ANTIARRHYTHMIC PROPERTIES OF MARCAINE

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Marcaine (bupivacaine) is used in anesthesiology as a long-acting local anesthetic [6]. At the same time marcaine also possesses antiarrhythmic properties. Experiments on dogs anesthetized with halothane have shown that marcaine considerably increases the arrhythmogenic dose of adrenalin, injected intravenously [2] and abolishes arrhythmias induced in dogs by strophanthin overdosage for a longer time than lidocaine [3]. However, prospects for the use of marcaine as an antiarrhythmic agent are not yet clear [4, 5].

The object of this investigation was a comparative pharmacologic study of the antiarrhythmic properties of marcaine and lidocaine on experimental models of arrhythmias. Lidocaine closely resembles marcaine in chemical structure and is widely used in clinical practice as an antiarrhythmic drug.

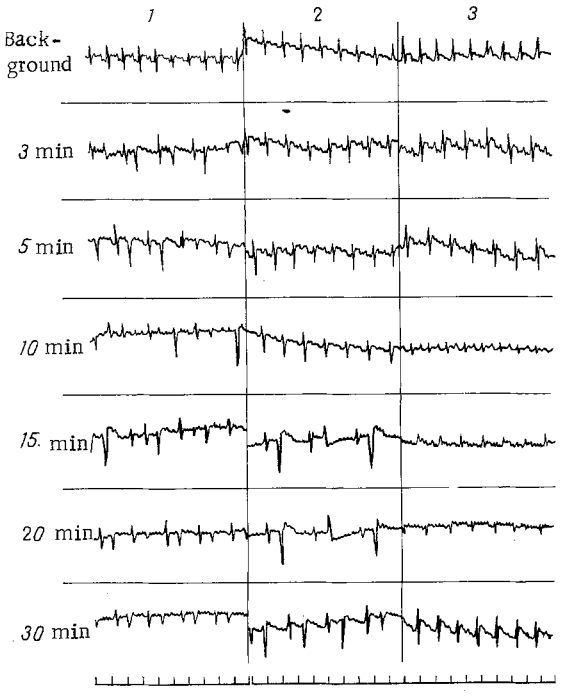

Fig. 1. Effect of marcaine and lidocaine on arrhythmia induced by intravenous injection of aconitine (40 μg/kg) in rats. 1) Development of disturbances of cardiac rhythm by aconitine; 2, 3) preventive action of lidocaine (8 mg/kg) and marcaine (5 mg/kg) respectively.

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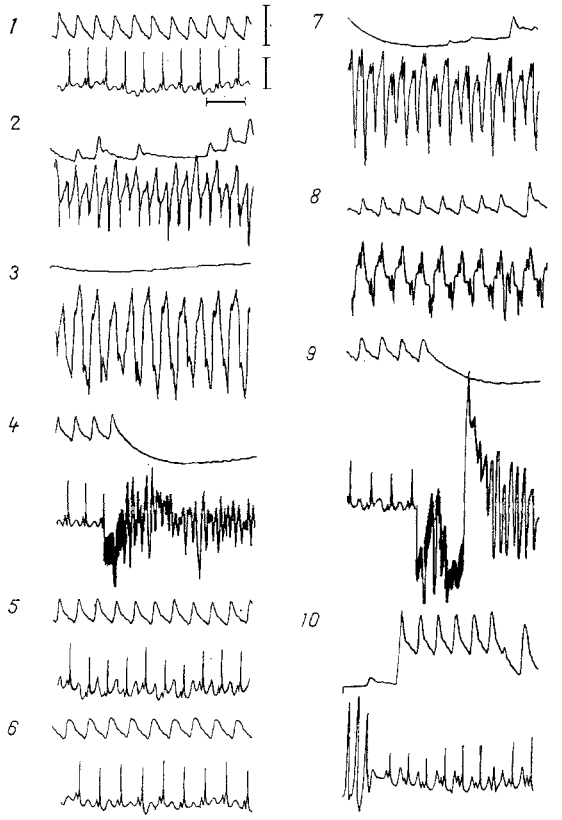

Fig. 2. Effect of lidocaine on cardiac rhythm binding and threshold of ventricular fibrillation in cat. For each pair of traces: top — pulse pressure (calibration 20 mm Hg), bottom — ECG (calibration 1 mV). Time marker 0.8 sec. 1) Background; 2) highest reproducible frequency (4 Hz); 3) rhythm of 4.5 Hz not bound by the heart; 4) fibrillation in response to burst of pulses with frequency of 50 Hz and strength of 3 mA; 5) after defibrillation by a 300 V discharge; 6) 1 min after action of lidocaine in a dose of 5 mg/kg; 7) fastest reproducible frequency 3.5 Hz; 8) rhythm of 4 Hz not bound; 9) fibrillation in response to burst of pulses with frequency of 50 Hz and strength of 20 mA (threshold raised almost sevenfold); 10) spontaneous recovery from fibrillation after 1 min.

EXPERIMENTAL METHOD

The pharmacologic study of the antiarrhythmic properties of marcaine was undertaken by a combination of methods that are used to evaluate drugs with antiarrhythmic action. The following models of experimental arrhythmias were used: arrhythmias evoked by intravenous injection of aconitine and strophanthin, and also disturbances of the cardiac rhythm (including fibrillation) caused by electrical stimulation of the ventricles.

Aconitine arrhythmia was produced in noninbred waking male rats weighing 180-200 g. Aconitine was injected intravenously in a dose of 40 μg/kg. Disturbances of the cardiac rhythm of varied character (polytopic extrasystoles, ventricular tachycardia) developed after 1-3 min. The duration of arrhythmia was 1.5-2 h. The ECG was recorded in lead II after 3, 5, 10, 20, and 30 min. The substances for testing were injected intravenously 1 min before the injection of aconitine.

Disturbances of rhythm under the influence of strophanthin in a dose of 0.25 mg/kg (intravenously) [6] were obtained in experiments on 25 guinea pigs weighing 250-400 g. The arrhythmogenic dose of strophanthin was compared before and after injection of the test substances.

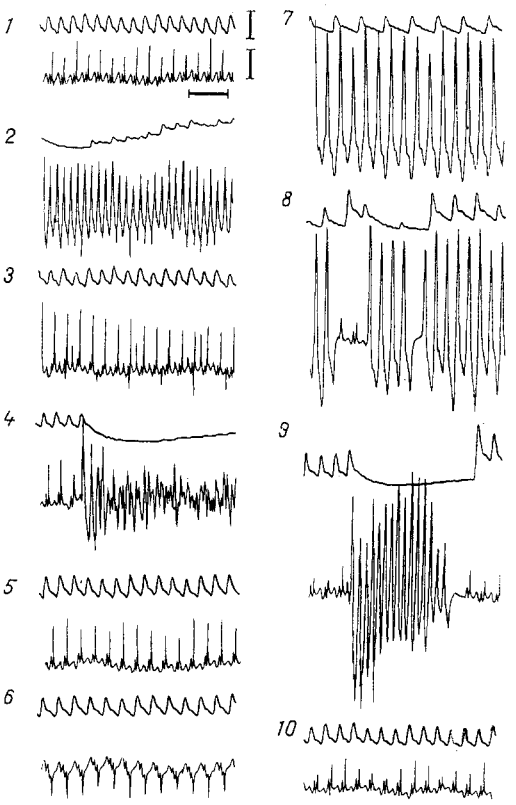

Fig. 3. Effect of marcaine on cardiac rhythm binding and threshold of ventricular fibrillation in cat. For each pair of traces: top — pulse pressure; bottom — ECG. 1) Background; 2) fastest reproducible frequency 5.5 Hz; 3) rhythm of 6 Hz not bound by the heart; 4) fibrillation in response to burst of pulses with a frequency of 50 Hz and strength of 0.6 mA; 5) after defibrillation by a 250 V discharge; 6) 1 min after intravenous injection of marcaine in a dose of 2 mg/kg; 7) fastest reproducible frequency 3 Hz; 8) rhythm of 3.5 Hz not bound by the heart; 9) episode of fibrillation in response to a burst of stimuli with a frequency of 50 Hz and a strength of 50 mA and spontaneous recovery from fibrillation; 10) 1 min after spontaneous recovery.

In experiments on cats anesthetized with pentobarbital, and with electrodes sutured to the myocardium of the right ventricle, an "ectopic focus" of excitation was created by electrical stimulation. To obtain single or grouped extrasystoles or to develop fibrillation, stimuli of different intensity were applied to the myocardium, through a current isolating system from a Sen-7103 electronic stimulator (Nihon Kohden, Japan).

The fibrillation threshold was determined by repeated scanning of the vulnerable period with series of 90 dc square pulses 4 msec in duration and of increasing strength (frequency 50 Hz) until fibrillation developed. The threshold was estimated as the minimal strength of current, in milliamperes, causing ventricular fibrillation. Defibrillation was produced by means of a defibrillating discharge of assigned strength, applied directly to the myocardium from the DI-03 apparatus.

The acute toxicity (LD_{50}) was determined in noninbred albino mice weighing 18-20 g, the drug being injected intravenously. ED_{50} was calculated by Litchfield's method [1]. The results were subjected to statistical analysis by Student's t test.

EXPERIMENTAL RESULTS

Lidocaine in a dose of 5 mg/kg was ineffective on the aconitine model, but when the dose was increased to 8 mg/kg it prevented its development, although only for 10 min. At the end of this time disturbances of the cardiac rhythm were observed (Fig. 1, 2).

Marcaine in a dose of 5 mg/kg, injected 1 min before aconitine, prevented the development of arrhythmia in 100% of cases (Fig. 1, 3). In this dose, however, marcaine had a marked toxic action (convulsions were observed in three of the 10 animals, and one animal died); LD_{50} for marcaine was 10 mg/kg.

In experiments on the strophanthin model disturbances of rhythm began 3 min after injection of the drug in a dose of 0.25 mg/kg. Initially the ECG revealed bradycardia, first- and second-degree atrioventricular conduction block, followed by polytopic ventricular extrasystoles, changing into ventricular tachycardia and fibrillation. In 90% of cases the animals died 10 min after injection of this dose of strophanthin.

Marcaine in a dose of 5 mg/kg raised the arrhythmogenic dose of strophanthin from 0.25 to 0.49 ± 0.01 mg/kg and prevented death of the animals before 10 min in 100% of cases.

Lidocaine in a dose of 5 mg/kg had a weak antiarrhythmic effect, but in a dose of 8 mg/kg it raised the arrhythmogenic dose of strophanthin, but only to 0.3 ± 0.4 mg/kg. The length of survival of the animals under these circumstances was lengthened from 10 to 24.1 ± 2.4 min.

In experiments on anesthetized cats, lidocaine in a dose of 5 mg/kg reduced imposition of a high-frequency pacemaker rhythm from the "ectopic focus" on the heart (Fig. 2, 8). The decrease in the highest possible reproducible frequency of "ectopic excitation" under the influence of lidocaine was associated with the lengthening of the effective refractory period by this drug. For ventricular fibrillation to develop, much stronger electrical stimulation was required than before injection of lidocaine (Fig. 2: 4, 9).

Marcaine in a dose of 2 mg/kg slowed the sinus rhythm and slowed conduction over the atria and along the atrioventricular bundle (Fig. 3: 6). Marcaine sharply reduced binding of the rhythm of excitation from the "ectopic focus" by the ventricles, evidence of its well-marked antiarrhythmic properties (Fig. 3: 7, 8). Marcaine raised the threshold of ventricular fibrillation sharply (on average tenfold) and reduced the voltage of the defibrillating discharge or even led to spontaneous recovery from fibrillation (Fig. 3: 9). The duration of action of marcaine and lidocaine was 60 and 30 min respectively.

The results are evidence that marcaine has marked antiarrhythmic and antifibrillatory properties. In the intensity and duration of its antiarrhythmic effect on the experimental models of arrhythmia used in these experiments marcaine was superior to lidocaine with which it was compared. However, it has a narrower latitude of therapeutic action than lidocaine. For instance, the antiarrhythmic index (LD_{50}/ED_{50}) for marcaine, according to results obtained with the aconitine model, was 3.33 compared with 5.8 for lidocaine. The narrow range of therapeutic doses and the marked toxic effects (convulsions) evidently are obstacles to the widespread introduction of the drug into clinical practice. However, the search for an equally effective but less toxic preparation with prolonged antiarrhythmic action among a series of analogs of marcaine would seem to be very promising.

LITERATURE CITED

1. M. L. Belen'kii, Elements of Quantitative Evaluation of the Pharmacologic Effect [in Russian], Riga (1959).
2. J. C. Chapin, L. G. Kushins, E. S. Munson, et al., Anesthesiology, 52, 23 (1980).
3. R. W. Dunbar, R. B. Boettner, R. N. Gatz, et al., Anesth. Analg., 49, 761 (1970).
4. R. H. Jong and J. D. Bonin, Anesth. Analg., 59, 401 (1980).
5. D. S. Moore, L. D. Bridenbaugh, G. E. Thomson, et al., Anesth. Analg., 57, 42 (1978).
6. H. I. Neumann, Zbl. Pharm., 110, 371 (1971).