JPP
Journal of
Pharmacy and Pharmacology

JPP 2001, 53: 1671–1678
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Received May 17, 2001
Accepted July 24, 2001
ISSN 0022-3573

Effects of the Class III antiarrhythmic agent dofetilide (UK-68,798) on L-type calcium current from rabbit ventricular myocytes

A. A. Paul, D. J. Leishman, H. J. Witchel and J. C. Hancox

Department of Physiology and Cardiovascular Research Laboratories, School of Medical Sciences, University Walk, Bristol, BS8 1TD, UK

A. A. Paul, H. J. Witchel, J. C. Hancox

Pfizer Central Research, Ion Channel Pharmacology group, Pfizer Global Research and Development, PC 155 Sandwich, Kent, CT13 9NJ, UK

D. J. Leishman

Correspondence: J. Hancox, Department of Physiology, School of Medical Sciences, University Walk, Bristol, BS8 1TD, UK. E-Mail: jules.hancox@bristol.ac.uk

Funding and acknowledgements: The calcium current experiments in this study were supported by Pfizer Global Research and Development. H. J. Witchel was supported by a grant (PG/98081) from the British Heart Foundation. J. C. Hancox thanks the Wellcome Trust for a Research Career Development Fellowship. We thank Kathryn Yuill and Lesley Arberry for assistance with myocyte isolation.

Abstract

The methanesulphonanilide agent dofetilide (UK-68,798) exerts Class III antiarrhythmic effects by inhibiting the cardiac rapid delayed rectifier potassium current (I_{Kr}) encoded by *HERG*. The aim of the present study was to determine whether dofetilide also exhibits Class IV (L-type calcium-channel blocking) effects. L-type calcium current ($I_{Ca,L}$) was measured from rabbit isolated ventricular myocytes, using the whole-cell patch-clamp technique under selective recording conditions. Positive control experiments demonstrated inhibition of $I_{Ca,L}$ elicited by pulses to +10 mV by both nifedipine and externally applied Ni^{2+} ions. Three concentrations of dofetilide were tested: 100 nM, 1 μM and 10 μM. $I_{Ca,L}$ magnitude was not significantly reduced by any of the concentrations tested ($P > 0.05$; n = minimum of seven cells per drug concentration). The inactivation time-course of $I_{Ca,L}$ was also unaffected by 10 μM dofetilide. Heterologously expressed HERG current (I_{HERG}) recorded from Chinese Hamster Ovary cells was extensively inhibited by 100 nM and 1 μM dofetilide, with inhibition at 1 μM not significantly different from 100% ($P > 0.1$). It is concluded that dofetilide produced no $I_{Ca,L}$ blocking effects at concentrations up to and exceeding that required for maximal I_{HERG} inhibition. The findings support the notion that dofetilide is a highly selective Class III antiarrhythmic agent, devoid of Class IV antiarrhythmic activity.

Introduction

Cardiac arrhythmias are a major source of morbidity and mortality. Antiarrhythmic therapy has traditionally centered on drugs that alter the function of one or more cardiac ion channel types so as to suppress arrhythmia generation or maintenance. The development of antiarrhythmic drugs has been significantly influenced by the Cardiac Arrhythmia Suppression Trial (Cardiac Arrhythmia Suppression Trial (CAST) Investigators 1989; Echt et al 1991; CAST II Investigators 1992), which showed that certain Vaughan-Williams Class I (Na-channel blocking) agents increased mortality in patients who had experienced myocardial infarction. A great deal of attention has since focused on Class III drugs, agents that prolong action potential duration (APD) and thereby refractoriness (Naccarelli et al 1999). Such agents would be expected to increase refractoriness without impairing conduction, an action that would be predicted to suppress re-entrant arrhythmias (Nattel 1999).

Although, in principle, a Class III antiarrhythmic action could result from either enhancement of depolarizing (inward sodium or calcium) ionic current or inhibition of repolarizing (outward potassium) current (Hancox et al 2000),

the majority of Class III agents in development or in use are potassium-channel blockers. Although the "Survival with Oral D-sotalol" (SWORD) trial concluded that prophylactic use of a specific potassium-channel blocker (D-sotalol) does not reduce mortality and might be associated with increased mortality in patients after myocardial infarction (Waldo et al 1996), this is not necessarily the case for all such agents. The methanesulphonanilide agent dofetilide (UK-68,798) exerts Class III effects owing to inhibition of the "rapid" sub-type of the cardiac delayed rectifier potassium current (I_{Kr}) (e.g. Sanguinetti & Jurkiewicz 1990; Jurkiewicz & Sanguinetti 1993). Dofetilide can be effective at suppressing both ventricular tachycardia and atrial fibrillation or flutter in humans (Bashir et al 1995; Kober et al 2000; Torp-Pedersen et al 2000). Its use appears to be associated with a relatively low incidence of the arrhythmia *torsade de pointes* (Ferguson 1998) and the drug appears relatively safe in the settings of heart failure and myocardial infarction (Falk & Decara 2000; Torp-Pedersen et al 2000).

Although dofetilide is commonly considered to be a highly selective Class III agent (Gwilt et al 1991; Rasmussen et al 1992; Kiehn et al 1994; Falk & Decara 2000), one study has reported a reduction of calcium current during dofetilide exposure (Tohse & Kanno 1995). The aim of the present study was to determine if dofetilide can exert blocking effects on ventricular L-type calcium current ($I_{Ca,L}$) under selective recording conditions for this current, and at a physiologically relevant temperature.

Materials and Methods

Chemicals and drugs

Aristar grade chemicals were used for cell-isolation solutions (BDH Laboratory Supplies, Poole, Dorset, UK). Type 1A collagenase was supplied by Worthington Biochemical Corporation (NJ) and type XIV protease was supplied by Sigma (Poole, Dorset, UK). Analar grade chemicals (BDH Laboratory Supplies) were dissolved in de-ionized water (Milli-Q; Millipore) to make external and internal solutions. Nifedipine (Sigma) was dissolved in dimethylsulfoxide (DMSO) to give a 20 mM stock solution, which was protected from light. Nickel chloride (Sigma) was dissolved in de-ionized water to give a 0.5 M stock solution.

Dofetilide (UK-68,798; Pfizer Global Research, Sandwich, Kent, UK) was dissolved in DMSO to produce a 20 mM stock solution. This was serially diluted in DMSO so that similar aliquots were added to the external solution to produce the various test concentrations of the drug (100 nM, 1 μM and 10 μM). In each case, 10 μL DMSO was added to 20 mL of external solution, producing a final DMSO concentration of 0.05%.

Isolation and preparation of ventricular myocytes for recording

Male New Zealand White rabbits (1.8–2.5 kg) were killed by cervical dislocation (a method which was sanctioned by the Home Office) and hearts were rapidly removed. Ventricular myocytes were then isolated from the right ventricle, using a modification of the method described by Hancox et al (1993) (note that the EGTA concentration added to the perfusate was 100 μM and not 100 mM as published). Isolated cells were stored in a high-K, low-Ca (KB) storage solution comprised of (mM): 100 L-glutamate, 30 KCl, 5 Na-pyruvate, 20 taurine, 5 creatine, 5 succinic acid, 2 Na_2ATP, 5 β-OH pyruvate, 20 glucose, 5 $MgCl_2$, 1 EGTA, 10 HEPES, titrated to a pH of 7.2 by the addition of KOH. For recording, a suspension of myocytes in KB solution was placed in a chamber (with a volume of 0.5 mL) mounted on an inverted microscope (Nikon Diaphot) and superfused at 35–37°C with standard Tyrode's solution containing (mM): 130 NaCl, 4 KCl, 2 $CaCl_2$, 1 $MgCl_2$, 10 glucose, 5 HEPES, titrated to a pH of 7.4 by the addition of NaOH. Perfusion was started at a slow rate and gradually increased (to 3.5 mL min^{-1}). In this way, the flow-rate could be increased without cells becoming dislodged, and as the calcium-containing bath solution replaced KB, the cells were slowly re-exposed to calcium.

Experimental solutions and conditions for $I_{Ca,L}$ measurement

The whole-cell patch-clamp technique was used. Patch pipettes (Corning 7052 glass; AM Systems) were pulled to resistances of ~ 2 MΩ (using either a Flaming-Brown puller (Sutter Instruments) or a Narashige PP83) and fire-polished to 3–5 MΩ (Narashige MF83 microforge). Recordings of membrane currents were made using an Axopatch 1D amplifier (Axon Instruments, CA) with a CV-4 headstage. Normally ~ 80–90% of the pipette series resistance was compensated.

A Cs^+-based internal dialysis solution was used for all $I_{Ca,L}$ recordings; its composition was as follows (mM): 113 CsCl, 10 NaCl, 10 HEPES, 0.4 $MgCl_2$, 5 glucose, 5 K_2ATP, 10 BAPTA, titrated to pH 7.2 with CsOH. Apart from the standard Tyrode's solution in which cells were bathed until whole-cell clamp, all external solutions were applied using a multi-barrelled, warmed

application device capable of exchanging local bathing solution in < 1 s (Levi et al 1996). For most experiments, the control solution was standard K^+-free Tyrode's solution, in order to inhibit inwardly rectifying K current. During experiments both control and test solutions were applied from the device. External solutions for recording $I_{Ca,L}$ were applied at a temperature of 35–37°C.

Transient expression of HERG and solutions for HERG current (I_{HERG}) measurement

To put the findings of experiments testing for effects of dofetilide on $I_{Ca,L}$ in context, additional experiments were performed in which we tested (under our conditions) the effect of the drug against its intended target (channels responsible for the I_{Kr}). Heterologously expressed HERG channels are commonly used to test drugs that act on I_{Kr}, and we adopted this approach in the present study. cDNA coding for the HERG channel subunit was donated by Dr Mike Sanguinetti and Dr Mark Keating. It was subcloned into pGW1H (generously supplied by British Biotech, Oxford), which contains a CMV promoter to drive expression of the insert. Chinese Hamster Ovary (CHO) cells were maintained as described previously (Hancox et al 1998). Cells were plated onto small sterilized glass coverslips. After 24 h, the cells were co-transfected with 3:1 HERG cDNA: green fluorescent protein (GFP) in pCMX (donated by Dr Jeremy Tavare) using the recommended lipofectamine (BRL) protocol. In some experiments, successfully transfected cells were identified by detecting membrane expression of the CD8 antigen using beads (Dynal, Brombrough, UK) coated with an anti-CD8 antibody (Jurman et al 1994). The procedures used in our laboratory for identification of successful transfection using CD8 and GFP have been described recently (Paul et al 2001).

Standard Tyrode's solution was used as external bathing medium for HERG experiments. The pipette solution for these experiment contained (mM): 110 KCl, 5 K_2ATP, 0.4 $MgCl_2$, 10 HEPES, titrated to pH of 7.1 by adding KOH. The composition of this solution was similar to that used in recent studies of HERG in our laboratory (Hancox et al 1998; Paul et al 2001). External solutions for recording I_{HERG} were applied at a temperature of 35–37°C.

Generation of protocols, data acquisition and analysis

Voltage-clamp command signals were generated by a Digidata 1200 interface (Axon Instruments) and 'WinWCP' (program supplied free of charge by John Dempster, Strathclyde University). Data were recorded directly on-line using a Viglen EX personal computer. Membrane currents were sampled at 2 kHz.

Data were analysed using WinWCP to measure $I_{Ca,L}$ amplitude (taken as the difference between peak inward current, and current at the end of the test-pulse used to elicit the current). $I_{Ca,L}$ values, together with corresponding pulse number, were exported to FigP (Biosoft) via Excel to produce hardcopy data-plots. These programs were also used to measure I_{HERG} tail amplitude. Numerical values are expressed, where appropriate, as mean ± s.e.m.; n values refer to the number of cells for particular observations. A minimum sample size of seven cells (from two or more different hearts) was used to test each concentration of dofetilide.

Statistical comparisons

To quantify the effect of dofetilide on $I_{Ca,L}$, data from experiments on a number of myocytes were pooled at each of the drug concentrations tested. Two methods were used to compare control and test solutions. The first method (Method A) involved obtaining the values for mean amplitude of $I_{Ca,L}$ for each cell throughout the entire duration of dofetilide exposure and comparing this with the mean amplitude in control solution throughout the period of exposure. The second method (Method B) involved comparing the control $I_{Ca,L}$ value with the mean current amplitude for the last five pulses during dofetilide exposure. Results were expressed in terms of absolute current magnitude, and as percentage change of control current.

To compare mean absolute $I_{Ca,L}$ amplitudes before and during exposure to a particular concentration of dofetilide, pair-wise comparison was made between current in the presence of dofetilide and its respective control using a two-tailed, paired Student's *t*-test (Systat and Minitab; Systat Inc. and Minitab Inc., respectively). To determine whether percentage changes from control $I_{Ca,L}$ at three different dofetilide concentrations were significant, analysis of variance was used (Systat and Instat; Systat Inc. and GraphPad Software Inc., respectively). For all comparisons, P values of < 0.05 were taken as statistically significant.

Results and Discussion

The voltage protocol used to elicit $I_{Ca,L}$ was similar to that used in previous studies of this current using isolated cardiomyocytes (e.g. Hancox & Convery 1997; Dooley et al 1999; Hobai et al 2000). The protocol and

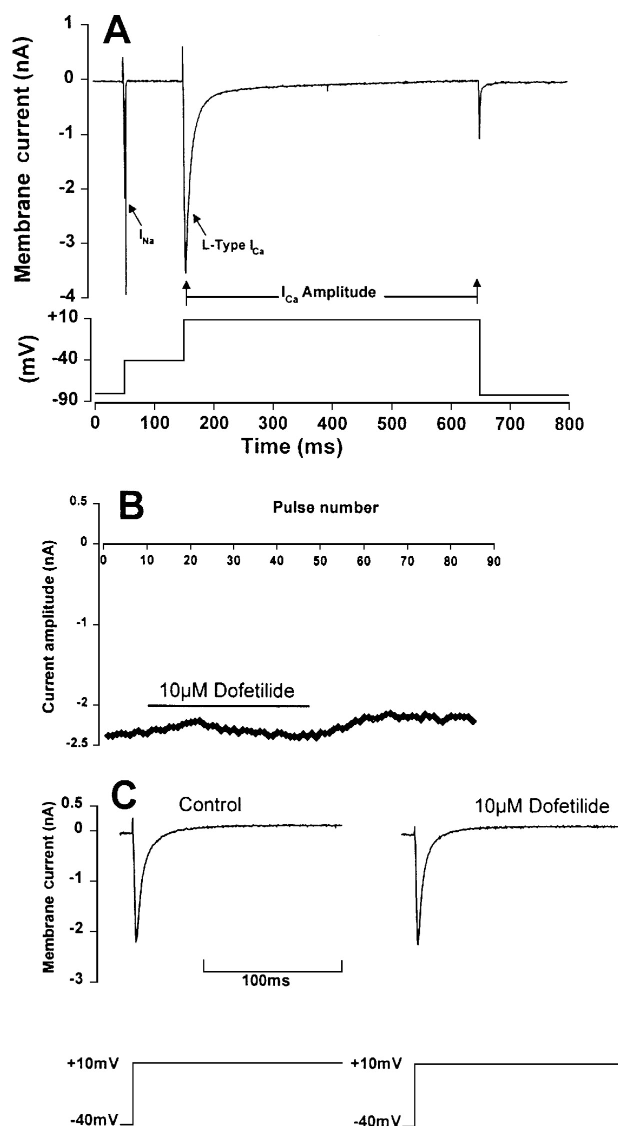

Figure 1 Dofetilide and $I_{Ca,L}$. A. Voltage protocol (lower trace) used to study $I_{Ca,L}$, together with a representative record of current elicited by this protocol (upper trace). B. A plot of the time-course of $I_{Ca,L}$amplitude during an experiment investigating the action of 10 μM dofetilide. Horizontal bar denotes the period of dofetilide exposure. C. Individual records of $I_{Ca,L}$ in control solution and in the presence of 10 μM dofetilide. The drug exerted no significant effect on $I_{Ca,L}$ magnitude.

representative currents elicited are shown in Figure 1A. From a holding potential of −80 mV, a 100-ms duration step to −40 mV activated and then inactivated fast Na current. This was followed by a 500-ms duration test pulse from −40 to +10 mV to activate an $I_{Ca,L}$. At the end of the test pulse, membrane potential was returned to −80 mV. The pulse frequency was 0.33 Hz. $I_{Ca,L}$ amplitude was measured as the difference between the peak inward current at the start of the test-pulse and the end-pulse current.

Positive controls using known $I_{Ca,L}$ blockers

Although the protocol described above and the identity of the currents shown in Figure 1A are well known, we applied known inhibitors of $I_{Ca,L}$ to demonstrate inhibition of ventricular $I_{Ca,L}$ under the conditions of this study. Externally applied Ni^{2+} (5 mM) produced a rapid inhibition of $I_{Ca,L}$. In six cells, Ni^{2+} blocked $I_{Ca,L}$ by 96.47±2.25%, consistent with previous data regarding the effects of Ni^{2+} on this current (Hobai et al 2000). The dihydropyridine $I_{Ca,L}$ blocker, nifedipine (20 μM), was also applied and produced a mean $I_{Ca,L}$ inhibition of 77.20±4.12% (n = 6 cells). Nifedipine inhibits $I_{Ca,L}$ with the greatest affinity in the inactivated state (e.g. Mery et al 1996; Shen et al 2000) and the negative holding potential and pulse frequency utilized in these experiments would have facilitated recovery from inactivation between successive test pulses. Thus, incomplete block of $I_{Ca,L}$ under these conditions might not be unexpected. Collectively, the data with Ni^{2+} and nifedipine confirmed that the voltage protocol used was appropriate for detection of pharmacological inhibition of $I_{Ca,L}$.

Negative control testing the solvent (DMSO) for dofetilide

Further control experiments were performed in which DMSO was added to the control solution at the same concentration as would be present in experiments with dofetilide (0.05%). No significant reduction in $I_{Ca,L}$ amplitude was observed in the presence of DMSO ($P >$ 0.2), consistent with previous data from Ogura et al (1995), suggesting little effect of DMSO on Ca current at concentrations between 0.1 and 10%. Thus, any effect that dofetilide exerted on $I_{Ca,L}$ would not be attributable to the use of DMSO as solvent for the agent.

Effects of dofetilide on $I_{Ca,L}$

The concentrations of dofetilide used for testing against $I_{Ca,L}$ were chosen with reference to those known to inhibit native cardiac I_{Kr} and its cloned equivalent HERG. Jurkiewicz & Sanguinetti (1993) reported an IC50 of 31.5 nM for ventricular I_{Kr}. A K_D for dofetilide binding to its high-affinity site of 20 nM has also been reported (Fiset et al 1996). For heterologously expressed HERG channels, IC50 values of 12–35 nM have been found (Kiehn et al 1996; Snyders & Chaudhary 1996).

Table 1 Summary of the effects of dofetilide on $I_{Ca,L}$.

Dofetilide concn	Control $I_{Ca,L}$ (nA)	Dofetilide $I_{Ca,L}$ Method A (nA)	Dofetilide $I_{Ca,L}$ Method B (nA)	Replicates (n)	Paired *t*-test *P*
100 nM	2.47 ± 0.17	2.55 ± 0.21	2.71 ± 0.25	7	Method A: ($P > 0.2$) Method B: ($P > 0.05$)
1 μM	2.56 ± 0.20	2.53 ± 0.21	2.59 ± 0.21	7	Method A: ($P > 0.3$) Method B: ($P > 0.5$)
10 μM	2.03 ± 0.17	2.00 ± 0.15	2.04 ± 0.16	23	Method A: ($P > 0.4$) Method B: ($P > 0.6$)

$I_{Ca,L}$ amplitude was measured in control solution and using Methods A and B in the presence of dofetilide. Values are expressed as mean ± s.e.m.

Concentrations of dofetilide expected to produce high levels of I_{Kr}/HERG block (100 nM, 1 μM and 10 μM) were used to test for $I_{Ca,L}$ inhibitory effects.

Figure 1B shows a continuous plot of $I_{Ca,L}$ amplitude against test-pulse number during an experiment investigating the effects of 10 μM dofetilide (the highest concentration tested). There was no consistent decrease in $I_{Ca,L}$ amplitude during the period of exposure to dofetilide. Figure 1C shows individual current records from this cell for $I_{Ca,L}$ in control solution and in the presence of 10 μM dofetilide. It can be seen that $I_{Ca,L}$ amplitude was little affected by exposure to dofetilide. To test whether the effects of dofetilide on $I_{Ca,L}$ amplitude were significant, mean data were compared using Methods A and B, described above. Table 1 summarizes the experimental findings, expressing mean data in terms of absolute current magnitude for each dofetilide concentration. Irrespective of whether Method A or B was used, there was no statistically significant effect of dofetilide on $I_{Ca,L}$ amplitude. Similar findings were obtained when, for the same experiments, data were expressed as percentage change of control current. For Method A, the mean percentage changes in control $I_{Ca,L}$ amplitude produced by 100 nM, 1 μM and 10 μM dofetilide were 2.58 ± 2.40, −1.37 ± 1.53, and −0.08 ± 1.81 %, respectively. These values were not significantly different from one another or a zero percentage change in $I_{Ca,L}$ ($P > 0.3$, analysis of variance). For Method B, the mean % changes in control $I_{Ca,L}$ amplitude produced by 100 nM, 1 μM and 10 μM dofetilide were 8.64 ± 4.22, 1.26 ± 2.08, and 2.21 ± 2.22 %, respectively. These values were also not significantly different from one another or from a zero percentage change in $I_{Ca,L}$ ($P > 0.6$, analysis of variance).

In addition to assessing the action of dofetilide on $I_{Ca,L}$ amplitude, we investigated whether the time-course of current inactivation during the depolarizing pulse to + 10 mV was affected by exposure to the agent at the highest drug concentration tested (10 μM). $I_{Ca,L}$ inactivation was well-described by a bi-exponential decline (e.g. Hobai et al 2000). For control, the fast inactivation time constant (τ_f) was 15.95 ± 3.72 ms, and the slow inactivation time constant (τ_s) was 98.18 ± 14.97 ms. For $I_{Ca,L}$ in the presence of dofetilide assessed using Method A, τ_f was 14.25 ± 2.47 and τ_s was 94.39 ± 10.97 ms. Using Method B, τ_f was 14.51 ± 2.83 and τ_s was 99.84 ± 14.55 ms. Using both Methods A and B, τ_f and τ_s in the presence of dofetilide did not differ significantly from control ($P > 0.20$, analysis of variance). Thus, the agent did not significantly alter the inactivation time-course of $I_{Ca,L}$.

Effects of dofetilide on heterologously expressed HERG

The results shown in Figure 1 and Table 1 are consistent with a lack of significant effect of dofetilide on ventricular $I_{Ca,L}$. However, it was important to confirm that this was not attributable to a lack of biological activity of the dofetilide sample used in our study. To confirm that dofetilide was effective against its target, we tested the effects of the agent on heterologous I_{HERG} recorded from CHO cells. To elicit I_{HERG}, depolarizing test pulses to + 30 mV were applied from a holding potential of − 40 mV (pulse frequency 0.25 Hz) and the amplitude of the tail current on repolarization to − 40 mV was monitored (e.g. Paul et al 2001). Steady-state I_{HERG} tail amplitude in the presence of dofetilide was measured and the percentage blockade determined. The effects of 100 nM and 1 μM dofetilide were tested. Figure 2 shows representative records of I_{HERG} in normal solution and in the presence of 1 μM dofetilide. Current inhibition in this cell was essentially complete. For 11 cells, 1 μM dofetilide blocked the I_{HERG} tail by 97.91 ± 0.55 %. The

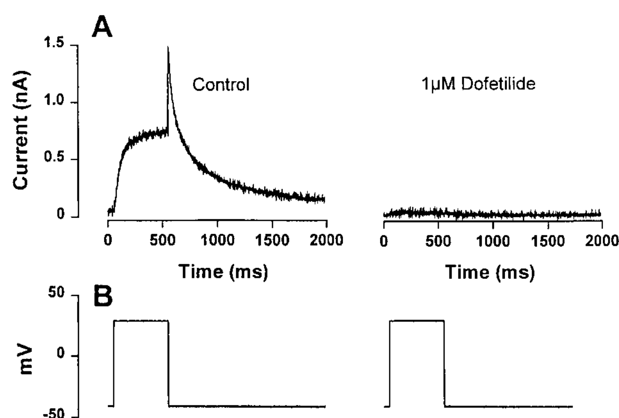

Figure 2 Dofetilide and HERG. A. I_{HERG} elicited by test pulses from −40 mV to +30 mV. The left panel shows control current and the right panel shows current after exposure to 1 μM dofetilide. B. The voltage protocol applied to elicit I_{HERG}.

extent of the blockade at this concentration was not significantly different from 100% inhibition ($P > 0.1$). For 13 cells, 100 nM dofetilide produced a 68.61 ± 8.40% inhibition of the I_{HERG} tail. These data confirmed the Class III activity of our sample of dofetilide, and are consistent with the potent I_{Kr}/HERG blockade reported previously for the compound (Jurkiewicz & Sanguinetti 1993; Fiset et al 1996; Kiehn et al 1996; Snyders & Chaudhary 1996).

Results in context

Although some work on dofetilide suggested that dofetilide did not significantly affect inward I_{Ca} (Gwilt et al 1991; Kiehn et al 1994), in contrast with the present experiments, neither of those studies were conducted using selective recording conditions for $I_{Ca,L}$, nor were the experiments by Kiehn et al (1994) conducted at a physiologically relevant temperature. A study of rabbit isolated sinoatrial nodal myocytes did report decreased I_{Ca} during dofetilide application (Tohse & Kanno 1995). In reporting a decrease in cardiac I_{Ca} during dofetilide exposure, Tohse & Kanno (1995) acknowledged that their reported current alteration "may be attributed to the 'run down' phenomenon". Gwilt et al (1991) also observed some time-dependent reduction in I_{Ca} in their experiments; however, the reduction was not significantly different between cells exposed to dofetilide and cells that had not received this treatment. $I_{Ca,L}$ measurement can be susceptible to time-dependent changes in amplitude owing to alterations in whole-cell access (series resistance alterations owing to either improvement or deterioration in access are possible) or to progressive current run-down. The two-fold method of data analysis that we used aimed to take such variations into account and, thereby, to highlight any consistent trend for actions of dofetilide on $I_{Ca,L}$. Method A produced a value for mean $I_{Ca,L}$ amplitude throughout the entire exposure period; this would have minimized the effect of transient variations of amplitude that could have been independent of drug action. However, although this method would have revealed any consistent (and rapid onset) effect of the drug, it would not have necessarily shown effects that progressively increased with pulse number. Method B, however, relied on current measurement after the drug had been applied for a series of pulses. This, together with the large sample size used to investigate the highest drug concentration tested (23 cells for 10 μM dofetilide), would very likely have revealed any genuine inhibitory effect of the drug on $I_{Ca,L}$, irrespective of drug-unrelated fluctuations of current during experiments. Moreover, under similar conditions, we were able to observe $I_{Ca,L}$ blockade both with Ni^{2+} and nifedipine, and we obtained I_{HERG} inhibition by dofetilide concentrations that left $I_{Ca,L}$ unaffected. Considered together, these findings argue strongly against any Ca-channel blocking (Class IV) activity of dofetilide under the conditions of our study.

Selective I_{Kr} blockers are commonly associated with reverse rate-dependent effects on cardiac action potentials, (Camm & Yap 1999; Hancox et al 2000). This may predispose, at slow rates, towards *torsade de pointes* (Witchel & Hancox 2000), which is associated at the cellular level with events termed "early-after-depolarizations" (EADs; e.g. Zhou et al 1995). However, despite potent I_{Kr}-blocking activity, dofetilide appears to be comparatively safe, even post-infarction (Ferguson 1998; Falk & Decara 2000; Torp-Pedersen et al 2000), making it a Class III agent of particular note. EADs are believed to result from reactivation of $I_{Ca,L}$ during slowed repolarization (January & Riddle 1989; Makielski & January 1998). Therefore, concomitant inhibition of $I_{Ca,L}$ and I_{Kr} is one potential mechanism by which proarrhythmic risk with I_{Kr} blockade can be attenuated (Bril et al 1998; Faivre et al 1999). However, since our results are inconsistent with combined Class IV and Class III activity of dofetilide, it seems reasonable to conclude that other facets of the action of this drug or its clinical use must account for its safety profile. One important factor may be careful patient monitoring started before drug administration commences. In this respect, recent data suggest that QT dispersion may not have prognostic value for patients with heart failure (Brendorp et al 2001a); however, baseline QT_c interval length might be a useful guide for selecting which

patients with heart failure may benefit from prophylactic antiarrhythmic treatment (Brendorp et al 2001b).

Conclusion

Under the conditions of this study, dofetilide exerted an I_{HERG}-blocking effect that was comparable with levels reported previously. In contrast, dofetilide (100 nM, 1 μM and 10 μM) did not inhibit rabbit ventricular $I_{Ca,L}$. Our findings are therefore consistent with dofetilide showing high selectivity for inhibition of I_{HERG}/native I_{Kr} over $I_{Ca,L}$. Thus, dofetilide is a selective Class III agent, without Class IV (Ca-channel blocking) activity.

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