

Figure 2:

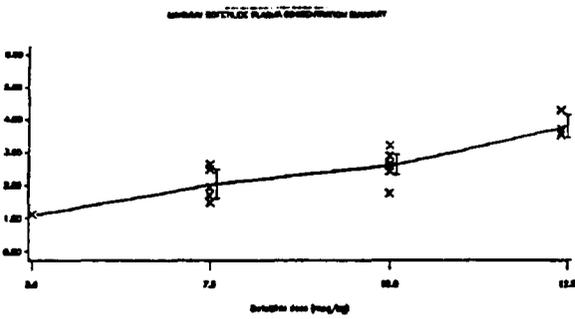


Figure 3:

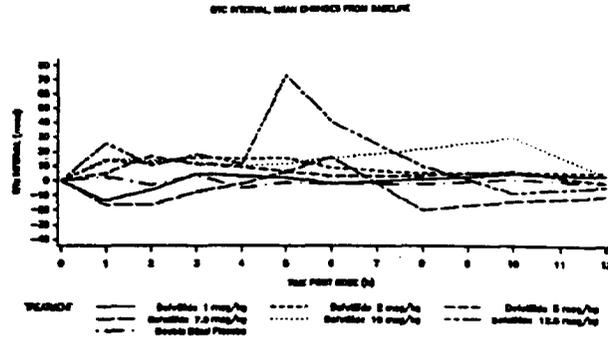
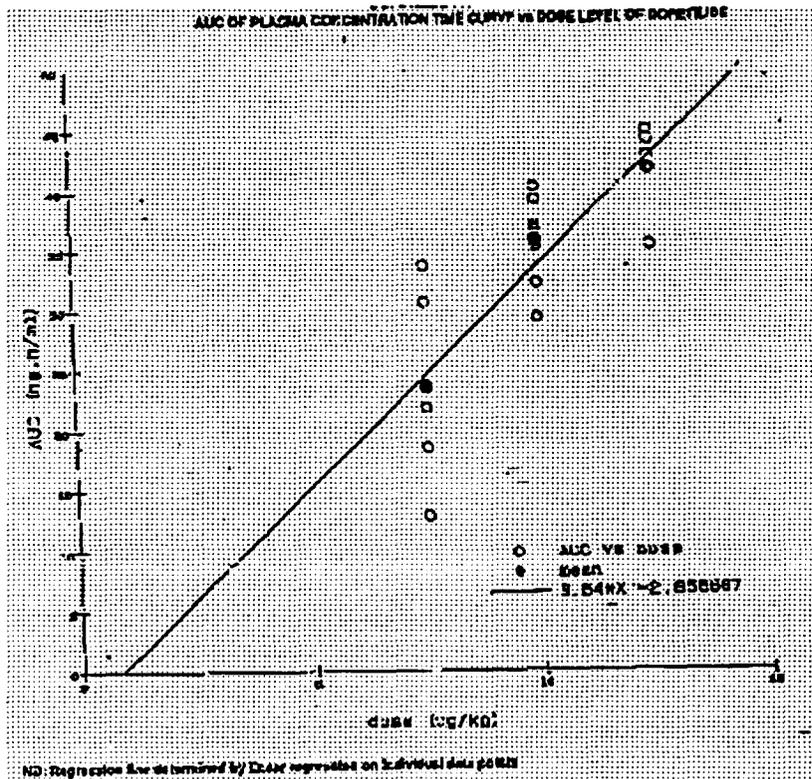


Figure 4:



**CONCLUSIONS:** The data obtained from the study demonstrated a linear relationship between plasma concentration (C<sub>max</sub> and AUC) and dose. Plasma concentrations declined with a mean elimination rate constant between 0.081 and 0.090h<sup>-1</sup> corresponding to harmonic mean half-life values of 7.5-8.6 hours. The percentage of dose excreted unchanged in the urine for doses 7.5mcg/kg, 10mcg/kg and 12.5mcg/kg were 58%, 64% and 67% respectively. Due to the diverse range of changes in QTc observed, the definition of a meaningful change for this population was not clear. Therefore it was not possible to establish the dose of dofetilide required to produce a “measurable” change in QTc.

## **SINGLE DOSE-RANGING STUDY**

**STUDY 115-202**

**VOLUMES: 2.22**

**INVESTIGATOR AND LOCATION:**

**STUDY DATE:** June 1988 - January 1989.

### **OBJECTIVES:**

To assess the safety and toleration of dofetilide. To examine the pharmacokinetic profile of dofetilide and to establish the dose required to produce measurable changes in the QT interval of the ECG.

### **FORMULATIONS:**

Dofetilide, solution for oral administration, 5 mg/100ml, FIDs 0954 (lot 733-37) and 0925 (lot 763-01)

Placebo solution, 0.002M HCl, FID 0925 (lot 733-34) and lot 763-06

### **STUDY DESIGN:**

This was a single-blind, placebo-controlled study using 5 escalating doses of dofetilide and one dose of placebo. Subjects were randomized in equal numbers into two groups to receive placebo and 1, 2, 5, 7.5 and 10 mcg/kg dofetilide. Each dose was given on a separate day and each study day was separated by at least 7 days. Progression to higher doses of dofetilide was determined by the safety and toleration of the preceding doses. Subjects were randomized into 2 groups of 6 to receive all 5 doses of dofetilide. Placebo was administered on the second day of dosing for group I subject numbers 4, 5, and 6; in group II, placebo was assigned to all subjects on Day 1 only. Blood samples were not required from any subjects on treatment days 1 and 2 (i.e. following the 1 mcg/kg and either 2 mcg/kg or placebo doses for group I subjects and following placebo and the 1mcg/kg dose for group II). At all other doses, blood (4 ml) samples were collected for estimation of plasma levels of dofetilide just prior to dosing and at 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 24, 48 and 72 hours post-dose. Labelled plasma samples were to be stored at -20°C until assayed. Urine samples were collected during the 2-hour period immediately prior to dosing and over the following periods post-dose: 0-12 hours, 12-24 hours and 24-48 hours. Volumes were recorded and two 9ml aliquots were labelled and stored at -20°C until assayed.

### **ASSAY:**

DATA ANALYSIS: AUC, Cmax, Tmax, Kel, t½ and urinary excretion were determined.

RESULTS: Tables 1-2 and Figures 1-4 summarize the pharmacokinetics and pharmacodynamics data obtained from the study.

Table 1.

Pharmacokinetics Results: (Means ± S.D.)	Dofetilide 1mcg/kg	Dofetilide 2mcg/kg	Dofetilide 5mcg/kg	Dofetilide 7.5mcg/kg	Dofetilide 10mcg/kg	Placebo
Cmax (ng/ml)	-	0.54 ± 0.11	1.29 ± 0.29	2.43 ± 0.84	2.77 ± 0.39	-
Tmax (h)	-	2.50 ± 1.50	2.40 ± 1.20	2.00 ± 1.30	1.20 ± 0.40	-
AUCt (ng.h/ml)	-	3.81 ± 0.70	13.62 ± 2.22	21.83 ± 3.50	29.47 ± 3.40	-
AUC (ng.h/ml)	-	-	15.82 ± 2.50	24.84 ± 3.31	33.00 ± 2.99	-
Kel (/h)	-	-	0.090 ± 0.013	0.091 ± 0.011	0.082 ± 0.012	-
T1/2 (h) (harmonic mean)	-	-	7.7	7.6	8.4	-
% excreted in urine	44.3 ± 15.5	51.0 ± 22.9	62.2 ± 11.8	68.8 ± 15.9	57.8 ± 15.8	-
<b>Pharmacodynamics</b>						
<b>Results:</b>						
Mean increase in QTc interval from baseline (msec, 2 hours post-dose) ± S.E.	1.40 ± 4.06	6.70 ± 6.41	22.35 ± 5.05	9.02 ± 8.06	34.04 ± 17.80	-1.72 ± 7.60
		<i>Dofetilide</i>	<i>Placebo</i>			

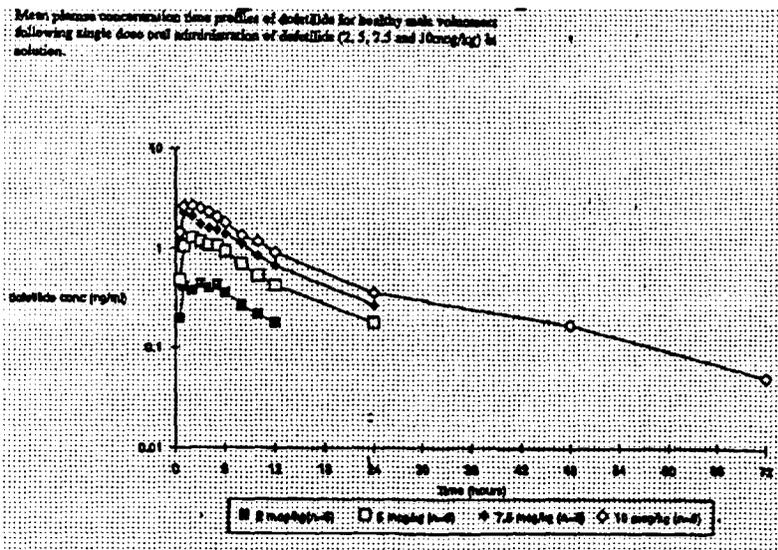
Table 2:

QTc INTERVAL, MEAN CHANGES FROM BASELINE

QTc INTERVAL BAZETS (msec)

TREATMENT		TIME POST DOSE (h)							
		BASE-LINE	1	2	4	8	12	24	
DOFETILIDE 1 mcg/kg ORAL SOLUTION	MEAN	409.95	-3.40	1.40	-3.27	-5.07	-6.60	-6.68	
	S.E.	3.12	3.67	4.06	2.65	2.96	3.42	4.26	
	N	11	11	11	11	11	11	11	
DOFETILIDE 2 mcg/kg ORAL SOLUTION	MEAN	409.97	-2.18	6.70	6.80	3.45	-5.29	1.24	
	S.E.	3.61	4.48	6.41	7.00	4.43	4.64	6.21	
	N	10	10	10	10	10	10	10	
DOFETILIDE 5 mcg/kg ORAL SOLUTION	MEAN	407.89	12.67	22.35	19.19	16.64	6.09	-0.66	
	S.E.	5.79	4.13	5.05	3.11	6.37	3.36	4.24	
	N	10	10	10	10	10	10	10	
DOFETILIDE 7.5 mcg/kg ORAL SOLUTION	MEAN	417.20	2.47	9.02	4.89	-1.00	-1.29	-12.01	
	S.E.	6.27	14.97	4.08	6.04	2.41	6.12	4.42	
	N	8	8	8	8	8	8	8	
DOFETILIDE 10 mcg/kg ORAL SOLUTION	MEAN	403.24	39.35	34.04	37.01	20.15	6.67	9.36	
	S.E.	9.92	20.78	17.80	14.30	9.62	5.09	2.18	
	N	8	8	8	8	8	8	8	
PLACEBO	MEAN	404.74	-0.36	-1.72	2.68	2.10	-2.42	-0.64	
	S.E.	3.95	6.99	7.60	6.74	5.60	4.17	3.22	
	N	11	11	11	11	11	11	11	

Figure 1:



## **PHARMACOKINETIC-PHARMACODYNAMIC STUDY**

**STUDY 115-308**

**VOLUMES: 2.222**

**INVESTIGATOR AND LOCATION:** [REDACTED]

**STUDY DATE:** December 1990 - April 1993.

### **OBJECTIVES:**

To assess efficacy, pharmacokinetics, electrophysiological effects (EP), safety and toleration of oral dofetilide in subjects with susceptible to sustained ventricular tachycardia (VT).

### **RATIONALE**

The most widely used drugs for treatment of arrhythmias are the Class I anti-arrhythmic drugs. However, despite their generally good efficacy, they have some disadvantages, including a potential for negative inotropy due to blockade of fast sodium channels, which is their primary mode of action. Dofetilide, currently in late phase development for the treatment of a broad range of supraventricular and ventricular tachyarrhythmias, is a selective potassium channel blocker which has shown no pre-clinical evidence of cardiac depression. This study was intended to examine the ability of dofetilide to prevent or reduce the clinical inducibility of sustained ventricular tachycardia (VT) and examine safety in susceptible subjects.

### **FORMULATIONS:**

250mcg dofetilide capsules FID No. 0963 Lot No. 842-47 & 904-21

500mcg dofetilide capsules FID No. 0964 Lot No. 503-04

Dosing Oral 250, 500, 750 and 1000 mcg twice daily (bd)

Duration 3-6 day acute phase with optional 12 month chronic phase

### **STUDY DESIGN:**

This was a multicentre, open study in subjects from a patient population which was susceptible to sustained VT. Subjects who had a clinical requirement for invasive electrophysiological investigation underwent PES to induce sustained VT before and after treatment with dofetilide. Four groups of eight subjects were given twice daily oral treatment with dofetilide 250, 500, 750 or 1000 mcg for a minimum period of three days (acute phase), escalation of dose being dependent on the safety and toleration of the previous treatment. Each subjects' final dose was to be taken the evening before the second programmed electrical stimulation (PES) procedure. At the discretion of the investigators, subjects who responded to study treatment continued on dofetilide for a period of 12 months (chronic phase). Blood samples for the determination of plasma concentrations of dofetilide were obtained immediately before, then 2, 4 and 12 hours after the initial dose of study drug on the first and final days of dosing during the acute phase.

**ASSAY:** {

DATA ANALYSIS: AUC, Cmax, Tmax, and CL/F were determined.

RESULTS: Table 1 and Figures 1-10 summarize the pharmacokinetics and pharmacodynamics data obtained from the study.

Table 1.

**Pharmacokinetic parameters of dofetilide**

Parameter	250	500	750	1000
C <sub>max</sub> Day 1 (ng/ml)	1.08 ± 0.53 (6)	1.99 ± 0.60 (7)	3.94 ± 2.00 (4)	5.19 ± 1.03 (9)
C <sub>max</sub> Day 3 (ng/ml)	1.75 ± 0.57 (6)	3.52 ± 0.44 (8)	5.95 ± 2.41 (4)	8.80 ± 2.22 (8)
T <sub>max</sub> Day 1 (h)	3.1 ± 1.1 (6)	2.6 ± 1.0 (7)	2.5 ± 1.0 (4)	4.2 ± 2.9 (9)
T <sub>max</sub> Day 3 (h)	3.5 ± 4.1 (6)	2.9 ± 3.9 (8)	2.1 ± 1.6 (4)	2.3 ± 1.2 (8)
AUC <sub>0-∞</sub> Day 1 (ng·h/ml)	8.7 ± 3.5 (5)	14.2 ± 2.5 (7)	25.2 ± 10.3 (4)	41.4 ± 12.3 (8)
AUC <sub>0-∞</sub> Day 3 (ng·h/ml)	15.4 ± 4.6 (5)	30.5 ± 4.4 (7)	48.1 ± 27.5 (3)	78.8 ± 19.3 (7)
CL/F Day 3 (L/h)	17.6 ± 5.6 (5)	16.7 ± 2.2 (7)	19.2 ± 9.8 (3)	13.4 ± 3.3 (7)

Values are mean ± SD (n)

Figure 1:

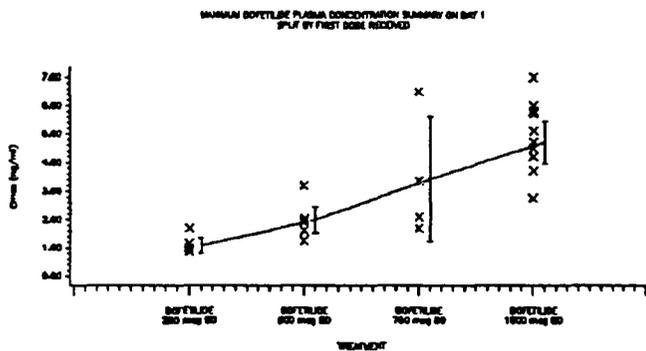


Figure 2:

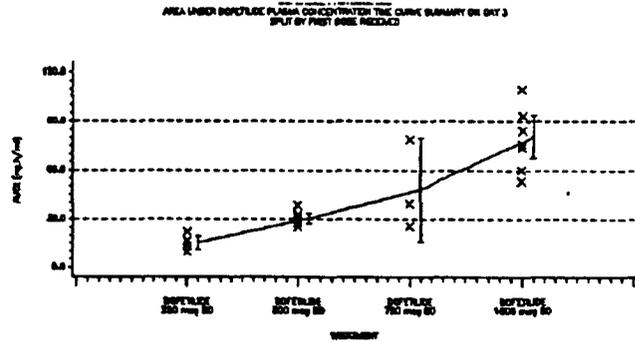


Figure 3:

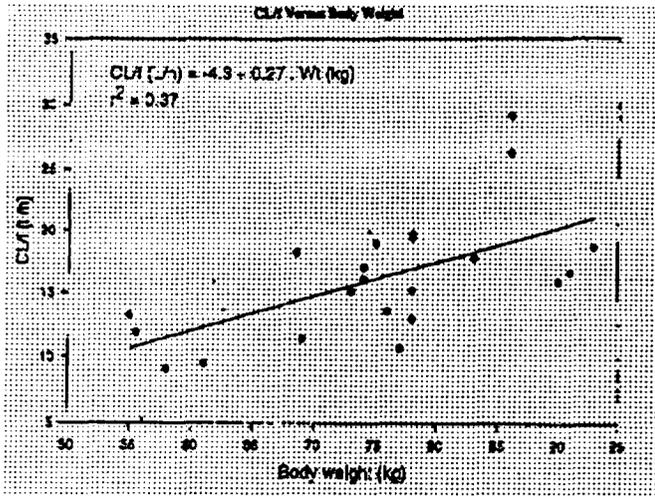


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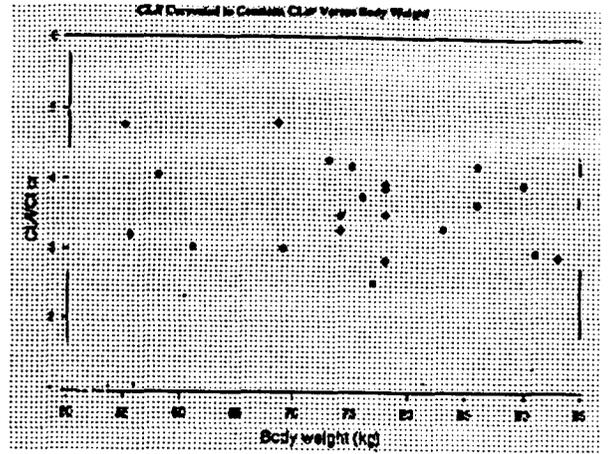


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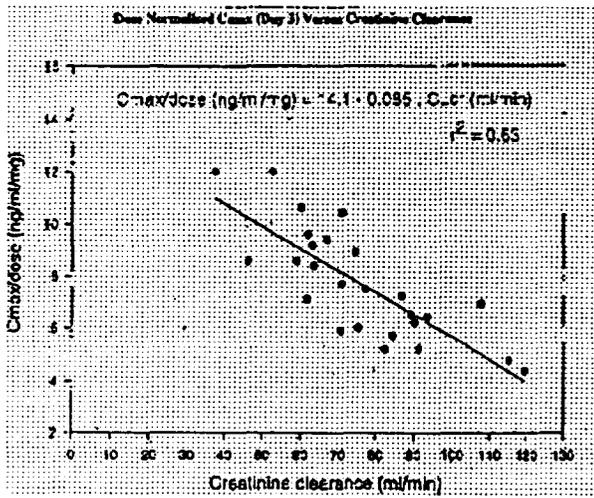


Figure 6:

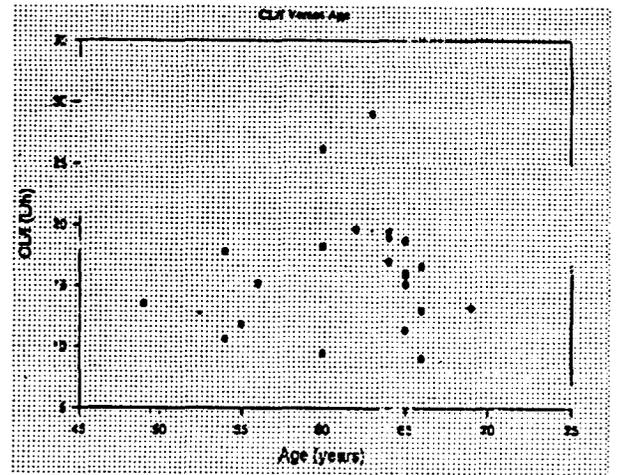


Figure 7:

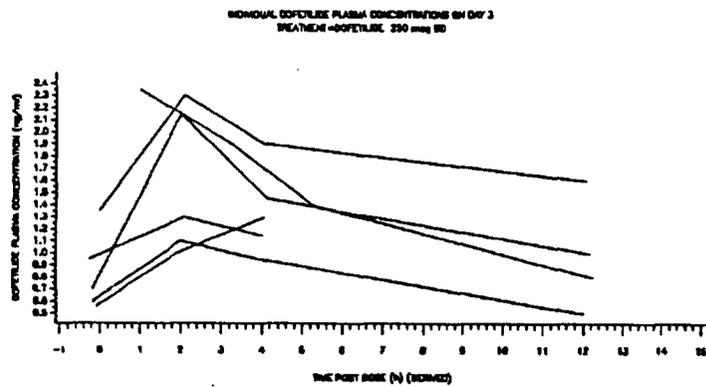
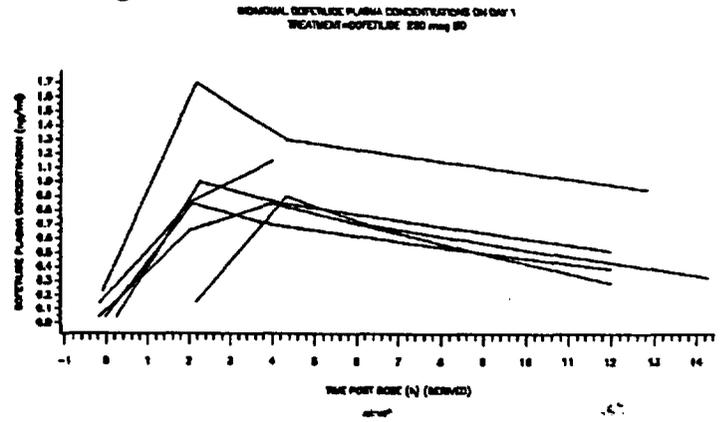
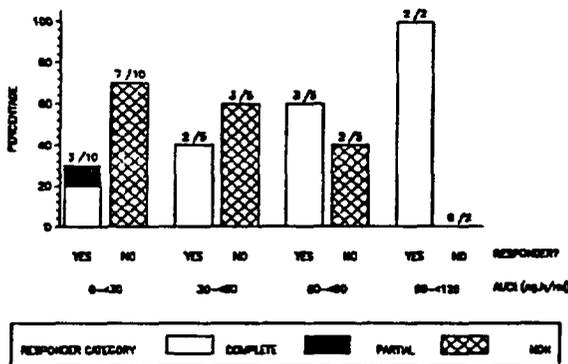


Figure 8:



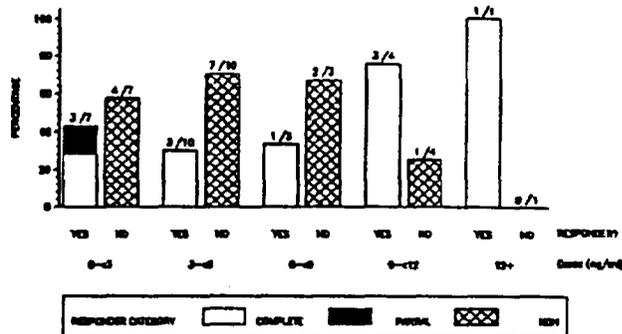
**Figure 9:**

RELATIONSHIP BETWEEN RESPONSE AND AREA UNDER DOFETILIDE PLASMA CONCENTRATION CURVE ON DAY 3



**Figure 10:**

RELATIONSHIP BETWEEN RESPONSE AND MAXIMUM DOFETILIDE PLASMA CONCENTRATION ON DAY 3



**CONCLUSIONS:**

Data obtained from the study showed both AUC and Cmax increased with dose although there was some between-subject variability. Accumulation ranged between 1.6 - 2.2, which was consistent with the known half-life of 9 - 12 hours. The possible relationship between oral clearance and left ventricular ejection fraction, age, body weight, and creatinine clearance was investigated. No significant correlation was found with left ventricular ejection fraction or age. There was a weak correlation with body weight ( $r^2 = 0.37$ ) but a strong correlation with creatinine clearance ( $r^2 = 0.70$ ). Thus:

$$CL/F (L/h) = 1.71 + 0.19.Clcr (ml/min)$$

When oral clearance was corrected for creatinine clearance, then the relationship with body weight disappeared. In addition, there was a direct relationship when dose-normalised Cmax values were correlated with Clcr. These findings suggest that the major determinant of between-subject variability in exposure to dofetilide is creatinine clearance.

The relationship between QTc and plasma concentration was explored. There were insufficient data to determine pharmacokinetic-pharmacodynamic parameters. The relationship between efficacy and plasma concentration was explored. Using the day 3 AUC, values, the percentage of subjects having efficacy increased in line with increasing exposure (with exposure of 0-30 ng.h/ml the response was 50%, between 30-60 it was 60%, between 60-90 it was 80% and over 90 it was 100%). The existence of a clear exposure-efficacy relationship in the absence of a clear dose-response relationship can possibly be accounted for by the between patient variability introduced into the pharmacokinetics by differing degrees of renal impairment (as evaluated by creatinine clearance).

## PHARMACOKINETIC-PHARMACODYNAMIC STUDY

STUDY 115-310

VOLUMES: 2.67

INVESTIGATOR AND LOCATION: [

STUDY DATE: July 1991 to October 1993.

### OBJECTIVES:

To assess the short-term efficacy (using programmed electrical stimulation, PES), safety and toleration of escalating doses of dofetilide administered orally (capsule) to subjects with confirmed AVNRT or AVRT. The study was also used to obtain information about the electrophysiology (EP) and pharmacokinetics (PK) of dofetilide.

### FORMULATIONS:

Dosage Form Dofetilide capsules 250 mcg (FID No. 0963: Lot Nos. 904-21, 503-15, 842-33, 503-18, 904-15, 503-16 and 842-47) and 500 mcg (FID No. 0964: Lot Nos. 503-04, 842-49 and 904-22).

Dosing: Oral 250 mcg bid, 750mcg bid or 1250 mcg bid.

Duration Minimum: 3-day acute phase with optional 12-month chronic phase.

### STUDY DESIGN:

A multicentre, open-label, dose-ranging study designed to evaluate the short-term efficacy, safety and toleration of dofetilide when administered orally, by capsule, to subjects with AVNRT or AVRT, induced by PES. Short-term efficacy was assessed during acute treatment (minimum of 3 days) by measuring the effect of dofetilide on inducibility of AVNRT/AVRT using PES. The EP and PK profiles of dofetilide were also assessed during this period. Subjects showing a complete or partial response to dofetilide during the acute phase were, at the discretion of the investigator, invited to continue dofetilide treatment during a 12-month chronic phase. Blood samples for estimation of dofetilide concentrations were collected at the following time points: immediately prior to the initial dofetilide dose and then 1, 2, 4, 6, 8 and 12 hours after the morning dose on Day 1; pre-dose and 2 hours after the morning dose on the Day 2; the day before the second electrophysiological investigation at the same time points as Day 1 the day of the second electrophysiological investigation at 1, 12, 18, 24, 36 and 48 hours after dosing (if possible). During the chronic phase of the study, a blood sample for determination of dofetilide plasma concentrations was to be obtained at each visit.

ASSAY: [

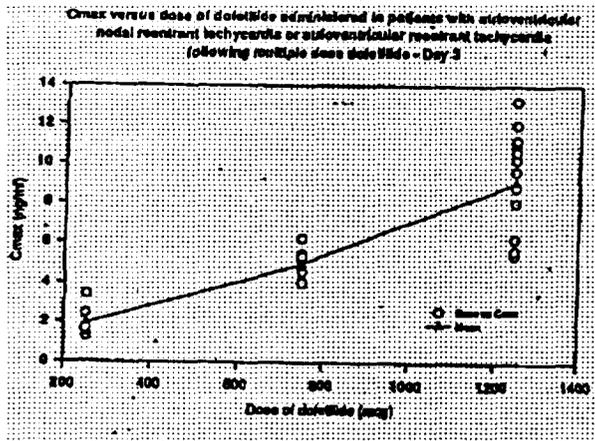
**DATA ANALYSIS:** AUC, Cmax, Tmax, and CL/F were determined. The data were examined for relationship between oral clearance and age, body weight, LVEF and creatinine clearance. Also, the relationships between QTc and plasma concentration, and efficacy and plasma concentration were tested.

**RESULTS:** Table 1 and Figures 1-10 summarize the pharmacokinetics and pharmacodynamics data obtained from the study.

**Table 1:**  
**Pharmacokinetics**  
(mean ± SD):

	Dose bid (n)		
	250mcg (n=6)	750mcg (n=8)	1250 (n=13)
Cmax Day 1 (ng/ml)	1.45 ± 0.80	3.46 ± 0.94	6.22 ± 1.36
Cmax Day 3 (ng/ml)	1.92 ± 0.83	4.95 ± 0.72	9.03 ± 2.66
Tmax Day 1 (h)	2.38 ± 1.36	1.91 ± 1.05	2.08 ± 0.95
Tmax Day 3 (h)	3.29 ± 1.51	1.84 ± 1.03	1.82 ± 1.07
AUC <sub>t</sub> Day 1 (ng.h/ml)	8.71 ± 2.96	20.91 ± 3.65	38.49 ± 8.32
AUC <sub>t</sub> Day 3 (ng.h/ml)	14.65 ± 6.39	36.83 ± 7.21	64.20 ± 15.71
CL/F Day 3 (L/h)	19.93 ± 8.18	21.12 ± 4.49	20.48 ± 4.53

**Figure 1:**



**Figure 2:**

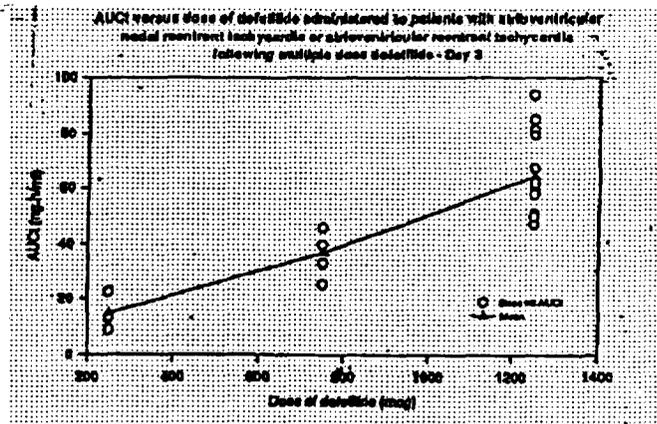


Figure 3:

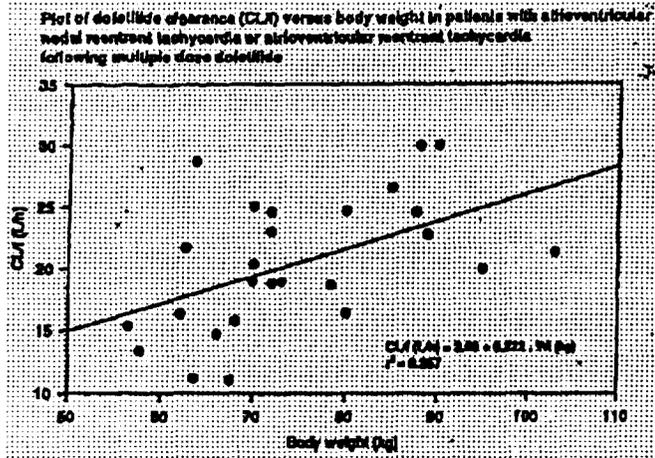


Figure 4:

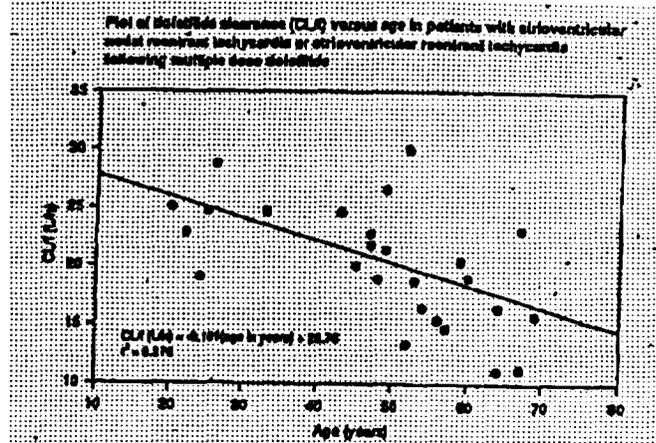


Figure 5:

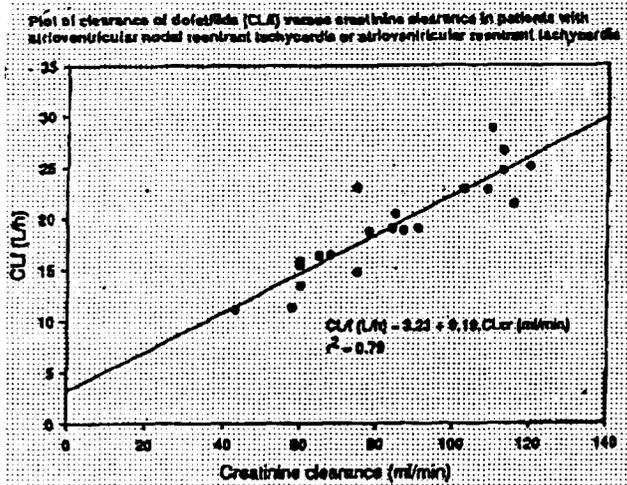


Figure 6:

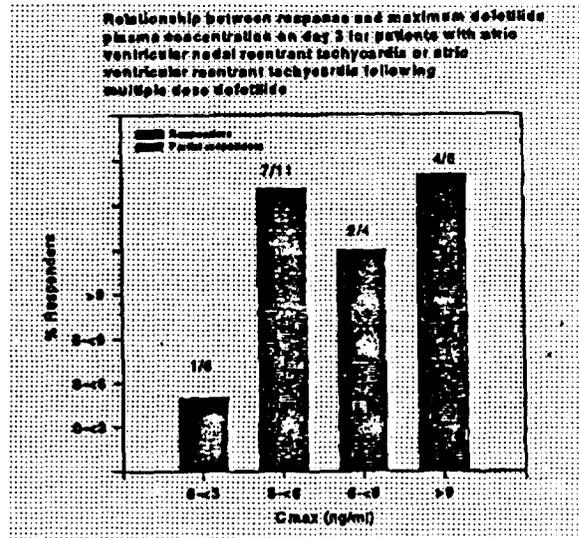
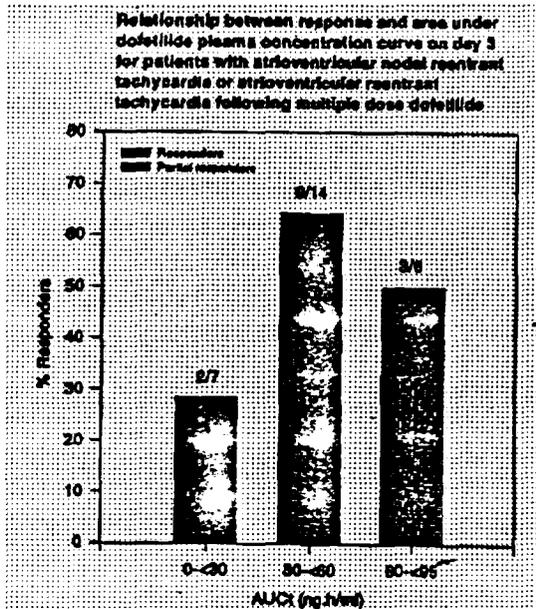


Figure 7



### CONCLUSIONS:

The data obtained from the study showed that  $C_{max}$  and  $AUC_t$  values generally increased linearly with dose, although there was some between-subject variability. Accumulation was in the range 1.4 to 2.0 and consistent with the known half-life (approximately 9 to 12 hours) of dofetilide. There was no correlation between dofetilide clearance and LVEF. There was a weak correlation between dofetilide clearance and age ( $r^2 = 0.28$ ) and body weight ( $r^2 = 0.26$ ) and a strong correlation between dofetilide clearance and creatinine clearance ( $r^2 = 0.79$ ). When dofetilide clearance was corrected for creatinine clearance, the weak relationships with age and body weight were no longer demonstrated. There was a correlation ( $r^2 = 0.64$ ) between dose normalised  $C_{max}$  and creatinine clearance. The data support dosage adjustment recommendations based on creatinine clearance in order to achieve a consistent exposure in subjects with impaired renal function. There were trends towards increasing duration of QT interval and  $QT_c$  (Bazett's) with dose. There was weak evidence for a relationship between maximum plasma concentration ( $C_{max}$ ), exposure ( $AUC_t$ ) and efficacy. No subjects with  $C_{max}$  concentrations below 3 ng/ml were classified as responding to dofetilide treatment. While subjects with  $C_{max}$  concentrations > 3 ng/ml had a response rate of 36%. For  $AUC_t$ , 14% of responding subjects had  $AUC_t$  values < 30 ng.h/ml whilst 46% had  $AUC_t$  values > 30 ng.h/ml. The relationship between plasma concentration and  $QT_c$  was not explored because the nature of the subjects' underlying cardiac disease made the ECG data not suitable for analysis.

## **MULTIPLE DOSE PHARMACOKINETIC STUDY**

**STUDY 115-203**

**VOLUMES: 2.23**

**INVESTIGATOR AND LOCATION:**

**STUDY DATE:** September 1988 - January 1989.

### **OBJECTIVES:**

To investigate the pharmacokinetics of four oral dose levels of dofetilide and to compare the safety and toleration of dofetilide with placebo during 10 days treatment in normal subjects.

### **Drug Administration:**

Test Product: Dofetilide, solution for oral administration, 5 mg/100ml, FIDs: 0954, lot 733-37; and 2 mg/100ml, FID 0958, lots 763-01, 763-02, 763-04 and 733-48  
Diluent and Reference Placebo solution: 0.002M HCl, FID: 0925, lots 763-01, 763-06, 763-09, 733-34 and 733-36.

Dosing: Dofetilide, 100 mcg bd, 200 mcg bid, 200 mcg od or 400 mcg bid (appropriate aliquots made up to 100 ml with diluent), or placebo, given for 10 days. Morning doses were given between 7.30 a.m. and 9.30 a.m., 1 hour before a carbohydrate breakfast. Evening doses were given approximately 12 hours later on Days 1-9.

### **STUDY DESIGN:**

This was a two centre, double-blind, placebo-controlled, sequential, parallel group study. At each centre, 4 groups of 8 subjects were studied. Each group consisted of 4 dofetilide and 4 placebo treated subjects. Dofetilide was administered at four dose levels: 100 mcg bid, 200 mcg od, 200 mcg bid and 400 mcg bid. The study was carried out sequentially, so that progression to higher doses of dofetilide was determined by the safety and toleration at the preceding dose levels. Blood (4-5 ml) samples were collected for estimation of plasma levels of dofetilide just prior to dosing and at 1, 2, 3, 4, 6, 8 and 12 hours post-dose on Days 1 and 10. Additional samples were collected 24 hours after the morning dose on Day 1 and at 24, 36, 48, 72 and 96 hours after the morning dose on Day 10. On Days 3 to 9 inclusive, a sample was collected just prior to the morning dose only. Plasma samples were to be stored at -20°C until assayed.

Urine was collected during the 2-hour period immediately prior to the initial dose of dofetilide or placebo and over the following periods after the morning dose on Days 1-10: 0-12 hours and 12-24 hours. Volumes were recorded and two 9ml aliquots from each 12-hour period on Days 1 and 10 were to be labelled and stored at -20°C until assayed.

### **ASSAY:**

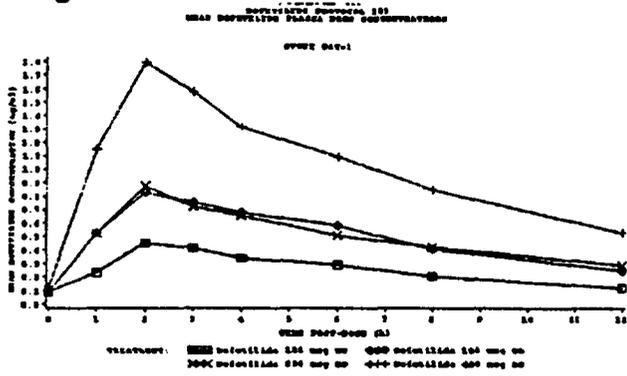
**DATA ANALYSIS:** AUC, Cmax, Tmax, Kel, t1/2 and CL<sub>R</sub> were determined. The change from baseline in QTc and QT and the maximum change from baseline in QTc and QT were analysed.

**RESULTS:** Table 1 and Figures 1-6 summarize the pharmacokinetics and pharmacodynamics data obtained from the study.

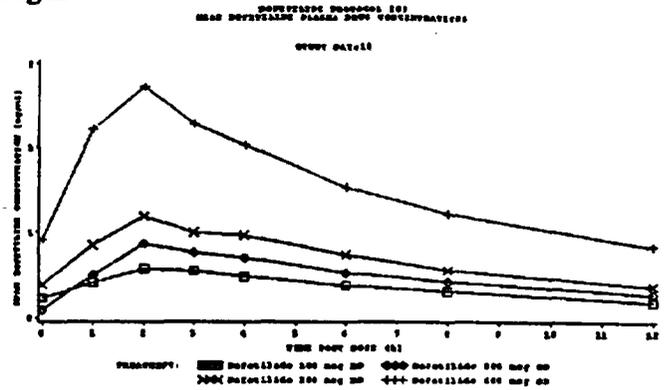
**Table 1:**

<b>Pharmacokinetics Results:</b>	Dofetilide 100mcg bd	Dofetilide 200mcg od	Dofetilide 200mcg bd	Dofetilide 400mcg bd	Placebo
<b>Day 1 (Means)</b>					
Cmax (ng/ml) a	0.50	0.83	0.83	1.81	-
Tmax (h) a	2.5	2.1	2.6	2.0	-
AUCtau (ng.h/ml) a	3.0	7.7	5.8	12.5	-
<b>Day 10</b>					
Cmax (ng/ml) a	0.59	0.87	1.19	2.73	-
Tmax (h) a	2.6	2.1	2.3	1.9	-
Kel (h) a	0.081	0.120	0.098	0.076	-
t1/2 (h) b*	8.6	5.8	7.1	9.1	-
AUCtau (ng.h/ml) a	4.4	7.6	8.5	19.1	-
Renal Clearance (ml/min) a	287	289	217	195	-
a arithmetic mean b harmonic mean					
*Calculated as $\ln(2) / \text{mean (Kel)}$					
<b>Pharmacodynamics Results:</b>					
Max increase in QTc from baseline on Day 1 (msec)	-6.09	28.58	18.55	58.91	14.68
Max increase in QTc from baseline on Day 10 (msec)	2.18	24.17	41.60	53.41	14.77
AUEC change from baseline QTc on Day 1 (msec.h)	-131.53	174.18	107.09	368.95	56.45
AUEC change from baseline QTc on Day 10 (msec.h)	-93.15	141.34	203.05	418.09	37.86

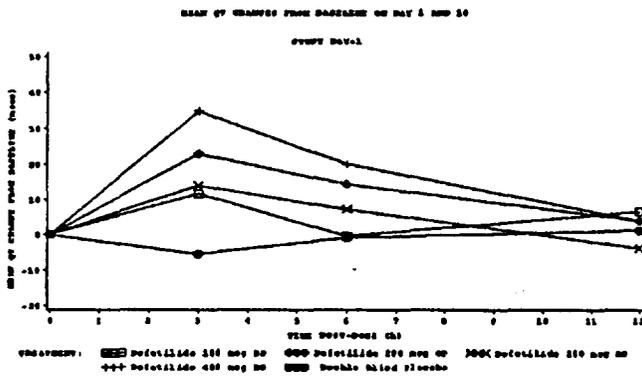
**Figure 1:**



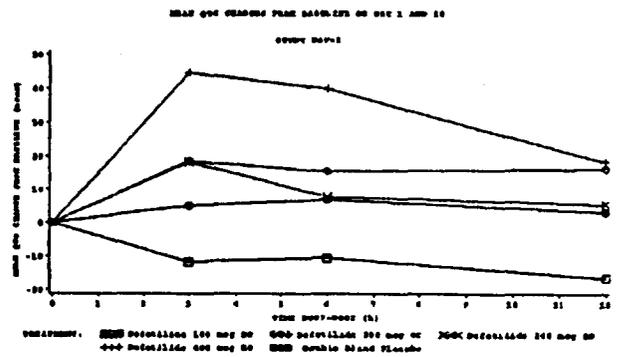
**Figure 2:**



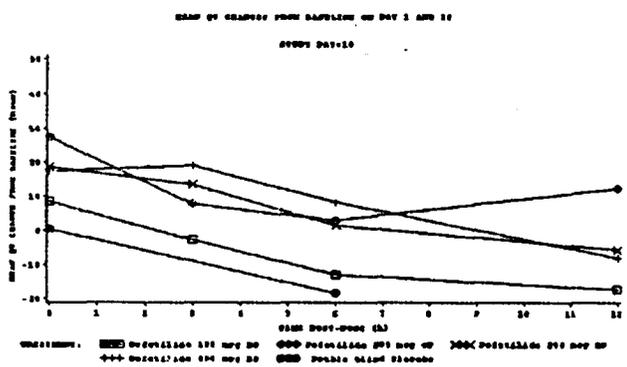
**Figure 3:**



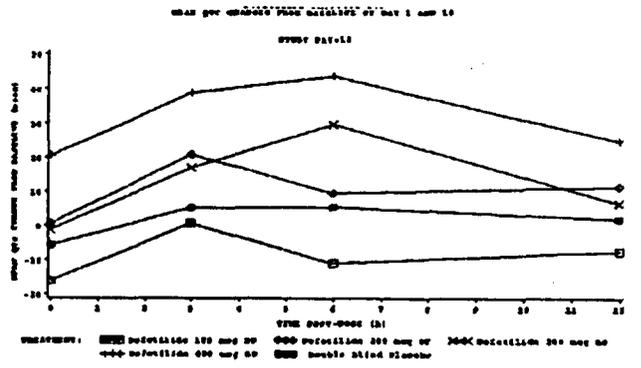
**Figure 4:**



**Figure 5:**



**Figure 6:**



**CONCLUSIONS:**

Comparison of the Day 1 and Day 10 AUC<sub>tau</sub> values showed that although no significant accumulation of dofetilide was observed on once daily dosing, accumulation was observed under a twice daily dosing regimen (increase in C<sub>max</sub> and AUC<sub>t</sub> from Day 1 to Day 10), with an approximate linear increase in exposure with dose. Steady state plasma dofetilide concentrations were reached by Day 3. Mean changes from baseline in QTc values showed increases at 3, 6 and 12 hours after the first dose in all but the 100mcg bid group. The mean maximum changes in QTc interval from baseline and the AUEC for the QTc/time relationship on Days 1 and 10 approximately increased with dose but not with time. Thus, with the exception of the 200 mcg bid group, the pharmacokinetic accumulation of dofetilide under twice daily dosing was not reflected in the pharmacodynamic response, indicated by changes in the QTc interval.

APPEARS THIS WAY  
ON ORIGINAL

## PHARMACOKINETIC-PHARMACODYNAMIC STUDY

STUDY 115-105

VOLUME: 1.20

INVESTIGATOR AND LOCATION: [

STUDY DATE: May 1991 - March 1994.

### OBJECTIVES:

1) To evaluate the hemodynamic and electrophysiologic effects of orally administered dofetilide in subjects with ventricular tachycardia and impaired left ventricular function (i.e., left ventricular ejection fraction = 20-30%); 2) To evaluate the relationship between plasma concentrations of dofetilide and changes in hemodynamic and electrophysiologic parameters; 3) To assess the safety of orally administered dofetilide in subjects with impaired left ventricular function.

### DRUG ADMINISTRATION:

Dosage Form: Dofetilide 250 mcg (FID No. 0963) or 500 mcg (FID No. 0964) capsules; or placebo capsules (FID No. 0034).

Dosing: Dofetilide 250 mcg, 500 mcg or placebo three times daily (tid).

Duration: Three days, minimum of 6 doses.

### STUDY DESIGN:

This was a multicenter, randomized, double-blind study of orally administered dofetilide or placebo in subjects with nonsustained or sustained ventricular tachycardia (VT) and impaired left ventricular function. Thirty subjects were screened in two phases. In the first phase, 12 subjects were randomized (2:1) to receive either 250 mcg dofetilide tid (8 subjects) or placebo (4 subjects) after a 3-day wash-out period of all other antiarrhythmic medication. After baseline hemodynamic measurements were made, a standard electrophysiology protocol was implemented. Subjects had to have inducible VT to qualify for randomization. After subjects had received study drug for 3 days, hemodynamic and electrophysiology measurements were repeated. Only after this group completed the study and safety and toleration were analyzed was the second group randomized (2:1) to receive either 500mcg dofetilide tid (12 subjects) or placebo (5 subjects) again after a 3-day wash-out period followed by 3 days of study treatment. On study day 6, blood samples (6 ml) were to be collected after the hemodynamic measurements, at the end of the EP protocol, and at 1, 2, 3, 6, 8, 12, and 16 hours after electrical stimulation.

ASSAY: [

**DATA ANALYSIS:** AUC, Cmax, Tmax, and CL/F were determined. The data were examined for relationship between oral clearance and age, body weight, LVEF and creatinine clearance. Also, the relationships between QTc and plasma concentration, and efficacy and plasma concentration were tested.

**RESULTS:** Tables 1-2 and Figures 1-5 summarize the pharmacokinetics and pharmacodynamics data obtained from the study.

**Table 1:**

Subject	Cmax (ng/ml)	Tmax (hr)	AUC(0-8) (ng·hr/ml)	CLp (L/hr)
<b>0.25 mg TID</b>				
514-0002				
514-0003				
514-0004				
514-0006				
514-0007				
514-0008				
514-0011				
514-0012				
Mean	2.07	4.1	13.7	19.03
SD	0.65	2.4	4.0	6.02
CV(%)	31	58	28	32
<b>0.5 mg TID</b>				
514-0019				
514-0022				
514-0023				
514-0028				
514-0030				
528-0001				
528-0002				
528-0004				
Mean	5.50	2.9	36.7	15.29
SD	2.98	1.7	19.7	7.36
CV(%)	54	57	54	48

Table 2:

CARDIAC INTERVALS MEAN CHANGE FROM BASELINE - QT, QTc (MSR)

MEASUREMENT	TREATMENT GROUP	Baseline		Change from B/L		
		Mean	S.E.	N	Mean	S.E.
QT Interval (msec)	Defetillide 250 mg tid	384.82	9.23	8	44.63	11.48
	Defetillide 600 mg tid	383.60	10.98	8	71.60	14.06
	Double Blind Placebo	382.14	27.94	7	6.00	25.14
QTc Interval - CRF (msec)	Defetillide 250 mg tid	443.63	15.63	8	24.25	21.37
	Defetillide 600 mg tid	452.34	9.62	8	49.00	19.46
	Double Blind Placebo	443.00	26.65	7	2.87	32.68

QT Interval (msec) :  
 LS Mean Difference (Defetillide 250 mg tid-Double Blind Placebo) =41.48 with 95% CI (-2.83, 85.79).  
 LS Mean Difference (Defetillide 600 mg tid-Double Blind Placebo) =67.42 with 95% CI (23.12, 111.7).

QTc Interval - CRF (msec) :  
 LS Mean Difference (Defetillide 250 mg tid-Double Blind Placebo) =22.33 with 95% CI (-26.1, 70.78).  
 LS Mean Difference (Defetillide 600 mg tid-Double Blind Placebo) =66.26 with 95% CI (7.65, 104.9).  
 D: 17DEC96 - 06MAR97  
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Figure 1. Plasma Concentration of Defetillide Sampling From the Oral Administration of 0.25 mg Three Times Daily to Subjects in part of left to right to placebo

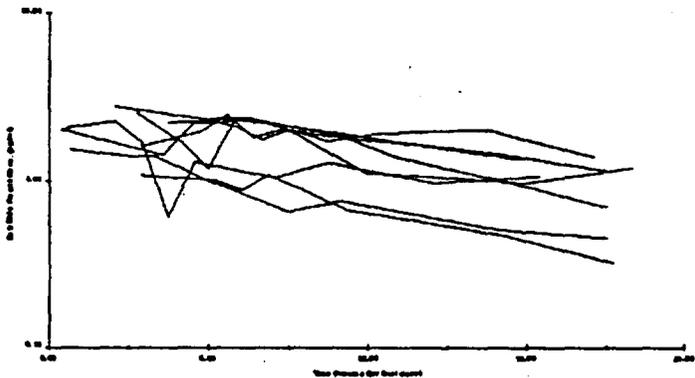


Figure 2. Plasma Concentration of Defetillide Sampling From the Oral Administration of 0.25 mg Three Times Daily to Subjects in part of left to right to placebo

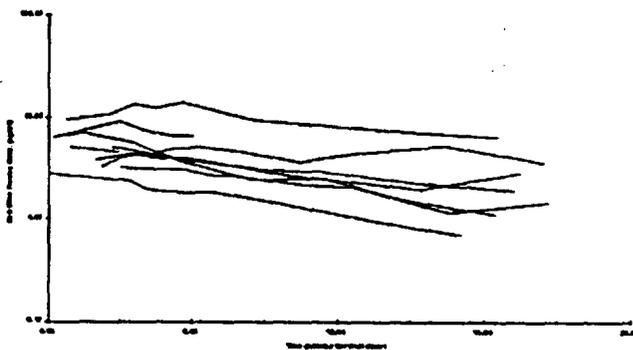


Figure 1. Relationship Between Age and Clearance of Dofetilide in Subjects with an Adjusted Left Ventricular Ejection Fraction of About 50% (N=10) (Dose 500 mg)

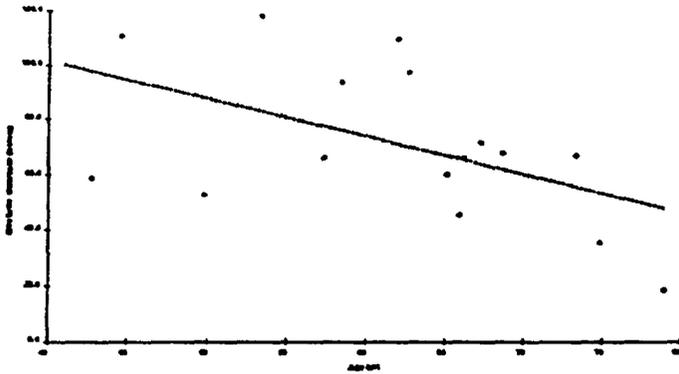
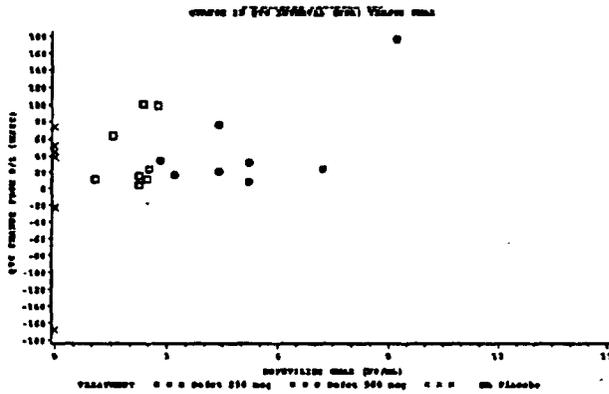
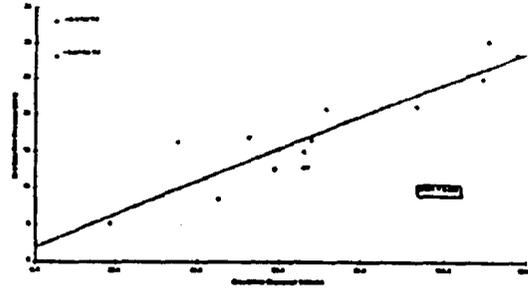


Figure 2. Relationship Between the Mean Values of Dofetilide and Clearance of Dofetilide in Subjects with an Adjusted Left Ventricular Ejection Fraction of About 50% (N=10) (Dose 500 mg)



### CONCLUSIONS:

The mean Cmax and AUC(0-8) values increased in concert with the dose administered to these subjects. There was no clear and consistent relationship between plasma dofetilide (i.e., Cmax) and cardiac index, QTc or RVERP. There was no clear and consistent relationship between plasma dofetilide (i.e., Cmax) and cardiac index, QTc or RVERP.

There was a reduction in oral clearance with advancing age (~40% reduction over interval 45 to 75 years). This finding is likely attributable to reduced renal function in the elderly. There was no relationship between the severity of left ventricular impairment (as assessed by left ventricular ejection fraction) and the oral clearance of dofetilide.

## **PHARMACOKINETIC-PHARMACODYNAMIC STUDY**

**STUDY 115-250**                      **VOLUME: 2.58**

**INVESTIGATOR AND LOCATION:** (

**STUDY DATE:** May 1993 - January 1994.

### **OBJECTIVES:**

To determine the effect of dofetilide on the QT interval and QT dispersion at different heart rates and to determine the effect of heart rate on the QT interval-plasma concentration relationship.

### **DRUG ADMINISTRATION:**

Dosage Form: Dofetilide suitable for oral dosing was provided as 1x250 mcg capsules for 250 mcg dosing, or 3x250 mcg capsules for 750 mcg dosing (FID No. 0963, Lot No. 503-18). Matching placebo capsules were also provided (FID No. 0034, Lot No. 748-16).

### **STUDY DESIGN:**

The study was of a double-blind, placebo-controlled, three-way crossover design, and evaluated the QT change at the time of the expected maximum and minimum prolongation after dofetilide or placebo at different heart rates induced by exercise. Subjects were randomised to a sequence of three treatments comprising dofetilide 250 mcg or 750 mcg b.i.d. or placebo b.i.d. All subjects were given a total of 7 doses of dofetilide or placebo over 3.5 days with a minimum 7-day washout period between each treatment period. On each treatment period, blood samples (approximately 4ml) were at pre-morning dose and 2 hours post-dose on Day 4.

### **ASSAY:** (

**DATA ANALYSIS:** C<sub>min</sub> and C<sub>2h</sub> were determined. For each treatment period, the relationship between QT interval prolongation and plasma dofetilide concentration at different heart rates was analysed both before and after study drug administration on Day 4. The relationship between dofetilide-induced QT prolongation at different heart rates and dofetilide plasma concentrations during each of the treatment periods (both trough and peak on Day 4) was investigated by means of graphical representation.

**RESULTS:** Table 1 and Figures 1-4 summarize the pharmacokinetics and pharmacodynamics data obtained from the study.

**Table 1:**

**Pharmacodynamic Results:**

Parameter (msec) (mean±SD)	RR interval ‡	Dofetilide 250mcg	Dofetilide 750mcg	Placebo
QT interval (trough)	500	315.67±10.59	329.10±17.64**	302.57±7.98
	900	372.34±23.07	389.94±23.93**	366.03±16.71
QT interval (peak)	500	327.84±20.06*	347.63±31.65**	304.39±14.46
	900	381.40±24.75*	412.38±32.98**	353.65±14.37
QT dispersion (peak)	500	30.21±14.72	52.47±34.30	30.79±15.03
	900	35.48±13.20	39.73±11.56	33.36±12.88

‡ Results shown are for selected RR intervals only (heart rates 120 and 67bpm, respectively).

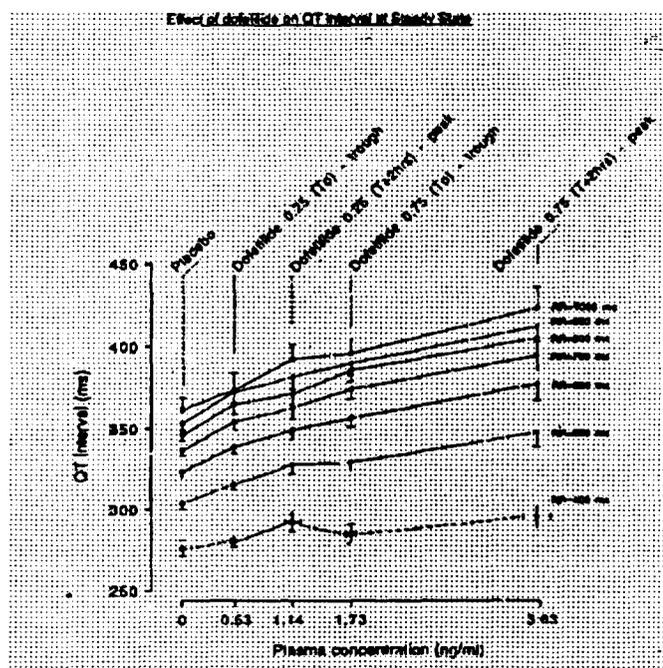
p values <0.05 for comparison of: \* dofetilide 250mcg vs placebo

\*\* dofetilide 750mcg vs dofetilide 250mcg

**Pharmacokinetic Results:**

Plasma concentration (mean ±SD)	Dofetilide 250mcg ng/ml	Dofetilide 750mcg ng/ml	Placebo ng/ml
Trough	0.53±0.13	1.73±0.18	<0.05
Peak	1.14±0.28	3.65±0.48	<0.05

**Figure 1:**



**Figure 2:**

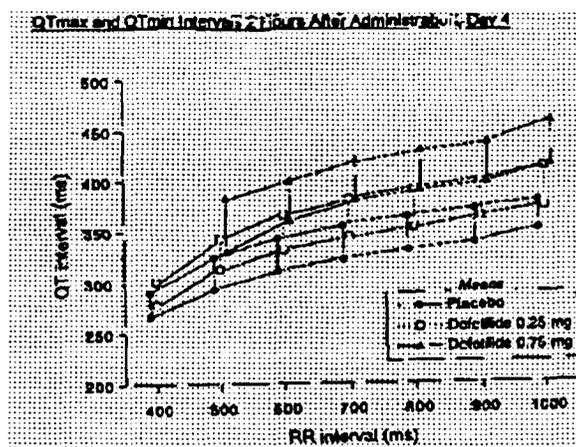


Figure 3:

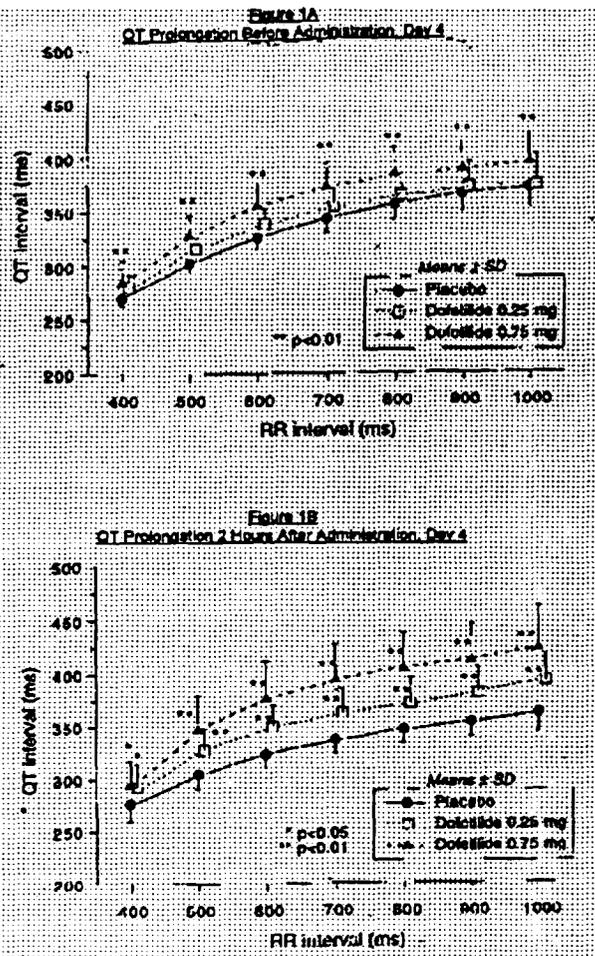
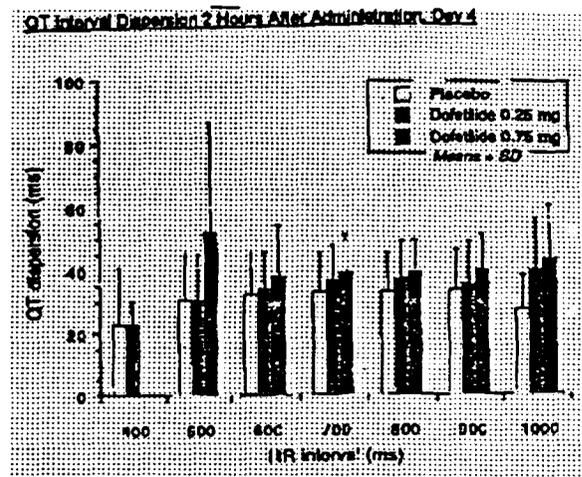


Figure 4:



### CONCLUSIONS:

The data obtained from the study indicate that dofetilide-induced QT prolongation was dose and plasma concentration-dependent, i.e. the higher the dose of dofetilide given the higher the plasma concentration of dofetilide, and the greater the QT prolongation. The limited range of doses used here give results which are consistent with the dose of dofetilide being directly related to subsequent plasma concentration, and with plasma concentration being directly related to QT prolongation. However, additional data are required before any definite conclusions about these relationships can be made.

## PHARMACOKINETIC-PHARMACODYNAMIC STUDY

STUDY 115-209

VOLUME: 2.30

### INVESTIGATOR AND LOCATION:

STUDY DATE: May 1990 - June 1991.

### OBJECTIVES:

To assess the safety and toleration of dofetilide in subjects with DDD pacemakers; to determine the effect of dofetilide and placebo on certain cardiac electrophysiological parameters and to obtain pharmacokinetic information about dofetilide following oral administration to subjects with heart disease.

### DRUG ADMINISTRATION:

Test Product Dofetilide capsules, 250mcg (FID: 0963, lot 904-01) and 500mcg (FID: 0964, lots 904-02 and 904-05)

Reference Placebo capsules (FID 0034: lot 748-06)

### STUDY DESIGN:

This was a multicentre, double-blind, placebo-controlled, crossover study. On the first of two study days, subjects were randomly allocated to receive placebo or dofetilide (250 or 500mcg capsule). On the second study day, after a wash-out period of between 3 and 10 days, subjects were to receive the alternative treatment. Blood samples (4ml) were collected just prior to dosing and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8 and 24 hours post-dose. Labelled plasma samples were stored at -20°C until assayed. All subjects had a permanent implantation of dual chamber programmable pacemakers, allowing electrophysiological measurements to be made under conditions of electrical stimulation. From these pacemakers, the following measurements were to be performed during the baseline period and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8 and 24 hours post-dose in as many of the subjects as possible: RR, QRS, JT and JTc, QT and QTc and sinus cycle length during sinus rhythm. All these intervals were to be recorded during sinus rhythm as an average of six consecutive sinus beats.

### ASSAY:

**DATA ANALYSIS:** Mean pharmacokinetic parameters ( $\pm$  S.D.) were calculated. Maximum change from baseline for both VERP and QT were analysed. Separate analyses were performed for each dose level of dofetilide and for the

two paced cycle lengths.

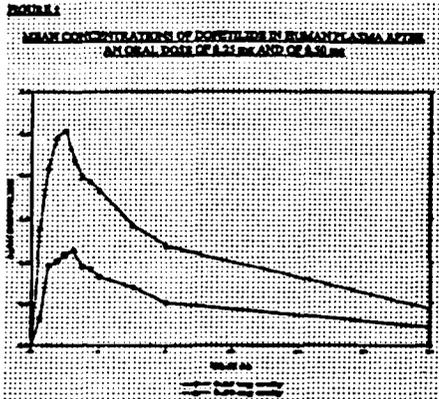
**RESULTS:** Tables 1-2 and Figures 1-4 summarize the pharmacokinetics and pharmacodynamics data obtained from the study.

Table 1: Pharmacodynamic Parameters

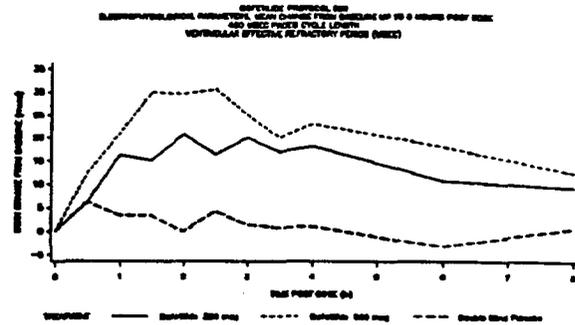
<b>Electrophysiology Results:</b>	<i>Dofetilide</i>	<i>Placebo</i>	<i>p-values</i>
450msec Paced Cycle Length	<i>250mcg</i>		
Max. Change from b/l (means)			
QT (msec)	35 ± 8	16 ± 13	0.0825
VERP (msec)	26 ± 6	15 ± 12	0.0705
600msec Paced Cycle			
QT (msec)	34 ± 16	11 ± 11	0.0400
VERP (msec)	33 ± 13	13 ± 9	0.0195
	<i>Dofetilide</i>	<i>Placebo</i>	<i>p-values</i>
450msec Paced Cycle Length	<i>500mcg</i>		
Max. Change from b/l (means)			
QT (msec)	46 ± 25	9 ± 14	0.0225
VERP (msec)	37 ± 11	8 ± 11	< 0.0001
600msec Paced Cycle			
QT (msec)	50 ± 18	6 ± 9	0.0016
VERP (msec)	56 ± 37	15 ± 9	0.0113

Table 2: Mean (SD) Pharmacokinetic Parameters

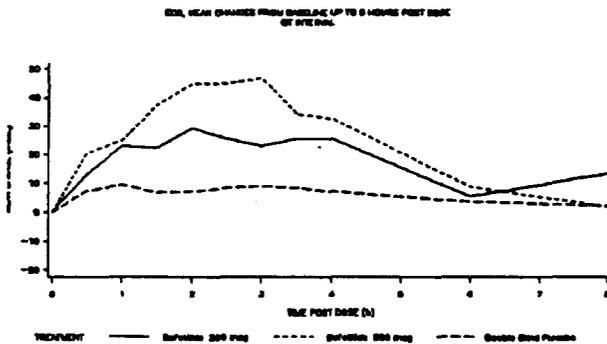
Dose	Cmax (ng/ml)	AUC(O-24) (ng.h/ml)	Tmax (h)
0.25 mg	1.32 (0.31)	12.2 (3.0)	2.0 (0.7)
0.5 mg	3.0 (1.2)	26.1 (6.4)	2.0 (1.2)



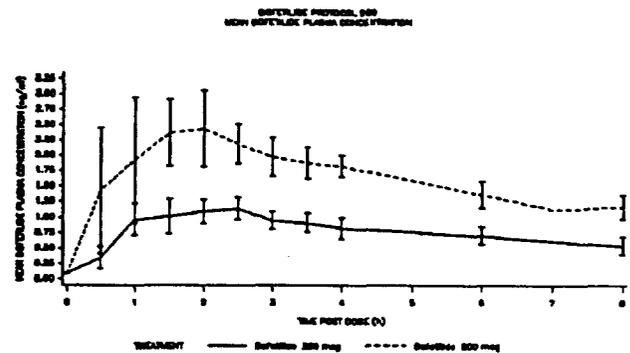
**Figure 2:**



**Figure 3:**



**Figure 4:**



**CONCLUSIONS:** There were no differences between groups in baseline VERP or QT at either paced rate and both increased to a similar degree when pacing rate decreased. Parity was maintained with dose between both paced rates. Maximum increases from baseline observed after 500mcg dofetilide were statistically significantly different from placebo for QT interval and VERP at each paced rate, but after 250mcg dofetilide, only the QT and VERP changes under conditions of 600msec pacing achieved statistical significance.

## PHARMACOKINETIC-PHARMACODYNAMIC STUDY

STUDY 115-229

VOLUME: 2.45

INVESTIGATOR AND LOCATION:

STUDY DATE: July to December 1990.

### OBJECTIVES:

To assess the pharmacodynamics (QTc prolongation), pharmacokinetics, safety and toleration of dofetilide after 5 days oral administration in twice daily and thrice daily regimens.

### DRUG ADMINISTRATION:

Test Product: Dofetilide, FID# 0963, Lot# 904-04; 330 mcg FID# 1060, Lot# 904-17; 500 mcg FID# 0964, Lots# 904-05 and 904-22.

Matmatched placebo capsules FID# 0034, Lot# 748-06.

Dosing: Capsules containing dofetilide or placebo were to be taken with 240 ml water at 08.00, 15.30, 20.00 and 23.00. Each regimen was taken for 5 consecutive days.

### STUDY DESIGN:

This was an exploratory, double-blind, randomized, crossover study. Subjects attended 2 treatment periods, with 6 or more days between. Three separate groups, each of at least 8 subjects recruited sequentially, were received 2x5 days treatment with dofetilide: either 330mcg tid and 500 mcg bid, 500 mcg tid and 750 mcg bid or 1250 mcg bid and 830 mcg tid. The order in which the two treatment regimens were to be taken by each subject was assigned randomly.

Blood samples (5 ml) were taken immediately before dosing and at the following times after the morning (08.00 h) dose on Days 1 and 5: 1, 2, 3, 4, 6 and 7.5 hours (i.e. immediately prior to the 15.30 dose); 8.5, 9.5, 10.5 and 12 hours (i.e. immediately prior to the 20.00 dose); 13, 14 and 15 hours (i.e. immediately prior to the 23.00 dose) and 16, 20 and 24 hours (prior to any 08.00 dose). Blood samples were also obtained before the first dose (08.00) on Days 3 and 4, at 14.00 and 23.00 on Day 6, and at 08.00 and 23.00 on Day 7. Thus, on Days 6 and 7 blood samples were to be taken 15, 24, 33 and 48 hours after the final dose of study medication.

Twelve lead ECGs were recorded after a minimum of 15 minutes of supine rest at the following times: at 08.00, 09.00, 10.00, 11.00, 12.00, 14.00, 15.30, 16.30, 17.30, 18.30, 20.00, 21.00, 22.00, 23.00, 24.00 and 04.00 during the 24 hours pre-dose; at times corresponding to those of blood sampling for the pharmacokinetic determinations, i.e. 1, 2, 3, 4, 6, 7.5, 8.5, 9.5, 10.5, 12, 13, 14, 15, 16, 20 and 24 hours on Days 1 and 5; before dosing on Days 3 and 4; at 14.00 and 23.00 on Day 6, and at 08.00 and 23.00 on Day 7. Further recordings were made at 2-hourly intervals from 08.00 until 14.00, and at 16.15, 18.00 and 20.00 on Days 2-4 inclusive of each treatment period.

ASSAY:

**DATA ANALYSIS:** Mean pharmacokinetic parameters ( $\pm$  S.E.) were calculated. Maximum change from baseline for QT were analysed. Plots of plasma dofetilide concentration versus change in QTc were constructed for each treatment regimen following the first dose on Days 1 and 5.

**RESULTS:** Table 1 and Figures 1-12 summarize the pharmacokinetics and pharmacodynamics data obtained from the study.

Table 1: Pharmacokinetics/Pharmacodynamics Parameters (Means + SE)

	330mcg tid	500mcg bid	500mcg tid	750mcg bid	830mcg tid	1250mcg bid
Day 1						
Cmax (ng/ml)	1.70 $\pm$ 0.07	2.64 $\pm$ 0.11	2.26 $\pm$ 0.09	3.54 $\pm$ 0.21	3.55 $\pm$ 0.14	5.47 $\pm$ 0.28
Tmax (h)	2.29 $\pm$ 0.18	2.00 $\pm$ 0.31	2.13 $\pm$ 0.13	2.13 $\pm$ 0.13	2.29 $\pm$ 0.18	1.57 $\pm$ 0.20
AUC $\tau$ (ng.h/ml)	8.61 $\pm$ 0.43	17.03 $\pm$ 0.82	10.81 $\pm$ 0.34	23.55 $\pm$ 1.32	18.89 $\pm$ 0.75	37.50 $\pm$ 1.27
Slope*(msec/ng/ml)	20.7 $\pm$ 4.5	15.6 $\pm$ 2.4	18.1 $\pm$ 4.5	14.5 $\pm$ 4.1	15.1 $\pm$ 3.3	16.2 $\pm$ 2.7
Day 5						
Cmax (ng/ml)	3.04 $\pm$ 0.19	3.80 $\pm$ 0.19	4.78 $\pm$ 0.25	5.23 $\pm$ 0.28	7.71 $\pm$ 0.60	10.07 $\pm$ 0.70
Tmax (h)	2.29 $\pm$ 0.18	2.00 $\pm$ 0.22	2.00 $\pm$ 0.00	1.89 $\pm$ 0.40	2.14 $\pm$ 0.14	1.57 $\pm$ 0.30
AUC $\tau$ (ng.h/ml)	16.75 $\pm$ 0.86	25.39 $\pm$ 1.48	25.54 $\pm$ 1.74	37.50 $\pm$ 2.62	40.10 $\pm$ 2.05	62.07 $\pm$ 2.92
Kel (/h)	0.070 $\pm$ 0.0020	0.068 $\pm$ 0.0029	0.073 $\pm$ 0.0024	0.069 $\pm$ 0.0022	0.073 $\pm$ 0.0023	0.069 $\pm$ 0.0026
Slope*(msec/ng/ml)	16.0 $\pm$ 4.1	13.2 $\pm$ 2.3	13.0 $\pm$ 2.9	13.3 $\pm$ 2.2	11.2 $\pm$ 1.6	11.1 $\pm$ 2.1

Where  $\tau$  is the dosing interval of 8 hours for tid and 12 hours for bid

\* = Slope of  $\Delta$ QTc/ plasma dofetilide concentration  $\pm$  SD

Figure 1:

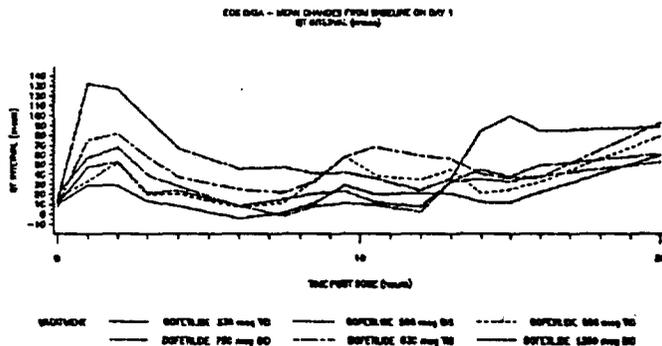
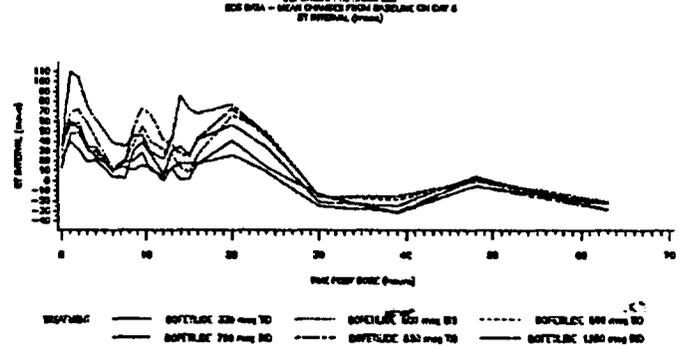
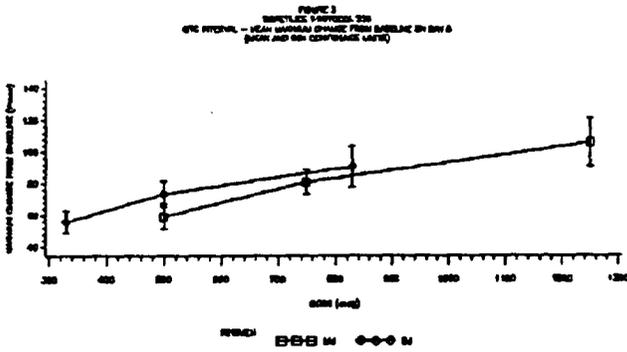


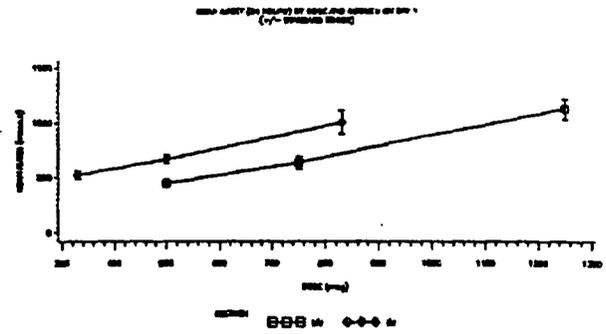
Figure 2:



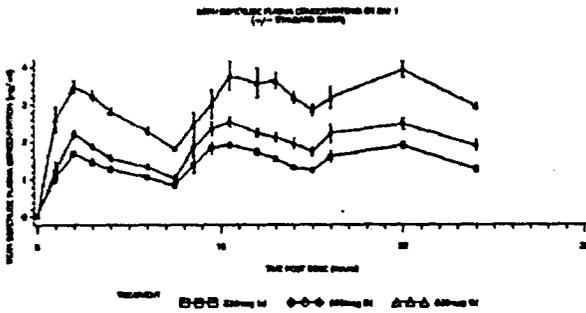
**Figure 3:**



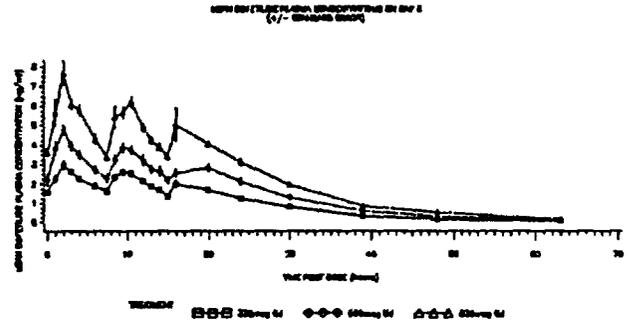
**Figure 4:**



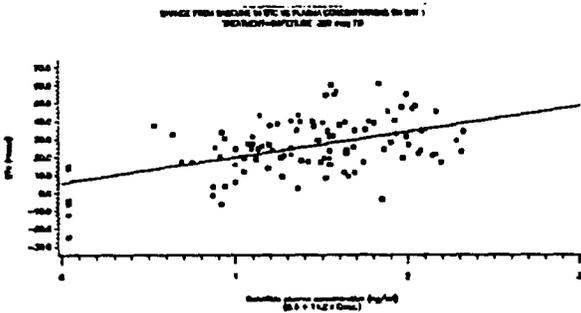
**Figure 5:**



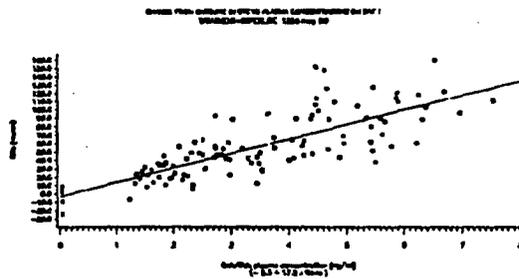
**Figure 6:**



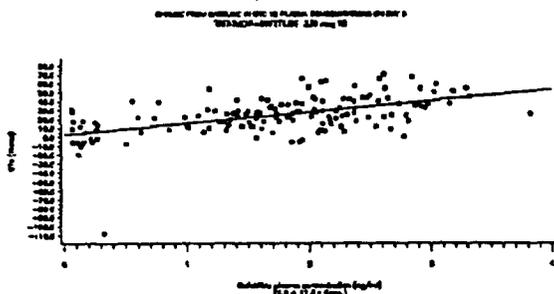
**Figure 7**



**Figure 8**



**Figure 9**



**Figure 10**

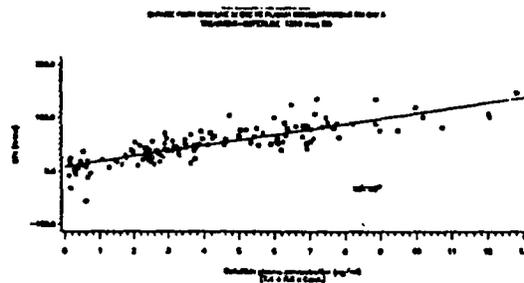


Figure 11

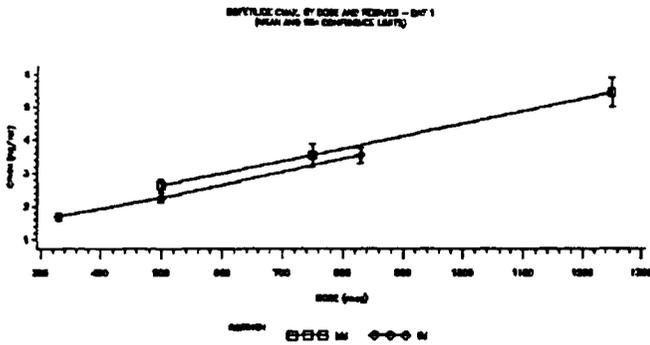
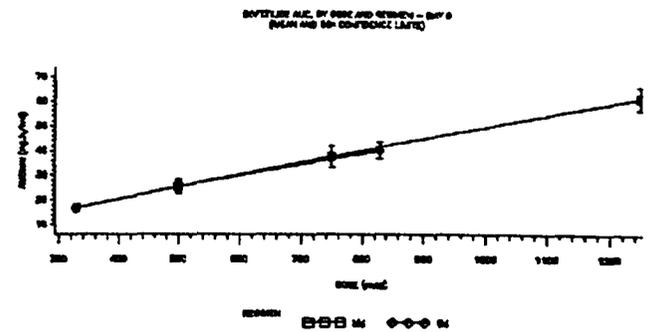


Figure 12:



**CONCLUSIONS:**

The pharmacokinetics of dofetilide after oral administration were linear with dose, regardless of the dosing frequency. They showed the predictable accumulation, reaching a steady state by Day 5. This accumulation was independent of the dosing regimens used. In contrast, increases in QTc remained constant over the dosing cycles, thus the relationship between QTc and plasma concentration (Slope) was significantly different between Days 1 and 5. Slope on Day 5 was essentially similar across all doses, indicating that the frequency of dose administration does not affect this response. The profiles of QTc changes closely followed those of the plasma concentrations with each dose and dosing regimen indicating that movements of dofetilide to the effect compartment were limited by the absorption process after oral administration.

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## PHARMACOKINETIC-PHARMACODYNAMIC STUDY

STUDY 115-239

VOLUME: 2.52

INVESTIGATOR AND LOCATION:

STUDY DATE: January - March 1992.

### OBJECTIVES:

To assess the pharmacokinetics, pharmacodynamics, safety and toleration of 1.0mg dofetilide capsules during and after 24 days of twice daily dosing and to compare these with a group intermittently dosed with dofetilide.

### DRUG ADMINISTRATION:

Test Product: Dofetilide, 500mcg capsules: FID 0964 Lot No. 503-04

Reference: Therapy Identical placebo capsules: FID 0034 Lot No. 748-16

### STUDY DESIGN:

This was a single-blind, randomised, placebo-controlled, parallel group, multiple dose study. Subjects were randomized in equal numbers into one of three groups receiving either 1.0mg dofetilide twice daily (Group 1), or matching placebo (Group 2), or 1.0mg dofetilide dosed intermittently (Group 3). Subjects in Group 3 received a single dose of 1.0mg dofetilide 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. Dofetilide pharmacodynamics were assessed by comparison of the maximum changes in QTc from baseline to Day 24 and by the change from baseline in the mean slope of the plasma concentration versus change in QTc curve. Dofetilide pharmacokinetics were derived at fixed times and compared between the continuous and intermittent dosing groups. Laboratory safety tests, electrocardiographic and haemodynamic measurements were repeated at intervals up to 48 hours after the completion of dosing.

Blood plasma samples were collected at the following times during the study: pre-dose and at the following times relative to the morning dose on Days 1, 5, 10, 17 and 24: 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10 and 12 hours. The last sample was to form the pre-dose sample for the 8 p.m. dose. Additional collections at 18, 24, 30, 36 and 48 hours were to be made after the morning dose on Day 24. Labelled plasma samples were stored at -20°C until assayed.

Urine samples were taken on Days 1, 5, 10, 17 and 24. On these days, two 12-hour collections were to be made to correspond to the dosing intervals 8 a.m. to 8 p.m. and 8 p.m. to 8 a.m. Collection volumes were to be recorded and a 10ml aliquot from each period frozen at -20°C.

Three-lead ECGs were recorded during the 24 hours before the first dose (prior to the 8 a.m. dose of placebo) and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10 and 12 hours post-dose. Additional 3-lead ECGs were to be recorded at the times of each blood sampling for dofetilide assay and on all other treatment days prior to the 8 a.m. dose and at 0.5, 1, 1.5, 2, 3 and 4 hours after the 8 a.m. dose.

**ASSAYS:**

**DATA ANALYSIS:** Cmax, Cmin, Tmax, AUC(0-12), Kel, CLr, half-life and amount of dofetilide excreted in urine are were calculated. Maximum change from baseline for QT were analysed. Plots of plasma dofetilide concentration versus change in QTc were constructed .

**RESULTS:** Tables 1-7 and Figures 1-6 summarize the pharmacokinetics and pharmacodynamics data obtained from the study.

Table 1:

MAXIMUM QTc (MSEC) INTERVAL BY DAY

TREATMENT		DAY									
		B/L	1	2	3	4	5	10	17	24	
DOFETILIDE Continuous 1000mcg BID	Mean	373.1	443.3	453.3	450.2	464.3	460.0	460.0	466.3	462.2	
	S.E.	4.6	7.9	9.0	8.1	9.1	6.6	6.2	8.2	7.0	
	N	8	8	8	8	8	8	8	8	8	
DOFETILIDE Intermittent 1000mcg	Mean	387.1	472.0	406.1	397.4	395.8	466.5	466.7	469.2	457.5	
	S.E.	6.6	18.1	6.7	6.1	5.9	14.4	18.1	16.0	10.1	
	N	8	8	8	8	8	8	8	7	8	
Placebo	Mean	377.2	393.5	397.6	390.7	396.0	393.6	398.9	396.2	394.8	
	S.E.	4.8	4.3	6.5	6.8	6.9	7.4	5.3	5.6	7.8	
	N	8	8	8	8	8	8	8	8	8	

Table 2:

ANALYSIS OF MAXIMUM CHANGE IN QTC (MSEC) FROM BASELINE ON DAY 24. SUMMARY

TREATMENT		Baseline	Change to day 24
DOFETILIDE Continuous 1000mg BID	Mean	272.1	69.1
	S.E.	4.6	5.0
	N	8	8
DOFETILIDE Intermittent 1000mg	Mean	267.1	70.4
	S.E.	6.4	8.0
	N	8	8
Placebo	Mean	277.2	17.6
	S.E.	4.8	5.6
	N	8	8

Table 3:

MEAN SLOPE OF PLASMA CONCENTRATION VS CHANGE IN QTC RELATIONSHIP (MSEC/NG/ML)

TREATMENT		DAY RELATIVE TO START OF STUDY THERAPY				
		1	5	10	17	24
DOFETILIDE Continuous 1000mg BID	MEAN	14.20	9.05	8.61	8.83	8.60
	S.E.	1.68	0.79	0.73	0.71	0.81
	N	8	8	8	8	8
DOFETILIDE Intermittent 1000mg	MEAN	16.12	15.27	15.44	15.88	16.72
	S.E.	1.77	2.05	2.00	1.68	1.24
	N	7	7	7	6	7

Table 4:

ANALYSIS OF MEAN CHANGE IN SLOPE (MSEC/NG/ML). SUMMARY

TREATMENT		Change in Slope from Day 1			
		5	10	17	24
DOFETILIDE Continuous 1000mg BID	MEAN	-5.15	-5.59	-5.28	-5.80
	S.E.	1.27	1.22	1.49	1.68
	N	8	8	8	8
DOFETILIDE Intermittent 1000mg	MEAN	-0.76	-0.69	-0.22	-1.60
	S.E.	0.61	0.91	1.12	1.11
	N	7	7	6	7
P-Value*		0.011	0.008	0.022	0.027

Table 5:

PHARMACOKINETIC PARAMETERS, SUMMARY

			DAY RELATIVE TO START OF STUDY THERAPY				
			1	5	10	17	24
C <sub>max</sub> (ng/ml)	DOFETILIDE Continuous 1000mg BID	MEAN	4.79	7.10	6.99	7.08	6.99
		S.E.	0.27	0.54	0.47	0.51	0.25
		N	8	8	8	8	8
	DOFETILIDE Intermittent 1000mg	MEAN	4.61	4.74	4.48	4.99	5.01
		S.E.	0.34	0.48	0.40	0.40	0.39
		N	8	8	8	7	8
T <sub>max</sub> (h)	DOFETILIDE Continuous 1000mg BID	MEAN	3.12	1.04	2.21	2.12	2.28
		S.E.	0.23	0.33	0.21	0.28	0.26
		N	8	8	8	8	8
	DOFETILIDE Intermittent 1000mg	MEAN	2.61	2.54	2.56	2.50	2.69
		S.E.	0.33	0.25	0.29	0.28	0.21
		N	8	8	8	7	8
AUC (0-12h) (ng.h/ml)	DOFETILIDE Continuous 1000mg BID	MEAN	31.82	47.30	47.54	48.52	48.40
		S.E.	1.51	1.80	1.82	2.77	2.69
		N	8	8	8	8	8
	DOFETILIDE Intermittent 1000mg	MEAN	32.23	31.59	32.05	31.70	33.17
		S.E.	2.25	2.21	1.82	2.54	2.23
		N	8	8	8	7	8
C <sub>min</sub> (ng/ml)	DOFETILIDE Continuous 1000mg BID	MEAN	1.37	1.68	1.70	1.91	2.14
		S.E.	0.07	0.04	0.15	0.16	0.11
		N	8	8	8	8	8
	DOFETILIDE Intermittent 1000mg	MEAN					
		S.E.					
		N	8	8	8	8	8

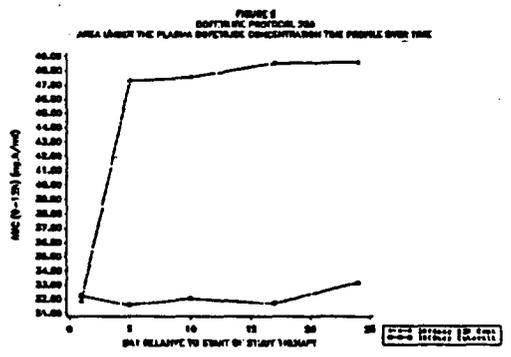
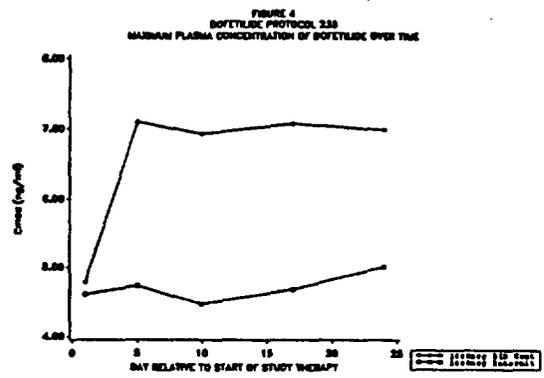
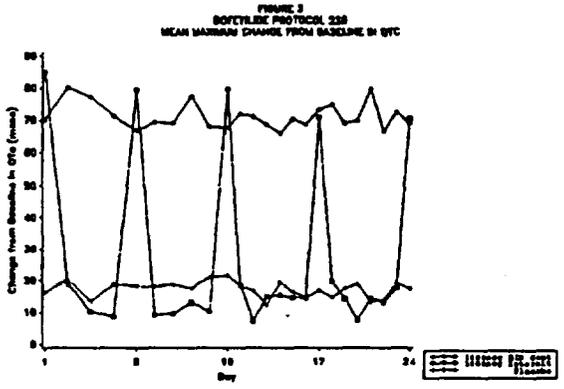
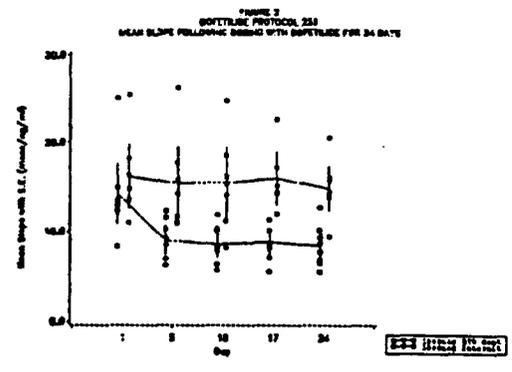
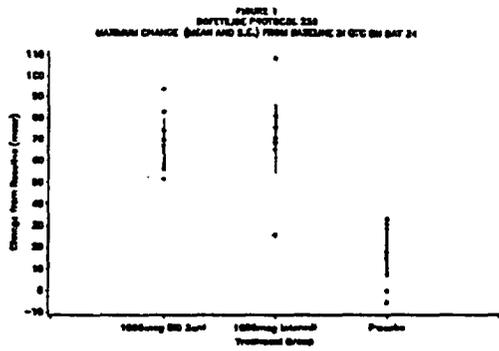
Table 6: Renal Clearance of Dofetilide (Mean ±SD)

Dosing Regimen	CL <sub>r</sub> (ml/min)				
	Day 0	Day 4	Day 9	Day 16	Day 23
Continuous	289 ±80	282 ±60	273 ±50	3219 ±97	281 ±68
intermittent	298 ±104	276 ±71	272 ±101	284 ±81	285 ±116

Table 7:

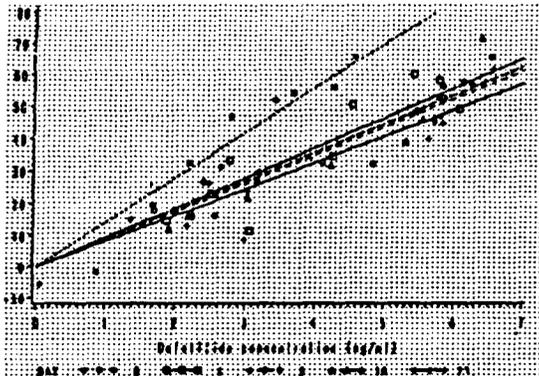
AMOUNT OF DOFETILIDE EXCRETED IN URINE (%), OVER EACH 12 HOUR COLLECTION PERIOD

AMOUNT OF DOFETILIDE EXCRETED (ng)		DAY RELATIVE TO START OF STUDY THERAPY									
		1		5		10		17		24	
		0-12	12-24	0-12	12-24	0-12	12-24	0-12	12-24	0-12	12-24
DOFETILIDE Continuous 1000mg BID	MEAN	518.66	393.92	776.67	725.78	771.71	710.28	902.61	612.66	822.89	266.19
	S.E.	40.71	35.53	41.64	59.22	31.41	89.10	65.65	65.69	81.52	10.09
	N	8	8	8	8	8	8	8	8	8	8
DOFETILIDE Intermittent 1000mg	MEAN	347.20	154.99	326.39	144.21	312.89	127.61	455.09	132.96	344.54	158.14
	S.E.	52.39	15.06	31.15	19.28	70.94	17.33	73.11	21.43	73.22	11.58
	N	8	8	8	8	8	8	8	8	8	8

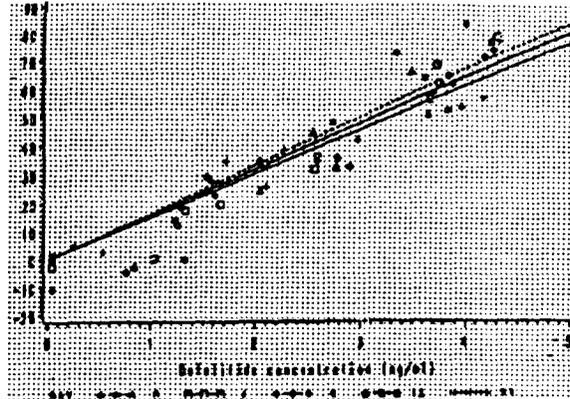


**Figure 6: Mean changes in QTc versus dofetilide concentration**

**(a) continuous regimen**



**(b) intermittent regimen**



**CONCLUSIONS:**

Oral administration of twice daily dofetilide over 24 days resulted in accumulation with steady state concentrations achieved by Day 5. The pharmacokinetic parameters that resulted following intermittent (single dose) administration showed no accumulation and demonstrated low intra-subject variability. The maximum change in QTc from baseline to Day 24 was statistically significantly greater for subjects receiving either continuous or intermittent dofetilide than for those receiving placebo alone. In contrast to the plasma levels, the response to continuous twice daily dosing dofetilide, as measured by changes in QTc, increased from baseline to Day 2 but thereafter showed an attenuation which was not progressive beyond Day 5. Single doses of dofetilide in the intermittently treated group gave reproducible changes in QTc.

The difference between the mean change from Day 1 in the slope of the QTc/plasma dofetilide relationship in the continuously and intermittently dosed dofetilide groups was statistically significant ( $p < 0.05$ ). Within the continuous dofetilide group, after an initial drop in the value of the mean slope between the first and fifth days, there was little variation after Day 5; i.e. the change in slope over the first five days was not progressive after Day 5. The value of the mean slope recorded for the intermittent group was consistent at all assessment times.

## **PHARMACOKINETIC-PHARMACODYNAMIC STUDY**

**STUDY 115-245**

**VOLUME: 2.52**

**INVESTIGATOR AND LOCATION:**

**STUDY DATE:** January - March 1993.

**OBJECTIVES:** To compare QTc changes and the QTc-plasma drug concentration relationship for dofetilide and sotalol. To determine the effect of multiple dosing on these parameters.

### **DRUG ADMINISTRATION:**

Dosage Form Oral dofetilide capsules 750 mcg FID: 0963, Lot No: 503 - 18 (3 x 250 mcg).

Oral sotalol tablets (240 mg) sourced locally (1.5 x 160 mg).

Oral propranolol tablets (80 mg) sourced locally (2 x 40 mg).

Dosing: Dofetilide or sotalol twice daily for five days then once daily for one day. At least nine days after last dose, the alternate treatment twice daily for five days then once daily for one day.

### **STUDY DESIGN:**

An open, randomized, two-way crossover study in healthy male subjects and a washout period of at least seven days (i.e. nine days after the last dose). Subjects were randomized to receive oral treatment with dofetilide 750 mcg followed by sotalol 240 mg or vice versa. Prior to study drug administration, recordings of QT interval and heart rate after exercise and propranolol (80 mg) were used to determine the relationship of QT and heart rate for each individual. Thus, any effect of treatment on QTc interval could be divorced from any heart rate effects.

Blood samples were to be to determine dofetilide and sotalol plasma concentrations at the same times for both study periods; Day 1 - prior to and 0.5, 1, 2, 3, 4, 5, 6, 8, 10 and 12 hours post first dose and prior to (same as 12 hours post first dose) and 2, 3, and 4 hours post second dose; Day 2 - prior to and 2, 3, and 4 hours post each dose; Days 3, 4, and 5 - prior to and 2, 3, and 4 hours post the first dose only; Day 6 - prior to and 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 18, 24, 36, and 48 hours post dose. The samples were stored at -20°C until assayed. A resting 3-lead ECG recording was also taken at these times to enable investigation of any correlation in changes in QTc interval with changes in plasma concentration.

### **ASSAYS:**

**DATA ANALYSIS:** C<sub>max</sub>, C<sub>min</sub>, T<sub>max</sub>, AUC(0-12), K<sub>el</sub>, CL<sub>r</sub>, half-life and amount of dofetilide excreted in urine are were calculated. Maximum change from baseline for QT were analysed. Plots of plasma dofetilide or sotalol concentration versus change in QTc were constructed. The following pharmacokinetic/pharmacodynamic parameters were analyzed:

(Slope Day 1 - Slope Day 6) / Slope Day 1

**RESULTS:** Table 1 and Figures 1-5 summarize the pharmacokinetics and pharmacodynamics data obtained from the study.

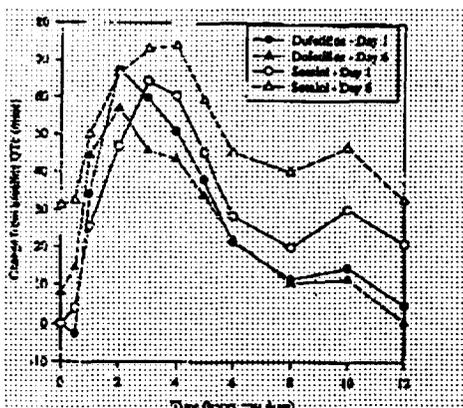
**Table 1:**

**Pharmacokinetic and Pharmacokinetic/Pharmacodynamic Results:**

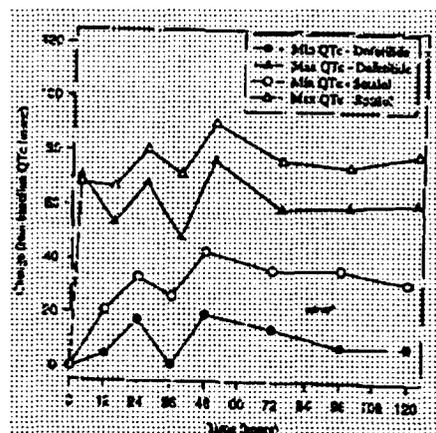
Dofetilide 750mcg Mean ± SD	Dose 1	Dose 11	Sotalol 240mcg Mean ± SD	Dose 1	Dose 11
C <sub>max</sub> (ng/ml)	3.04 ± 0.44	5.08 ± 0.78	C <sub>max</sub> (mcg/ml)	1.97 ± 0.43	3.32 ± 0.36
T <sub>max</sub> (h)	2.13 ± 0.83	1.88 ± 0.83	T <sub>max</sub> (h)	2.75 ± 0.89	3.13 ± 0.99
AUC <sub>t</sub> (ng.h/ml)	n/a	54.36 ± 5.84	AUC <sub>t</sub> (mcg.h/ml)	n/a	49.07 ± 4.42
AUC <sub>0-12h</sub> (ng.h/ml)	23.36 ± 3.24	n/a	AUC <sub>0-12h</sub> (mcg.h/ml)	13.83 ± 3.42	n/a
K <sub>el</sub> (h)	n/a	0.082 ± 0.004	K <sub>el</sub> (h)	n/a	0.064 ± 0.007
Half Life (h)	n/a	8.41	Half Life (h)	n/a	10.81
Slope (msec/ng/ml)*	23.67 ± 4.73	13.52 ± 3.27	Slope (msec/mcg/ml)*	36.89 ± 9.04	23.53 ± 6.93

n/a = not applicable, Slope = slope of regression line of QTc versus plasma concentration, \* = comparison of change in slope [(Day 1 - Day 6)/Day 1] between treatments: p value = 0.1664

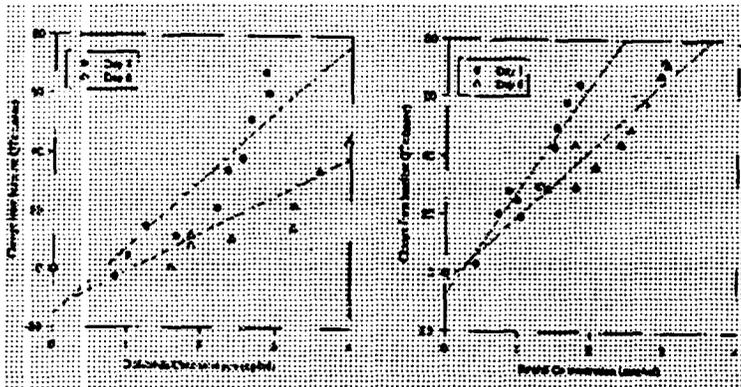
**Fig. 1: Change in Baseline QTc versus time**



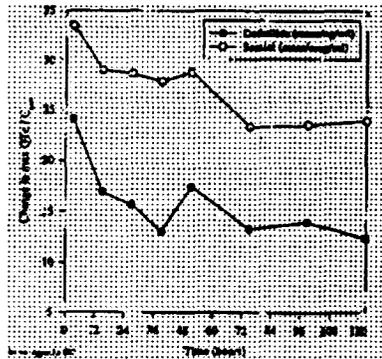
**Fig. 2: Min and Max QTc versus Time**



**Fig. 3: QTc change versus concentration**

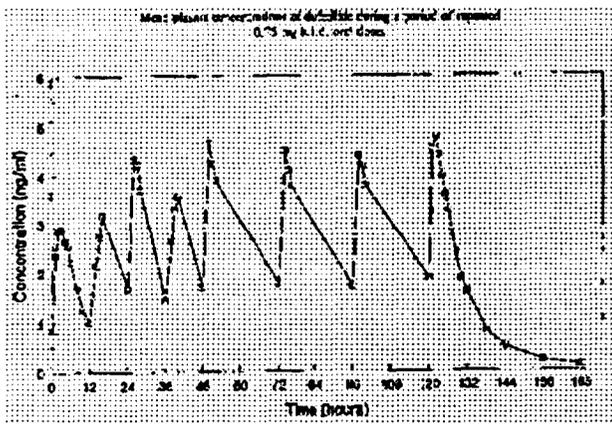


**Fig. 4 : Max QTc change/Cmax versus time**

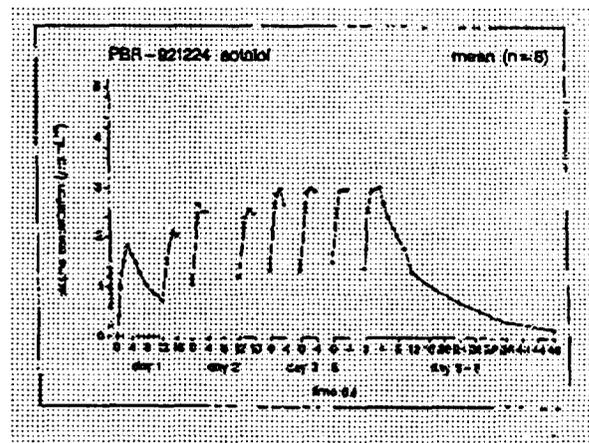


**Fig. 5: Mean Plasma Concentration versus Time**

**(a) Dofetilide**



**(b) Sotalol**



## **CONCLUSIONS:**

The data obtained from the study showed dofetilide and sotalol have a similar pharmacokinetic profile. On both Day 1 and Day 6, the maximum prolongation of QTc (QTc max) was reached between 2-4 hours for both dofetilide and sotalol, with the maximum QTc for sotalol occurring slightly later than for dofetilide. This was consistent with the values for Tmax, which was reached slightly later with sotalol compared to dofetilide. The pattern of changes in QTc min and QTc max throughout the study were also similar for both treatments. The relationship of changes in QTc with plasma concentration showed that with dofetilide the slopes for Day 1 (23.67 msec/ng/ml) and Day 6 (13.52 msec/ng/ml) were lower than with sotalol for Day 1 (36.89 msec/mcg/ml) and Day 6 (23.53 msec/mcg/ml). However, the ratio of the reduction in slope between Day 1 and Day 6 was similar for both treatment groups; dofetilide 0.43 and sotalol 0.35, and there was no evidence of a statistically significant difference between the ratios for each treatment group ( $p=0.1664$ ). This suggests that there is an attenuation in sensitivity of QTc to plasma concentration for both dofetilide and sotalol, and that it is similar for both treatments. Further evidence of a similar attenuation for both treatments was observed when changes from baseline in maximum QTc were normalised for plasma concentration. These values decreased to a constant level by approximately the fourth dose for both study treatments which suggests that attenuation in sensitivity is complete at approximately 48 hours. Since plasma concentrations (Cmax) also reached steady state around this time, the attenuation seems to follow the same time course as increase in Cmax.

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## **BIOAVAILABILITY / BIOEQUIVALENCE STUDY**

**STUDY 115-210**

**VOLUMES: 2.31**

**INVESTIGATOR AND LOCATION:**

**STUDY DATE:** March - April 1989.

**OBJECTIVES:** To investigate the safety and toleration, and pharmacokinetics of single doses of dofetilide administered as a solution and as a capsule.

### **FORMULATIONS:**

Oral dofetilide capsules, 500 mcg, FID No. 0964, Lot No. 772-02

Oral dofetilide solution, 500 mcg/100 ml, FID No. 0992, Lot No. 772-763-23

### **STUDY DESIGN:**

The study design was a two-way cross-over in which twelve subjects were to be randomized to receive a single oral dose of 500 mcg dofetilide as two formulations, capsule and solution. Half the subjects received the dofetilide solution in the first study period followed by the capsule seven days later in the second study period. The other half received the dofetilide capsule in the first study period followed by the solution seven days later in the second study period. Plasma dofetilide, ECG, haemodynamic and full safety assessments were made throughout the study. Blood samples for the determination of plasma dofetilide concentrations were collected prior to (0 hours) and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 24, 48 and 72 hours after dosing.

### **ASSAYS:**

### **DATA ANALYSIS:**

C<sub>max</sub>, T<sub>max</sub>, AUC<sub>t</sub>, AUC, K<sub>el</sub> and t<sub>1/2</sub> were calculated.

**RESULTS:** Table 1 and Figures 1-3 summarize the pharmacokinetic data obtained from the study.

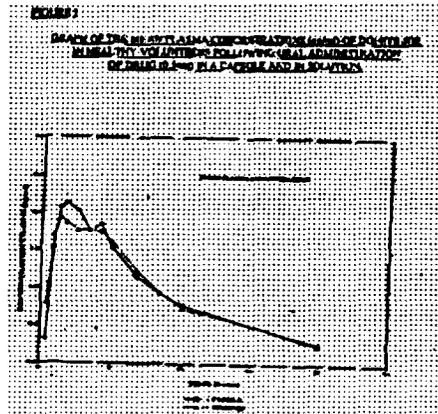
**Table 1. Bioequivalence of the two formulations**

**Pharmacokinetic Results:**

**Dofetilide 500mcg Oral**

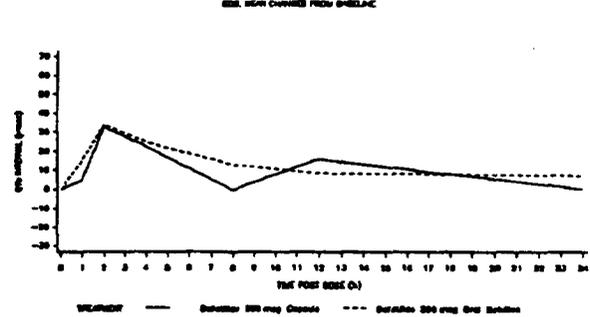
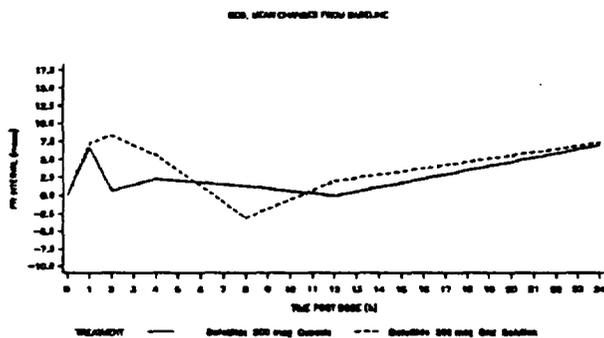
1. Pharmacokinetics (Mean ± SD* n = 11**)		Capsule	Solution	90% CI's	
				lower	Upper
	Cmax (ng/ml)	2.28 ± 0.94 <sup>a</sup>	2.08 ± 0.41 <sup>a</sup>	80%	109%
	Tmax (h)	2.3 ± 0.8	2.6 ± 1.5	N/A	
	AUCt (ng.h/ml)	22.52 ± 6.87	21.76 ± 3.22	N/A	
	AUC (ng.h/ml)	25.21 ± 7.81 <sup>b</sup>	24.93 ± 3.80 <sup>b</sup>	90%	112%
	Kel (h)	0.097 ± 0.0009 <sup>c</sup>	0.093 ± 0.015 <sup>c</sup>	-0.01	0.01
	11/2 (h)	7.2	7.5	N/A	

KEY: \* = Non-adjusted mean ± standard deviation, \*\* = one subject was excluded for insufficient data. a, b, and c = There were no significant differences between the adjusted means of the two formulations: p ≥ 0.05 and lower and upper 90% confidence intervals of Kel lay either side of zero and of anti-logged Cmax and AUC lay either side of 100%. CI's = Confidence intervals, N/A = no analysis performed



**Figure 2: Mean QT Changes**

**Figure 3: Mean QTC Changes**



**CONCLUSIONS:** The data obtained from the study showed that dofetilide capsule formulation and dofetilide solution are bioequivalent.

## IN VITRO METABOLIC STUDIES

**PROTOCOL NUMBER:** UK-68,798/DM/06/93

**STUDY DATES:** May to July 1993

**INVESTIGATOR AND LOCATION:**

**OBJECTIVE:** To compare the effect of dofetilide on the rate of metabolism of phenytoin to its 4-hydroxy metabolite (CYP2C9), bufuralol to 1-hydroxybufuralol (CYP2D6) and felodipine to its pyridine (CYP3A4) to that of three existing anti-arrhythmic agents (amiodarone, flecainide and quinidine), in human liver microsomes.

**PROCEDURES:** Probe substrates for the three major drug metabolising P450 isozymes were co-incubated with these agents and IC50 values calculated. The substrate concentration chosen was that which had previously been determined to be at the Km of the enzyme. The concentrations of anti-arrhythmics were in the range 0.01-100  $\mu$ M. The probe substrates phenytoin (CYP2C9), bufuralol (CYP2D6) and felodipine (CYP3A4) were used to determine cytochrome P450 activities in control human liver microsomes produced from a combination of samples from 8 human livers. At substrate concentrations of 20  $\mu$ M phenytoin, 10  $\mu$ M bufuralol and 25  $\mu$ M felodipine the rates of metabolite formation were previously calculated to be 4 pmol/mg/min, 14.3 pmol/mg/min and 78.6 pmol/mg/min, respectively. The following procedures were used:

**Phenytoin 4-hydroxylase (CYP2C9):** Incubations (final volume 120  $\mu$ l) were carried out at 20  $\mu$ M phenytoin and 2 mg microsomal protein/ml for 1h in the presence and absence of the compounds under investigation. After 1h incubations were stopped by the addition of 10  $\mu$ l perchloric acid followed by 10 ml internal standard (phenobarbitone 0.1mg/ml). The precipitated microsomal protein was pelleted by centrifugation at 3000rpm for 5min. The supernatant was removed and 80  $\mu$ l of this injected onto the HPLC.

**Bufuralol 1-hydroxylase (CYP2D6):** Incubations (final volume 120  $\mu$ l) were carried out at 10  $\mu$ M bufuralol and 0.25 mg microsomal protein/ml for 30 minutes in the presence and absence of the compounds under investigation. After 30 minutes incubations were stopped by the addition of 10 ml perchloric acid. The precipitated microsomal protein was pelleted by centrifugation at 3000 rpm for 5 min. The supernatant was removed and 80  $\mu$ l of this injected onto the HPLC.

**Felodipine oxidase (CYP3A4):** Incubations (final volume 1 ml) were carried out at 25  $\mu$ M felodipine and 1 mg microsomal protein for 10 minutes in the presence and absence of the compounds under investigation. After 10 minutes incubations were stopped by the addition of 4 ml t-butylmethyl ether followed by 5  $\mu$ l internal standard (nifedipine 0.1mg/ml, or UK-57699 0.1 mg/ml for quinidine samples). Samples were extracted on a rotary mixer for 15 minutes followed by separation of the organic layer using centrifugation at 3000rpm for 5 minutes. The ether layer was pipetted into tapered tubes and evaporated to dryness under nitrogen. The residue was resuspended in 100  $\mu$ l mobile phase and 80  $\mu$ l was injected onto HPLC.

## DATA ANALYSIS: Calculation of IC50 Values.

IC50 values were calculated from a plot of % inhibition against the log of the anti-arrhythmic concentration using the SIGFIT programme within the BIostat package.

## RESULTS:

### Inhibition of Phenytoin 4-hydroxylase

Co-incubation of dofetilide (0.01-100  $\mu\text{M}$ ) with phenytoin in suspensions of microsomes had only a small effect on the rate of formation of 4-hydroxyphenytoin (10% inhibition at 100 $\mu\text{M}$  dofetilide). In contrast both amiodarone and flecainide inhibited the formation of the 4-hydroxy metabolite with IC50's of  $25 \pm 3 \mu\text{M}$  and  $49 \pm 7 \mu\text{M}$  respectively. At the maximum concentration of quinidine (100 $\mu\text{M}$ ) investigated the rate of 4-hydroxyphenytoin formation was inhibited by 50%, suggesting that quinidine is a weak inhibitor of CYP2C9.

### Inhibition of Felodipine oxidase (Figures 1-4)

The metabolism of felodipine to its pyridine metabolite was not inhibited by any of the anti-arrhythmic agents at the concentrations used in this study (0.01-100 $\mu\text{M}$ ).

### Inhibition of Bufuralol 1-hydroxylase (Figures 5-8)

Dofetilide had little effect on the metabolism of the CYP2D6 probe substrate bufuralol (20% inhibition at 100  $\mu\text{M}$  dofetilide). In contrast both quinidine and flecainide were potent inhibitors of 1'-hydroxybufuralol formation (IC50's of  $0.25 \pm 0.08 \mu\text{M}$  and  $0.44 \pm 0.16 \mu\text{M}$  respectively). Amiodarone was found not to inhibit CYP2D6 over the concentration range studied.

Figure 1.

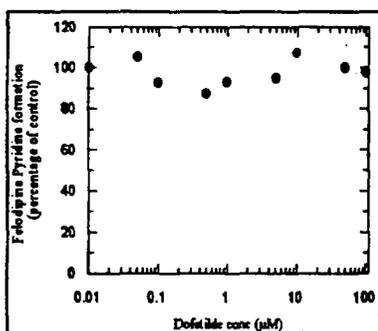


Figure 2.

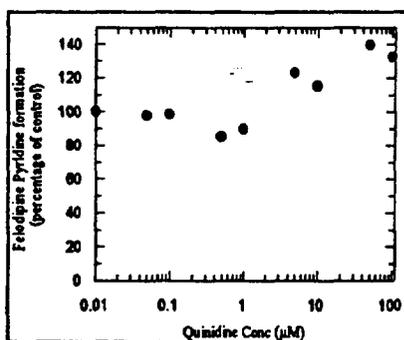


Figure 3.

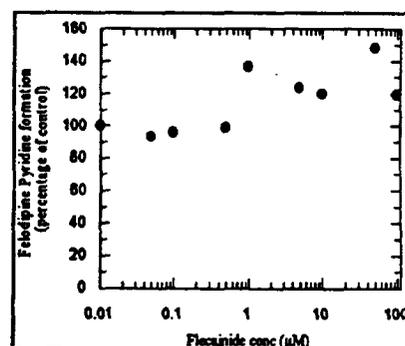


Figure 4.

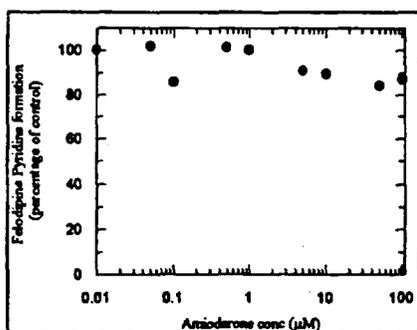


Figure 5.

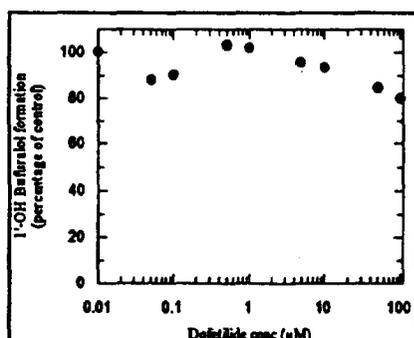


Figure 6.

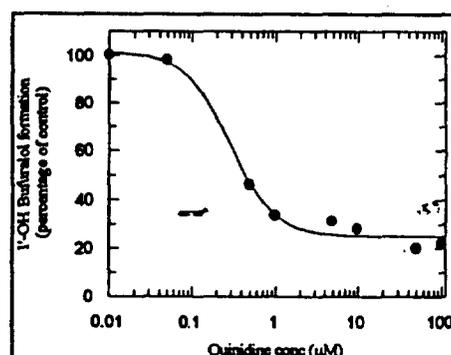


Figure 7.

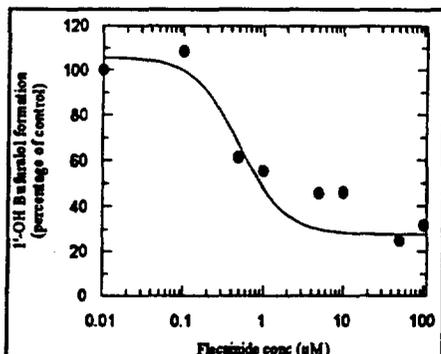
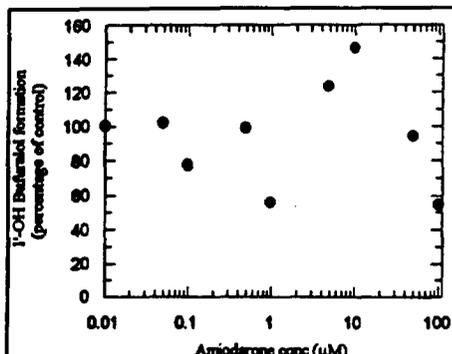


Figure 8.



**CONCLUSIONS:** The results show that dofetilide does not significantly inhibit CYP2C9, CYP2D6 and CYP3A4 over the concentration range 0.01-100 µM. In comparison quinidine and flecainide are both potent inhibitors of CYP2D6 (IC<sub>50</sub>=0.25 µM and 0.44 µM respectively). Flecainide and amiodarone are also inhibitors of CYP2C9 (IC<sub>50</sub>=48.5 µM and 25 µM respectively). These data are in accord with clinical experience. Co-administration of flecainide and propranolol has been reported to result in raised plasma concentrations of both compounds. Quinidine has also been shown to inhibit the metabolism of flecainide, encainide, propafenone and propranolol, resulting in increased plasma concentrations of these compounds. Drug interactions between amiodarone and phenytoin have been reported, as have amiodarone and warfarin with increased plasma concentrations of phenytoin and warfarin. In conclusion, dofetilide has not been shown to inhibit the three major drug metabolising isozymes over the concentration range studied. The concentrations used in this study were four orders of magnitude in excess of the clinical concentrations of dofetilide (less than 0.005 µM). In contrast the antiarrhythmic agents used as positive controls (flecainide, quinidine and amiodarone) have been shown to inhibit CYP2C9 and CYP2D6. These *in vitro* data suggest that dofetilide is unlikely to be implicated in P450-mediated drug interactions but a perfect correlation between *in vitro* and *in vivo* metabolic data has not been established (there have been both false positive and false negative predictions).

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## **IN VITRO PROTEIN BINDING STUDIES**

**PROTOCOL NUMBER:** UK-68,798/DM/12/87

**STUDY DATES:** May to June 1987

**INVESTIGATOR AND LOCATION:**

**OBJECTIVE AND RATIONALE:** The extent to which a drug binds to plasma proteins can effect the interpretation of efficacy, toxicity and pharmacokinetic data. This study compares the binding of dofetilide to the plasma proteins of rat and dog (the species used in toxicity testing) with that in man. The initial plasma concentrations of drug investigated were 100 and 10 ng/ml.

### **PROCEDURES:**

Plasma containing [<sup>14</sup>C]-dofetilide at a concentrations of 10 and 100 ng/ml were prepared in rat, dog and human plasma. And protein binding studies were conducted using equilibrium dialysis. Samples of plasma containing [<sup>14</sup>C]-dofetilide (1 ml) were dialysed against isotonic, pH 7.4 buffer (1 ml) for 5 h at 37°C in a rotating dialyser (Dianorm, M.S.E. Ltd.). The radioactivity in samples (0.5ml) of buffer and plasma from each half-cell was measured by liquid scintillation counting in Instagel (Packard Instruments Ltd.).

### **DATA ANALYSIS:**

The percentage of [<sup>14</sup>C]-dofetilide in plasma which was bound to plasma proteins at equilibrium was determined using the formula

$$\% \text{ bound} = 100 - \frac{(\text{concentration } [^{14}\text{C}]\text{-dofetilide in buffer} \times 100)}{\text{concentration } [^{14}\text{C}]\text{-dofetilide in plasma}}$$

where the concentrations of [<sup>14</sup>C]-dofetilide were determined from the radioactivity (d.p.m.) per 0.5 ml sample.

**RESULTS:** Table 1 summarizes the result obtained from the study.

**TABLE 1**

**PERCENTAGE OF [<sup>14</sup>C]-DOFETILIDE BOUND TO PLASMA PROTEINS OF RAT, DOG AND MAN**

Results are mean of five determinations.

Species	% Dofetilide bound to plasma protein	
	100ng/ml	10ng/ml
Rat	53 (62)	62 (8.6)
Dog	54 (68)	56 (6.3)
Man	64 (72)	68 (6.9)

Figures in brackets are plasma concentrations of dofetilide (ng/ml) at equilibrium.

**CONCLUSIONS:** The results show that when the initial concentration of dofetilide was 100ng/ml the percentages of drug bound were 53%, 54% and 64% in rat, dog and man respectively. At a concentration of 10 ng/ml the percentages of drug bound were 62%, 56% and 68% respectively. In view of the high free fraction the differences in binding between species are not significant and there is low potential for drug-drug interactions.

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