ANTIARRHYTHMIC ACTIVITY OF QUATERNARY DERIVATIVES OF TRIMECAINE IN EXPERIMENTAL VENTRICULAR ARRHYTHMIAS

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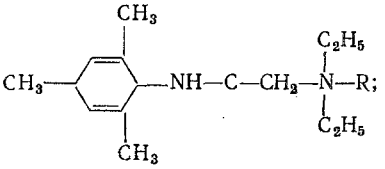
KEY WORDS: quaternary derivatives of trimecaine; antiarrhythmic action; ventricular arrhythmia; strophanthin poisoning.

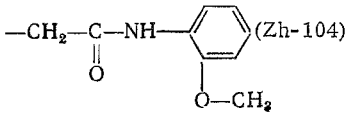
The local anesthetic trimecaine [9], like lidocaine, is becoming the drug of choice for the treatment of cardiac arrhythmias complicating acute myocardial infarction [7, 10]. However, because of its short half-breakdown time [8] trimecaine, if given intravenously, has a comparatively short antiarrhythmic action [2, 3, 6].

There are indications in the literature that conversion of the nitrogen in the lidocaine molecule into the ammonium state yields compounds (methyl lidocaine, OX-572) with a longer antiarrhythmic action [12, 13]. This paper gives the results of an experimental study of the antiarrhythmic action of several quaternary derivatives of trimecaine (QDT) in ventricular arrhythmias induced by disturbance of the myocardial blood supply and poisoning with a cardiac glycoside.

The QDT tested contained the following radicals attached to the quaternary nitrogen atom:

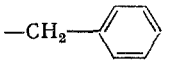


R—CH_3 (Zh-87)
—CH_2—CH_3 (Zh-88)
—CH_2—CH=CH_2 (Zh-92)



(Zh-104)

(Zh-112)



EXPERIMENTAL METHOD

Experiments were carried out on 23 dogs weighing 8-17 kg and 90 cats weighing 1.9-3.2 kg, anesthetized with pentobarbital sodium (30 mg/kg).

Experimental ventricular tachyarrhythmia was induced in dogs by occluding the descending branch of the left coronary artery (OCA) as described previously [3]. The experiments were carried out 24-48 h after OCA. The QDT for testing were injected intravenously in a single dose or, if necessary, repeated at intervals of 10-20 min in doses of 0.25-2.5 mg/kg (equivalent to 1-6% of LD_{50} for mice), until a lasting antiarrhythmic effect was achieved. By using the standardized experimental conditions, activity of the QDT could be estimated from the value of the effective accumulated dose.

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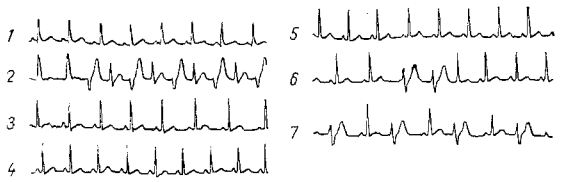

Fig. 1. Antiarrhythmic action of Zh-104. ECG of dog in standard lead II: 1) initially, 2) 24 h after OCA, 3-7) 10, 40, 120, 240, and 270 min respectively after injection of 0.8 mg/kg of Zh-104.

TABLE 1. Antiarrhythmic Activity and Duration of Antiarrhythmic Effect of QDT and of Certain Other Drugs in Experimental Ventricular Arrhythmias

Preparation	LD_{50} for mice by intraperitoneal injection, mg/kg	Effective dose, mg/kg		Duration of antiarrhythmic effect in arrhythmia after OCA, *min*	Literature source
		strophanthin arrhythmia	arrhythmia after OCA		
Zh-87	45,5±4,2	5,1±1,0	10,7±1,4	155±36 (60—220)	—
Zh-88	32,6±2,5	3,9±0,7	4,3±0,6	107±35 (40—160)	—
Zh-92	46,5±1,9	3,2±0,7	2,8±0,5	117±18 (50—190)	—
Zh-104	48,3±2,9	1,1±0,3	0,9±0,2	154±32 (60—240)	—
Trimecaine	180,0±11,5	7,4±1,3	16,0±1,4	7—10	[3, 9]
Quinidine	66,9	25	5,5—15,0	5—30	[15, 16]
Ajmalin	150±5	2,7±0,35	8,8±1,2	Up to 40	[1]
Lidocaine	128±9,2	6,9±1,0	2,5—5,0	Not more than 5	[3, 9, 14]
Methyl lidocaine	—	4,0—10,0	4,0—10,0	60—180	[13]
QX-572	—	3,0—50,0	3,0—50,0	30—60	[12]

Ventricular arrhythmia was induced in cats by intravenous injection of ouabain in a dose of 70 ± 8 μg/kg. The QDT were injected intravenously in the above-mentioned doses 3-5 min after the onset of arrhythmia and until impulse formation in the ventricles was suppressed and the correct sinus rhythm restored.

The effect of the QDT on tolerance of the cats to the toxic action of ouabain also was studied 24 h after the formation of a myocardial infarct. Disturbance of the coronary circulation was simulated by OCA, and the methods of determining the minimal arrhythmogenic dose and the lethal dose of ouabain, by which the sensitivity of the animals to the cardiac glycosides was estimated, were described previously [4]. The ECG was recorded in standard lead II.

EXPERIMENTAL RESULTS

After OCA ventricular polytopic tachycardia developed in all the experimental dogs after 18-24 h, with a heart rate of 178 ± 11 beats/min, and 80-90% of the contractions were ectopic in origin. The arrhythmia continued for 2-3 days, gradually subsiding.

All the QDT tested were able to inhibit ventricular tachycardia induced in dogs by OCA and to restore a stable and regular sinus rhythm (Fig. 1). The antiarrhythmic activity of the QDT and the duration of their antiarrhythmic effect largely depended on the character of the radical attached to the quaternary nitrogen atom.

The most active compounds on this model of arrhythmia were QDT with a benzene group in the radical (Zh-104). After intravenous injection in a dose of 0.9-0.2 mg/kg compound Zh-104 gradually (in the course of 8 min) and completely suppressed ectopic impulse formation and led to restoration of a regular sinus rhythm, which remained stable for 1-4 h. Meanwhile some degree (7%) of slowing of the heart rate was observed.

High antiarrhythmic activity also was exhibited by compound Zh-92, containing an unsaturated hydrocarbon as the radical. In an effective dose of 2.8 ± 0.5 mg/kg this substance abolished ventricular arrhythmia after 3.0 ± 0.2 min and restored the sinus rhythm, the effect lasting 50-190 min (117 ± 18 min), while at the same time the heart rate was slowed by 11%.

QDT containing saturated hydrocarbons as the radicals (Zh-88 and Zh-87) were rather less active. Their effective doses were 4.3 ± 0.6 and 10.7 ± 1.4 mg/kg respectively; in most experiments the antiarrhythmic effect of both these compounds lasted 1-3.5 h.

TABLE 2. Effect of QDT on Tolerance of Cats to Strophanthin 24 h after OCA

Experimental conditions	Dose of QDT, mg/kg	Number of experiments	Dose of ouabain, μg/kg			
			arrhythmogenic		lethal	
			$M \pm m$	% of control	$M \pm m$	% of control
Intact animals	—	5	82,0±2,0	—	124,3±2,1	—
24 h after OCA (control)	—	5	56,1±2,9	100	110,0±2,4	100
Injection of:						
Zh-87	3,2	5	85,0±9,0	152	144,0±13,0	131
Zh-92	1,6	6	86,0±9,0	154	143,0±8,0	130
Zh-104	0,5	6	113,0±8,0	202	165±7,0	150
Zh-112	0,5	6	111,2±6,0	198	173,0±15,0	157

Comparison of the results of these experiments with data in the literature for quinidine, lidocaine, trimecaine, QX-572, and methyl lidocaine, obtained on the same model of ventricular arrhythmia, showed that the QDT are much superior to the drugs mentioned above in their antiarrhythmic activity and in the duration of their antiarrhythmic effect (Table 1).

Control experiments with strophanthin arrhythmia showed that in animals receiving 70 ± 8 μg/g of ouabain, ventricular arrhythmia developed after 20-25 min and all the animals died during the next 45-65 min, with evidence of increasing disorganization of their cardiac rhythm.

The antiarrhythmic effect of the QDT in strophanthin arrhythmia developed 1-9 min after intravenous injection and it was manifested as inhibition of ectopic impulse formation, abolition of the disturbances of conduction, and restoration of the sinus rhythm, accompanied by some slowing of the heart rate. All animals receiving the QDT survived.

The effective dose of the various QDT in strophanthin arrhythmia varied from 1.1 to 5.1 mg/kg and depended on the character of the radical attached to the quaternary nitrogen atom (Table 1). The compound containing a benzene group as the radical (Zh-104) proved to be the most active. Next followed QDT containing unsaturated (Zh-92) and saturated (Zh-88 and Zh-87) hydrocarbon groupings.

The ability of the QDT to inhibit strophanthin arrhythmia and to protect poisoned animals against death indicates that these substances may be used to abolish or prevent arrhythmias due to glycoside poisoning.

With this consideration in mind, it was also decided to study to what extent this effect is exhibited in experimental myocardial infarction when sensitivity to cardiac glycosides is considerably increased [4].

The results indicated (Table 2) that QDT significantly increased the tolerance of cats with an experimentally induced myocardial infarct to the toxic action of ouabain. This property is present to the highest degree in QDT containing a benzene group as the radical attached to the quaternary nitrogen atom (Zh-104 and Zh-112). For comparison it may be noted that trimecaine, under similar experimental conditions, gave a similar effect in a dose of 25 mg/kg.

The results of these experiments thus show that conversions of the nitrogen atom in the trimecaine molecule into the quaternary state yields compounds with higher antiarrhythmic activity and with a longer and more stable antiarrhythmic action. These properties are expressed to the greatest degree in QDT containing a benzene or unsaturated hydrocarbon group as the radical attached to the quaternary nitrogen atom.

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FENIBUT BINDING WITH BICUCULLINE-INSENSITIVE GABA RECEPTORS IN THE RAT BRAIN

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Fenibut (β-phenyl GABA) has a sedative and tranquilizing action [5]. Many of the effects of fenibut have been shown to resemble those of GABA-mimetic substances [4]. Because of the structural similarity of GABA and fenibut it can be postulated that fenibut affects GABA-ergic processes in the CNS. Fenibut has not yet been found to affect the activity of enzymes participating in GABA metabolism [2] and, in addition, fenibut has no action on reassimilation of GABA [3].

Since the effect of fenibut on GABA receptors has received little study, it was decided to investigate the action of fenibut on GABA binding with GABA receptors in the rat brain.

EXPERIMENTAL METHOD

Male Wistar rats weighing 250-300 g were used. Binding of [^{3}H]-GABA was determined in the corpus striatum. The membrane fraction was obtained as follows: the rat was decapitated and the corpus striatum quickly removed in the cold and homogenized in 60 volumes of cold Tris-HCl buffer, pH 7.4, with a knife homogenizer (8000 rpm, 60 sec). The resulting suspension was centrifuged at 30,000g for 30 min at 4°C. The residue was left to stand overnight at −20°C. Next day the residue was kept for 15 min at room temperature, then suspended in the initial volume of the same buffer, and again homogenized and centrifuged at 30,000g. The residue was again allowed to stand overnight at −20°C. The residue was then rehomogenized and centrifuged another four times at 30,000g. After the last centrifugation the residue was rehomogenized in the same volume of buffer. The reaction of binding of [^{3}H]-GABA with receptors was carried out in the absence of NaCl at 0°C for 10 min and in the presence of 2.5 μM $CaCl_2$ and 50 μM (+)-bicuculline at 20°C (10 min). The reaction mixture contained: 0.9 ml of membrane protein suspension, 6 nM labeled GABA (50 Ci/mmole, from Amersham Corporation, England). Specific binding of the label with GABA receptors was determined from the difference between binding of the label in the presence and absence of 100 μM unlabeled GABA in the reaction mixture. The reaction was stopped by addition of 4 ml of cold Tris-HCl buffer, pH 7.4 (2°C), and rapid filtration through glass filters of the GFB type (from Whatman, England). The filters were washed three times with 4 ml of the same buffer and transferred

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