Class I and III antiarrhythmic actions of prazosin in guinea-pig papillary muscles

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1 The electrophysiological effects of prazosin, a highly specific α_1 -adrenoceptor antagonist, on trans-membrane action potential characteristics were studied in guinea-pig papillary muscles.

2 At concentrations between 10^{-6} M and 10^{-5} M, prazosin produced a concentration-dependent decrease in the maximum upstroke velocity (V_{max}) and a progressive lengthening of the action potential duration at 50% (APD₅₀) and 90% (APD₉₀) of repolarization. The prolongation of the APD₅₀ and APD₉₀ values was independent of the frequency of stimulation. The prolongation of the APD₉₀ was accompanied by a parallel lengthening of the effective refractory period (ERP) and thus, the ERP/APD₉₀ ratio remained unaltered at all drug concentrations tested.

3 In the presence of prazosin, 5×10^{-6} M, the percentage of V_{max} block increased with the frequency of stimulation, the inhibitory effect being more marked at fast driving rates (frequency-dependent V_{max} block). At 3 Hz, the onset kinetics of the frequency-dependent V_{max} block was better fitted by a biexponential function, the K values of the fast (K_1) and slow components (K_2) being 0.254 ± 0.037 AP⁻¹ and 0.045 ± 0.010 AP⁻¹, respectively. However, prazosin did not produce tonic V_{max} block.

4 The recovery time constant (τ_{re}) from the frequency-dependent V_{max} block was prolonged from 19.6 ± 2.5 ms to 24.4 ± 5.5 s. This result indicated that prazosin can be considered as a slow kinetics Na channel blocker.

5 Prazosin, 5×10^{-6} M, shifted the membrane responsiveness curve in a hyperpolarizing direction, which indicated that the blockade of sodium channels increased at less negative potentials (voltage-dependent V_{max} block).

6 It is concluded that in guinea-pig papillary muscles, prazosin inhibited the V_{max} and lengthened the duration of the action potentials, thus exhibiting both class I and class III antiarrhythmic actions, respectively, that were possibly unrelated to blockade of myocardial α_1 -adrenoceptors.

Keywords: Prazosin; ventricular muscles; action potentials; action potential duration; frequency-dependent V_{max} block

Introduction

The effectiveness of α_1 -adrenoceptor antagonists on catecholamine-induced cardiac arrhythmias in animals has been known for more than 40 years (for review, see Benfey 1980; 1982). Phentolamine and prazosin inhibited the ventricular arrhythmias occurring after coronary occlusion and during reperfusion (Sheridan *et al.*, 1980; Stewart *et al.*, 1980) as well as those induced by ouabain (Ettinger *et al.*, 1969) and chloroform (Vargaftig & Coignet, 1969). In addition, α_1 -adrenoceptor antagonists suppressed ventricular tachyarrhythmias in patients with myocardial infarction (Gould *et al.*, 1975) and in circumstances where β -adrenoceptor antagonists were inactive (Sheridan *et al.*, 1980; Benfey, 1982). Even although it may be expected that at high concentrations α_1 -adrenoceptor antagonists might antagonize arrhythmias in conditions not involving α_1 -adrenoceptor stimulation, the mechanisms responsible for the antiarrhythmic effects are still unknown (Benfey, 1982; Ferrier & Carmeliet, 1990).

Previous electrophysiological studies in different animal species have demonstrated that α_1 -adrenoceptor antagonists inhibited the maximum upstroke velocity (V_{max}) and lengthened the action potential duration (Quadbeck & Reiter, 1975; Sada, 1978; Northover, 1983; Dukes & Vaughan Williams, 1984; Rosen *et al.*, 1984; Tohse *et al.*, 1986; Himmel *et al.*, 1991). These results suggested that α_1 -adrenoceptor antagonists may exhibit class I (Na channel blocking properties) and class III antiarrhythmic properties, respectively, according to the classification of Vaughan Williams (1984). Most sodium (Na) channel blocking drugs have been shown to have important frequency (use)-dependent effects on the V_{max} of the cardiac action potential (Hondeghe & Katzung,

1977; Tamargo *et al.*, 1992) and the analysis of the onset and offset kinetics of the frequency-dependent V_{max} block has been used for the subclassification of cardiac Na channel blockers into three subgroups, i.e., fast, intermediate, and slow kinetics drugs (Campbell, 1983; Vaughan Williams, 1984). In contrast, the prolongation of the action potential duration produced by most class III antiarrhythmic drugs decreased at fast rates, i.e., they exhibited a 'reversed use-dependence' (Hondeghe & Snyders, 1990). Even when in some studies the inhibitory effects of phentolamine and prazosin on V_{max} increased with the frequency of stimulation (Sada, 1978; Northover, 1983; Tohse *et al.*, 1986) the frequency-dependent effects of α_1 -adrenoceptor antagonists on V_{max} and APD have not been thoroughly studied.

Therefore, the present study was undertaken to: (1) investigate the frequency-dependent effects of prazosin, a highly specific α_1 -adrenoceptor antagonist (Williams *et al.*, 1981), on V_{max} and APD in guinea-pig papillary muscles, and (2) compare its effects with those previously described in this cardiac tissue with other antiarrhythmic drugs.

Methods

Experimental procedure

Guinea-pigs of either sex, weighing 250–350 g, were killed by a blow on the neck. The hearts were rapidly excised, and papillary muscles (<1 mm in diameter) were dissected from the right ventricle and superfused continuously at a constant rate of 7 ml min⁻¹ with Tyrode solution of the following composition (mM): NaCl 125, KCl 5.4, CaCl₂ 1.8, MgCl₂ 1.05, NaHCO₃ 24, NaH₂PO₄ 0.42 and glucose 11. The solu-

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tions were bubbled with 95% O₂:5% CO₂ (pH = 7.4) and the temperature was kept constant at 34 ± 0.5°C. The preparations were initially driven at 1 Hz and a period of at least 1 h was allowed for equilibration during which a stable impalement was obtained. Driving stimuli were rectangular pulses (2 ms duration, twice threshold strength) delivered to the preparation from a multipurpose programmable stimulator (Cibertec CS-220).

Transmembrane action potentials were conventionally recorded through glass microelectrodes filled with 3 M KCl (tip resistance of 8–15 MΩ). The microelectrode was connected via Ag-AgCl wire to a high-input impedance, capacity neutralizing amplifiers (WPI model 701). The V_{max} of the action potential was obtained by electronic differentiation (Delpón *et al.*, 1992). Stimulus intensity and duration were adjusted throughout each experiment to maintain a constant latency (1–2 ms) between stimulus and upstroke of action potential. Both action potential and V_{max} were displayed on a storage oscilloscope (Tektronix 5104N) and photographed with a kymographic Grass camera (Model C-4). Film analysis was used to measure resting membrane potential (RMP), action potential amplitude (APA), V_{max} , action potential duration at 50% (APD₅₀) and 90% of repolarization (APD₉₀) and effective refractory period (ERP). The ERP was determined by introducing premature test-stimuli of twice threshold strength at progressively earlier diastolic intervals applied every 8th basic beat (Delpón *et al.*, 1992). All experimental results were obtained from a single continuous impalement through the whole experiment. In some experiments following the equilibration period, the effects of prazosin on APD₅₀ and APD₉₀ values at steady state were studied in muscles stimulated at different driving rates (0.1–3 Hz).

To study the frequency-dependent effects of prazosin on V_{max} , preparations were driven at a basal rate of 0.02 Hz. Following the equilibration period, the preparations were driven by trains of stimuli at various rates ranging from 0.5 to 3 Hz for 40 s (0.5, 1 and 2 Hz) and 16 s (3 Hz). Resting periods of 5 min, which were sufficient to ensure full recovery from the frequency-dependent decrease in V_{max} , were interposed between the trains of stimuli (Delpón *et al.*, 1992). The rate of onset of V_{max} block in the presence of prazosin was quantified by determining the rate constant of this process, described as the reciprocal of the action potential number (AP⁻¹). Recovery of V_{max} from the frequency-dependent block was studied by applying a single test stimulus at various coupling intervals after a stimulation train for 20 s at 3 Hz (Delpón *et al.*, 1992).

The effect of prazosin on the relationship between V_{max} and the resting membrane potential, i.e., membrane responsiveness, was studied in papillary muscles driven at 0.01 Hz and the resting potential was depolarized in a stepwise manner by increasing the [K]_o from 2 to 15 mM (Delpón *et al.*, 1992). The V_{max} was measured each time after an equilibration period of 8 min. After obtaining control data, [K]_o was returned to 2 mM and the procedure repeated 30 min after exposure to prazosin, 5 × 10⁻⁶ M.

Drugs

Prazosin hydrochloride (Sigma Chemical Ltd., London) as a powder was initially dissolved in distilled deionized water and further dilutions were carried out in Tyrode solution to obtain the desired final concentrations.

Throughout the paper, data are expressed as the mean ± s.e.mean and Student's *t* test for paired observations was used to estimate the significance of differences from control values. For statistical comparison of more than two groups, a one-way analysis of variance was performed (Wallenstein *et al.*, 1980). A *P* value of less than 0.05 was considered as significant. A nonlinear least squares fitting routine was used to determine the rate constant for the onset block of V_{max} and the time constant of recovery from block V_{max} .

Results

Effects on action potential characteristics

The effects of prazosin in a range of concentrations between 10⁻⁷ M and 10⁻⁵ M on the electrophysiological characteristics of the ventricular action potentials were studied in nine guinea-pig papillary muscles constantly driven at 1 Hz. The results obtained under control conditions and 30 min after each increment in drug concentration are summarized in Table 1. At 10⁻⁷ M, prazosin had no significant effects on the characteristics of the action potential. At higher concentrations it produced a progressive decrease (*P* < 0.05) in V_{max} , which reached significant values at 5 × 10⁻⁶ M and 10⁻⁵ M. This effect was not accompanied by significant changes in action potential amplitude or in the resting membrane potential. However, the most representative effect of prazosin was a progressive slowing in the rate of repolarization during phases 2 and 3 of the ventricular action potential, leading to a concentration-dependent lengthening of the APD₅₀ and APD₉₀ values. This prolongation reached significant values at concentrations ≥ than 10⁻⁶ M (*P* < 0.05). The prolongation of the APD₉₀ was accompanied by a parallel lengthening of the ERP and hence, the ERP/APD₉₀ ratio remained unaltered at all drug concentrations tested. Thus, in seven papillary muscles driven at 1 Hz the values for the ERP and ERP/APD₉₀ ratio averaged 194.8 ± 18.4 ms and 1.03 ± 0.07 in the absence and 225.7 ± 30.3 ms and 1.04 ± 0.04 in the presence of 10⁻⁵ M prazosin, respectively.

Frequency-dependent V_{max} block

The effectiveness of Na channel blockers in inhibiting the fast inward Na current (*I*_{Na}) is strongly dependent on the frequency of stimulation (Hondeghe & Katzung, 1977; Campbell, 1983; Tamargo *et al.*, 1992). In order to study the effect of the stimulation frequency on the V_{max} block induced by prazosin, preparations were driven at a basal rate of 0.02 Hz and trains of pulses at different rates (0.5–3 Hz) separated

Table 1 Electrophysiological effects of prazosin on action potentials in guinea-pig ventricular papillary muscles driven at 1 Hz

Drug concentration (M)	RMP (mV)	APA (mV)	V_{max} (V s ⁻¹)	APD ₅₀ (ms)	APD ₉₀ (ms)
0	86 ± 1	120 ± 1	179 ± 18	154 ± 11	186 ± 9
10 ⁻⁷	86 ± 1	120 ± 1	179 ± 19	157 ± 10	190 ± 9
10 ⁻⁶	86 ± 1	119 ± 1	178 ± 17	168 ± 10	202 ± 8*
5 × 10 ⁻⁶	85 ± 1	118 ± 2	161 ± 15*	171 ± 12*	208 ± 12*
10 ⁻⁵	85 ± 1	118 ± 1	145 ± 14*	182 ± 11**	223 ± 13**

x ± s.e.mean, *n* = 9

P* < 0.05; *P* < 0.001.

from one another by a rest period of 5 min were applied. In the presence of prazosin, 5×10^{-6} M, the inhibition of the $\dot{V}_{\max}$ of the first action potential of each train, i.e. tonic $\dot{V}_{\max}$ block, averaged $0.6 \pm 0.3\%$ ($n = 8$), this effect being independent of the frequency of stimulation tested. In fact, as previously reported by Tohse *et al.* (1986), sometimes prazosin slightly increased, instead of decreasing, the $\dot{V}_{\max}$ of the first action potential. These results suggested that at this concentration, prazosin had no affinity for the rested state of the Na channel.

In the absence of prazosin the repetitive stimulation of the papillary muscles produced a gradual decrease of $\dot{V}_{\max}$ from the value of the first action potential to a new steady-state and this decrease increased with the frequency of stimulation (frequency-dependent $\dot{V}_{\max}$ block). Table 2 shows that when the stimulation rate increased from 0.5 to 3 Hz the $\dot{V}_{\max}$ block progressively augmented from $0.7 \pm 0.3\%$ to $16.1 \pm 1.5\%$. Figure 1 shows the percentage decrease in $\dot{V}_{\max}$ from the first action potential of the train to the new steady-state level obtained in a typical experiment in the presence of prazosin, 5×10^{-6} M. It can be observed that the percentage of $\dot{V}_{\max}$ block increased with the frequency of stimulation. As summarized in Table 2, prazosin induced a significant frequency-dependent $\dot{V}_{\max}$ block at all the rates of stimulation tested but the inhibitory effect was more marked at fast (1–3 Hz, $P < 0.001$) than at slow driving rates (0.5 Hz, $P < 0.05$).

The onset kinetics of frequency-dependent $\dot{V}_{\max}$ block can be defined as an event-dependent process, that can be fitted by a single or biexponential function (Courtney, 1987; Delpon *et al.*, 1992). The onset rate constant per action potential [K/AP] at which $\dot{V}_{\max}$ decreased to a new steady-state level in the presence of 5×10^{-6} M prazosin was calculated from the exponential fit of the $\dot{V}_{\max}$ values obtained during the train of action potentials. As is shown in Table 3, the onset rate constant of $\dot{V}_{\max}$ block was dependent on the stimulation frequency, being always higher at lower stimulation frequencies. In muscles driven at 0.5 and 1 Hz, the onset kinetics were fitted by a single exponential curve, the K values being $0.177 \pm 0.039/AP$ and $0.064 \pm 0.004/AP$, respectively. However, at 2 Hz and 3 Hz, the onset kinetics of the frequency-dependent $\dot{V}_{\max}$ block was better fitted by a biexponential

function, the K values of the fast (K_1) and slow components (K_2) being $0.301 \pm 0.036/AP$ and $0.040 \pm 0.006/AP$ at 2 Hz and $0.254 \pm 0.037/AP$ and $0.045 \pm 0.010/AP$ at 3 Hz, respectively.

Effects of prazosin on the recovery process of $\dot{V}_{\max}$

The effects of prazosin on the recovery kinetics of frequency-dependent $\dot{V}_{\max}$ block were also studied in papillary muscles driven every 5 min by a train of stimuli at a frequency of 3 Hz for 20 s and a test-stimulus was applied at variable coupling intervals from 500 ms to 10 s. Recovery from fre-

Figure 1 Frequency-dependent $\dot{V}_{\max}$ block obtained in the presence of prazosin (5×10^{-6} M) in guinea-pig papillary muscles driven by trains of stimuli at various rates of stimulation (0.5, 1, 2 and 3 Hz). The percentage of $\dot{V}_{\max}$ normalized by the value of the first action potential of the train [$\dot{V}_t/\dot{V}_c$ (%), $\dot{V}_t = \dot{V}_{\max}$ of the action potentials of the train, $\dot{V}_c = \dot{V}_{\max}$ of the first action potential of the train] was plotted against the number of consecutive beats of the train: (●) 0.5 Hz; (○) 1 Hz; (▲) 2 Hz; (△) 3 Hz.

Table 2 Effects of prazosin (5×10^{-6} M) on the frequency-dependent $\dot{V}_{\max}$ block in guinea pig papillary muscles

Frequency of stimulation (Hz)	Frequency-dependent $\dot{V}_{\max}$ block (%) Control (%)	Prazosin (%)
0.5	0.7 ± 0.3	$2.4 \pm 0.5^*$
1	3.4 ± 0.8	$9.9 \pm 1.3^{**}$
2	10.7 ± 1.1	$21.9 \pm 1.6^{**}$
3	16.1 ± 1.5	$28.6 \pm 2.4^{**}$

$x \pm$ s.e.mean, $n = 8$

* $P < 0.05$; ** $P < 0.001$.

Table 3 Rate constants of development of frequency-dependent $\dot{V}_{\max}$ block (K) in the presence of prazosin (5×10^{-6} M)

Frequency of stimulation (Hz)	Onset rate per AP	
	K_1/AP	K_2/AP
0.5	—	0.177 ± 0.039
1.0	—	0.064 ± 0.004
2.0	0.301 ± 0.036	0.040 ± 0.006
3.0	0.254 ± 0.037	0.045 ± 0.010

$x \pm$ s.e.mean, $n = 7$

Figure 2 Effects of prazosin (10^{-5} M) on the recovery process of $\dot{V}_{\max}$ block after trains of action potentials at 3 Hz for 20 s. $\dot{V}_c$: $\dot{V}_{\max}$ of the first action potential of the train; $\dot{V}_t$: $\dot{V}_{\max}$ of the test response. Time: interval (s) between the last action potential of the train and the test response. First-order regressions of the slow component were fitted by the method of least squares.

Table 4 Duration of action potential at 50% (APD₅₀) and 90% (APD₉₀) of repolarization in absence and presence of prazosin 5×10^{-6} M at different frequencies of stimulation

Frequency of stimulation (Hz)	Control APD ₅₀	Control APD ₉₀	Prazosin APD ₅₀	Prazosin APD ₉₀
0.1	170 ± 10	199 ± 10	195 ± 12*	233 ± 14*
0.5	172 ± 9	202 ± 10	197 ± 9*	239 ± 11*
1	163 ± 9	195 ± 9	191 ± 13*	235 ± 13*
2	134 ± 5	166 ± 6	162 ± 10*	203 ± 11*
3	112 ± 3	145 ± 4	133 ± 6*	175 ± 7*

x ± s.e.mean, n = 6

*P < 0.01.

Figure 3 Relationship between the increment of the action potential duration values measured at 50% (APD₅₀, ○) and 90% (APD₉₀, ●) repolarization induced by prazosin (5×10^{-6} M) and the frequency of stimulation. The increment of action potential duration values was obtained from paired experiments. Each point represents the mean ± s.e.mean of six experiments.

quency-dependent V_{max} block occurred as a biexponential process for which the time constant of the slow component can be taken as the recovery time constant (τ_{re}). Figure 2 shows the recovery process of V_{max} . In order to ensure a high degree of V_{max} block, these experiments were performed in the presence of a high concentration of prazosin (10^{-5} M) and the duration of the conditioning train was increased to 20 s. Under control conditions, the τ_{re} was 19.6 ± 2.5 ms, whereas in the presence of prazosin the τ_{re} was prolonged to 24.4 ± 5.5 s ($P < 0.001$). The y-intercept of the recovery of V_{max} , which can be taken as the fraction of Na channels blocked (Valenzuela *et al.*, 1989), rose to a value of $26.1 \pm 4.1\%$. In another three muscles prazosin, 5×10^{-6} M, prolonged the τ_{re} to a similar extent (24.4 ± 5.3 s, $P > 0.05$). These results indicated that prazosin can be considered as a slow kinetics Na channel blocker, i.e. it exhibits class Ic antiarrhythmic actions.

Effects of prazosin on APD at different frequencies

The lengthening of the ventricular action potential produced by 5×10^{-6} M prazosin was studied in six papillary muscles driven at various frequencies of stimulation. The basic driving rate was changed at 5 min intervals from 0.1 to 3 Hz. In the absence of prazosin an increase in the frequency of stimulation progressively shortened both the APD₅₀ and APD₉₀ values. Prazosin significantly prolonged the APD₅₀ and APD₉₀ values ($P < 0.01$) at all driving rates over control values (Table 4). However, as is shown in Figure 3, when the

Figure 4 Effect of prazosin 5×10^{-6} M on the relationship between V_{max} and the resting membrane potential at which the action potential is generated (i.e., membrane responsiveness). Ordinate scale: normalized V_{max} values ($V s^{-1}$). Abscissa scale: membrane potential (mV). Controls (●), prazosin (○).

results were expressed as a percentage change, the prolongation of the APD values was similar at all driving rates tested ($P > 0.05$). These results indicated that the effects of prazosin on APD₅₀ and APD₉₀ values were independent of the frequency of stimulation.

Effect on membrane responsiveness

The relationship between V_{max} and the membrane resting potential from which the action potential arises, i.e. membrane responsiveness, was studied in four papillary muscles driven at a basal rate of 0.01 Hz, so that the diastolic interval was much longer than the τ_{re} . The resting membrane potential was depolarized stepwise to approximately -60 mV by increasing the $[K]_o$ from 2 to 15 mM and the V_{max} value was measured when the resting membrane potential reached steady-state values at each $[K]_o$. Results of a typical experiment are shown in Figure 4. It can be observed that 5×10^{-6} M prazosin shifted the membrane responsiveness curve along the voltage axis in a hyperpolarizing direction by 4.1 ± 0.5 mV. These results indicated that the blockade of Na channels produced by prazosin increased at less negative potentials (voltage-dependent block).

Discussion

The results of the present study demonstrated that prazosin, a highly selective α_1 -adrenoceptor blocking drug, inhibited

$\dot{V}_{max}$, an indirect index of the I_{Na} , and prolonged the APD of the guinea-pig ventricular muscle fibres in a concentration-dependent manner. The inhibition of $\dot{V}_{max}$ appeared at concentrations at which prazosin had no effect on the resting membrane potential which suggested that the drug exhibits Na channel blocking properties, e.g., class I antiarrhythmic actions. These results confirmed and extended previous evidence that prazosin inhibited the $\dot{V}_{max}$ in rat (Northover, 1983), guinea-pig (Himmel *et al.*, 1991) and rabbit ventricular muscles (Dukes & Vaughan Williams, 1984; Tohse *et al.*, 1986) and dog Purkinje fibres (Rosen *et al.*, 1984).

The voltage- and frequency-dependent blockade of $\dot{V}_{max}$ produced by prazosin can be interpreted within the framework of the 'modulated receptor hypothesis' proposed to explain the interactions between local anaesthetic and antiarrhythmic drugs with Na channels (Hondegheem & Katzung, 1977; Tamargo *et al.*, 1992). According to this hypothesis, the affinity of the drug receptor differs in the three different receptor conformations (rested, activated and inactivated). In our experiments prazosin decreased only slightly, and sometimes increased, the $\dot{V}_{max}$ of the first beat of the train. These results indicated that prazosin has no affinity for rested channels at concentrations at which the drug produced frequency-dependent $\dot{V}_{max}$ block.

During repetitive stimulation, Na channels spend proportionately more time in the activated and/or inactivated state and the time for recovery during the diastole is shortened. Thus, if prazosin exhibited a higher affinity for the activated or inactivated state than for the resting state of the channel and prolonged the τ_{re} , an accumulation of blocked channels would be expected at increasing driving rates (i.e., frequency-dependent $\dot{V}_{max}$ block). At 3 Hz the onset rate value of the frequency-dependent $\dot{V}_{max}$ block produced by 5×10^{-6} M prazosin was $0.045 \pm 0.010/\text{AP}$, a value between that described for procainamide, an intermediate kinetics Na channel blocker, and flecainide, a slow kinetics blocker (Hondegheem & Katzung, 1977; Campbell, 1983; Tamargo *et al.*, 1992). In rabbit papillary muscles treated with $10 \mu\text{M}$ prazosin and driven at 1 Hz, Tohse *et al.* (1986) obtained a K value of $0.042 \pm 0.006/\text{AP}$, which is slower than that obtained in the present experiments at the same driving rate ($0.064 \pm 0.004/\text{AP}$). The discrepancy between these values can be attributed not only to the fact that the experiments were performed in different animal species but also at different drug concentrations, since the value of K increased with drug concentration (Courtney, 1987). As previously described for phentolamine (Northover, 1983), prazosin-induced $\dot{V}_{max}$ block increased when the extracellular K concentration was raised. Since the inactivated state of the Na channel predominates at depolarized membrane potentials, this result suggests that the drug exhibits a high affinity for the inactivated state of the Na channel.

The recovery kinetics of $\dot{V}_{max}$ from the frequency-dependent block is one of the most reliable parameters to subdivide Na channel blockers (Hondegheem & Katzung, 1977; Campbell, 1983; Tamargo *et al.*, 1992). In the present experiments prazosin prolonged the τ_{re} value to 24 s, suggesting that it binds with a slow dissociation constant to the inactivated Na channels. The τ_{re} value is similar to that described for encainide (20.3 s; Campbell, 1983) and thus, it may be considered as a member of the Na channel blockers with slow kinetics, i.e., class Ic antiarrhythmic drugs. This value, however, is significantly shorter than that described in rabbit papillary muscles (39.97 ± 1.2 s; Tohse *et al.*, 1986). Since the τ_{re} is independent of drug concentration and in both experimental designs its value was determined after applying a train of pulses until a steady-state $\dot{V}_{max}$ block was achieved, the discrepancy may result from the different species used (rabbit vs guinea-pig). The main repolarizing current in rabbit ventricular muscle fibres is the transient outward current, I_{to} (Giles & Imaizumi, 1988), which is not present in guinea-pig ventricular cells, where the delayed rectifier K current (I_K) is the main determinant for repolarization (Matsuura *et al.*,

1987). Because the I_{to} is rapidly activated (Giles & Imaizumi, 1988), the $\dot{V}_{max}$ observed in rabbit papillary muscles may reflect not only changes of the I_{Na} , but also of the I_{to} . In contrast, since I_K activates only after several hundred milliseconds (Matsuura *et al.*, 1987), this current would possibly not interfere with the determination of the $\dot{V}_{max}$ values.

The most characteristic effect of prazosin was a decrease in the slopes of phases 2 and 3 of repolarization that prolonged the APD₅₀ and APD₉₀ values. This effect was accompanied by a parallel prolongation of the ERP, and thus, the ERP/APD₉₀ ratio remained unchanged. These results are consistent with those previously described with prazosin in rat (Northover, 1983), guinea-pig ventricular muscle (Himmel *et al.*, 1991), rabbit (Dukes & Vaughan Williams, 1984; Tohse *et al.*, 1986) and dog Purkinje fibres (Rosen *et al.*, 1984), and suggest that prazosin may also exhibit class III antiarrhythmic actions according to Vaughan Williams' classification (1984). Although this paper is not concerned with the ionic mechanisms that determine the prazosin effect on repolarization, the prolongation of the APD can be related to an increase in the slowly inactivating Na and the inward L-type Ca currents (I_{Ca}) and/or to a decrease in outward K currents. The former possibility can be excluded since inhibition of inward Na currents would shorten, but not lengthen, the APD. Moreover, at concentrations at which prazosin lengthened the APD it had no effect on the slowly inactivating Na channels (Ferrier & Carmeliet, 1990). Thus, the most likely explanation for the prolongation of the APD would be an inhibition of the I_K (Ferrier & Carmeliet, 1990). Since stimulation of α_1 -adrenoceptor agonists also prolonged the APD in papillary muscles, it seems unlikely that the prolongation of the APD induced by prazosin could be related to the blockade of α_1 -adrenoceptors (Dukes & Vaughan Williams, 1984).

It has been shown that the ability of most class III antiarrhythmic drugs to prolong the APD is diminished at fast heart rates and augmented by bradycardia, i.e. they exhibited reverse frequency-dependence (Hondegheem & Snyders, 1990). In the present experiments, prazosin prolonged the APD to a similar extent at all stimulations tested. Thus, prazosin as previously described with amiodarone (Hondegheem & Snyders, 1990; Nattel, 1991) can be considered as a class III drug without reverse frequency-dependence. A homogeneous prolongation of the APD reducing the dispersion of ventricular refractoriness can explain the effectiveness of prazosin against ischaemia- and reperfusion-induced ventricular arrhythmias (Sheridan *et al.*, 1980; Davey, 1980).

Prazosin plasma levels present a marked intersubject-variability, but in patients with chronic heart failure, peak plasma concentrations after 1 and 4 mg of prazosin averaged 23 ± 10.5 and $254 \pm 48 \text{ ng ml}^{-1}$ (Wood *et al.*, 1976; Silke *et al.*, 1981). These levels are higher than those used in the present experiments and suggests that possibly its antiarrhythmic properties may be unrelated to its specific α_1 -adrenoceptor blocking properties. In fact, it has been proposed that prazosin might have antiarrhythmic efficacy in the settings in which sympathetic activity is not a prominent factor in the induction of the arrhythmia (Dukes & Vaughan Williams, 1984; Ferrier & Carmeliet, 1990).

In conclusion, in guinea-pig papillary muscles prazosin inhibited the $\dot{V}_{max}$ and lengthened the duration of the action potentials, thus exhibiting both class I and class III antiarrhythmic actions, respectively, which were possibly unrelated to blockade of myocardial α -adrenoceptors.

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