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# Cardiac effects of quinidine on guinea-pig isolated perfused hearts after *in vivo* quinidine pretreatment

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**1** Experimental and clinical studies suggest that class I and class III antiarrhythmic drugs may be subject to pharmacological tolerance during long term treatment, leading to loss of therapeutic effectiveness.

**2** The aim of this study was to ascertain whether prolonged *in vivo* treatment with the Class Ia agent quinidine can modify cardiac (electrical and mechanical) responses to the drug.

**3** A group of guinea-pigs ($n=7$) were treated intraperitoneally (q.d.) for 6 days with 75 mg $kg^{-1}$ quinidine sulphate. Preliminary pharmacokinetic experiments indicated that this dose could attain plasma concentrations similar to those that are therapeutic in man (2–5 mg $l^{-1}$). A control group ($n=7$) received a saline solution for the same period.

**4** Twenty-four hours after the last administration hearts were removed and retrogradely perfused at constant flow (stimulation frequency: 2.5 Hz). The following parameters were measured: maximal derivative of intraventricular pressure ($dP/dt_{max}$); coronary perfusion pressure (Cp); PR, QRS and JT intervals, on surface ECG. The effects of quinidine on these parameters were measured at different concentrations (2, 4, 8, 12, 16, 20 $\mu$M) and compared in the two experimental groups.

**5** In the control group quinidine decreased in a dose-dependent manner dP/dt and increased PR and QRS intervals. JT interval was increased at the lowest concentrations and decreased at the highest (biphasic effect). Cp did not change significantly.

**6** In the pretreated group quinidine qualitatively produced the same effects on dP/dt and ECG intervals as in control group. Also the magnitude of these effects was not significantly different between the two groups. In contrast with findings in control experiments, Cp was significantly decreased by increasing quinidine concentration. Mean baseline Cp was higher in pretreated than in the control group (though not significantly, $P=0.072$) and quinidine addition abolished this difference. Thus, it is suggested that quinidine withdrawal induced a rebound increase in coronary tone, due to the unmasking of vasoconstrictor homeostatic mechanisms elicited by the *in vivo* vasodilating effect of the drug.

**7** In conclusion, our data do not support the possibility that tolerance ensues during long term quinidine treatment, at least as far as electrophysiological and contractility effects are concerned. Further experimental work is needed to explain the appearance of a coronary vasodilating effect in pretreated hearts.

**Keywords:** Antiarrhythmic agents; quinidine; tolerance

## Introduction

In recent years several studies (Duff *et al*., 1985; Kennedy *et al*., 1989; Capucci *et al*., 1990; Le Coz *et al*., 1992; Boriani *et al*., 1993) have suggested that the efficacy or the electrocardiographic effects of antiarrhythmic drugs may decrease under chronic treatment. Capucci *et al*. (1990) showed that the minimal effective concentration of propafenone and its active metabolite, 5-OH-propafenone, were substantially higher during chronic treatment when compared to acute treatment. Another study by the same group (Boriani *et al*., 1993) correlated plasma concentrations of flecainide with QRS changes after single and long-term administration and found that the slope of the linear correlation was steeper at the first dose than after multiple dosing. Interestingly, a class III drug, sotalol, has also been found (Le Coz *et al*., 1992) to produce a QTc prolongation during repeated oral administration, which was, on average 4.1% less than the value predicted from single administration. In the study by Kennedy *et al*. (1989), the long-term antiarrhythmic efficacy of moricizine was irreversibly lost in 14% of patients, despite persistence of plasma levels within the therapeutic range and therapeutic effectiveness was restored by increasing the drug dose. The same observation was made by Duff *et al*. (1985), who found that 2 of 17 patients did not respond to chronic quinidine, although plasma concentrations were equal to those which had been effective during the acute intravenous test. In all these therapeutic studies it is unclear whether loss or decrease in therapeutic effectiveness was due to spontaneous variability of cardiac arrhythmias or to a true pharmacological tolerance. Indeed, other clinical investigations (McCollam *et al*., 1989; Salerno *et al*., 1990) did not find any decline in the therapeutic efficacy of class I antiarrhythmic drugs during long term treatment. A molecular basis for the tolerance hypothesis has recently been provided by an experimental study in rats (Taouis *et al*., 1991), which showed the development of up-regulation of cardiac sodium channels (dose-dependent and reversible upon drug withdrawal) over a 6-day treatment with the Na channel blocker, mexiletine. At present it is unknown whether these molecular changes are specifically related to this drug or are secondary to Na channel blockade *per se*. Furthermore, possible functional consequences of the cardiac effects of class I drugs have not yet been investigated. In order to verify the tolerance hypothesis at a pharmacodynamic level too, we studied the influence of prolonged quinidine administration to guinea-pigs on the *in vitro* quinidine effects on the isolated perfused heart. Quinidine was chosen as the prototype of class Ia agents with mixed Na channel- and K channel-blocking activities, because it permits the investigation of possible onset of tolerance on a wider spectrum of electrophysiological parameters.

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## Methods

### *Pharmacokinetic study*

A preliminary pharmacokinetic study was carried out in Dunkin-Hartley albino guinea-pigs to determine the quinidine dose necessary to produce pharmacologically active plasma concentrations. The time course of plasma concentrations was determined after i.p. administration of two different quinidine doses: 50 mg $kg^{-1}$ ($n=3$) and 100 mg $kg^{-1}$ ($n=3$). The animals were anaesthetized (urethane 2 g $kg^{-1}$, i.p., + atropine 0.05 mg $kg^{-1}$, i.p., every 20–40 min), the carotid artery was cannulated and blood was sampled at 5 min, 15 min, 30 min, 1 h, 1.5 h, 2 h, 3 h, 4 h and 6 h after quinidine administration. Blood was centrifuged and plasma was frozen at −20°C until the assay was performed. Quinidine was assayed by means of a specific and sensitive h.p.l.c. method with fluorimetric detection (Leroyer *et al*., 1982). In our laboratory the detection limit was 10 ng $ml^{-1}$ and the coefficient of variation at 1 mg $l^{-1}$ was 3.5%.

The following model-independent parameters were calculated: the peak concentration (Cmax), the 6 h concentration ($C_{6h}$), the area under the concentration-time curve ($AUC_{0-6\,h}$), the average concentration within the 6 h sampling interval ($=AUC_{0-6\,h}/6$). A monoexponential equation was used to fit the final decay of each curve ($C=C_O.e^{-k.t}$) and the corresponding final $t_{1/2}$ was calculated ($t_{1/2}=0.693/k$). The steady state minimum plasma concentration ($Cmin_{SS}$) expected following multiple drug administrations was extrapolated from the equation: $Cmin_{SS}=C_O.e^{-k.\tau}/(1-e^{k.\tau})$), where $\tau$ is the dosing interval (Gibaldi & Perrier, 1975), and $C_O$ and $k$ are the experimental parameters of the monoexponential equation.

### *Pharmacodynamic study*

Dunkin-Hartley albino guinea-pigs of either sex (body weight: 250–350 g) were treated q.d. intraperitoneally for 6 days with either saline solution (control group, $n=7$) or 75 mg $kg^{-1}$ quinidine sulphate (test group, $n=7$). At the end of the treatment period, the animals were killed by cervical dislocation 24 h after the last drug administration and the heart was rapidly removed and retrogradely perfused at constant flow rate (≈8 ml $g^{-1}$ tissue $min^{-1}$) with a peristaltic micropump (Gilson Minipuls 2 HP2/HF), as previously described (Padrini *et al*., 1992). The perfusion medium was a modified Krebs-Henseleit solution (mM: NaCl 118, KCl 4.7, $CaCl_2$ 2.5, $MgSO_4$ 1.2, $NaHCO_3$ 25, $KH_2PO_4$ 1.2, glucose 11.1 and Na pyruvate 2) bubbled with an $O_2$: $CO_2$ gas mixture (95%:5%) and maintained at 37°C (pH 7.4±0.01). Sinus node was excised and the hearts were driven at a frequency of 2.5 Hz, through platinum electrodes placed on the right atrium (stimulus strength = 1.5 times the threshold value; duration = 0.5 ms). A rubber balloon filled with water (filling pressure: 10 $cmH_2O$) and connected to a mechano-electrical transducer (M.A.R.B., P82) was inserted into the left ventricle to measure changes in intraventricular pressure. Heart contractility was measured as the maximal positive derivative of the left ventricle pressure ($+dP/dt_{max}$). Surface ECG was recorded by means of two electrodes, one placed on the crux cordis and the other on the left ventricle free wall (Yang *et al*., 1995). The signal was amplified and monitored with a digital memory oscilloscope (PM 3331, Philips), connected to a printer. The main ECG intervals (PR = atrio-ventricular conduction time; QRS = intra-ventricular conduction time; JT = duration of ventricular depolarization) were measured directly on the screen by use of vertical cursors. Coronary perfusion pressure was monitored with a water manometer ($cmH_2O$) to assess the change in coronary vessel resistance. In our experimental conditions all the parameters measured remained quite stable for at least 2 h.

After a stabilization period of 30 min, quinidine sulphate was added in steps to obtain concentrations of 2, 4, 8, 12, 16, and 20 μM (1 μM ≈0.4 mg $l^{-1}$). The effects of each drug concentration were measured after an equilibration time of 15 min as fractional change from baseline. Preliminary experiments showed that a 15 min exposure to the drug was sufficient to reach a steady change for all the parameters measured.

Data are presented as mean±s.d. The concentration-effect curves obtained in control and quinidine pretreated hearts were compared by means of two way-ANOVA followed, if necessary, by Student's multiple $t$ test with the Bonferroni correction.

## Results

### *Pharmacokinetic study*

The time courses of quinidine plasma levels in each experiment are illustrated in Figure 1a and the mean (±s.d.) values of $C_{max}$, $C_{6\,h}$ and average concentration ($AUC_{0-6\,h}/6$) after 50 mg $kg^{-1}$ and 100 mg $kg^{-1}$ are shown in Table 1. While 50 mg $kg^{-1}$ generally achieved concentrations which are subtherapeutic in man (range: 2–5 mg $l^{-1}$ ≈5–13 mM), in some cases 100 mg $kg^{-1}$ gave rise to supratherapeutic peak concentrations (close to 10 mg $l^{-1}$). Thus, the intermediate dosage of 75 mg $kg^{-1}$ daily was used for chronic treatment.

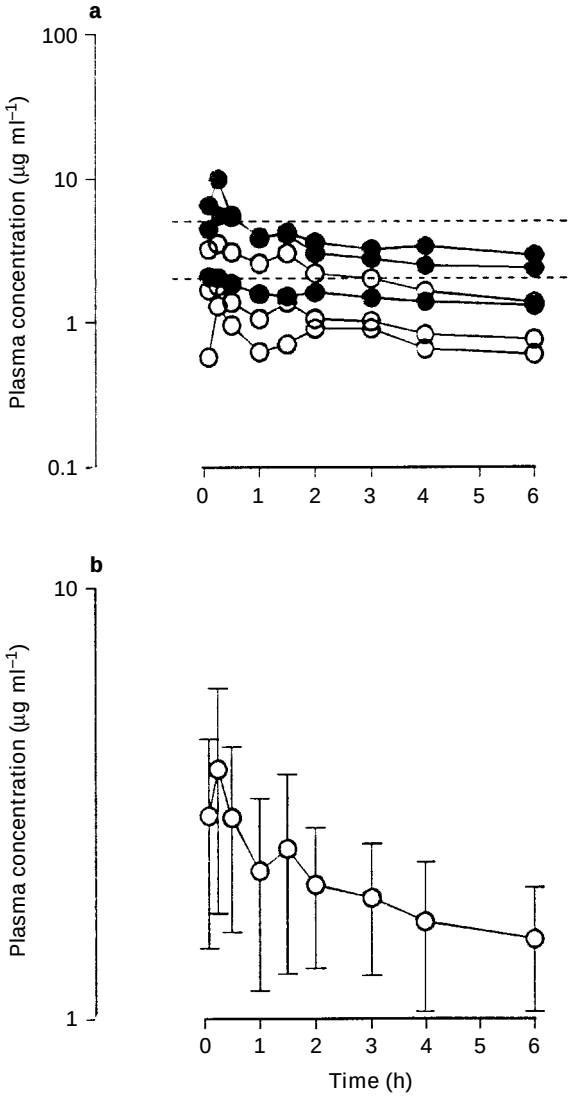


**Figure 1** (a) Time courses of quinidine plasma levels after administration of 50 mg $kg^{-1}$ (open circles) and 100 mg $kg^{-1}$ (solid circles); the dashed lines denote the therapeutic range in man (2–5 mg $l^{-1}$). (b) Time course of mean quinidine plasma levels normalized for a dose of 75 mg $kg^{-1}$ ($n=6$); vertical lines show s.d.

The mean (±s.d.) plasma level profile, normalized for the dose of 75 mg $kg^{-1}$, is illustrated in Figure 1b. Since secondary peaks occurred 1.5 h after drug administration, the exponential regression analysis was applied to data from the 2nd hour onwards (namely, in the log-linear phase of concentration decay). Y-axis intercept ($C_O$) and $t_{1/2}$ of the normalized decay curves were $2.39 \pm 1.05$ mg $l^{-1}$ and $10.2 \pm 3.5$ h, respectively. Because of the relatively slow decay of plasma concentrations compared to the short sampling time (6 h), the $t_{1/2}$ value calculated must be considered with caution. Provided that the $t_{1/2}$ value is correct, quinidine plasma concentration expected 24 h after the last 75 mg $kg^{-1}$ dose ($C_{min,ss}$) is 0.58 mg $l^{-1}$ (see Methods).

### *Pharmacodynamic study*

The baseline values of the ECG intervals (PR, QRS, JT), ventricular contractility ($+dP/dt_{max}$) and coronary pressure parameters measured did not significantly differ between the control and the treated group (Table 2). However, in the case of QRS duration and coronary pressure the mean values were greater in the treated group and the differences approached the significance level ($P \leqslant 0.10$).

The concentration-effect curves for each parameter measured as shown in Figures 2–6. Quinidine induced a marked dose-dependent decrease in ventricular contractility (Figure 2): the highest concentration tested (50 $\mu$M) depressed $+dP/dt_{max}$ to about 20% of its basal value without reaching the plateau of the effect. As expected, both atrio-ventricular conduction time (PR interval, Figure 3) and intraventricular conduction time (QRS interval, Figure 4) were prolonged by the drug. However, while the maximum effect on atrio-ventricular conduction was always attained without the occurrence of blocks, in 12 out of 14 experiments quinidine concentrations equal to or greater than 16 mM gave rise to intraventricular conduction disturbances, leading to sharp changes in QRS complex shape. In the presence of an altered pattern of ventricular activation, QRS measurement does not reflect the degree of Na channel blockade. For this reason QRS curves in Figure 4 are shown up to 12 mM.

Quinidine effect on ventricular depolarization (JT interval) was biphasic, with a prolongation at the lowest concentrations (up to 4 mM) and shortening at the highest (Figure 5).

At any concentration, drug effects on ECG and contractility were not significantly less in the pretreated compared to the control group. Thus, no sign of tolerance was present. Indeed, at most quinidine concentrations QRS, PR and JT changes were slightly greater in the pretreated group (Figures 2–4).

Surprisingly, the effect of quinidine on the coronary bed was different in the two experimental groups. Coronary perfusion pressure was significantly decreased by quinidine in the pretreated group but not in controls (Figure 6). In spite of this, analysis of variance did not reveal any significant difference between the two curves. In control experiments, coronary perfusion pressure underwent non significant changes from the baseline, with a slight increase occurring at the lowest concentrations and a slight decrease at the highest. In contrast, in the pretreated group the coronary response to quinidine was a uniform, significant decrease in perfusion pressure (Figure 6a). If absolute (instead of fractional) changes are considered (Figure 6b), it appears that baseline pressure was higher in the pretreated group than in controls ($80.8 \pm 7.8$ vs $68.3 \pm 13.1$ $cmH_2O$, $P = 0.072$) and that quinidine dose-dependently reduced this difference, so that at the highest con-

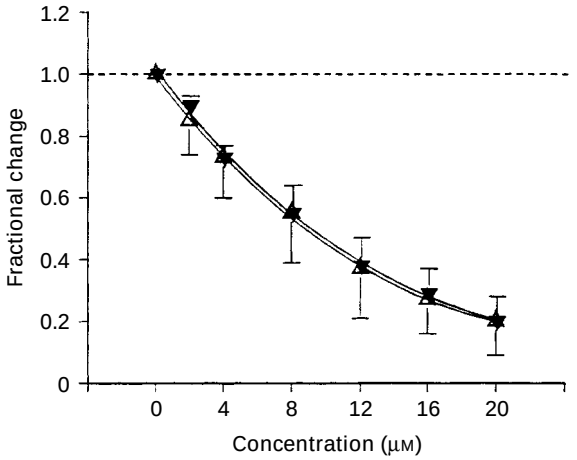


**Figure 2** Concentration-response curves for effect of quinidine on contractility ($+dP/dt_{max}$). Open triangles: controls ($n = 7$); solid triangles: quinidine pretreated group ($n = 7$). Vertical lines show s.d.

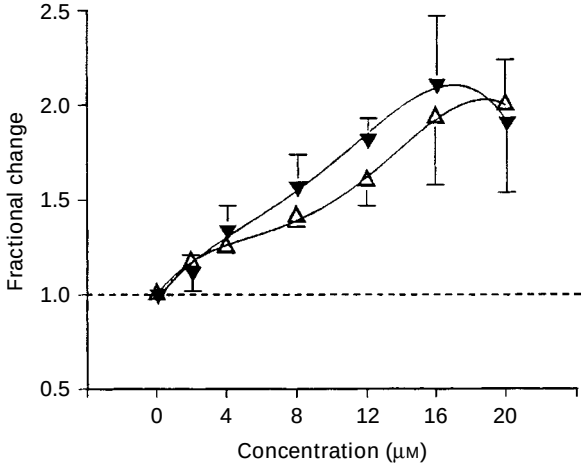


**Figure 3** Concentration-response curves for effect of quinidine on intraventricular conduction time (PR interval). Open triangles: controls ($n = 7$); solid triangles: quinidine pretreated group ($n = 7$). Vertical lines show s.d.

**Table 1** Results of the preliminary pharmacokinetic study

| *Dose* (mg $kg^{-1}$) | *Peak concentration* (mg $l^{-1}$) | *6 h concentration* (mg $l^{-1}$) | *Average concentration* (mg $l^{-1}$) |
|---|---|---|---|
| 50 ($n = 3$) | $2.18 \pm 0.94$ | $1.00 \pm 0.26$ | $1.29 \pm 0.22$ |
| 100 ($n = 3$) | $5.81 \pm 3.20$ | $1.80 \pm 0.79$ | $2.83 \pm 1.17$ |

Data shown are means ± s.d.

**Table 2** Baseline values of the parameters measured

| | *Parameters* | | | | |
|---|---|---|---|---|---|
| | *PR* (ms) | *QRS* (ms) | *JT* (ms) | $+dP/dt_{max}$ (mmHg $s^{-1}$) | *Coronary pressure* ($cm\ H_2O$) |
| Controls ($n = 7$) | $47.6 \pm 6.1$ | $21.8 \pm 1.8$ | $179.0 \pm 7.6$ | $862.7 \pm 385.6$ | $68.3 \pm 13.1$ |
| Treated ($n = 7$) | $49.1 \pm 11.8$ | $25.7 \pm 5.0$ | $180.4 \pm 13.0$ | $594.8 \pm 248.4$ | $80.8 \pm 7.8$ |
| *P* value | 0.28 | 0.10 | 0.82 | 0.18 | 0.072 |

Data shown are means ± s.d.

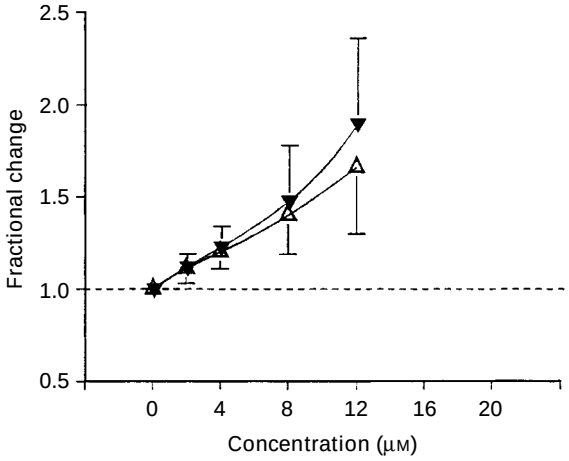


**Figure 4** Concentration-response curves for effect of quinidine on atrioventricular conduction time (QRS interval). Open triangles: controls ($n=7$); solid triangles: quinidine pretreated group ($n=7$). Data corresponding to quinidine concentrations higher than 12 $\mu$M are not shown due to intraventricular conduction disturbances (see Results). Vertical lines show s.d.

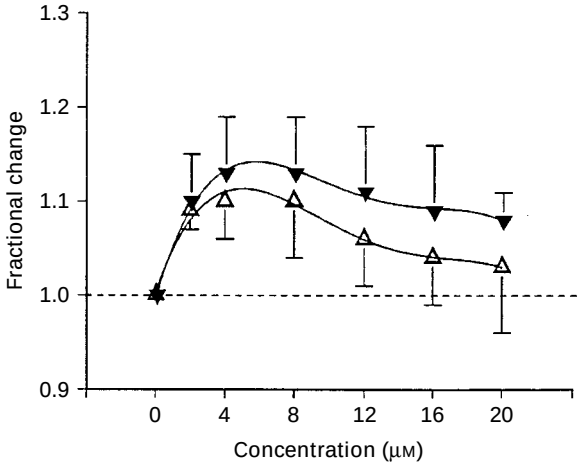


**Figure 5** Concentration-response curves for effect of quinidine on ventricular repolarization time (JT interval). Open triangles: controls ($n=7$); solid triangles: quinidine pretreated group ($n=7$). Vertical lines show s.d.

centration the pressure was the same in the two groups ($60.9\pm7.1$ vs $61.6\pm6.3$ cm$H_2O$).

To sum up, as far as contractility and ECG intervals are concerned, these data suggest that a 6-day quinidine treatment does not change heart responsiveness to the drug. Conversely, coronary bed sensitivity seemed to be altered with long term treatment, with the emergence of a vasodilating effect.

## Discussion

In agreement with current knowledge about the pharmacological properties of quinidine, the results of our investigation indicate that this drug affects several parameters of heart function in a dose-dependent manner. In view of the manifold pharmacological activities of quinidine (Campbell, 1983; Motulsky *et al.*, 1984; Hondeghem & Matsubara, 1988; Balser *et al.*, 1991; Hatem *et al.*, 1992; Mariano *et al.*, 1992; Wyse *et al.*, 1993), it is conceivable that the mechanism of action may differ according to the type of effect. In this sense, QRS prolongation is related to the blocking activity of sodium channels (Hondeghem & Matsubara, 1988), PR prolongation to the block of sodium and calcium channels (Hatem *et al.*, 1992) and JT

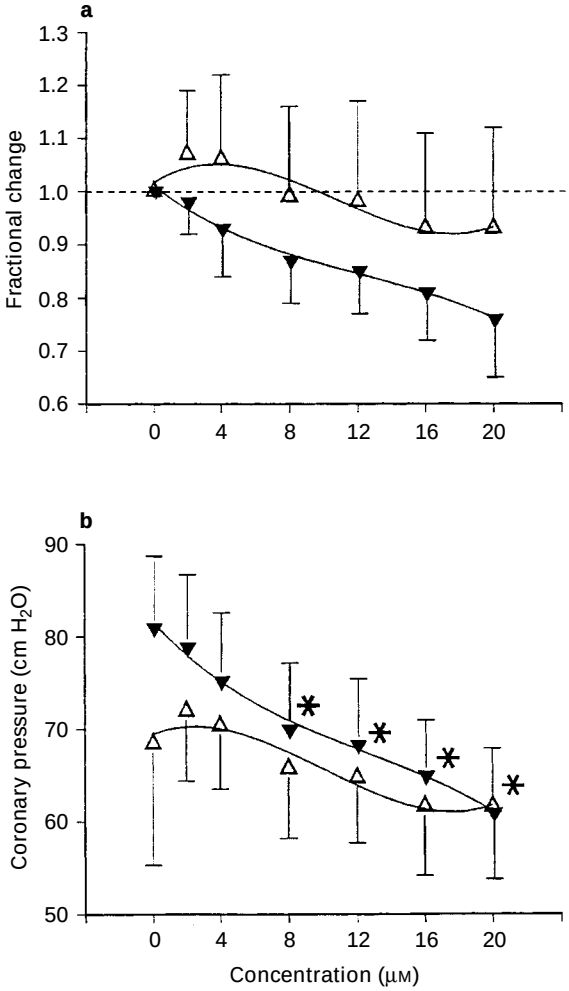


**Figure 6** Concentration-response curves for effect of quinidine on coronary perfusion pressure. Open triangles: controls ($n=7$); solid triangles: quinidine pretreated group ($n=7$). (a) Fractional changes from baseline. (b) Absolute pressure values; asterisks indicate significant changes ($P<0.05$) from baseline. Vertical lines show s.d.

prolongation to the block of a potassium channel (Balser *et al.*, 1991). The JT shortening observed by us at the highest quinidine concentrations agreed with a similar effect, seen by others, on the action potential duration of guinea-pig ventricular myocytes (Campbell, 1983) and Purkinje fibres (Wyse *et al.*, 1993). The underlying mechanism has been ascribed to a blockade of the small persisting component of the sodium inward current during the action potential plateau. The marked negative inotropic effect of quinidine may, as for all Na channel blockers, be partly due to an increased $Ca^{2+}$ outflow through the $Na^+/Ca^{2+}$ exchanger and, partly, to the concomitant $Ca^{2+}$ entry blocker activity.

Surprisingly, in control experiments quinidine did not produce a clear vasodilating effect on the coronary bed. While *in vivo* quinidine decreases blood pressure through both an $\alpha$-blocking and a direct myolytic mechanism (Motulsky *et al.*, 1984; Mariano *et al.*, 1992), *in vitro* (in the absence of an adrenergic tone) $\alpha$-receptor blockade is unlikely to produce relaxation of vascular smooth muscle. On the other hand, it has been shown that quinidine is more potent in relaxing rat aorta than pig coronary arteries (Perez-Viscaino *et al.*, 1994). Thus, factors such as animal species or vascular district may be important in determining the magnitude of the vasodilating effect. It is even more difficult to explain why coronary dilatation occurred in the quinidine pretreated group. Since the baseline coronary pressure tended to be higher in pretreated animals than in controls and the addition of quinidine abolished the difference, it can be hypothesized that chronic, *in vivo*

quinidine treatment may really have induced a coronary dilatation but that a homeostatic adaptation could also ensue, which was able to overcome the vasodilating effect. If so, when the drug was withdrawn, a rebound increase in coronary tone occurred, which was fully antagonized by the *in vitro* re-exposure to the drug. More work is needed to confirm and explain these findings. In contrast with the vascular effects, the electrophysiological and inotropic effects of quinidine on myocardial tissue were not significantly different in the pretreated group than in controls. These findings substantially agree with the persistence of therapeutic efficacy during long-term treatment observed in some clinical studies with class 1a and 1c drugs (McCollam *et al*., 1989; Salerno *et al*., 1990), but differ from those previously obtained by other authors (Duff *et al*., 1985; Kennedy *et al*., 1989; Capucci *et al*., 1990; Le Coz *et al*., 1992; Boriani *et al*., 1993). It could be argued that either the duration of quinidine pretreatment or the steady state plasma concentrations attained were not adequate for tolerance to develop. However, Taouis *et al*. (1991) found that following 6 days of administration of mexiletine in rats (50 mg $kg^{-1}$ daily, s.c.) the Na channel number gradually rose during the first 3 days of treatment and remained steady over the next period, suggesting that channel up-regulation requires just a few days. The same authors observed that such changes occurred despite the very low mexiletine levels detected in plasma ($<0.1$ mg $l^{-1}$) and they concluded that sodium channel regulation in rats is exquisitely sensitive to the drug. In this regard it should also be recalled that Na channel blockade induced by class 1 antiarrhythmic drugs is frequency-dependent and that small rodents physiologically have a very high sinus rate ($\approx 300$ beats $min^{-1}$). Therefore, it is presumed that substantially lower plasma concentrations are needed in rats and guinea-pigs compared to man to obtain the same degree of Na channel blockade. On the contrary, the depolarization effects of quinidine, due to K channel blockade and characterized by a reverse use-dependence (Balser *et al*., 1991), should be less marked in guinea-pigs than in man.

In our experiments quinidine plasma levels measured (or extrapolated) were within (or close to) the therapeutic range in man, so that we can reasonably assume that *in vivo* drug treatment was 'effective', at least as far the interaction with Na channel is concerned. Why, then, did not tolerance to QRS and contractility effects of quinidine ensue, as expected from the study with mexiletine? First, since the animal species used in the two studies was different, a specific species-sensitivity may be involved. Second, although both drugs act at the level of Na channel (as local anaesthetics or class 1 agents), substantial differences exist in the interaction with their substrate as far as both the channel state and the kinetics of interaction are concerned: in fact, quinidine binding occurs during the active state of the Na channel (phase 0 of the action potential) (Hondeghem & Matsubara, 1988), whereas mexiletine interacts with the channel during phase 2 (inactivated state) (Kodama *et al*., 1987) and both association and dissociation time constants are much shorter for mexiletine than for quinidine. At present, no data are available about the influence of the above factors on the attitude to the various class 1 agents to induce up-regulation of Na channels, but the possibility that the intimate mechanism of the drug-receptor interaction could play a role in the process cannot be ruled out and also, consequently, certain agents may require longer periods of treatment to elicit clear tolerance phenomena.

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## References


BALSER, J.R., BENNETT, P.B., HONDEGHEM, L.M. & RODEN, D.M. (1991). Suppression of time-dependent outward current in guinea pig ventricular myocytes. Actions of quinidine and amiodarone. *Circ. Res*., **69,** 519–529.

BORIANI, G., CAPUCCI, A., STROCCHI, E., CALLIVA, R., SANTARELLI, A., BIFFI, M. & MAGNANI, B. (1993). Flecainide acetate: concentration-response relationship for antiarrhythmic and electrocardiographic effects. *Int. J. Clin. Pharmacol. Res*., **8,** 211–219.

CAMPBELL, T.J. (1983). Kinetics of onset of rate-dependent effects of class I antiarrhythmic drugs are important in determining their effects on refractoriness in guinea-pig ventricle, and provide a theoretical basis for their subclassification. *Cardiovasc. Res*., **17,** 433–452.

CAPUCCI, A., BORIANI, G., MARCHESINI, B., STROCCHI, E., TOMASI, L., BALDUCCELLI, M., FRABETTI, L., AMBROSIONI, E. & MAGNANI, B. (1990). Minimal effective concentration values of propafenone and 6-hydroxy-propafenone in acute and chronic therapy. *Cardiovasc. Drug Ther*., **4,** 281–287.

DUFF, H.J., WYSE, D.G., MANYARI, D. & MITCHELL, L.B. (1985). Intravenous quinidine: relations among concentration, tachyarrhythmia suppression and electrophysiological actions with inducible sustained ventricular tachycardia. *Am. J. Cardiol*., **55,** 92–97.

GIBALDI, M. & PERRIER, D. (1975). *Pharmacokinetics*. pp. 97–128, New York: Marcel Dekker, Inc.

HATEM, S., LE GRAND, B., LE HEUZEY, J.Y., COUETIL, J.P. & DEROUBAIX, E. (1992). Differential effects of quinidine and flecainide on plateau duration of human atrial action potential. *Basic Res. Cardiol*., **87,** 600–609.

HONDEGHEM, L.M. & MATSUBARA, T. (1988). Quinidine blocks cardiac sodium channels during opening and slow inactivation in guinea-pig papillary muscle. *Br. J. Pharmacol*., **93,** 311–318.

KENNEDY, H.L., SPRAGUE, M.K., HOMAN, S.M., SEILER, S.M., WIENS, R.D., JANOSIK, D.L., REDD, R.M. & BUCKINGHAM, T.A. (1989). Natural history of potentially lethal ventricular arrhythmias in patients treated with long-term antiarrhythmic drug therapy. *Am. J. Cardiol*., **64,** 1289–1297.

KODAMA, I., TOYAMA, J., TAKANAKA, C. & YAMADA, K. (1987). Block of activated and inactivated sodium channels by Class-I antiarrhythmic drugs studied by using maximum upstroke velocity (Vmax) of action potential in guinea-pig cardiac muscles. *J. Mol. Cell. Cardiol*., **19,** 367–377.

LEROYER, R., JARREAU, C. & PAYS, M. (1982). Specific determination of quinidine and metabolites in biological fluids by reversed-phase high-performance liquid chromatography. *J. Chromatogr. Biochem. Appl*., **228,** 336–371.

LE COZ, F., FUNCK-BRENTANO, C., POIRIER, J.M., KIBLEUR, Y., MAZOIT, F.X. & JAILLON, P. (1992). Prediction of sotalol-induced maximum steady-state QTc prolongation from single-dose administration in healthy volunteers. *Clin. Pharmacol. Ther*., **52,** 417–426.

MARIANO, D.J., SCHOMER, S.J. & REA, R.F. (1992). Effects of quinidine on vascular resistance and sympathetic activity in humans. *J. Am. Coll. Cardiol*., **20,** 1411–1416.

MCCOLLAM, P.L., BAUMAN, J.L., BECKMAN, K.J. & HARIMAN, R.J. (1989). A simple method of monitoring antiarrhythmic drugs during short- and long-term therapy. *Am. J. Cardiol*., **63,** 1273–1275.

MOTULSKY, H.J., MAISEL, A.S., SNAVELY, M.D. & INSEL, P.A. (1984). Quinidine is a competitive antagonist at alpha 1- and alpha 2-adrenergic receptors. *Circ. Res*., **55,** 376–381.

PADRINI, R., BOVA, S., CARGNELLI, G., PIOVAN, D. & FERRARI, M. (1992). Effects of pinacidil on guinea-pig perfused heart with particular references to the proarrhythmic effect. *Br. J. Pharmacol*., **105,** 715–719.

PEREZ-VIZCAINO, F., FERNANDEZ DEL POZO, B., ZARAGOZA, F. & TAMARGO, J. (1994). Voltage- and time-dependent inhibitory effects on rat aortic and porcine coronary artery induced by propafenone and quinidine. *Br. J. Pharmacol*., **113,** 1281–1288.

SALERNO, D.M., FIFIELD, J. & HODGES, M. (1990). Antiarrhythmic drug therapy for suppression of ventricular arrhythmia: Experience with 122 patients treated for two years. *J. Clin. Pharmacol*.. **30,** 226–234.

TAOUIS, M., SHELDON, R.S. & DUFF, H.J. (1991). Upregulation of the rat cardiac sodium channel by in vivo treatment with a class I antiarrhythmic drug. *J. Clin. Invest.*, **88,** 375–378.

WYSE, K.R., YE, V. & CAMPBELL, T.J. (1993). Action potential prolongation exhibits simple dose-dependence for sotalol, but reverse dose-dependence for quinidine and disopyramide: Implications for proarrhythmia due to triggered activity. *J. Cardiovasc. Pharmacol.*, **21**, 316–322.

YANG, Q., PADRINI, R., BOVA, S., PIOVAN, D. & MAGNOLFI, G. (1995). Electrocardiographic interactions between pinacidil, a potassium channel opener and class I antiarrhythmic agents in guinea-pig isolated perfused hearts. *Br. J. Pharmacol.*, **114,** 1745–1749.

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