. 1).

2. **Drug influences on the contractile tension of atria driven by electrical stimulation**

Each drug tested reduced the contractile tension of left atria driven by electrical stimulation. The drugs which, at concentrations lower than $10^{-6}$, could reduce the tension by 50% or more of that of the control rate were cocaine, lidocaine, propranolol, and quinidine; the drugs which required concentrations of from $10^{-6}$ to $10^{-5}$ to reduce it to the same degree were ajmaline and diphenylhydantoin; procainamide and trimetazidine required concentrations higher than $10^{-5}$ to reveal the same effect (Fig. 2).

3. **Drug influences on the functional refractory period of atrial muscle**

At high concentrations, each drug tested except diphenyl-hydantoin could increase the functional refractory period of the left atrial muscle. The drugs which, at concentrations lower
Fig. 4. This figure is made from Figs. 1 and 2, and shows the relations between the drug effects on the beat rate of the right atrium and those on the contractile tension of the left atrium expressed by percent of the respective controls: each line shows how strong the drug can reduce the tension in its concentration in which the drug decreases the beat rate at a given degree.

Fig. 5. This figure is made from Figs. 1 and 3, and shows the relations between the drug effects on the beat rate of the right atrium and those on the functional refractory period of the left atrial muscle: each line shows how long the drug can prolong the refractory period in its concentration in which the drug decreases the beat rate at a given degree.

Fig. 6. This figure is made from Figs. 2 and 3, and shows the relations between the drug effects on the contractile tension and those on the functional refractory period of left atrial muscle: each line shows how long the drug can prolong the refractory period in its concentration in which the drug decreases the contractile tension at a given degree.

trimetazidine required a concentration higher than $10^{-5}$, but diphenyl-hydantoin could scarcely yield this effect at any concentration (Fig. 3).

**DISCUSSION**

Figs. 4, 5, and 6 facilitate discussion of the above obtained results. Fig. 4 shows the relation between the drug effects on the beat rate of the right atrium and those on the contractile tension of the left atrium expressed by percent of the respective controls. For example, in the concentration in which ajmaline reduces the beat rate by 40% of that of the control, the drug simultaneously reduces the contractile tension by 25% of that of the control. As for lidocaine, the concentration which reduces the contractile tension by 55% of that of the control is that which reduces the beat rate by only 10%. Therefore, the main character of ajmaline can be assumed to be one which reduces beat rate, and that of lidocaine, one which reduces contractile tension. The character of diphenyl-hydantoin, procainamide, propranolol, and trimetazidine is to reduce contractile tension rather than beat rate, while cocaine and quinidine tend to reduce beat rate rather than contractile tension in each high concentration.

In the Fig. 5, the relations between the drug effects on the functional refractory period of the
left atrial muscle and on the beat rate are shown. Except diphenylhydantoin, each drug tends to increase the refractory period by 100% or more of that of the control already at the respective concentrations by which each drug reduces the beat rate by 60%. However, it is characteristic of ajmaline to already reduce the beat rate by 20% at the concentration by which the refractory period begins to increase, and that quinidine reduces the beat rate by over 50% at the concentration by which the refractory period has been increased by 100%, although this drug can increase the period even to a small degree at the concentration by which the drug can scarcely suppress the beat rate.

The relation between the drug effects on the functional refractory period and on the contractile tension of the left atrium are shown in the Fig. 6. The drugs, which can prolong the refractory period by 100% at the respective concentrations by which they can depress the contractile tension by 50% or less of that of the controls, are ajmaline, cocaine, and trimetazidine. The other 5 drugs can scarcely prolong the refractory period by 100% without a strong depression of over 60% of the contractile tension; this is especially true of diphenylhydantoin which can hardly be expected to prolong the refractory period at any concentration.

Thus, the characteristics of the above 8 kinds of drugs have been compared as to the interrelation of their effects on the functional refractory period, contractile tension, and beat rate of isolated atria, though the examination was experimental. As an anti-arrhythmic which can prolong the refractory period of atrial muscle, diphenylhydantoin would scarcely qualify; ajmaline tends to reduce the beat rate; and lidocaine, quinidine, procainamide, and propranolol reduce contractile tension, although some of these drugs are clinically used. Cocaine might be effective on atrial arrhythmia because of its strong effect on refractory period and its weak effect on beat rate and contractile tension, were it not for its deleterious side effects. Trimetazidine also has a relatively stronger effect on refractory period than on beat rate or contractile tension.

But, further experiments with these drugs are required in order to clarify whether their characteristic actions on beat rate and contractile tension are main effects or only side effects when each drug is to be evaluated as an effective anti-arrhythmic, and to clarify also whether or not their actions on the ventricular muscle would be the same. Despite limitation to their effects on the atrium alone, this knowledge of the special characteristics of these drugs might be of value when considering their use as anti-arrhythmics.

REFERENCES