Pharmacodynamic effect of continuous vs intermittent dosing of dofetilide on QT interval

Michael J. Allen,¹ Stuart D. Oliver,² Margaret W. Newgreen¹ & Donald J. Nichols¹

¹Pfizer Global Research and Development, Ramsgate Road, Sandwich, Kent UK, CT13, 9NJ and ²Covance Medical Research Unit, Springfield House, Hyde Street, Leeds, UK, LS2 9NG

Aims To investigate the pharmacokinetics and pharmacodynamics of dofetilide 1 mg twice daily continuously for 24 days compared with intermittent single dose treatments.

Methods A randomized, single-blinded, placebo-controlled, parallel-group, multiple-dose study design was utilized. Healthy male volunteer subjects were randomized into three groups. Group 1 received dofetilide 1.0 mg twice daily for 23 days and once on day 24. Group 2 received matching placebo capsules under the same regimen as group 1. Group 3 received a single dose of dofetilide 1.0 mg on days 1, 5, 10, 17, and 24 with identical placebo capsules administered at all other times to match the dosing pattern of the other groups.

Results Continuous administration of dofetilide resulted in the achievement of steady-state concentrations by day 5. Pharmacokinetic parameters following intermittent treatment showed no accumulation. Maximum daily QTc interval (mean $\pm$ s.e. mean) increased in response to continuous twice-daily dofetilide from baseline (373 ± 5) to day 2 (453 ± 9) but thereafter decreased slightly, but not beyond day 5, by which time the mean maximum QTc was 440 ± 7 ms. In contrast, single doses of dofetilide in the intermittently treated group led to reproducible increases in QTc. Thus mean ($\pm$ s.e. mean) maximum QTc increased from a baseline of 387 ± 7 – 467 ± 14 , 467 ± 18 , 469 ± 14 and 458 ± 10 ms on days 5, 10, 17 and 24, respectively. In view of the pharmacokinetic accumulation on continuous dosing, the attenuation of responsiveness is best represented by the slope of the QTc *vs* plasma concentration relationship. In the continuously treated group, an initial decrease in the value of the mean slope between day 1 (14.2 ± 1.7 ms/ng ml⁻¹) and day 5 (9.1 ± 0.8 ms/ng ml⁻¹) did not progress beyond day 5. The mean difference in slopes (95% CI) between the intermittent and continuously treated groups were 4.4 (1.3, 7.4) on day 5, 4.9 (1.6, 8.2) on day 10, 5.2 (1.1, 9.2) on day 17 and 4.4 (0.4, 8.4) on day 24.

Conclusions With continuous twice-daily administration the QT interval responsiveness to dofetilide is greater after the first dose than it is at steady state. After day 5 the relationship between dofetilide plasma concentration and its QT interval effect is predictable and stable over time.

Keywords: dofetilide, pharmacodynamics, pharmacokinetics, QT interval

Introduction

Dofetilide, a new potassium channel-blocking agent, selectively inhibits the rapidly activating, delayed rectifier potassium current (I_{Kr}) [1, 2] with little or no impact on

other cardiac potassium channels (I_{K1} , I_{Ks}) or other cardiac ion channels including I_{to} [3–6].

In keeping with its capacity for specific I_{Kr} blockade, dofetilide induces concentration-dependent prolongation of both the effective refractory period (ERP) and action potential duration (APD) in a range of cardiac preparations, without any detectable impact on cardiac resting membrane potential or conduction velocity [2–4]. An increase in ERP and APD is associated with an increase in QT interval. Thus, QT interval

Correspondence: Dr M. J. Allen, Pfizer Global Research and Development, Ramsgate Road, Sandwich CT13 9NJ, Kent UK. Tel.: 01304 648532; Fax: 01304 652144; E-mail: michael_allen@sandwich.pfizer.com

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represents a marker of the electrophysiologic activity of this agent.

In a previous study [7], daily doses of dofetilide 1.0, 1.5, and 2.5 mg were administered to healthy men for 5 days either two or three times a day. The results of this study demonstrated that the slope of the line relating the change in QTc interval to plasma concentration was less steep on day 5 than after the first dose of dofetilide, regardless of frequency, suggesting a degree of attenuation of effect with repeat dosing. Although published data suggest that with repeated oral dosing, steady state is achieved with this agent within 5 days [8], it was not known whether the attenuation of QTc response would be progressive beyond day 5. Thus, it was important to assess the relationship of plasma concentration of dofetilide to changes in QT interval both before and after steady-state pharmacokinetics were achieved and beyond 5 days of dosing.

The aim of this study was to investigate the course and extent of this apparent attenuation of QT responsiveness to dofetilide through assessment of the pharmacokinetics and evaluation of the effect on QT interval of dofetilide 1.0 mg twice daily (a high dose) and dofetilide 1.0 mg administered as intermittent single doses over a period of 24 days.

Methods

Study design

In the 2 weeks before the start of this single-blind, randomized, placebo-controlled, parallel-group, multiple-dose study, healthy male volunteers provided written informed consent and underwent a pre-study examination. A resting 12-lead ECG and 2-channel 24 h ambulatory ECG (Holter) recording were obtained, and blood and urine samples were taken for routine haematologic and biochemical testing and urinalysis.

A sufficient number of volunteers were screened to ensure that 24 evaluable subjects would complete the study. At entry, subjects were randomized in equal numbers to three groups. Group 1 received dofetilide 1.0 mg twice daily for 23 days and only once on day 24. Group 2 received matching placebo capsules under the same regimen as group 1. Group 3 received a single dose of dofetilide 1.0 mg on the mornings of days 1, 5, 10, 17, and 24 with identical placebo capsules administered at all other times to match the dosing pattern of groups 1 and 2. A dose of placebo was given to all subjects at 08.00 h on day 0, the first day of the study.

Before dosing and periodically after dosing, blood samples were taken to monitor plasma concentrations of dofetilide and for routine laboratory safety tests. Blood pressure, heart rate, 3- and 12-lead ECGs, and 24 h

ambulatory (Holter) ECGs were monitored at fixed times throughout the study. Urine was also collected over 12 h periods at intervals during the study for dofetilide assay. A final examination, including physical examination, laboratory tests, blood pressure and heart rate measurement, and 12-lead ECG, was performed 48 h after the last dose and was repeated 2 weeks after the completion of the study at the follow-up visit.

Every subject was required to conform to the inclusion/exclusion criteria outlined in Table 1. The protocol was reviewed and approved by the local ethics committee, and the study was conducted in accordance with the revised Declaration of Helsinki. The study was sponsored by Pfizer and conducted at the Covance Medical Research Unit in Leeds, UK.

Pharmacokinetic analysis

Blood samples for estimation of plasma concentrations of dofetilide were collected before dosing and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, and 12 h after the morning dose on days 1, 5, 10, and 17. Additional samples were taken at 18, 24, 30, 36, and 48 h after the morning dose on day 24. Two 12 h

Table 1 Inclusion and exclusion criteria.

<i>Inclusion criteria</i>
Healthy men: 18–45 years
Weight: 60–90 kg (in range for height and frame size)
HR (after 5 min supine): 55–100 beats min ⁻¹
Supine BP (after 5 min): (90/60–150/90 mmHg)
Written informed consent
<i>Exclusion criteria</i>
Any clinically significant disease
History of asthma, eczema, any other allergic condition, previous drug hypersensitivity. History of cardiac dysrhythmias.
Family history of sudden death before age 40 years
Any significant abnormality of resting ECG or 24 h Holter recording; subjects with resting QTc ≥ 420 ms
Any clinically significant abnormality after prestudy laboratory data and full physical examination. (All laboratory tests in normal range except for bilirubin, alkaline phosphatase, and urea, 10% of normal range)
Prescribed or OTC drug use (except paracetamol) 2 weeks before study
Experimental drug use within 3 months before study
Drug abuse or alcohol consumption (>28 units/week)
Smoking (>5 cigarettes/day or equivalent)
HBsAg or HBcAb positive
Blood donation (during or 1 month before or after study)
Any condition likely to effect absorption of study drug
Mental, physical, or social factors that might interfere with study completion

HR = heart rate; BP = blood pressure; ECG = electrocardiogram; OTC = over the counter; HBsAg = hepatitis B surface antigen; HBcAb = hepatitis B core antibody.

urine samples were collected on days 1, 5, 10, 17, and 24 between morning and evening dosing. All samples were stored at -20°C prior to assay.

Concentrations of dofetilide in plasma and urine were analysed in duplicate by automated double-antibody radioimmunoassay with detection by liquid scintillation analysis [3]. The lower limit of quantification was 0.05 ng ml^{-1} . Within the range $0.1\text{--}1.2\text{ ng ml}^{-1}$ the coefficient of variation of the assay ranged between 7.9% and 14.4%. The between batch variation ranged between 11.0% and 23.4%.

The following pharmacokinetic parameters were derived from the assay data: C_{max} (ng ml^{-1}); t_{max} (h); $\text{AUC}(0, 12\text{ h})$ ($\text{ng ml}^{-1}\text{ h}$) the apparent terminal phase rate constant (K_{el} [h^{-1}]); the mean half-life ($t_{1/2}$ [h]), calculated as $\ln 2/\text{mean } K_{\text{el}}$; and amount of dofetilide (ng) excreted in the urine in 12 h.

Pharmacodynamic measurements

Three-lead ECGs were recorded before the first placebo dose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, and 12 h after the placebo dose. Thereafter, 3-lead ECGs were recorded during the day at the same time as blood samples were taken for the dofetilide assay. For all other treatment days, ECGs were recorded before the morning dose and at 0.5, 1, 1.5, 2, 3, and 4 h after dosing. QT and other ECG time intervals were measured using electronic calipers on computer-captured ECG signals from the analogue output of a Hewlett Packard ECG recorder. On the few occasions when the electronic data capture failed, measurements were made with a digitizing pad from the paper traces. For each subject, measurements were taken from the same lead, and the preferred lead was lead II. To calculate QTc intervals for each subject, Bazett's formula was applied to the 3-lead ECG data. The slope ($\text{ms}/\text{ng ml}^{-1}$) of the change in QTc *vs* dofetilide plasma concentration was analysed to evaluate the sensitivity of QT prolongation to dofetilide exposure.

Safety measures

Twelve-lead ECGs were recorded before the morning dose on days 1, 5, 10, 17, and 24; 2 h after the evening dose on days 1, 2, 3, and 4; and 48 h after the final dose and at follow-up. In addition, Holter monitoring provided 24 h electrocardiographic data at the prestudy screening visit, at baseline (day 0), and on days 2, 5, 10, 17, and 24. Blood pressure and heart rate (after 5 min of supine rest) were measured before dosing, and at 1, 2, and 4 h after the morning dose during the 24 h before the first dose and on days 1, 5, 10, 17, and 24.

Treatment was stopped immediately if there was any indication of an adverse electrophysiologic event: QTc

interval $>600\text{ ms}$ on one recording or two incidences of QTc intervals $>550\text{ ms}$; an increase in premature ventricular complexes or nonsustained ventricular tachycardia equivalent to or in excess of the number calculated according to the CAPS algorithm [9]; new sinus pause $>2.5\text{ s}$ in sinus rhythm; new sinus bradycardia ($<40\text{ beats min}^{-1}$ for $>30\text{ s}$); new third-degree atrio-ventricular or sinoatrial block when the dominant rhythm was sinus rhythm.

Statistical analyses

The maximum change in QTc from baseline to day 24 was subjected to analysis of variance, with baseline QTc as a covariate in the model (baseline QTc was taken as the mean of the pretreatment QTc values). For the maximum change from baseline of QTc on day 24 pairwise comparisons were made between each of the three treatment groups. Using a two-sample *t*-test, the change from day 1 in the mean slope of QTc to dofetilide plasma concentration was compared between the intermittently and continuously treated dofetilide subjects on days 5, 10, 17, and 24. A change in slope of 30% was chosen as a clinically meaningful degree of response attenuation. No adjustments were made for multiple comparisons.

Results

Study population

Of the 26 healthy men randomized to treatment, 10 received continuous dofetilide, 8 received intermittent dofetilide, and 8 received placebo.

In the continuously treated dofetilide group, two subjects were discontinued for reasons probably related to treatment. The first subject was withdrawn after 2 days because of QTc interval prolongation of $>550\text{ ms}$; the second was withdrawn after 5 days of treatment because of nonsustained ventricular tachycardia.

Pharmacokinetics

Steady-state levels of dofetilide were reached by day 5 in subjects treated continuously with dofetilide. Mean maximum ($\pm\text{s.e. mean}$) plasma concentration was $4.79 \pm 0.27\text{ ng ml}^{-1}$ on day 1 rising to 7.10 ± 0.54 on day 5 and was thereafter similar on days 10, 17, and 24 (Table 2). Mean $\text{AUC}(0, 12\text{ h})$ was $31.82 \pm 1.51\text{ ng ml}^{-1}\text{ h}$ on day 1 rising to 47.30 ± 1.80 on day 5 and was thereafter similar on days 10, 17, and 24 (Table 2). Mean C_{max} for the intermittently treated group on day 1 was $4.61 \pm 0.34\text{ ng ml}^{-1}$ on day 1 and was similar on days 5, 10, 17, and 24. Mean $\text{AUC}(0, 12\text{ h})$ was $32.23 \pm 2.35\text{ ng ml}^{-1}\text{ h}$ on day 1 and similar on days 5, 10, 17, and 24

Table 2 Pharmacokinetic parameters (mean $\pm$ s.e. mean) for continuously or intermittently administered dofetilide for 24 days.

	Study treatment day				
	1	5	10	17	24
$C_{\max}$ (ng ml $^{-1}$)					
Cont	4.79 $\pm$ 0.27	7.10 $\pm$ 0.54	6.93 $\pm$ 0.47	7.08 $\pm$ 0.51	6.99 $\pm$ 0.35
Int	4.61 $\pm$ 0.34	4.74 $\pm$ 0.48	4.48 $\pm$ 0.40	4.69 $\pm$ 0.40*	5.01 $\pm$ 0.39
$t_{\max}$ (h)					
Cont	3.13 $\pm$ 0.23	1.94 $\pm$ 0.33	2.31 $\pm$ 0.21	2.13 $\pm$ 0.28	2.38 $\pm$ 0.36
Int	2.81 $\pm$ 0.33	2.56 $\pm$ 0.35	2.56 $\pm$ 0.29	2.50 $\pm$ 0.38*	2.69 $\pm$ 0.21
AUC(0, 12 h) (ng ml $^{-1}$ h)					
Cont	31.82 $\pm$ 1.51	47.30 $\pm$ 1.80	47.54 $\pm$ 1.82	48.52 $\pm$ 2.77	48.60 $\pm$ 2.69
Int	32.23 $\pm$ 2.35	31.59 $\pm$ 2.21	32.05 $\pm$ 1.82	31.70 $\pm$ 2.54*	33.17 $\pm$ 2.33

All values $n=8$ except * ($n=7$).

Cont = continuously; Int = intermittently.

(Table 2). The similarity of $C_{\max}$ and AUC(0, 12 h) values between day 1 of the continuously treated group and days 1, 5, 10, 17, and 24 for the intermittently treated group suggests low inter and intrasubject pharmacokinetic variability. Mean K_{el} for subjects dosed continuously was 0.073 ± 0.002 h $^{-1}$ compared with 0.088 ± 0.003 h $^{-1}$ for intermittent dosing, while mean elimination half-lives were 9.55 and 7.88 h for these groups, respectively. Mean pharmacokinetic parameters are summarized in Table 2.

Pharmacodynamics

For both dofetilide-treated groups, the change in QT interval from baseline increased gradually to a maximum value 2 h after administration and then declined, while negligible changes in QT interval were observed in the placebo group over the same period (11.5 ± 3.9 ms). The maximum change in QTc from baseline to day 24 was 69.1 ± 5.0 ms (baseline 373.1 ± 4.6 ms) for the continuously treated group and 70.4 ± 8.0 ms (baseline 387.1 ± 6.6 ms) for the intermittently treated group. The change from baseline to day 24 was significantly greater for subjects receiving either continuous or intermittent dofetilide than for those receiving placebo alone ($P < 0.0001$ vs placebo); however, there was no statistically significant difference between the two dofetilide-treated groups. The levels of maximum change in QTc from baseline in the group treated intermittently with dofetilide dropped to a similar level to those in the placebo group on the days when placebo was administered (Figure 1). In contrast to the pharmacokinetic accumulation of dofetilide to steady state by day 5 with continuous dosing of dofetilide, the QTc response increased from baseline to day 2 but thereafter showed a marginal decrease, which did not progress further after day 5. Single intermittent doses of dofetilide resulted in reproducibly intermittent increases in QTc (Figure 1).

Figure 1 Mean maximum change in QTc interval from baseline over 24 days in subjects dosed with placebo (+) or dofetilide 1 mg twice daily administered continuously (◆) or intermittently (□).

In view of the pharmacokinetic accumulation between days 1 and 5, the responsiveness to dofetilide is best represented by the relationship between plasma dofetilide concentrations and change in QTc. Mean values for the slopes of the plasma concentration vs change in QTc curve over the 24 day dosing period for the two groups receiving dofetilide are presented in Figure 2. A summary analysis of the change in slope from day 1 is shown in Table 3. After an initial drop in mean slope from 14.20 ± 1.68 ms/ng ml $^{-1}$ on day 1 to 9.05 ± 0.79 ms/ng ml $^{-1}$ on day 5, there was little variation within the continuously treated dofetilide group (8.40 ± 0.81 – 9.05 ± 0.79 ms/ng ml $^{-1}$). The value of the mean slope recorded for the intermittent group was consistent and in the range 15.37 ± 2.05 – 16.13 ± 1.77 ms/ng ml $^{-1}$ at all assessment times.

There was no evidence that dofetilide clinically affected systolic or diastolic blood pressure, heart rate, or electrocardiographic intervals other than QT with intermittent or continuous dosing.

Discussion

This study revealed three important findings:

1. Continuous administration of dofetilide 1 mg twice daily for 24 days resulted in steady-state concentrations achieved by day 5.

2. Changes in QTc interval that occurred in response to continuous twice-daily dofetilide increased from baseline to day 2 but did not progress thereafter and the mean maximum QTc decreased slightly between days 2 and 5.

3. A statistically significant difference occurred in the slopes of the change from baseline QTc *vs* plasma dofetilide concentration curves over 24 days between the intermittent and continuous dofetilide groups, indicating a reduced but not progressive responsiveness with continued exposure.

Figure 2 Mean slope of plasma dofetilide concentration *vs* change in QTc over 24 days in subjects treated continuously (light grey) or intermittently (black) with dofetilide. The bars above each column represent 1 standard error of the mean.

There are published data on the plasma pharmacokinetics of dofetilide administered as a single oral dose, and the relationship between the resultant pharmacokinetic and pharmacodynamic changes over periods up to 48 h after dosing [10, 11]. However, this study is a comparison of the pharmacokinetic/pharmacodynamic characteristics of dofetilide during repeated intermittent and continuous oral dosing over an extended period.

Establishing a relationship between plasma concentrations and pharmacodynamic effect, assessed in this study by measurement of the QTc interval, was necessary to confirm the predictability of clinical effect based on the pharmacokinetic characteristics of a given dosing regimen. This predictability is particularly important because prolongation of QT interval is both a risk factor for proarrhythmic events and a marker of the desired pharmacology of class III antiarrhythmic agents, such as dofetilide, which achieve their antiarrhythmic effect by prolongation of repolarization. Thus, predictability of the relationship between pharmacokinetic and pharmacodynamic effect is central to both the clinical safety and potential efficacy profile of dofetilide. Although this study was conducted using a dofetilide dose 2–4 times higher than recommended in clinical practice, it has provided further insight into the relationship between dosing regimen and the plasma pharmacokinetic and the pharmacodynamic effect of this agent.

The data from the intermittent dosing component of this study are consistent with published data, with peak plasma concentrations being reached in 2.5–3 h, and elimination half-life from the plasma occurring in the published range of 6–13 h (mean ~7.9 h) [12–14]. This consistency was maintained throughout the study at each of the intermittent doses (Table 2), with low inter- and intra-subject variability in pharmacokinetic parameters. Comparison of such parameters throughout the 24 day study showed no significant differences between plasma concentrations on each day of dosing or between the amounts of dofetilide excreted in the urine over 24 h

Table 3 Summary analysis of mean ($\pm$ s.e. mean) changes of plasma dofetilide concentration *vs* change in QTc relationship.

Dofetilide 1 mg dosing group	Day 1 slope	Change in slope from day 1 (ms/ng ml^{-1})			
		Day 5	Day 10	Day 17	Day 24
Cont	14.2 ± 1.7	-5.2 ± 1.3	-5.6 ± 1.2	-5.4 ± 1.5	-5.8 ± 1.5
Intermittent*	16.1 ± 1.8	-0.8 ± 0.6	-0.7 ± 0.9	-0.2 ± 1.1	-1.4 ± 1.1
Mean difference in change in slope		4.4	4.9	5.2	4.4
95% confidence interval of difference		1.3, 7.4	1.6, 8.2	1.1, 9.2	0.4, 8.4
P value between treatments		0.011	0.008	0.023	0.037

*Slope of plasma concentration *vs* change in QTc not calculated for one subject in intermittent dofetilide group since data were not amenable to regression analysis. Only QTc data for this subject was analysed and tabulated.

Cont = continuously, twice daily oral doses of dofetilide 1 mg (all values $n=8$); Int = intermittently, single oral doses of dofetilide 1 mg ($n=7$).

(Table 2). Drug accumulation was not evident in the intermittent group.

In the continuous dosing group mean pharmacokinetic values on day 1 were comparable with those with intermittent dosing. However, it is clear from the data that continuous administration resulted in accumulation, and steady-state dofetilide plasma concentrations were reached by day 5 of the dosing schedule and maintained throughout the rest of the study (Table 2).

Both intermittent and continuous dosing resulted in significant increases in QTc interval when compared with placebo. However, comparison of changes in QTc values elicited by the two dosing schedules revealed important differences. Intermittent, reproducible changes on the day of dosing, with recovery of QTc interval to baseline on those days where dofetilide was not administered, were seen with intermittent treatment alone. Previous analysis of QTc response to different oral doses of dofetilide suggested that with repeat, continuous dosing prolongation of repolarization might be attenuated [7]. If the attenuation progressed over time, implications for the therapeutic utility of this agent would be obvious. However, previous studies generated data for only 5 days. The present study clearly demonstrates that this attenuation effect does not progress beyond day 5, a point by which steady-state pharmacokinetics is reached. This study also showed that, in response to repeat dosing, the QTc increased from baseline during days 1 and 2 but not in the same proportion to the expected or measured plasma drug concentrations thereafter. If anything, the mean maximum QTc fell between days 2 and 5. This apparent decrease in the responsiveness of prolongation of repolarization to dofetilide is best reflected in the slope of the plasma concentration *vs* QTc curve over the same period. These data demonstrate that there is no further attenuation of responsiveness beyond day 5.

A possible interpretation of the finding would be that responses were saturated at the drug concentrations seen around day 2 (i.e. that subjects had reached a plateau on their concentration-response relationships). However, the attenuation of responses between days 1 and 5 was seen in all subjects, regardless of the absolute plasma concentrations, and was also seen in a previous study at much lower doses and plasma drug concentrations [7]. The reasons for the short-term attenuation of effect observed in this study are unclear but it may be an adaptational response to sustained exposure to dofetilide.

In this study, the increase in QTc prolongation that occurred by day 2 may be an indicator of maximum risk of prodysrhythmia. It is advantageous that this period of maximum risk occurs early in a dosing schedule when a patient is still under medical supervision. In clinical practice, dofetilide is administered during a hospital stay lasting 3 days, and ECG monitoring during that period

should reduce the risk of prodysrhythmia [15]. In contrast, 1 month treatment with oral sotalol 160–320 mg day⁻¹ enhances its effect on ventricular repolarization and thus the degree of QTc prolongation increases [16]. It has been suggested that this may represent an adaptational response to chronic β -adrenoceptor blockade [17]. It is likely that the attenuation of dofetilide-induced QTc interval prolongation that occurs with repeated dosing may potentially limit the development of prodysrhythmia to the early dosing period, although the significance of this phenomenon in patients with cardiac dysrhythmias is unclear at present.

In conclusion repeated dosing with oral dofetilide causes the change in QT interval to peak on day 2 and attain a steady state by day 5. The short-term attenuation effect on QT prolongation, which is a decreased responsiveness to drug rather than pharmacokinetic in origin, does not progress with long-term dofetilide dosing.

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