Br. J. Pharmacol. (1988), **95**, 1039–1046

Electrophysiological mechanism for the antiarrhythmic action of propafenone: a comparison with mexiletine

Sandra Amerini, *Roberto Bernabei, *Pierugo Carbonin, Elisabetta Cerbai, [1]Alessandro Mugelli & *Marco Pahor

Department of Pharmacology, University of Florence, Florence and *Gerontology Division, Catholic University, Rome, Italy

1 The antiarrhythmic potency of propafenone was evaluated in the guinea-pig isolated heart; arrhythmias were induced with (a) digitalis intoxication and (b) hypoxia followed by reoxygenation.

2 Propafenone, 0.5 μM, was found to be the minimal but effective antiarrhythmic concentration. The antiarrhythmic activity of propafenone developed slower than that of 10 μM mexiletine, which was the lowest effective concentration under the same experimental conditions.

3 The electrophysiological effects of propafenone were then studied on sheep cardiac Purkinje fibres (manifesting oscillatory afterpotentials and triggered automaticity induced by barium or strophanthidin) and compared with those of 10 μM mexiletine.

4 Both 0.5 μM propafenone and 10 μM mexiletine consistently blocked triggered activity in sheep Purkinje fibres. The onset of the effect of propafenone was slower than that of mexiletine.

5 Unlike mexiletine, propafenone did not reduce the amplitude of oscillatory afterpotentials.

6 In contrast, propafenone significantly reduced $\dot{V}_{max}$ in barium- and strophanthidin-treated preparations.

7 It is concluded that the antiarrhythmic action of propafenone on digitalis- and reoxygenation-induced arrhythmias is probably due to an electrophysiological mechanism different from that of mexiletine. Mexiletine, by reducing the amplitude of oscillatory afterpotentials, prevents the attainment of the threshold; propafenone, by reducing the excitability of the cell, increases the threshold and consequently an oscillatory afterpotential of the same amplitude will not generate arrhythmias.

Introduction

The antiarrhythmic action of class I antiarrhythmic agents is generally referred to as their ability to reduce the fast sodium current, an effect which is simply revealed by the reduction of the maximum rate of depolarization ($\dot{V}_{max}$) (Vaughan Williams 1984). However, mexiletine, a class Ib antiarrhythmic agent, has been reported to exert its antiarrhythmic action on digitalis-, reperfusion- and reoxygenation-induced arrhythmias by selectively reducing oscillatory afterpotential amplitude (Amerini *et al.*, 1985a).

Oscillatory afterpotentials (delayed afterdepolarizations) are thought to be the possible electrophysiological stimulus responsible for the genesis of digitalis-, reperfusion- and reoxygenation-arrhythmias (Ferrier, 1977; Corr & Witkowsky, 1983; Manning & Hearse, 1984; Amerini *et al.*, 1985a).

Propafenone is an antiarrhythmic drug which has been shown to be effective in the treatment of supraventricular and ventricular arrhythmias (Connolly *et al.*, 1983; Chilson, *et al.*, 1985). Its pharmacological properties and clinical indications have been recently reviewed (Karaguezian *et al.*, 1985).

Microelectrode studies of isolated cardiac tissue have shown that propafenone decreases the maximum rate of depolarization of phase 0 of the action potential, without changing the resting membrane potential, in both atrial and ventricular muscle fibres (Ledda *et al.*, 1981; Kohlhardt, 1983; Tamargo

[1] Author for correspondence; present address: Institute of Pharmacology, University of Ferrara, Via Fossato di Mortara 64/b, Ferrara, Italy.

& Delgado, 1985). Propafenone also reduces the amplitude of delayed afterdepolarizations induced by ouabain in Purkinje fibres and ventricular muscle (Tamargo & Delgado, 1985). Finally propafenone shortens the effective refractory period (Ledda *et al.*, 1981; Tamargo & Delgado, 1985), exerts a β-adrenoceptor blocking action (Ledda *et al.*, 1981), and has calcium antagonistic activity (Ledda *et al.*, 1981; Delgado *et al.*, 1984).

We thought that it would be interesting to evaluate the antiarrythmic potency of propafenone in digitalis- and reoxygenation-induced arrhythmias that possibly share a common electrophysiological mechanism (Amerini *et al.*, 1985a). In an attempt to clarify the electrophysiological mechanism of its antiarrhythmic action, we evaluated the effect of propafenone on the transmembrane potential properties of Purkinje fibres exposed to barium or strophanthidin and manifesting oscillatory afterpotentials and triggered activity (Amerini *et al.*, 1985a,b). We, finally, compared the effects of propafenone with those of mexiletine under the same experimental conditions.

The two major aims of the study were: (1) to correlate the antiarrhythmic effect of propafenone with its main electrophysiological action; (2) to compare the electrophysiological profiles of antiarrhythmic concentrations of propafenone and mexiletine. Some of these results have been presented in abstract form (Cerbai *et al.*, 1987).

Methods

Studies in the isolated heart

Guinea-pigs (body weight 350–500 g) were injected with heparin, 100 u, and killed by a sharp blow at the base of the skull. The heart was immediately removed and mounted on a double-reservoir non-recirculating Langendorff apparatus perfused in a retrograde manner. Details of the technique have been described elsewhere (Carbonin *et al.*, 1981; Amerini *et al.*, 1985a). The hydrostatic aortic perfusion pressure was 8 kPa. The composition of the control medium was (mM): NaCl 117, KCl 4.6, $CaCl_2$ 2, $NaHCO_3$ 20, NaH_2PO_4 0.8, $MgCl_2$ 1 and glucose 5, equilibrated at 37°C with 95% O_2 and 5% CO_2. The CO_2 and O_2 partial pressure and the pH value of the perfusion fluid were monitored by means of a gas analyzer (Instrumentation Laboratory model 213).

Epicardial electrograms were recorded by means of an atraumatic electrode connected to an amplifier (E&M Instrument model V 1205). The left ventricular pressure was measured by inserting a 12 cm polyethylene catheter (0.5 mm diameter) into the left ventricle via the mitral valve. Left ventricular pressure and dP/dt were recorded by means of a pressure transducer (Statham P23) connected to a pressure amplifier (E&M Instrument model V 2203). All data were recorded on paper with an E&M Instrument model VR 12 Simultrace recorder. The coronary flow rate was measured by collecting the effluent.

Rhythm disturbances were subdivided into: (a) conduction disturbances (sinoatrial and atrioventricular blocks) and (b) ventricular tachyarrhythmias (VTAs) which include ventricular premature beats (VPBs), ventricular tachycardia (VT), and ventricular fibrillation (VF). A large and aberrant QRS complex and the absence of a preceding P wave identified VPBs. More than 5 consecutive VPBs were considered VT. Complete morphological irregularity of at least 10 complexes was considered VF.

After 20 min of control perfusion to obtain the stabilization of heart rate and ventricular function, the hearts in one group were exposed to hypoxia followed by reoxygenation and in a second group to perfusion with digitalis.

Hypoxia was produced by gassing the medium with a mixture of 95% N_2 plus 5% CO_2 (Po_2 <40 mmHg). During the hypoxic period the hearts were perfused with a glucose-free medium. After 15 min of hypoxia, the perfusion with the oxygenated medium was rapidly restored and maintained for 10 min (reoxygenation phase).

Digitalis intoxication was obtained by perfusing the heart with digoxin 1 μM for 30 min.

Electrophysiological studies

Sheep cardiac Purkinje fibres were excised from the ventricles and kept in oxygenated Tyrode solution until used. One strand was mounted in a tissue bath and superfused with Tyrode solution at a rate of 8 ml min^{-1}. The composition of the solution was (mM): NaCl 137, KCl 4, $NaHCO_3$ 11.9, NaH_2PO_4 0.42, $MgCl_2$ 0.5, $CaCl_2$ 2.7 and glucose 5. The concentration of $CaCl_2$ was changed in some experiments, as indicated. The Tyrode solution was equilibrated with 97% O_2 and 3% CO_2(pH 7.3–7.4).

The preparations were stimulated with rectangular pulses (0.5 to 1 ms in duration and 1.5 times the threshold) through bipolar silver electrodes electrically insulated except for the tip. Action potentials were recorded by means of two 3 M KCl-filled glass microelectrodes, one of which was inserted intracellularly and the other placed in the solution close to the preparation. Microelectrodes were coupled to two high-input impedance guard electrometer amplifiers (Bigongiari, Firenze). The action potential was displayed on a Tektronix model 5113 dual-beam

storage oscilloscope and recorded on an FM tape recorder (Racal 14 DS). The records were played back into a chart recorder (Gould Brush 2400). An automated analysis of action potential was performed, as previously described (Fusi *et al.*, 1984). Evaluation of the following parameters was carried out: action potential amplitude, overshoot, maximum diastolic potential, $\dot{V}_{max}$, action potential duration (APD_{-60} and APD_{90}).

Oscillatory afterpotentials (OAPs) were induced by exposing the preparations to low barium concentration or to strophanthidin, as described elsewhere (Mugelli *et al.*, 1983; Amerini *et al.*, 1985a,b). The drive stimulus was interrupted periodically (usually every min for 30 s) to assess the presence of OAP and triggered activity.

The drugs used in this study were chemically pure: strophanthidin (Sigma), digoxin (Boehringer-Biochemia-Robin), propafenone (Knoll), mexiletine (Boehringer-Ingelheim), $BaCl_2$.

Analysis of data

The analysis of data for significance was performed by means of Student's *t* test for paired data and of Fisher's exact test for the proportions. *P* values of <0.05 were considered significant.

Results

Effect of propafenone on digitalis-induced arrhythmias

Digoxin, 1 μM, induced ventricular tachyarrhythmias (VTAs) in 100% of the control hearts within 9 min. Propafenone, added to the perfusion medium when all the hearts exhibited digitalis-induced VTAs (i.e. after 9 min), was able to reduce the incidence of these VTAs. The lowest but significantly effective concentration proved to be 0.5 μM: this concentration, in fact, significantly reduced the incidence of VTAs after 18 min of perfusion. A lower concentration, 0.1 μM, was completely ineffective; 1 μM propafenone was already effective after 9 min of perfusion and completely abolished the VTAs induced by digoxin after 18 min (Figure 1). The antiarrhythmic action of propafenone was delayed compared with mexiletine. Mexiletine 10 μM was found to be the lowest effective concentration in the same experimental conditions (Amerini *et al.*, 1985a) and 10 μM mexiletine promptly abolished digitalis-induced VTAs and the hearts returned to normal sinus rhythm within 1 min (Amerini *et al.*, 1985a); however, with propafenone a similar effect was obtained after 9 to 18 min of perfusion (present results).

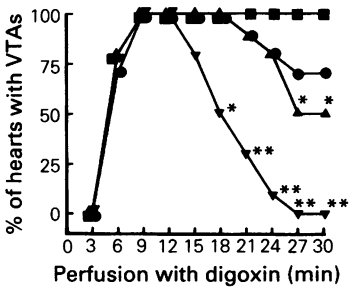

Figure 1 Percentage of hearts which developed ventricular tachyarrhythmias (VTAs) during perfusion with digoxin 1 μM of the guinea-pig isolated heart; (■): perfusion with digoxin (control); (●), (▲), and (▼): perfusion with digoxin plus propafenone 0.1, 0.5 or 1 μM respectively. $n = 10$ for each point. Propafenone was added to the medium after 9 min of perfusion with digoxin. $^*P < 0.05$; $^{**}P < 0.01$ vs control.

Effect of propafenone on reoxygenation-induced arrhythmias

Perfusion with a hypoxic glucose-free medium caused, as expected, a rapid decrease in ventricular rate (Carbonin *et al.*, 1981; Amerini *et al.*, 1985a). Reoxygenation was associated with the sudden development of ventricular tachyarrhythmias in 75–92% of the control hearts (Figure 2). The lowest effective concentration of propafenone on digitalis-induced VTAs (0.5 μM) was also effective on the VTAs occurring during the reoxygenation phase. The drug was added to the perfusion medium at the beginning of reoxygenation. Propafenone reduced the incidence of reoxygenation-induced VTAs, the

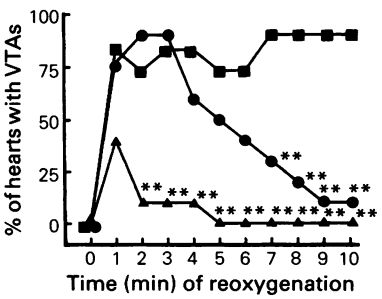

Figure 2 Percentage of hearts which developed ventricular tachyarrhythmias (VTAs) during reoxygenation of the guinea-pig isolated heart; (■, $n = 12$): control; (●, $n = 11$): perfusion with propafenone 0.5 μM, (▲) (data reported by Amerini *et al.*, 1985a): perfusion with mexiletine 10 μM ($n = 10$). $^*P < 0.05$, $^{**}P < 0.01$ vs control.

antiarrhythmic effect being statistically significant after 7 min of perfusion (Figure 2). The effect of propafenone was again delayed compared with mexiletine, as shown in Figure 2. Mexiletine (10 μM), in fact, significantly reduced reoxygenation-induced VTAs after only 2 min of perfusion (Amerini *et al.*, 1985a).

Effect of propafenone on Purkinje fibres manifesting oscillatory afterpotentials (OAPs) and triggered activity

The effects of propafenone on normal Purkinje fibres have been described previously (Ledda *et al.*, 1981; Dukes & Vaughan Williams, 1984; Tamargo & Delgado, 1985). We consequently studied only the effects of propafenone on preparations manifesting OAP and triggered activity.

Superfusion of Purkinje fibres with low barium concentrations or with strophanthidin typically causes the appearance of oscillatory afterpotentials and of subsequent triggered activity (Amerini *et al.*, 1985a).

Propafenone (0.5 μM) consistently blocked the triggered activity induced by barium or by strophanthidin. Figure 3 shows one such experiment: strophanthidin (0.3 μM) induced triggered activity which sometimes lasted for a long time, Figure 3a shows the self-sustained rhythm 1–2 min after its start. Propafenone (0.5 μM) was able to block such spontaneous activity in 6 min (Figure 3b). Typically the rhythm ceases with subthreshold damped oscillations. Similar results were obtained in barium-treated Purkinje fibres. The lower records (b) of Figure 4 show a representative experiment of a series of 4, in which similar results were obtained. In the presence of barium (10 μM) and high $[Ca^{2+}]_o$ (7.2 mM), a triggered rhythm ensued when stimulation was interrupted (Figure 4, controls a and b). Propafenone (0.5 μM) progressively blocked such activity within 8 min. The interruption of stimulation was now followed by a subthreshold oscillatory

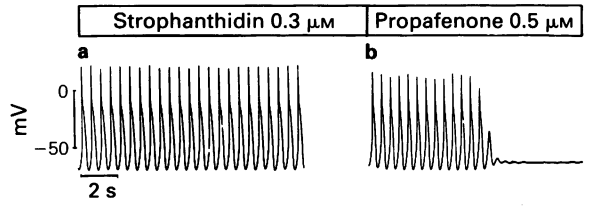

Figure 3 Effect of propafenone (b) on strophanthidin-induced triggered automaticity: (a) shows the automatic rhythm ensuing after the interruption of stimulation in the presence of strophanthidin; (b) was recorded 6 min after addition of propafenone.

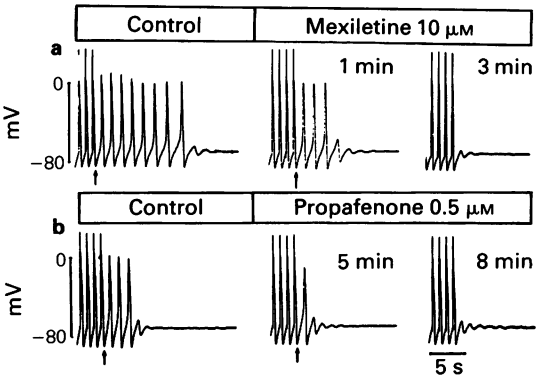

Figure 4 Comparison between the effects of mexiletine (a) and propafenone (b) on barium-induced triggered activity. Each panel shows the last 3–4 driven action potentials and the electrical activity during the interruption of the stimulation. Arrows indicate the first non-driven action potential.

afterpotential. The effect of mexiletine (10 μM) was practically indistinguishable from that of propafenone except for a faster onset. The concentration of mexiletine was chosen on the basis of our previous results (Amerini *et al.*, 1985a), showing that 10 μM mexiletine was the lowest fully antiarrhythmic concentration in digitalis-, reperfusion- and reoxygenation-induced arrhythmias in the isolated guinea-pig heart.

Oscillatory afterpotentials increase in amplitude as the cycle length of the previous drive decreases (Ferrier, 1977). Eventually, the threshold is reached

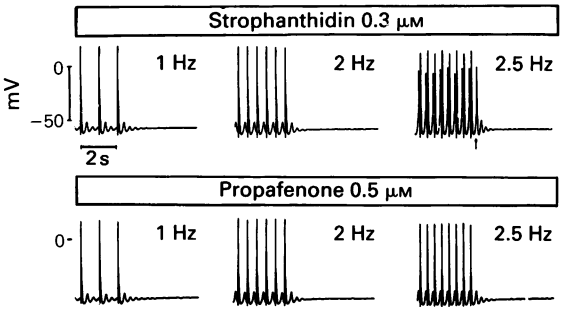

Figure 5 Effect of propafenone on strophanthidin-induced oscillatory afterpotentials and triggered extra beats. Each panel shows intracellular recording when the preparation is driven at different rates and during the subsequent interruption of the stimulation. The arrow indicates the triggered action potential recorded after the interruption of stimulation.

and a spontaneous beat occurs. Such behaviour is shown in the control records of Figure 5 and 6 (top traces). In the presence of strophanthidin every driven action potential is followed by a clearcut OAP which, in its turn, is followed by smaller ones. This is even more evident when the stimulation is interrupted. Their amplitude is clearly increased and time to peak is shortened by increasing the driving rate from 1 to 2 Hz. When the preparation is driven at 2.5 Hz, the oscillatory afterpotential reaches the threshold and every driven action potential is followed by a spontaneous one; these features are characteristic of digitalis-induced bigeminy (Kieval *et al.*, 1986). The arrows indicate the spontaneous action potentials during the interruption of the stimulation; since the following OAP does not reach the threshold, the rhythm ceases. Propafenone (0.5 μM) is clearly able to block the bigeminal rhythm (Figure 5 lower traces, right hand panel). However, it does not seem to reduce the amplitude of the oscillatory afterpotentials at 1 or 2 Hz. Figure 6 shows, for comparison, the effect of mexiletine (10 μM). Mexiletine, like propafenone, was able to block the triggered extra beats at 2.5 Hz, but, unlike propafenone, mexiletine clearly reduced the OAP amplitude in preparations driven at 1 or 2 Hz.

To gain further insight into the electrophysiological mechanisms of the antiarrhythmic action of propafenone, we studied its effect on action potential characteristics and on subthreshold OAP amplitude of Purkinje fibres exposed to barium or to strophanthidin.

Figure 7 shows one such experiment in the presence of strophanthidin. It is apparent that 0.5 and 1 μM propafenone did not modify the oscillatory

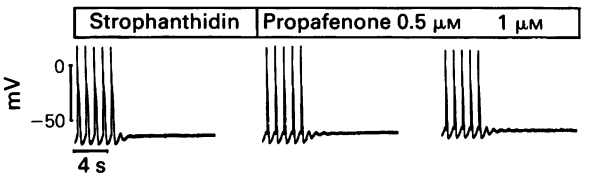

Figure 7 Effect of propafenone on strophanthidin-induced subthreshold oscillatory afterpotentials. Each panel shows the last 5 driven action potentials and the electrical activity during the interruption of stimulation.

afterpotential amplitude. However, these concentrations were fully active in reoxygenation- and digitalis-induced arrhythmias in the guinea-pig isolated heart, and blocked triggered activity induced in Purkinje fibres. Figure 8 summarizes the effects of propafenone (0.5 μM) on action potential characteristics. In 6 experiments in the presence of strophanthidin, propafenone (0.5 μM) significantly affected only $\dot{V}_{max}$, while OAP amplitude and action potential duration were not modified. Similar results were also obtained in 7 preparations manifesting OAP after exposure to barium (not shown).

Discussion

The present results demonstrate that: (1) in guinea-pig isolated heart propafenone exerts antiarrhythmic

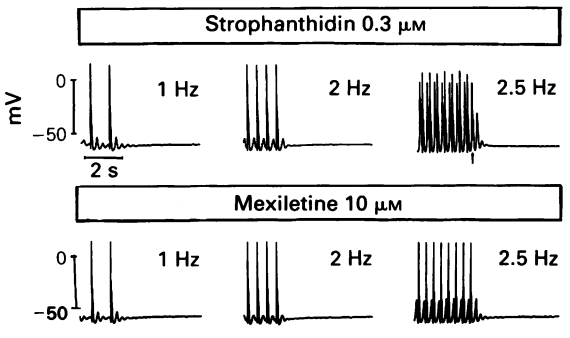

Figure 6 Effect of mexiletine on strophanthidin-induced oscillatory afterpotentials and triggered extra beats. Each panel is an intracellular recording when the preparation is being driven at different rates and during the subsequent interruption of stimulation. The arrow indicates the triggered action potential recorded after the interruption of stimulation.

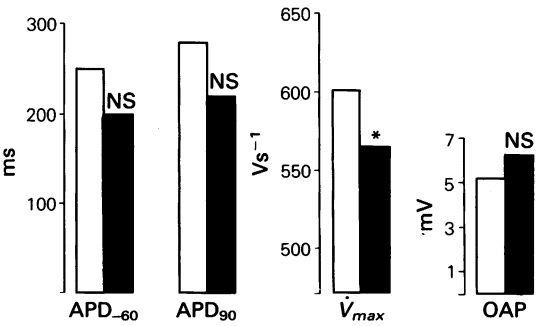

Figure 8 Effects of propafenone on action potential duration at −60 mV (APD_{-60}) and at 90% of repolarization (APd_{90})), $\dot{V}_{max}$ and oscillatory afterpotential (OAP) amplitude in Purkinje fibres superfused with strophanthidin. Open columns = control; solid columns = propafenone 0.5 μM ($n = 6$). *$P < 0.01$; NS = not significant.

activity on both digitalis- and reoxygenation-induced arrhythmias, the lowest effective concentration being 0.5 μM; (2) 0.5 μM propafenone, like 10 μM mexiletine, abolishes triggered activity in Purkinje fibres exposed to barium or strophanthidin; (3) propafenone and mexiletine, at the concentrations which abolish triggering, affect $\dot{V}_{max}$ and OAP amplitude differently: propafenone significantly reduces $\dot{V}_{max}$ but not OAP amplitude, mexiletine significantly reduces OAP amplitude but not $\dot{V}_{max}$.

The antiarrhythmic action of class I drugs is generally attributed to their interference with the Na^+ channels, resulting in a depression of the fast Na^+ current. We are aware that the effects we observed in driven Purkinje fibres cannot be extrapolated to the isolated heart. Both mexiletine and propafenone reduce the $\dot{V}_{max}$ of the cardiac action potential in a use- and voltage-dependent way (Kohlhardt & Seifert, 1980; 1983; Hohnloser *et al.*, 1982; Campbell, 1983).

The arrhythmias suppressed in the guinea-pig isolated heart by propafenone (present results) and by mexiletine (Amerini *et al.*, 1985a) were at high frequency (about 5 Hz for the reoxygenation-induced arrhythmias). Hypoxia (Moréna *et al.*, 1980) and digitalis (Vassalle & Musso, 1976) are also known to cause a partial depolarization of myocardial cells. Nevertheless, our results strongly support a different electrophysiological mechanism for the antiarrhythmic action of mexiletine and propafenone. In fact, at the concentrations which are significantly antiarrhythmic in the guinea-pig isolated heart, the two drugs clearly exert different electrophysiological effects. While both mexiletine and propafenone suppress triggered activity in barium- and strophanthidin-treated Purkinje fibres, only mexiletine (Amerini *et al.*, 1985a; present results) affects the OAP amplitude. Propafenone (0.5–1 μM), under the same experimental conditions, did not affect the OAP amplitude but significantly reduced $\dot{V}_{max}$, which in its turn was not reduced by mexiletine (Amerini *et al.*, 1985a).

Furthermore, on both digitalis- and reoxygenation-induced arrhythmias, the antiarrhythmic action of mexiletine occurred more rapidly than that of propafenone (Figures 1 and 2) and the suppression of triggered activity in Purkinje fibres was faster with mexiletine than with propafenone. The possibility cannot be excluded that the slower onset of action of propafenone depends on the fact that it does not directly affect the OAP amplitude.

Oscillatory afterpotentials are transient depolarizations that follow complete repolarization of a normal action potential. They are due to a transient inward oscillatory current (I_{os}), that is enhanced by all the interventions which increase intracellular calcium (Vassalle & Mugelli, 1981).

The mechanism underlying the I_{os} has not been established and the exact role of Ca^{2+} is still debated (Noble, 1984; Lin *et al.*, 1986; Kass *et al.*, 1978a). One possibility is that repolarization liberates calcium from an intracellular store (Ferrier, 1976), possibly the sarcoplasmic reticulum (Kass *et al.*, 1978a). Once freed, calcium would activate a non specific cation channel (Kass *et al.*, 1978a,b; Colquhoun *et al.*, 1981) which carries the transient inward oscillatory current. An alternative possibility is that calcium released inside the cell may stimulate the Na^+-Ca^{2+} exchanger. The process is electrogenic, since it extrudes calcium ions in exchange for an electrically greater quantity of sodium ions (Noble, 1984). This hypothesis is supported by recent voltage clamp data (Lin *et al.*, 1986), by the observation that the transient inward oscillatory current disappears in Na^+-free solution (Eisner *et al.*, 1983) and that its reduction by lidocaine is associated with a reduction in intracellular sodium activity (Eisner *et al.*, 1983; Sheu & Lederer, 1985). Consequently, any agent which reduces sodium entry should reduce oscillatory afterpotential amplitude, at least indirectly.

However, our data show that, at least acutely, agents which certainly interfere with the sodium channels, such as propafenone and mexiletine, have different effects on the oscillatory afterpotentials. We do not know the reason why mexiletine reduces OAP amplitude without affecting $\dot{V}_{max}$. We could not completely exclude the possibility that an effect on inward sodium current could contribute to the effect of mexiletine on OAP (Amerini *et al.*, 1985a), since the relationship between $\dot{V}_{max}$ measurements and fast sodium current is controversial (Cohen *et al.*, 1984). But certainly propafenone reduces $\dot{V}_{max}$ without affecting OAP amplitude at the concentration and under the conditions at which it abolishes arrhythmias and triggered activity that are likely to be due to OAP. It is worth noting that the two drugs exert different effects on action potential duration; mexiletine (10 μM) significantly reduces APD (Amerini *et al.*, 1985a), while propafenone only slightly reduces it as previously observed (Ledda *et al.*, 1981). Other studies (Dukes & Vaughan Williams, 1984) reported a slight lengthening of action potential duration in rabbit Purkinje fibres for comparable propafenone concentrations; the reason for this discrepancy is not obvious. However, on the whole, the experimental data demonstrate that the effects of mexiletine and propafenone on action potential duration are certainly different if not opposite. It is known that action potential duration strongly influences OAP amplitude (Henning & Wit, 1984), in agreement with voltage clamp data (Vassalle & Mugelli, 1981). It might therefore be suggested that the different effects caused by mexiletine and propafenone on action potential duration may explain their different effects on oscillatory after-

potential amplitude. However, a voltage clamp study is required to clarify the reason for these differences.

In conclusion, regardless of the exact mechanisms by which mexiletine reduces or propafenone does not reduce OAP amplitude, we can say that their antiarrhythmic action on those arrhythmias in which OAPs play a role, such as digitalis-, reoxygenation- and reperfusion-induced arrhythmias, is probably due to different electrophysiological mechanisms. In other words, mexiletine, by reducing OAP amplitude, prevents the attainment of the threshold and consequently the triggered rhythm will not occur. Propafenone, on the other hand, by reducing the excitability of the cell, increases the threshold; consequently an OAP of the same amplitude will not generate an automatic rhythm.

This work was supported by a grant from MPI 60%, University of Florence.

References

AMERINI, S., CARBONIN, P., CERBAI, E., GIOTTI, A., MUGELLI, A. & PAHOR, M. (1985a). Electrophysiological mechanisms for the antiarrhythmic action of mexiletine on digitalis- reperfusion- and reoxygenation-induced arrhythmias. *Br. J. Pharmacol.*, **86**, 805–815.

AMERINI, S., GIOTTI, A. & MUGELLI, A. (1985b). Effect of verapamil and diltiazem on calcium-dependent electrical activity in cardiac Purkinje fibres. *Br. J. Pharmacol.*, **85**, 89–96.

CAMPBELL, T.J. (1983). Resting and rate-dependent depression of maximum rate of depolarization ($\dot{V}_{max}$) in guinea-pig ventricular action potentials by mexiletine, dysopyramide and encainide. *J. Cardiovasc. Pharmacol.*, **5**, 291–296.

CARBONIN, P.U., DI GENNARO, M., VALLE, R. & WEISZ, A.M. (1981). Inhibitory effect of anoxia on reperfusion- and digitalis-induced ventricular tachyarrhythmias. *Am. J. Physiol.*, **240**, H730–H737.

CERBAI, E., PAHOR, M., CARBONIN, P.U., BERNABEI, R. & MUGELLI, A. (1987). Possible electrophysiological mechanism for the antiarrhythmic action of propafenone. *J. Mol. Cell. Cardiol.*, **19**, S11.

CHILSON, D.A., HEGER, J.J., ZIPES, D.P., BROWNE, K.F. & PRYSTOWSKY, E.N. (1985). Electrophysiological effects and clinical efficacy of oral propafenone therapy in patients with ventricular tachycardia. *J. Am. Coll. Cardiol.*, **5**, 1407–1413.

COHEN, C.J., BEAN, B.P. & TSIEN, R.W. (1984). Maximal upstroke velocity as an index of available sodium conductance. Comparison of maximal upstroke velocity and voltage clamp measurements of sodium current in rabbit Purkinje fibers. *Circ. Res.*, **54**, 636–651.

COLQUHOUN, D., NEHER, E., REUTER, H. & STEVENS, C.F. (1981). Inward current channels activated by intracellular Ca in cultured cardiac cells. *Nature*, **294**, 752–754.

CONNOLLY, S.J., KATES, R.E., LEBSACK, C.S., HARRISON, D.C. & WINKLE, R.A. (1983). Clinical pharmacology of propafenone. *Circ.*, **3**, 589–596.

CORR, P.B., WITKOWSKI, F.X. (1983). Potential electrophysiological mechanisms responsible for dysrhythmias associated with reperfusion of the ischemic myocardium. *Circ.*, **68**, I16–I24.

DELGADO, C., TAMARGO, J. & TEJERINA, T. (1984). The electrophysiological effects of propafenone on guinea-pig papillary muscles. *Br. J. Pharmacol.*, **81**, 171P.

DUKES, I.D. & VAUGHAN WILLIAMS, E.M. (1984). The multiple modes of action of propafenone. *Eur. Heart J.*, **5**, 115–125.

EISNER, D.A., LEDERER, W.S. & SHEU, S-S. (1983). The role of intracellular sodium activity in the antiarrhythmic action of local anesthetics in sheep Purkinje fibres. *J. Physiol.*, **340**, 239–257.

FERRIER, G.R. (1976). The effects of tension on acetylstrophanthidin-induced transient depolarizations and aftercontractions in canine myocardial and Purkinje tissues. *Circ. Res.*, **38**, 156–162.

FERRIER, G.R. (1977). Digitalis arrhythmias: role of oscillatory afterpotentials. *Prog. Cardiovasc. Dis.*, **19**, 459–474.

FUSI, F., PIAZZESI, G., AMERINI, S., MUGELLI, A. & LIVI, S. (1984). A low-cost microcomputer system for automated analysis of intracellular cardiac action potentials. *J. Pharmacol. Methods*, **11**, 61–66.

HENNING, B. & WIT, A.L. (1984). The time course of repolarization affects delayed afterdepolarization amplitude in atrial fibers of the canine coronary sinus. *Circ. Res.*, **55**, 110–115.

HOHNLOSER, S., WEIRICH, J. & ANTONI, H. (1982). Effects of mexiletine on steady-state characteristics and recovery kinetics of $\dot{V}$max and conduction velocity in guinea pig myocardium. *J. Cardiovasc. Pharmacol.*, **4**, 232–239.

KARAGUEUZIAN, H.S., PETER, T.C. & MANDEL, W.J. (1985). Propafenone. In *New Drugs Annual: Cardiovascular Drugs* ed. Scriabine, A. Vol. 3, pp. 285–299. New York: Raven Press.

KASS, R.S., LEDERER, W.J., TSIEN, R.W. & WEINGART, R. (1978a). Role of calcium ions in transient inward current induced by strophanthidin in cardiac Purkinje fibres. *J. Physiol.*, **281**, 187–208.

KASS, R.S., TSIEN, R.W. & WEINGART, R. (1978b). Ionic basis of transient inward current induced by strophanthidin in sheep cardiac Purkinje fibres. *J. Physiol.*, **281**, 209–226.

KIEVAL, R.S., JOHNSON, N.J. & ROSEN, M.R. (1986). Triggered activity as a cause of bigeminy. *J. Am. Coll. Cardiol.*, **8**, 644–647.

KOHLHARDT, M. (1983). Basic electrophysiological actions of propafenone in heart muscle. In *Cardiac Arrhythmias.* ed. Schlepper, M. & Olsson, B. pp. 91–101. Berlin: Springer Verlag.

KOHLHARDT, M. & SEIFERT, C. (1980). Inhibition of $\dot{V}$max of the action potential by propafenone and its voltage-, time- and pH-dependence in mammalian ventricular myocardium. *Naunyn-Schmiedebergs Arch. Pharmacol.*, **315**, 55–62.

KOHLHARDT, M. & SEIFERT, C. (1983). Tonic and phasic I_{Na} blockade by antiarrhythmics. Different properties of drug binding to fast sodium channels as judged from $\dot{V}$max studies with propafenone and derivatives in mammalian ventricular myocardium. *Pflüegers Arch.*, **396**, 199–209.

LEDDA, F., MANTELLI, L., MANZINI, S., AMERINI, S. & MUGELLI, A. (1981). Electrophysiological and antiarrhythmic properties of propafenone in isolated cardiac preparations. *J. Cardiovasc. Pharmacol.*, **3**, 1162–1163.

LIN, C.-I., KOTAKE, H. & VASSALLE, M. (1986). On the mechanism underlying the oscillatory current in cardiac Purkinje fibers. *J. Cardiovasc. Pharmacol.*, **8**, 906–914.

MANNING, A.S. & HEARSE, J. (1984). Reperfusion-induced arrhythmias: mechanism and prevention. *J. Mol. Cell. Cardiol.*, **16**, 497–518.

MORÉNA, H., JANSE, M.J., FIOLET, J.W.T., KRIEGER, W.J.G., CRIJNS, H. & DURRER, D. (1980). Comparison of the effects of regional ischemia, hypoxia, hyperkalemia, and acidosis on intracellular and extracellular and metabolism in the isolated porcine heart. *Circ. Res.*, **46**, 634–646.

MUGELLI, A., AMERINI, S., PIAZZESI, G. & GIOTTI, A. (1983). Barium-induced spontaneous activity in sheep cardiac Purkinje fibers. *J. Mol. Cell. Cardiol.*, **15**, 697–712.

NOBLE, D. (1984). The surprising heart: a review of recent progress in cardiac electrophysiology. *J. Physiol.*, **353**, 1–50.

SHEU, S-S. & LEDERER, W.J. (1985). Lidocaine's negative inotropic and antiarrhythmic actions. *Circ. Res.*, **57**, 578–590.

TAMARGO, J. & DELGADO, C. (1985). Electrophysiological effects of propafenone on isolated guinea-pig ventricular muscle and sheep Purkinje fibres. *Eur. J. Pharmacol.*, **118**, 331–340.

VASSALLE, M. & MUGELLI, A. (1981). An oscillatory current in sheep cardiac Purkinje fibers. *Circ. Res.*, **48**, 618–631.

VASSALLE, M. & MUSSO, E. (1976). On the mechanisms underlying digitalis toxicity in cardiac Purkinje fibers. *Rec. Adv. Stud. Cardiac Struct. Metab.*, **9**, 355–376.

VAUGHAN WILLIAMS, E.M. (1984). A classification of antiarrhythmic action reassessed after a decade of new drugs. *J. Clin. Pharmacol.*, **24**, 129–147.

(Received January 5, 1988
Revised May 4, 1988
Accepted July 8, 1988)