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Effects of dauricine, quinidine, and sotalol on action potential duration of papillary muscles *in vitro*[1]

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KEY WORDS dauricine; quinidine; sotalol; papillary muscles; action potentials

AIM: To compare the characteristics of dauricine, sotalol, and quinidine on action potential duration (APD). **METHODS:** Using intracellular microelectrode method to record APD in guinea pig papillary muscles. **RESULTS:** Dauricine 20 μmol·L^{-1} prolonged action potential at 90 % repolarization, the percent of APD prolongation were 22±8, 11±6, 9±5, 7±5, 6±3, 4.3±2.8, 4.5±2.8 at the cycle lengths of 200 - 2000 ms, dauricine became more effective in lengthening APD at short cycle lengths. The effect of dauricine on prolonging APD exhibited normal use-dependence, whereas quinidine 1 μmol·L^{-1} and sotalol 10 μmol·L^{-1} were less effective in lengthening APD at short cycle lengths. The effect of quinidine and sotalol on APD exhibited reverse use-dependence. **CONCLUSSION:** The effect of dauricine on APD depends on activation frequency.

At present, many drugs with class Ⅲ properties experimentally (including class I and class Ⅲ anti-arrhythmic drugs) exhibited reverse use-dependence[1]. As a result of reverse use-dependence, these drugs have less effect during tachycardias. Conversely, during bradycardia or after a long diastolic interval (eg, compensatory pause after ectopic), these drugs may induce maximum prolongation of action potential duration (APD). Excessive lengthening of APD with these drugs have been associated with development of early afterdepolarizations (EAD), triggered activity (TA), and even Torsade de Pointes (TdP). They suggested that the therapeutic potential of new class Ⅲ drugs should have a weak ability to prolong repolarization at fast heart rates, which would increase their effectiveness in terminating tachycardias[2,3].

Dauricine, a bisbenzyl tetrahydroisoquinoline derivative, was isolated from rhizome of *Menispermum dauricum* DC. Its anti-arrhythmic effect was found in animals[4,5], it prolonged APD with a use-dependent manner in canine Purkinje fibers[6]. In this study, we compare its electrophysiologic features on prolonging APD with quinidine and sotalol in guinea pig papillary muscles.

MATERIALS AND METHODS

Guinea pigs of either sex weighing 280 ± *s* 31 g (*n* = 34), provided from the Experimental Animal Center of Tongji Medical university, were decapitated and the hearts were superfused with cold Tyrode's solution. Isolated papillary muscle of right ventricle was mounted on a tissue bath and perfused with Tyrode's solution (35 ± 1 ℃) gassed with O_2. The Tyrode's solution contained NaCl 137, KCl 5.4, $CaCl_2$ 1.8, $MgCl_2$ 1.05, glucose 10, Tris 10 mmol·L^{-1} (pH 7.2 - 7.4).

The preparation was stimulated (Nihon Kohden, Japan) at a control basic cycle length of 1000 ms, 1 ms square wave, and 150 % of the diastolic threshold. Transmembrane potentials were led to the microelectrode amplifier (SWF-1, Chengdu Instrument Factory) by a standard intracellular glass electrode filled with KCl 3 mol·L^{-1} having resistance of 10 - 30 MΩ. The signals were displayed on oscilloscope (SBR-1, Shantou Electronic Instrument Factory) and fed to computer (Compaq 486).

(1) After a stabilization in Tyrode's solution for 1 h, the action potentials were recorded at cycle lengths of 200 - 2000 ms. Tissue was stimulated for at least 3 min at a cycle length before recording. Then the preparations were superfused with quinidine 1 μmol·L^{-1}, action potentials were recorded at various cycle lengths after 30 min. (2) Sotalol group. (3) Dauricine group.

Dauricine was kindly supplied by Dr PAN Xi-Ping (Pharmaceutical College of Tongji Medical University), was a white powder, M_r 624, mp 103 - 104 ℃, purity >99 %. It was dissolved in distilled water to 1 mmol·L^{-1}, and refrigerated. Sotalol and quinidine sulfate were purchased from Sigma, refrigerated stock solution of 10 mmol·L^{-1}.

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The statistical analysis of results were made with paired t-test and ANOVA.

RESULTS

Quinidine As the control, action potentials were recorded at 1, 2, and 3 h, the APD_{90} were 168 ± 18, 172 ± 19, and 171 ± 21 ms ($n = 4$) at the cycle of 1000 ms, the APD_{90} among 1, 2, 3 h were not significantly different ($P > 0.05$).

At quinidine 1 μmol · L^{-1}, APD_{90} was prolonged, particularly at longer cycle length. At the cycle lengths of 200, 300, 400, 600, 800, 1000, 2000 ms, the percent of APD_{90} prolongation were 2.8 ± 1.8, 6 ± 4, 9 ± 4, 9 ± 4, 11 ± 4, 13 ± 5, 16 ± 7 ($n = 10$), respectively. Quinidine became less effective in lengthening APD at short cycle lengths, its effect exhibited reverse use-dependence (Tab 1, Fig 1,2).

Sotalol At sotalol 10 μmol·L^{-1}, APD_{90} was prolonged, particularly at longer cycle length. At the cycle lengths of 200, 300, 400, 600, 800, 1000, 2000 ms, the percent of APD_{90} prolongation were 8.5 ± 1.8, 8.4 ± 1.7, 10.0 ± 2.6, 11 ± 3, 11 ± 3, 13 ± 4, 16 ± 4 ($n = 10$). respectively. Similar to quinidine, sotalol became less effective in lengthening APD at short cycle lengths, Its effect exhibited reverse use-dependence (Tab 1, Fig 1,2).

Dauricine At dauricine 20 μmol·L^{-1}, APD_{90} was prolonged, contrast to quinidine and sotalol, particularly at shorter cycle length. At the cycle lengths of 200, 300, 400, 600, 800, 1000, 2000 ms, the percent of APD_{90} prolongation were 22 ± 8,

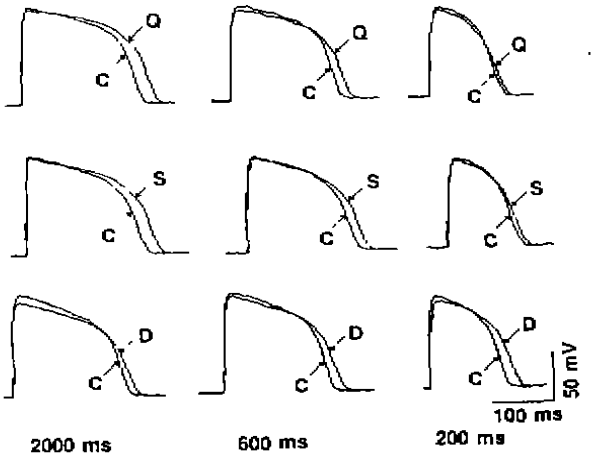

Fig 1. Effects of quinidine (Q), sotalol (S), dauricine (D) on action potential duration at verious cycle lengths in guinea pig papillary muscle. C = control.

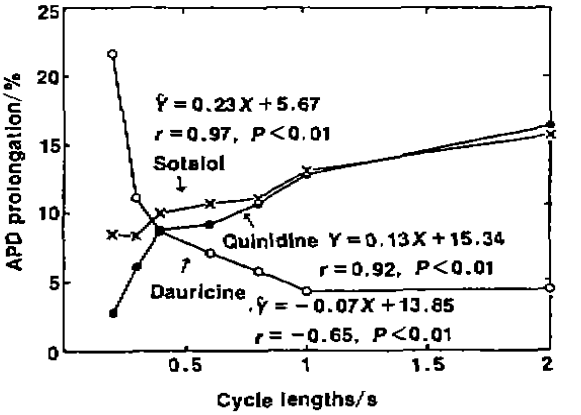

Fig 2. Use-dependence of dauricine on APD in guinea pig papillary muscles: contrast to quinidine and sotalol.

Tab 1. Effects of dauricine, quinidine, and sotalol on APD_{90} in guinea pig papillary muscles. ($n = 10$ muscles of 10 hearts), $\bar{x} \pm s$. $^aP > 0.05$, $^bP < 0.05$, $^cP < 0.01$ *vs* control.

Cycle lengths/ms	Action potential duration/ms							F
	200	300	400	600	800	1000	2000	
Control	98 ± 10	125 ± 15	138 ± 16	153 ± 16	160 ± 19	165 ± 20	169 ± 20	
Dauricine	120 ± 15^c	138 ± 18^c	151 ± 19^c	164 ± 19^c	169 ± 19^c	172 ± 20^b	176 ± 20^b	
Change (%)	22 ± 8	11 ± 6	8 ± 4	7 ± 3	6 ± 3	4.3 ± 2.8	4.5 ± 2.8	8.8^c
Control	92 ± 9	116 ± 14	125 ± 14	145 ± 16	156 ± 17	166 ± 18	175 ± 17	
Quinidine	93 ± 9^a	119 ± 15^a	137 ± 15^c	159 ± 16^c	173 ± 18^c	187 ± 19^c	203 ± 16^c	
Change (%)	2.8 ± 1.8	6 ± 4	9 ± 4	9 ± 4	11 ± 4	13 ± 5	16 ± 7	18.4^c
Control	95 ± 11	121 ± 12	129 ± 14	150 ± 15	161 ± 15	168 ± 17	177 ± 17	
Sotalol	103 ± 10^a	131 ± 13^c	142 ± 14^c	166 ± 15^c	179 ± 17^c	190 ± 17^c	205 ± 18^c	
Change (%)	8.5 ± 1.8	8.4 ± 1.7	10.0 ± 2.6	11 ± 3	11 ± 3	13 ± 4	16 ± 4	6.9^c

11 ±6, 9±5, 7±5, 6±3, 4.3±2.8, 4.5±2.8 (n = 10), respectively. Dauricine became more effective in lengthening APD at short cycle lengths, Its effect exhibited normal use-dependence (Tab 1, Fig 1,2).

DISCUSSION

Quinidine blocked Na^+ current and multiple cardiac K^+ currents. As a consequence of its K^+ channel-blocking actions, quinidine prolonged action potentials in most cardiac cells. This effect is most prominent at slow rates (reverse use-dependence). Quinidine consistently elicited EAD at slow heart beats[7]. It was estimated that 2 % – 8 % of patients who received quinidine therapy would develop marked QT interval prolongation and TdP[8]. Sotalol is non-selective β-adrenergic receptor antagonist that also prolonged APD by inhibiting delayed rectifier K^+ currents. Similar to quinidine, its effect on APD exhibited reverse use-dependence, sotalol caused EAD and TA *in vitro* and TdP in patients[9]. In this study, we found that quinidine and sotalol prolonged APD as use-dependence manner in guinea pig papillary muscles. The results were similar to those described above.

Our results suggested that dauricine exhibit normal use-dependence on prolonging APD contrast to quinidine and sotalol. Recently, we found that dauricine inhibited the EAD induced by quinidine. The studies indicate that dauricine may become the 'ideal' anti-arrhythmic drug. Obviously, it is very important to further study anti-arrhythmic properties and mechanism of dauricine on ionic channels in cardiac repolarization by comparison with quinidine or other class Ⅲ drugs.

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蝙蝠葛碱，奎尼丁和索他洛尔对离体乳头状肌动作电位时程的作用

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关键词 蝙蝠葛碱；奎尼丁；索他洛尔；乳头状肌；动作电位

目的：观察蝙蝠葛碱对豚鼠乳头状肌的动作电位是否具有使用依赖性特征，并与奎尼丁、索他洛尔作平行比较. 方法：利用细胞内微电极技术记录豚鼠乳头状肌跨膜动作电位. 结果：蝙蝠葛碱 20 μmol·L^{-1}能明显延长乳头状肌跨膜动作电位时程，在刺激周长为 200，300，400，600，800，1000，2000 ms 时，其延长动作电位时程的百分率分别为 22 ±8，11 ±6，9 ±5，7 ±5，6 ±3，4.3 ±2.8，4.5±2.8，蝙蝠葛碱延长动作电位时程作用于刺激周期较短时作用明显，呈使用依赖性特征. 而奎尼丁 1 μmol·L^{-1}和索他洛尔 10 μmol·L^{-1}延长动作电位时程作用随刺激周期延长而增强，呈现逆向使用依赖性特征. 结论：蝙蝠葛碱使用依赖性延长豚鼠乳头状肌动作电位时程.