Membrane Mechanisms of Antiarrhythmic Effect of Quaternidine

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Complex electrophysiological study of the effects of quaternidine carried out on intact hearts from cats, myocardial fragments from rats, and single ionic channels of large edible snail showed that quaternidine demonstrates properties of class 1B antiarrhythmic drug according to Vaughan-Williams nomenclature. This agent did not suppress nomotopic pacemaker automaticity, did not change conduction in ventricles, atria, and atrioventricular junction in hearts with preserved sinus rhythm, did not prolong refractoriness of the atria and atrioventricular junction, but prolonged efficient refractory period of heart ventricles. Quaternidine decelerated rapid depolarization of the action potential, but had no effect on its duration. It did not affect potassium conductance.

Key Words: *quaternidine; action potential; antiarrhythmic; heart; neurons; cat; rat; snail; electrophysiology*

Quaternidine (QN) is a new Russian-made antiarrhythmic drug, which is highly efficient in the treatment of ventricular rhythm disturbances of ischemic origin. The effect of QN after a single intravenous injection persists for 5-10 h [3]. It was hypothesized that QN belongs to class III antiarrhythmics by Vaughan-Williams nomenclature [5]. However, this hypothesis was not corroborated by membrane studies. Our aim was to study the complex of electrophysiological properties of QN.

MATERIALS AND METHODS

The effects of QN on excitability, refractoriness of the atria and ventricles, automaticity of cardiac pacemaker, and conductance of the atria, atrioventricular node, and ventricles were studied on mature artificially ventilated cats intraperitoneally narcotized with sodium thiopental (50 mg/kg) [4]. The heart was stimulated with a Kordelectro stimulator via platinum electrodes placed in atria and ventricles. Cardiac electrogram was recorded with ELKAR-2A pen-ink recorder. QN was administered to 7 animals in an efficient antiarrhythmic dose of 1 mg/kg [3]. The control group comprised 10 animals.

The effects of QN on the rate of rapid depolarization V_{max} and amplitude and duration of action potential (AP) were examined on papillary muscles isolated from the right ventricle of rat heart [1]. The effect of QN on potassium conductance was studied by patch clamp on potential-operated delayed rectifier K^+-channels in neurons isolated from peripharyngeal ring of large edible snail. The data were analyzed statistically using Student's *t* test for independent and nonindependent variables.

RESULTS

Electrophysiological experiment on cats showed that similarly to the standard class IB and III antiarrhythmics [5], QN had no effect on automaticity of the nomotopic pacemaker (duration of *PP*-interval and time of recovery of sinus node function) and it did not

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TABLE 1. Time-Dependence of Electrophysiological Parameters of Cat Heart during Application of QN (Percentage to Initial Values, *M*±*m*)

Parameter		Group	Time after application, min		
			10-20	20-30	40-50
PP		Control	111±6	121±4	128±5
		QN	110±4	119±5	125±7
Restoration time of sinus node function		Control	117±3	123±4	124±7
		QN	109±7	121±5	124±10
P		Control	100	100	100
		QN	100	100	100
PQ		Control	102±2	100	100
		QN	108±5	109±8	105±7
QRS		Control	103±3	103±3	103±3
		QN	110±11	113±9	110±5
ERP	atria	Control	102±3	107±3	112±5
		QN	104±2	113±3	120±8
	atrioventricular node	Control	108±7	114±6	125±12
		QN	105±3	111±4	130±8
	ventricles	Control	103±4	108±4	120±5
		QN	120±5*	127±5*	142±7*
Excitation threshold	atria	Control	112±12	112±12	112±12
		QN	115±5	117±6	120±8
	ventricles	Control	116±1	123±7	130±5
		QN	105±5	109±7	106±8

Note. $p<0.05$ *compared to the control.

inhibit conductance in the atria, ventricles, and atrioventricular node (duration of *P*, *PQ*, and *QRS* intervals, Table 1). QN did not modulate excitability of the atria and ventricles. By contrast to K^+-channel blockers, QN did not change the duration of efficient refractoriness period (ERP) in the atria and atrioventricular node, but prolonged ERP in ventricles 10 and 30 min postinjection by 17% and 19%, respectively ($p<0.05$).

Experiments on papillary muscles from rat heart showed that QN significantly decreased the rate of rapid depolarization, and this effect was dose-dependent (Table 2). In concentrations of 13 μM and 26 μM, QN decreased V_{max} by 18±3% and 45±4%, respectively. The amplitude of AP decreased only when QN was applied in high concentrations. An important feature was the absence of changes in AP duration mea-

TABLE 2. Effect of QN on AP of Isolated Papillary Muscle of Rat Right Ventricle Stimulated at 3 Hz (*M*±*m*, *n*=5)

Parameter	Initial data	QN, μM			
		13		26	
		abs.	%	abs.	%
AP amplitude, mV	104±2	102±1	98	94±2*	90
V_{max}, V/sec	124±2	102±5*	82	68±6*	55
AP duration at 80% repolarization amplitude, msec	88±10	86±17	98	86±9	98

Note. $p<0.05$ *compared to the initial data.

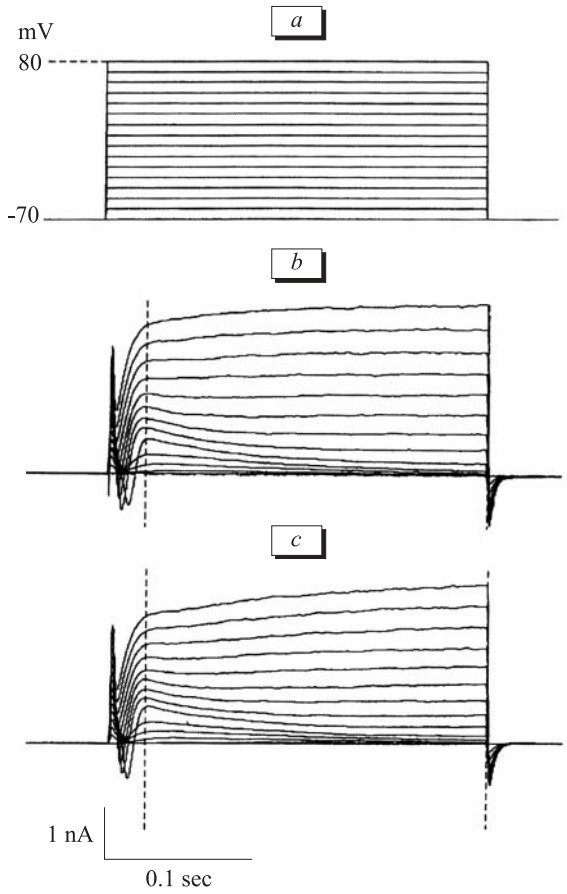

Fig. 1. Effect of QN on potassium currents in whole-cell voltage-clamped neuron isolated from large edible snail (*n*=5). *a*) rectangular voltage pulses with duration of 0.25 sec; *b*) control; *c*) QN, 10^{-4} M.

sured at 80% repolarization level. These data call in question the ability of QN to block K^+-channels, typical of class III antiarrhythmics.

The patch clamp experiments with potential-operated delayed rectifier K^+-channels showed that QN had no effect on parameters of these channels, when it was applied either to the outer or inner side of the membrane in concentrations up to 10^{-4} M. At this concentration, QN did not block potassium current through potential-operated delayed rectifier K^+-channels in whole-cell clamp experiments (Fig. 1). Insignificant decrease in ionic currents (about 15% at 80 mV) was most probably caused by progressive deterioration of the cell or by shifts in intracellular ionic composition due to diffusion of the ions from the pipette. This process was observed during the entire experiments and progressed with time.

When QN was applied to the inner surface of the membrane, the membrane potential was set to 0 in all cases (Fig. 2). Under these conditions, application of QN at 10^{-4} M produced no significant effect on channel performance.

The comparison of electrophysiological effects of QN with those produced by standard antiarrhythmics belonging to different classes makes it possible to classify QN according to the accepted nomenclature [5]. Since QN did not inhibit cardiac pacemaker, it cannot be placed among classes II or IV antiarrhythmics. Most probably, the absence of dromotropic effect during sinus rhythm excludes QN from the classes IA and IC antiarrhythmics. When applied to either face of the plasmalemma, QN did not increase the duration of AP and did not block potassium currents through potential-operated delayed rectifier K^+-channels in neurons isolated from large edible snail, so it cannot be related to class III antiarrhythmics.

We established that QN decreased the rate of AP upstroke and its amplitude, so this agent demonstrated properties of Na^+-channel blockers. Taken into consideration the complex of electrophysiological properties of QN and the data on its high efficiency in the treatment of ventricular rhythm abnormalities in contrast to supraventricular arrhythmias [2,3], QN can be referred to class IB antiarrhythmics according to Vaughan-Williams classification. In comparison to this group of antiarrhythmic preparations, the specific feature of QN is long-term pharmacokinetics, which evidently underlies the long-term effect of this drug.

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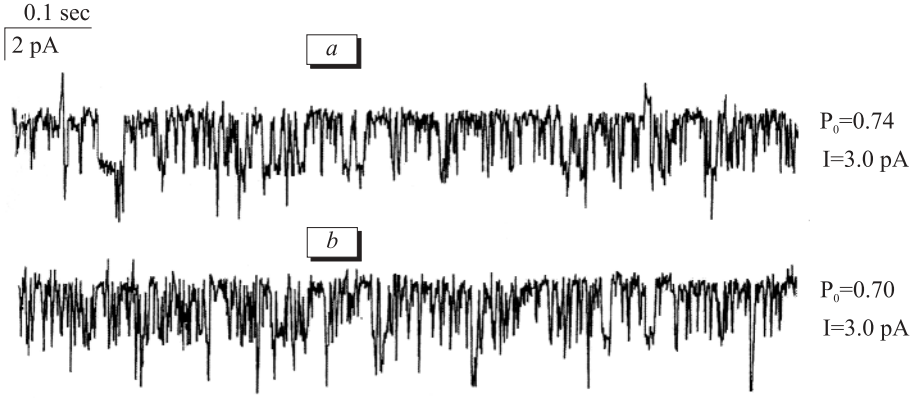

Fig. 2. Effect of QN on ionic currents flowing across 3 single potassium channels in plasmalemma fragment (*n*=6). *a*) control; *b*) QN, 10^{-5} M. P_0 is open state probability; I is current amplitude in single channels.

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