

DATA ANALYSIS:

AUC, C_{max}, and T_{max} were determined.

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

Table 1. PK Parameters for levonorgestrel and ethinyloestradiol

Parameter	OC + Dofetilide	OC + Placebo
levonorgestrel		
AUC _t (h*ng/ml)	123.5 (50.5)	106.7 (45.6)
C _{max} (ng/ml)	11.5 (4.1)	10.4 (3.0)
T _{max} (h)	1.6 (0.8)	1.4 (0.80)
	1.67 (1.05)	1.42 (0.56)
ethinyloestradiol		
AUC _t (h*pg/ml)	934.9 (682.3)	770.7 (585.7)
C _{max} (p/ml)	123.9 (53.9)	115.7 (30.4)
T _{max} (h)	2.2 (1.3)	2.2 (0.7)

OC = Oral Contraceptive

Table 2. Analysis of ethinylloestradiol pharmacokinetic parameters

COMPARISON: Dofetilide 750 mg b.i.d. - Double Blind Placebo

	LOG TRANSFORMED DATA			RATIO BETWEEN MEANS	ANTI-LOG*		P-VALUE
	DIFFERENCE BETWEEN ADJUSTED MEANS	90% CONFIDENCE LIMITS OF DIFFERENCE BETWEEN MEANS LOWER	UPPER		90% CONFIDENCE LIMITS OF RATIO BETWEEN MEANS LOWER	UPPER	
AUC (0-24h) (pg.h/ml)	0.19	-0.04	0.43	121.1%	95.7%	153.3%	0.1727
C _{max} (pg/ml)	0.03	-0.19	0.25	101.6%	82.4%	127.8%	0.6284

Table 3. Analysis of levonorgestrel pharmacokinetic parameters

	LOG TRANSFORMED DATA			RATIO BETWEEN MEANS	ANTI-LOG*		P-VALUE
	DIFFERENCE BETWEEN ADJUSTED MEANS	90% CONFIDENCE LIMITS OF DIFFERENCE BETWEEN MEANS LOWER	UPPER		90% CONFIDENCE LIMITS OF RATIO BETWEEN MEANS LOWER	UPPER	
AUC (0-24h) (ng.h/ml)	0.15	0.03	0.25	116.3%	105.6%	128.1%	0.0161
AUC (ng.h/ml)	0.18	0.07	0.30	119.9%	106.7%	134.6%	0.0197
C _{max} (ng/ml)	0.07	-0.11	0.25	107.6%	89.8%	128.9%	0.6863

Table 4. PK Parameters for Dofetilide

Parameter	Mean (SD)	Range
AUC _t (ng.h/ml)	50.3 (7.41)	
C _{max} (ng/ml)	8.0 (1.33)	
T _{max} (h)	2.0 (0)	

FIGURE 1.1
DOFETILIDE PROTOCOL 236
ETHINYLESTRODIOL PLASMA CONCENTRATION SUMMARY

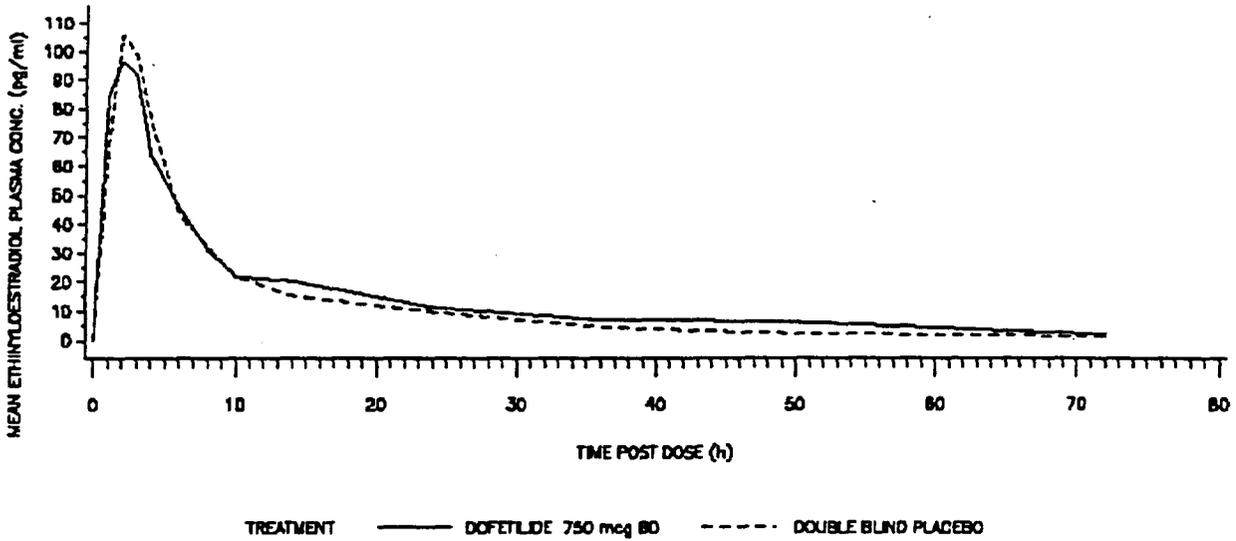
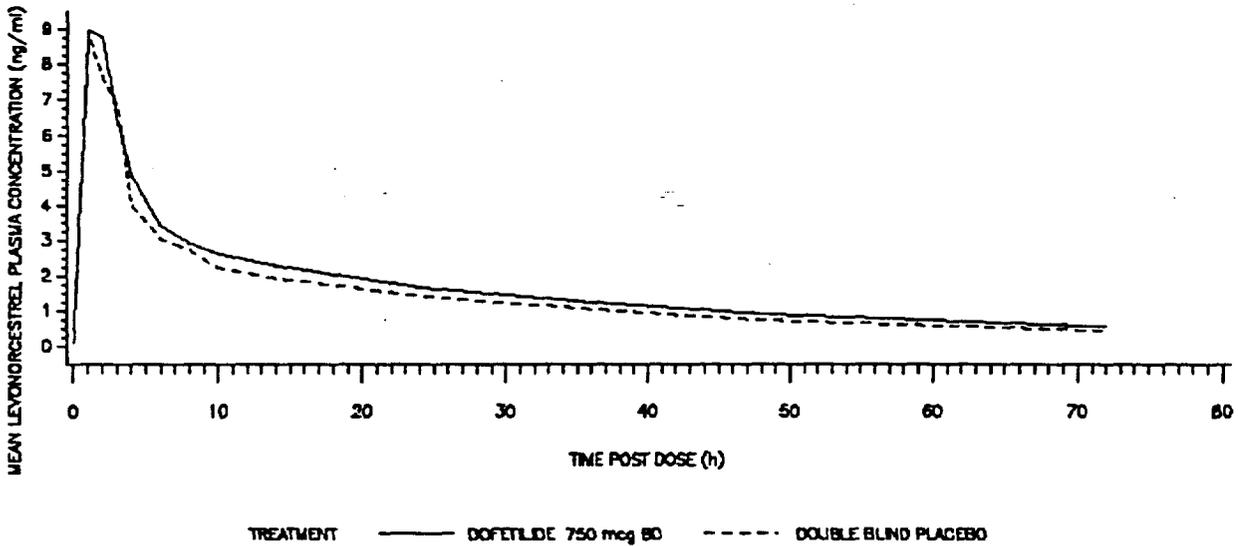


FIGURE 1.2
DOFETILIDE PROTOCOL 236
LEVONORGESTREL PLASMA CONCENTRATION SUMMARY



CONCLUSIONS: The results shows that when dofetilide is co-administered (was dosed at 750mcg twice daily for six days) with oral contraceptive containing ethinylestradiol and levonorgestrel (single dose) ethinylestradiol and levonorgestrel:

(1) The AUC of ethinylestradiol and levonorgestrel increased by 21% and 15% respectively but variability of the pharmacokinetic parameters were high (%CV - 40-75%).

(2) Compared to Study 115-001 (0.5 mg dofetilide BID, male subjects only, mean C_{max} of 2.4 ng/ml) and Study 115-014 (single dose of 0.5 mg dofetilide, mean C_{max} of 1.7 ng/ml for male and 2.4 ng/ml for female) it appears that the mean C_{max} of 8 ng/ml obtained from this study is rather high and suggests possible interaction of oral contraceptive with dofetilide.

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DOFETILIDE-PROPRANOLOL INTERACTION STUDY

STUDY 115-215 VOLUME: 2.36 PAGES: 1-229

INVESTIGATOR AND LOCATION: [

STUDY DATE: July - October 1989.

OBJECTIVES:

To investigate the effects of oral dofetilide, 250mcg b.i.d. for 4 days, on the pharmacodynamics and pharmacokinetics of steady-state propranolol and to evaluate the safety and toleration of the combination.

FORMULATIONS:

Dofetilide, FID 0963 Lot No. 772-04

Propranolol (Inderal), 40mg tablets, Lot No. 810-41

Identical placebo capsules: FID 0034 Lot No. 748-06

STUDY DESIGN:

This was a double-blind, placebo-controlled, randomized parallel group study. Each subject received propranolol 40mg b.i.d. on Days 1 to 8 inclusive and dofetilide, 250mcg, or matching placebo b.i.d. on Days 5 to 8, one hour before each propranolol dose. Propranolol pharmacodynamics were assessed on Days 4 and 8 by evaluation of ECG, heart rate, blood pressure and exercise induced tachycardia. Blood for determination of plasma propranolol concentrations were obtained immediately prior to the morning doses on Days 1 (baseline) to 8, with additional samples taken at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12 and 16 hours after the morning dose on Days 4 and 8 with a final sample 24 hours after dosing on Day 8. Blood for determination of plasma dofetilide concentrations were obtained immediately before the morning dose on Days 5 to 8 and before discharge on Day 9. Additionally, plasma concentrations of dofetilide were obtained from samples taken at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 16 and 24 hours post-dose on Day 8 which were extra to the requirements of the protocol.

ASSAYS:

DATA ANALYSIS:

AUC, Cmax, and Tmax were determined.

RESULTS: Tables 1-2 and Figures 1-3 summarize the data obtained from the study.

Table 1. Mean Propranolol Pharmacokinetics on Day 4 and Day 8 (Mean ± SE)

	Cmax (ng/ml)	Tmax (h)	AUCt (ng.h/ml)
Dofetilide			
Day 4	29.76 ± 7.84	1.64 ± 0.42	111.14 ± 29.37
Day 8	30.86 ± 6.66	2.07 ± 0.34	122.57 ± 26.71
Placebo			
Day 4	39.33 ± 3.96	1.14 ± 0.18	168.14 ± 19.81
Day 8	45.67 ± 6.11	1.07 ± 0.17	174.43 ± 25.58

Table 2. Propranolol Pharmacodynamics (Heart Rates, Mean ± SE)

	Before	After Exercise
Dofetilide		
Day 4	66.43 ± 2.95	143.57 ± 4.31
Day 8	68.14 ± 4.95	145.00 ± 4.09
Placebo		
Day 4	68.86 ± 4.51	138.43 ± 3.32
Day 8	64.86 ± 4.04	145.43 ± 5.40

DOFETILIDE PHARMACOKINETICS (Mean ± SD):

Mean Cmax - 1.72 ± 0.35 ng/ml
Mean AUC 0-12h - 11.88 ± 1.72 ng.h/ml

Figure 1. Mean Dofetilide Concentration on Day 8.

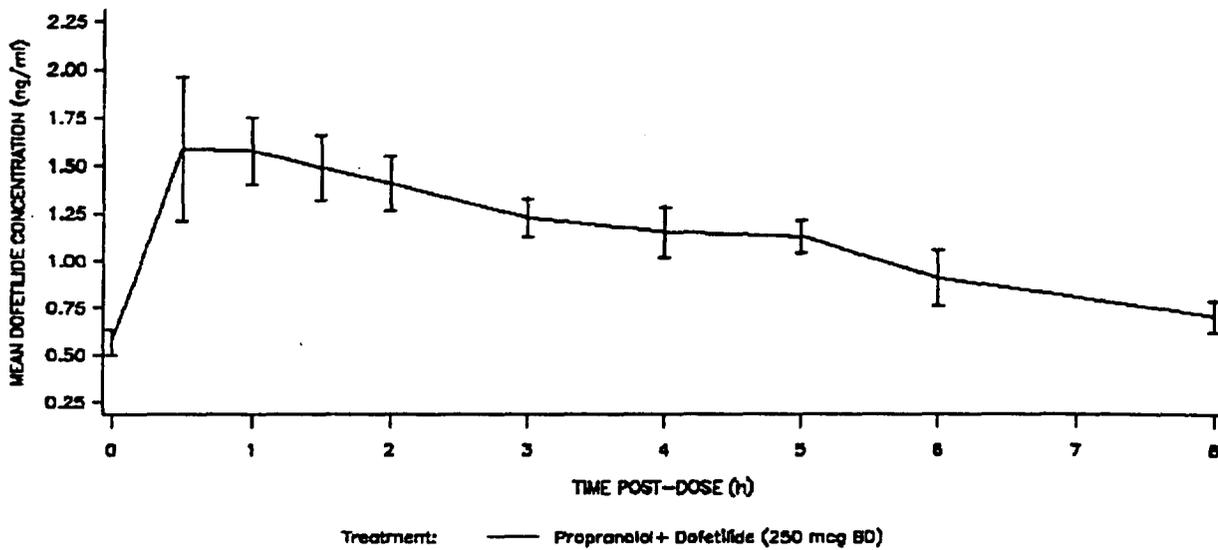


Figure 2. Mean Propranolol Concentrations

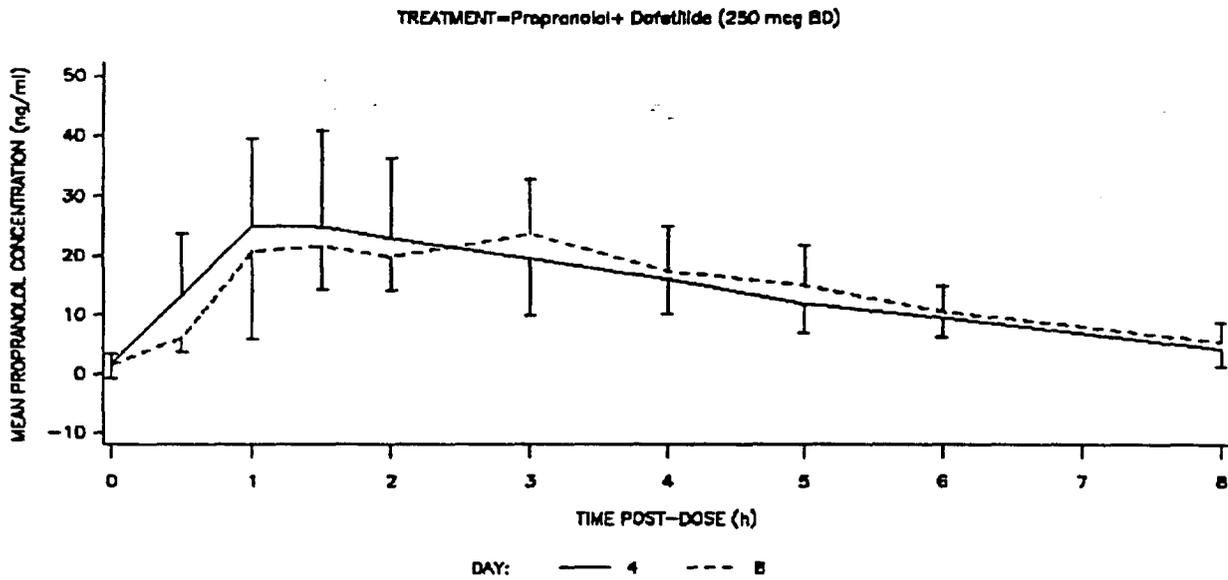
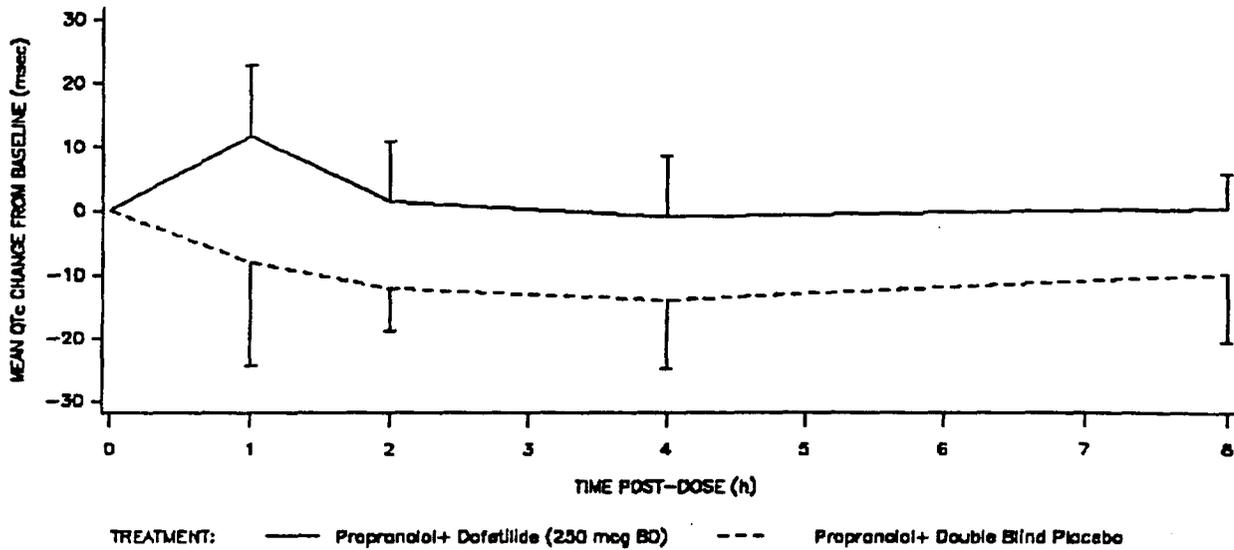


Figure 3. Mean QTc changes on Day 8



CONCLUSIONS:

- (1) Dofetilide did not alter the pharmacodynamics or pharmacokinetics of propranolol.
- (2) Compared to Study 115-001 (0.5 mg dofetilide BID, male subjects only, mean C_{max} of 2.4 ng/ml, mean AUC_{0-12h} of 18.4 ng.h/ml), the plasma levels of dofetilide (mean C_{max} of 1.72 ± 0.35 ng/ml, mean AUC_{0-12h} of 11.88 ± 1.72 ng.h/ml) obtained in this study (0.25 mg dofetilide BID) did not show that propranolol affects the pharmacokinetics of dofetilide. The comparison is however made difficult by the poor accuracy of the assay for the present study.

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DOFETILIDE-VERAPAMIL INTERACTION STUDY

STUDY 115-001

VOLUME: 1.29

PAGES: 1-395

INVESTIGATOR AND LOCATION: [

STUDY DATE: March 23 to June 1, 1993.

OBJECTIVES:

To determine whether any clinically significant pharmacokinetic or pharmacodynamic interaction occurs between dofetilide and verapamil. To examine the safety profile of dofetilide.

FORMULATIONS:

Dofetilide capsules: 500mcg FID No. 0964, Lot No. 503-20

Verapamil capsules: 80mg FID No. G00279AA, Lot No. ED-G-019-293

Placebo capsules FID No. 0034, Lot No. 748-17 and FID No. G00280AA, Lot No. ED- G-022-293

STUDY DESIGN:

This was a single-blind, placebo-controlled study with the following fixed sequence of study drug administration: Days 1-3 verapamil 80mg tid and placebo dofetilide bid, Days 4-6 placebo dofetilide bid and placebo verapamil tid, Days 7-11 dofetilide 500mcg bid and placebo verapamil tid, Days 12-14 dofetilide 500mcg bid and verapamil 80mg tid. Pharmacokinetic and pharmacodynamic evaluations were performed following morning study drug administration on Days 3, 6, 11, 12 and 14. Only the morning dose of active study drug was administered on Days 3, 11 and 14. All remaining doses on those days and all doses on Day 6 were placebo. Dofetilide and/ or verapamil plasma concentrations were monitored on Days 3, 11 and 14 at 0 (just prior to dosing) and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, and 24hrs post morning dosing and also on Day 12 at time points up to and including 8hrs post- dosing.

ASSAYS:

DATA ANALYSIS:

AUC, C_{max}, T_{max}, and Kel were determined. For pharmacodynamic analyses of dofetilide and verapamil, AUEC over selected intervals and E_{max} were determined.

Since only the morning dose was administered on Day 11, plasma concentrations of dofetilide on Day 12 were not considered at steady-state and were corrected for pre-dose concentrations using:

$$C_p(t)_{\text{corr}} = C_p(t)_{\text{meas}} - C_p(\text{predose}) \cdot e^{-K_{el} \cdot t}$$

RESULTS: Tables 1-4 and Figures 1-7 summarize the pharmacokinetic pharmacodynamic data obtained from the study.

Table 1. PK Parameters for Dofetilide

Parameter	Dofetilide (Day 11)	Verapamil + Dofetilide (Day 14)	90% CI
AUC ₀₋₄ (h*ng/ml)	7.4 (1.0)	9.2 (1.4)	104 - 152
AUC ₀₋₁₂ (h*ng/ml)	18.4 (3.4)	21.0 (3.7)	97 - 134
C _{max} (ng/ml)	2.4 (0.4)	3.4 (0.7)	110 - 186
T _{max} (h)	2.2 (1.4)	1.5 (0.5)	-
Kel (h ⁻¹)	0.0926 (0.011)	0.0932 (0.006)	-
Adjusted Values			
AUC ₀₋₈ (h*ng/ml)	9.9 (1.8)	11.1 (2.6)	82 - 154
C _{max} (ng/ml)	1.8 (0.4)	2.6 (0.6)	101 - 198

Geometric Mean (SD) except for T_{max} (Arithmetic mean)

Table 2. PK Parameters for Verapamil and Norverapamil

Parameter	Verapamil (Day 3)	Verapamil + Dofetilide (Day 14)	90% CI
Verapamil			
AUC ₀₋₄ (h*ng/ml)	519 (280)	574 (283)	87 - 140
AUC ₀₋₈ (h*ng/ml)	829 (472)	921 (454)	84 - 146
C _{max} (ng/ml)	230 (121)	244 (130)	68 - 166
T _{max} (h)	1.67 (1.05)	1.42 (0.56)	-
Norverapamil			
AUC ₀₋₄ (h*ng/ml)	539 (177)	573 (175)	89 - 126
AUC ₀₋₈ (h*ng/ml)	1029 (358)	1095 (357)	92 - 123
C _{max} (ng/ml)	177 (60)	179 (53)	81- 126
T _{max} (h)	2.46 (1.23)	1.79(0.45)	-

Table 3. PD (QTc) Parameters for Dofetilide

Parameter	Dofetile (Day 3)	Dofetilide+ Verapamil (Day 14)	Placebo
AUEC ₀₋₄ (msec.h)	43.7 (82.9)	26.8 (79.6)	-21.7 (59.0)
AUEC ₀₋₁₂ (msec.h)	50.6 (281.7)	-51.8 (195.0)	-39.2 (125.6)
E _{max} (msec)	34.5 (25.3)	32.1 (23.0)	15.5 (12.8)

Geometric Mean (SD)

Table 4. PD (PR interval) Parameters for Verapamil

Parameter	Verapamil (Day 3)	Dofetilide+ Verapamil (Day 14)	Placebo
AUEC ₀₋₄ (msec.h)	35.7 (29.6)	59.4 (40.0)	-11.2 (48.9)
AUEC ₀₋₈ (msec.h)	18.0 (71.3)	48.6 (81.6)	-53.9 (76.9)
E _{max} (msec)	25.8 (9.1)	30.8 (15.5)	9.3 (12.6)

Figure 1. Deltalide Mean Plasma Concentrations Following Multiple Oral Doses (500 mg q 12 h) in the Absence and Presence of Single and Multiple Oral Doses of Verapamil (50 mg q 8 h) to Healthy Male Subjects
 (Clinical Study #115-001-001, Dr. J. Vankar, Richmond, VA)

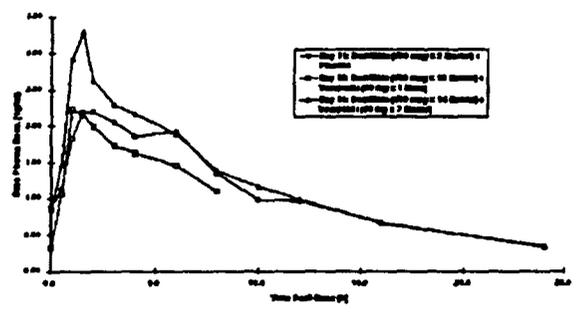


Figure 2. Verapamil Mean Plasma Concentrations Following Verapamil Administration (50 mg q 8h) in the Absence and Presence of Oral Doses of Deltalide (500 mg q 12h) to Healthy Male Subjects
 (Clinical Study #116-001-001, Dr. J. Vankar, Richmond, VA)

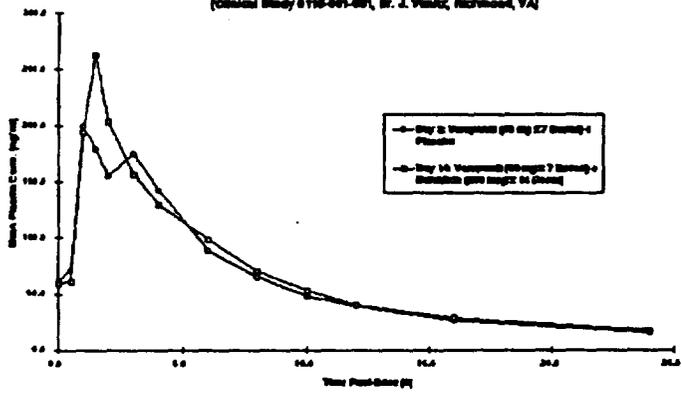


Figure 3. Nonverapamil Mean Plasma Concentrations Following Verapamil Administration (50 mg q 8h) in the Absence and Presence of Oral Doses of Deltalide (500 mg q 12h) to Healthy Male Subjects
 (Clinical Study #116-001-001, Dr. J. Vankar, Richmond, VA)

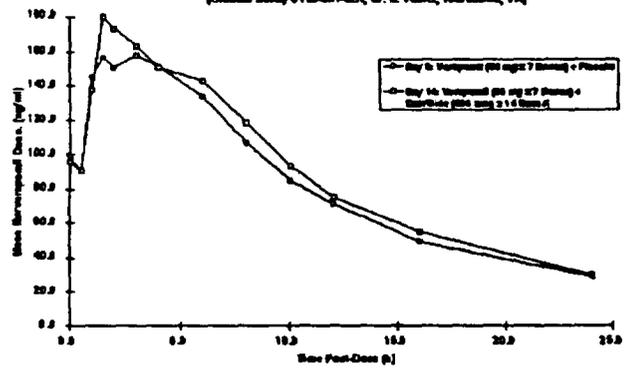


FIGURE 4
DOFETILIDE PROTOCOL 001
MEAN EXPERT LEAD II QTC CHANGES FROM PRE-DOSE ON DAYS 3, 6, 11, 12 AND 14

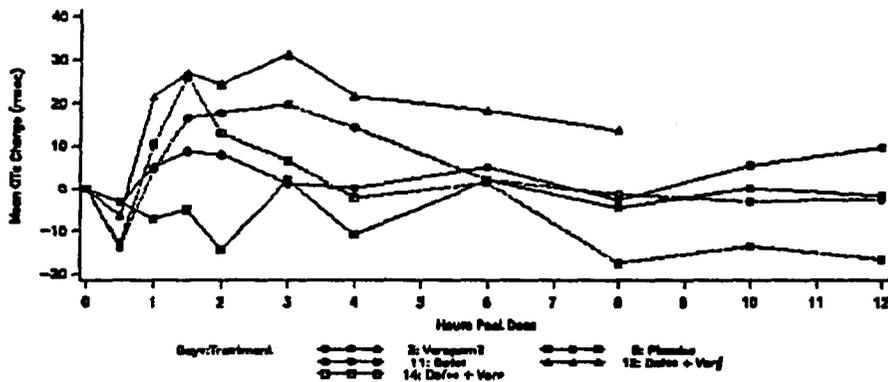


FIGURE 5
DOFETILIDE PROTOCOL 001
MEAN EXPERT LEAD II PR CHANGES FROM PRE-DOSE ON DAYS 3, 6, 11, 12 AND 14

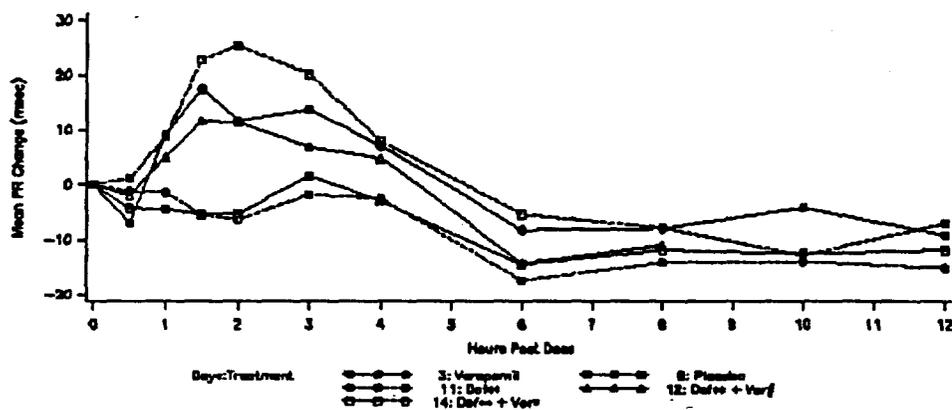


FIGURE 6
DOFETILIDE PROTOCOL 001
MEAN DOFETILIDE PLASMA CONCENTRATIONS AND MEAN EXPERT LEAD II QTC INTERVALS OVER TIME

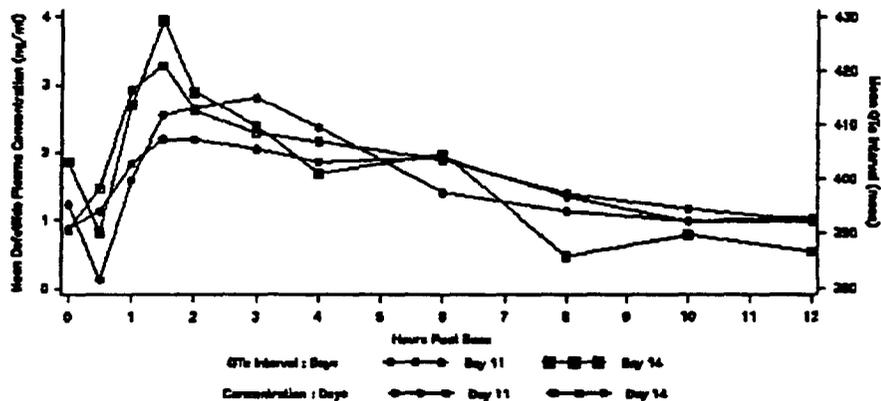
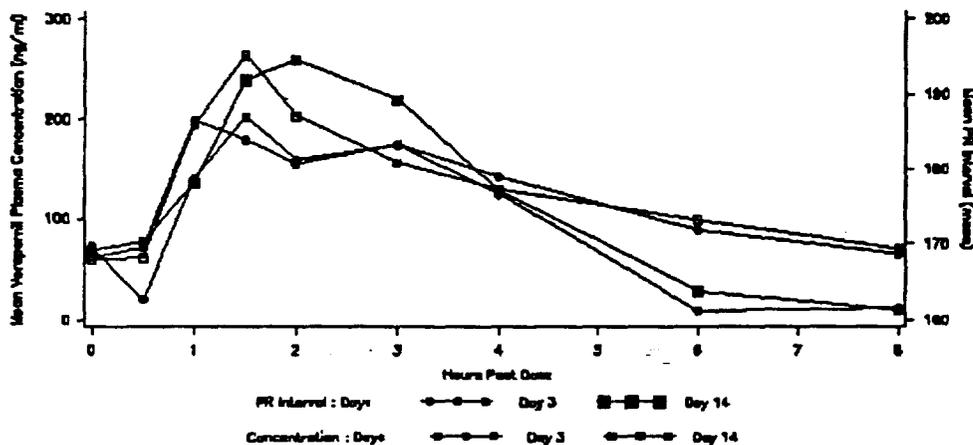


FIGURE 7
DOFETILIDE PROTOCOL 001
MEAN VERAPAMIL PLASMA CONCENTRATIONS AND MEAN EXPERT LEAD II PR INTERVALS OVER TIME



CONCLUSION: The results obtained from the study show that co-administration of 0.5 mg dofetilide with 80 mg verapamil

1. Cmax of dofetilide increased by 42% while AUC(0- 4) and AUC(0- 12) increased by 24% and 14% respectively and Tmax decreased from 2.2 hours to 1.5 hours. The increase in plasma levels is accompanied by QTc prolongation.
2. No change in verapamil or norverapamil pharmacokinetic parameters.

10 and 12 hours post dofetilide administration. Additional concentration measurements were obtained at 16, 24, 36, 48 and 72 hours post 10 dofetilide administration. Urine dofetilide concentrations were obtained from urine samples collected during the 12 hours following the morning dose of dofetilide on Day 4 and during the 24 hours following the last dose of dofetilide on Day 10.

ASSAYS:

DATA ANALYSIS:

AUC, Cmax, Tmax, and Kel were computed. Renal clearance (CLr) of dofetilide was determined on Day 4 as $A_e(0-12)/AUC(0-12)$ and on Day 10 as $A_e(0-24)/AUC(0-24)$. The maximum change in QTc (Emax) and the area under the QTc versus time curve (AUEC) was calculated up to 12 hours post dose.

RESULTS: Tables 1-3 and Figures 1-7 summarize the pharmacokinetic pharmacodynamic data obtained from the study.

Table 5.1 Summary of Mean Dofetilide Pharmacokinetic Parameters Following Multiple Oral Administration of 500 µg q. 12 h Alone and With Either Cimetidine 400 mg q. 12 h or Placebo q. 12 h to Healthy Male Subjects. (Clinical Study #115-004-501, Dr. G. Apstein, Columbus, OH)

Treatment Group ^a	N	AUC(0-12) ^b (ng·h/ml)	C _{max} ^b (ng/ml)	T _{max} (h)	K _{el} (h ⁻¹)	T _{1/2} (h)	CL _r (ml/min)
Day 4^c							
A	12	Mean 17.4 (SD) (2.7)	Mean 2.26 (SD) (0.37)	2.6 (1.0)	-	-	343.7 (73.4)
B	12	Mean 16.6 (SD) (3.8)	2.10 (0.41)	3.1 (2.1)	-	-	419.2 (85.4)
Day 10^c							
A	12	Mean 27.5 (SD) (6.2)	3.44 (0.62)	2.6 (1.4)	0.9534 (0.0104)	12.9 ^d -	192.9 (39.9)
B	12	Mean 17.3 (SD) (4.5)	2.17 (0.54)	2.3 (0.7)	0.851 ^d (0.0112)	12.8 ^{d,e} -	334.3 (121.5)

^a - Group A - Dofetilide (500 µg q. 12 h Days 1-10) + Cimetidine (400 mg q. 12 h Days 6-11)
Group B - Dofetilide (500 µg q. 12 h Days 1-10) + Placebo (q. 12 h Days 6-11)

^b - Means (SD) for AUC(0-12) and C_{max} are geometric

^c - Day 4 - Dofetilide alone 500 µg q. 12 h
Day 10 - Dofetilide 500 µg + Either Cimetidine 400 mg q. 12 h or Placebo q. 12 h

^d - ln 2/mean K_{el}

^e - n=10

Table 2. Statistical Analysis of Dofetilide PK Parameters

DOFETILIDE PROTOCOL 004 SUMMARY OF ANALYSIS OF DAY 10 VERSUS DAY 4 CHANGE IN DOFETILIDE PHARMACOKINETIC PARAMETERS							
Treatment		Day 4 ^a	Day 10 ^a	Ratio	Within Treatment Comparison 90% Confidence Limits	Between Treatment Comparison (p-value)	
Dofetilide 500 mg BID+ Cimetidine							
	AUC _t (ng·h/ml)	Mean S.D. N	17.40 2.64 12	27.49 3.17 12	1.58 0.16 12	(132.2%, 188.9%)	p <= 0.0001
	C _{max} (ng/ml)	Mean S.D. N	2.26 0.37 12	3.44 0.62 12	1.52 0.23 12	(115.7%, 200.4%)	p <= 0.0001
	T _{max} (h)	Mean S.D. N	2.59 0.97 12	2.63 1.40 12	0.04 1.63 12	(-3.3, 3.3)	p = 0.3095
	CL _r (ml/min)	Mean S.D. N	343.75 72.42 12	192.88 39.99 12	-150.88 76.70 12	(-286.9, -14.9)	p = 0.0921
Dofetilide 500 mg BID+ Placebo							
	AUC _t (ng·h/ml)	Mean S.D. N	16.56 3.80 12	17.35 4.55 12	1.03 0.09 12	(89.2%, 122.9%)	
	C _{max} (ng/ml)	Mean S.D. N	2.10 0.41 12	2.17 0.54 12	1.03 0.16 12	(78.4%, 135.7%)	
	T _{max} (h)	Mean S.D. N	3.09 2.13 12	2.25 0.72 12	-0.83 2.23 12	(-6.8, 3.3)	
	CL _r (ml/min)	Mean S.D. N	419.16 85.37 12	234.29 121.65 11	-89.76 89.69 11	(-250.8, 71.3)	

Table 3. Pharmacodynamic Parameters (Mean \pm SD) for Dofetilide

DOFETILIDE PROTOCOL 004
SUMMARY OF ANALYSIS OF DAY 10 VERSUS DAY 4 CHANGE IN EXPECT LEAD II QTC

Treatment		Day 4*	Day 10*	Difference	Within Treatment Comparison 95% Confidence Limits	Between Treatment Comparison (p-value)
Dofetilide 500 mg BID+ Cisatridine						
AUC ₀₋₂₄	Mean	199.90	206.02	6.12	(-276.3, 292.3)	p = 0.2137
(nmoles/h)	S.D.	178.81	208.09	127.78		
	N	12	12	12		
C _{max}	Mean	45.58	46.42	0.83	(-23.5, 25.2)	p = 0.4204
(nmoles)	S.D.	15.25	20.34	15.77		
	N	12	12	12		
Post-dose QTC	Mean	275.15	283.75	8.50	(-26.2, 43.2)	p = 0.6678
(nmoles)	S.D.	17.33	21.00	15.95		
	N	12	12	12		
Dofetilide 500 mg BID+ Placebo						
AUC ₀₋₂₄	Mean	257.50	175.17	-82.33	(-312.0, 347.3)	
(nmoles/h)	S.D.	190.01	193.39	197.19		
	N	12	12	12		
C _{max}	Mean	46.50	41.33	-5.17	(-46.3, 36.0)	
(nmoles)	S.D.	15.90	16.43	19.80		
	N	12	12	12		
Post-dose QTC	Mean	272.50	277.82	5.32	(-37.2, 47.9)	
(nmoles)	S.D.	24.15	26.32	19.32		
	N	12	12	12		

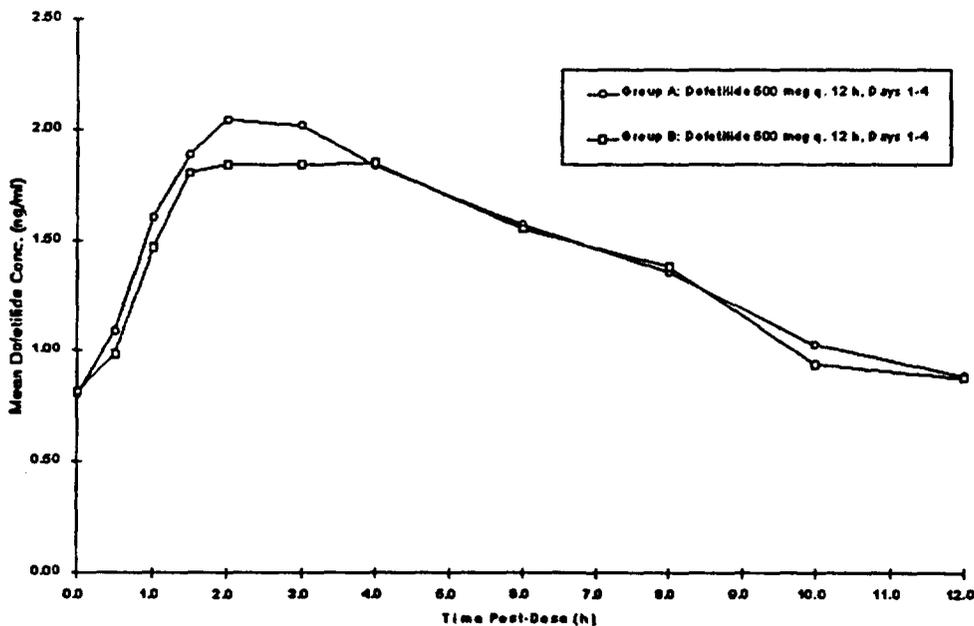
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Source: Appendix IV Tables 3.1 and 4

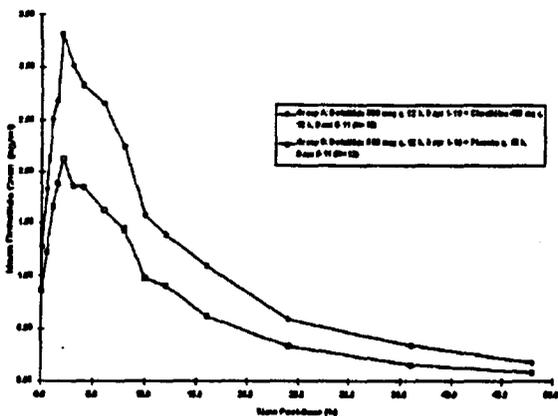
Means and standard deviations are arithmetic.
* Day relative to start of study therapy (Day 1).

Figure 1. Mean Dofetilide Plasma Concentrations on Day 4 Following Multiple Oral Doses of Dofetilide (500 mcg q. 12 to Healthy Male Subjects



Source Data: Appendix IIIB, Table 1

Figure 2. Mean Dofetilide Plasma Concentrations on Day 10 Following Multiple Oral Doses of Dofetilide (500 mg q. 12 h) With Either Clovidine (400 mg q. 12 h) or Placebo (q. 12 h) in Healthy Male Subjects



Source Data: Appendix III, Table 2

FIGURE 3
DOFETILIDE PROTOCOL 004
MEAN EXPERT LEAD II QTC CHANGES FROM PRE-DOSE ON DAYS 4 AND 10

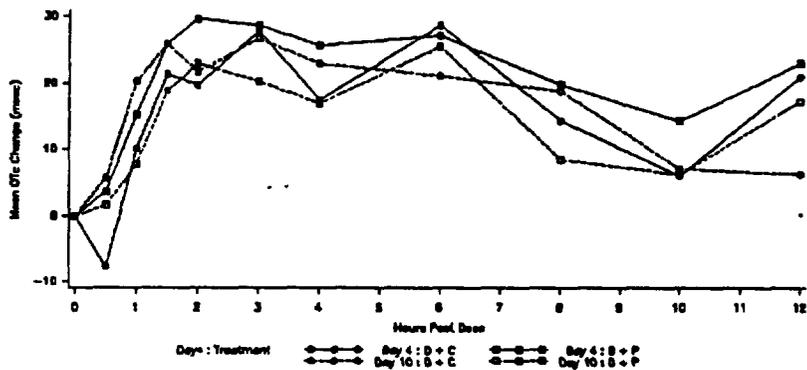


FIGURE 4
DOFETILIDE PROTOCOL 004
EXPERT LEAD II QTC EMAX VS CMAX

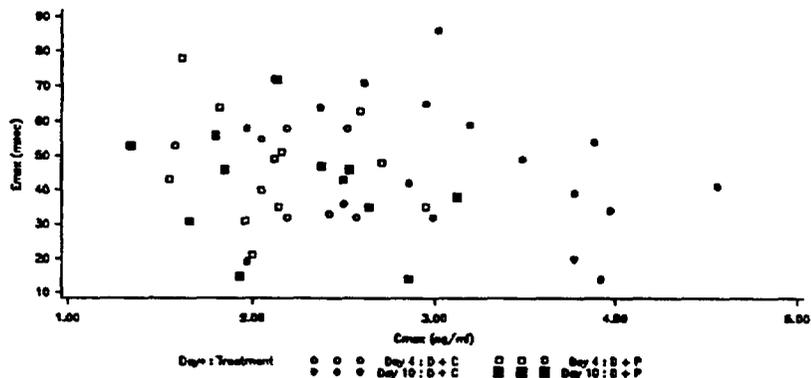


FIGURE 5
DOFETILIDE PROTOCOL 004
EXPERT LEAD II QTC EMAX VS AUCL

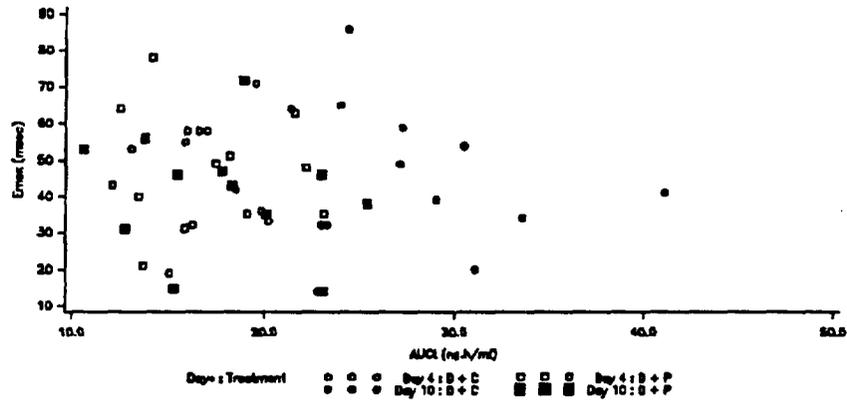


FIGURE 6
DOFETILIDE PROTOCOL 004
EXPERT LEAD II QTC AJECT VS CMAX

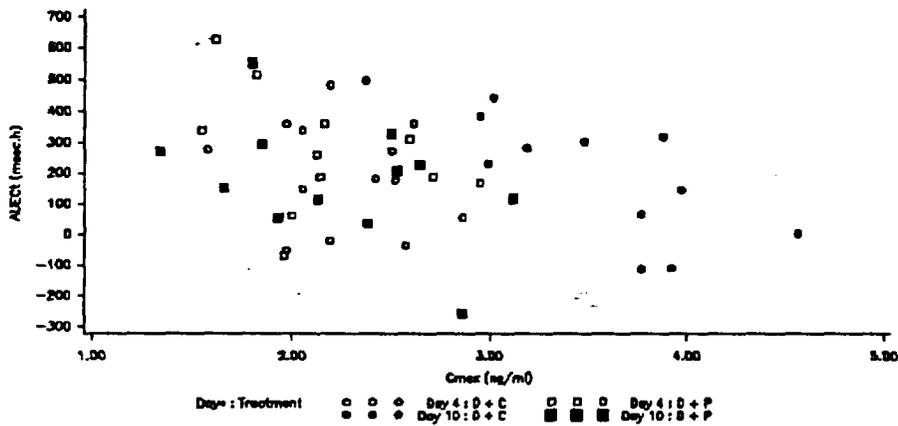
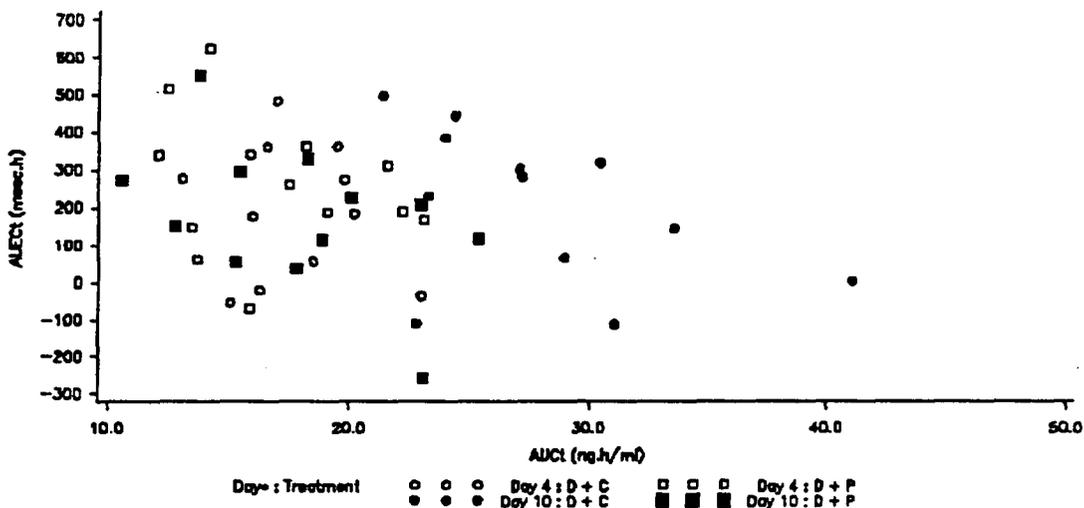


FIGURE 7
DOFETILIDE PROTOCOL 004
EXPERT LEAD II QTC AUECT VS AUCT



Conclusions: The concomitant administration of cimetidine with dofetilide resulted in an increase in AUC and C_{max}. The increases in mean C_{max} of 52% and in mean AUC_τ of 58% in the group treated with cimetidine plus dofetilide from Day 4 to Day 10 were statistically significant. In contrast, changes for mean C_{max} and mean AUC_τ for the group treated with placebo plus dofetilide from Day 4 to Day 10 were 3% and 5%, respectively, and were not statistically significant. A comparison between the two treatment groups showed a significant difference for AUC_τ and C_{max} ($p \leq 0.0001$). The mean dofetilide half-lives in the two treatment groups after 10 days of dosing were virtually the same.

Much of the increase in AUC and C_{max} for the subjects treated with dofetilide and cimetidine could be attributed to a 44% decrease in renal clearance, a decrease which was statistically significant. A decrease of 20% in mean renal clearance was also observed for the placebo plus dofetilide group, but this decrease was not statistically significant. In spite of the changes in pharmacokinetics upon concomitant administration with cimetidine, the pharmacodynamics of dofetilide as assessed by QTc intervals did not change. Neither AUEC or E_{max} changed significantly within the subject groups treated concomitantly with cimetidine or placebo. However, the variability in QTc was high. Given that the study was not powered on QTc but on AUC, which has low variability, this is not surprising. Also, in this study there was no apparent relationship between the pharmacodynamic (QTc) and the pharmacokinetic parameters which might be explained by the high variability in QTc and that only one dose strength of dofetilide was given.

PHARMACOKINETICS-PHARMACODYNAMICS STUDY

STUDY 115-221

VOLUME: 2.40

PAGES: 1-393

INVESTIGATOR AND LOCATION:

STUDY DATES: June to October 1990

STUDY OBJECTIVES:

To assess the pharmacokinetics and pharmacodynamics of dofetilide after three oral treatments and one intravenous infusion by investigating the relationship between plasma concentrations and QTc intervals and to evaluate safety and toleration of dofetilide after both routes of administration compared to placebo.

Drug administration:

Test product: Dofetilide: 25mcg/ml free base in solution for intravenous injection of 10mcg/kg FID 0952, Lot 916-11; 250mcg capsules, FID 0963, Lot 904-04; 500mcg capsules, FID 0964, Lot 904-02.

Reference therapy Matched placebo solution: FID 0950, Lot 788-49B; Matched placebo capsules FID 0034, Lot 748-06.

Diluent, for all iv doses - Mannitol solution (50mg/ml) with citric acid monohydrate solution (4mg/ml) adjusted to pH 3.5 with sodium hydroxide, FID 0950, Lot 916-10.

STUDY DESIGN:

This was a single blind study where 12 fasting, healthy, male subjects were allocated to receive three oral ascending doses of dofetilide (250, 750 and 1250mcg), with a single, oral dose of placebo and a single intravenous dose of dofetilide (10mcg/kg) randomly introduced into this sequence. Blood was sampled for plasma concentrations of dofetilide with coincident measurements of 12 lead ECGs up to 48 hours after each dose. Blood samples (5ml) for measurement of plasma concentrations of dofetilide were taken predose and at 5, 10, 15, 20, 30, 40, 50 minutes, then 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 18, 24, 32 and 48 hours after oral dosing or after the start of the iv infusion. The 30 minute sample coincided with the end of the infusion. Samples were stored at -20°C until analyzed.

ASSAYS:

DATA ANALYSIS:

C_{max}, T_{max}, AUC, AUC_t, Kel, T 1/2 and systemic bioavailability were computed. QTc values were calculated using Bazett's formula and AUEC_t (the area under the changes from baseline in QTc against time curve) was calculated over the first 12 hours using the linear trapezoidal rule. A biexponential disposition and monoexponential model with first order input were fitted to the iv and oral data respectively and used to examine the relationship between plasma concentrations of dofetilide and QTc. Hysteresis curves were collapsed and fitted to a linear model to yield slope values and the equilibration rate constant (KeO).

RESULTS: Tables 1-4 and Figures 1-6 summarize the data obtained from the study

Table 1. Pharmacodynamics of Dofetilide

DOFETILIDE PROTOCOL 111
MAXIMUM AND AUEC_t (12H) CHANGE FROM BASELINE QTc SUMMARY

TREATMENT		CHANGE FROM BASELINE QTc	
		MAXIMUM (ms) (n)	AUEC _t (0-12h) (ms.h) (n)
DOFETILIDE 10 mg/kg IV SOLUTION	MEAN	150.46	451.91
	S.E.	16.31	36.63
	N	7	7
DOFETILIDE 250 mg CAPSULE	MEAN	63.99	169.09
	S.E.	6.66	29.90
	N	7	7
DOFETILIDE 750 mg CAPSULE	MEAN	66.19	261.56
	S.E.	7.67	60.75
	N	7	7
DOFETILIDE 1750 mg CAPSULE	MEAN	91.84	330.01
	S.E.	10.46	89.56
	N	7	7
PLACEBO	MEAN	23.00	12.60
	S.E.	1.91	50.54
	N	7	7

D: 11JUN94
Y: 11JUN94 (10:00)

Source: Appendix IV Table 1.4

Table 2. Pharmacodynamics (change in QTc) of Dofetilide

DOFETILIDE PROTOCOL 211
ANALYSIS OF MAXIMUM CHANGE FROM BASELINE QTc SUMMARY

TREATMENT		MAXIMUM CHANGE FROM BASELINE QTc (secs)			
		BASELINE	OBSERVED	ADJUSTED*	% INCREASE FROM BASELINE
DOFETILIDE 10 mg/kg IV SOLUTION	MEAN	398.92	150.66	149.96	37.79
	S.E.	5.96	16.25	16.06	
	N	7	7	7	
DOFETILIDE 150 mg CAPSULE	MEAN	390.21	43.39	37.68	9.61
	S.E.	6.21	6.66	13.38	
	N	7	7	7	
DOFETILIDE 750 mg CAPSULE	MEAN	395.97	66.19	72.74	18.37
	S.E.	3.23	7.67	13.38	
	N	7	7	7	
DOFETILIDE 1250 mg CAPSULE	MEAN	403.99	91.36	91.87	22.74
	S.E.	3.93	10.66	19.09	
	N	7	7	7	
PLACEBO	MEAN	395.05	23.00	22.00	5.55
	S.E.	5.96	8.01	16.06	
	N	7	7	7	

IV vs placebo, p < 0.0001
 Pooled oral vs placebo, p = 0.0108
 Linear oral dose response relationship, p = 0.0161
 Quadratic oral dose response relationship, p = 0.6442

LINEAR DOSE RESPONSE EQUATION: MAXIMUM CHANGE FROM BASELINE QTc (secs) = 0.06 x (ORAL DOSE (mg)) + 37.1

Table 3. Pharmacokinetics of Dofetilide

DOFETILIDE PROTOCOL 211
PHARMACOKINETIC PARAMETERS SUMMARY

		TREATMENT			
		DOFETILIDE 10 mg/kg IV SOLUTION	DOFETILIDE 150 mg CAPSULE	DOFETILIDE 750 mg CAPSULE	DOFETILIDE 1250 mg CAPSULE
Cmax (ng/ml)	MEAN	9.94	0.99	2.30	4.98
	S.E.	1.00	0.07	0.30	0.25
	N	7	7	7	7
Tmax (h)	MEAN	0.48	3.00	1.74	3.39
	S.E.	0.62	0.63	0.25	0.21
	N	7	7	7	7
AUC (ng·h/ml)	MEAN	26.06	11.20	23.17	36.34
	S.E.	2.73	1.03	2.10	0.27
	N	7	7	7	7
Kel (1/h)	MEAN	0.0945	0.1824	0.0919	0.0973
	S.E.	0.0042	0.0072	0.0039	0.0045
	N	7	7	7	7
HALF LIFE (h)	MEAN*	7.04	6.77	7.54	7.93
SYSTEMIC AVAILABILITY	MEAN		0.91	0.91	0.93
	S.E.		0.04	0.04	0.04
	N		7	7	7

D: 20FEB95 - 15AUG95
 T: 15AUG95 (12:28)

Source: Appendix IIIC

* Mean half life calculated as ln(2) / mean(Kel)

Table 4. Pharmacokinetics-Pharmacodynamics Model Parameters

DOFETILIDE PROTOCOL 221
 PHARMACOKINETIC/PHARMACODYNAMIC MODEL SUMMARY

		TREATMENT		
		DOFETILIDE 10 mcg/kg IV SOLUTION	DOFETILIDE 750 mcg CAPSULE	DOFETILIDE 1250 mcg CAPSULE
SLOPE (msec/ng/ml)	MEAN	20.47	18.89	15.47
	S.E.	1.95	1.74	1.50
	N	6	6	7
Ke0 (/h)	MEAN	4.58	9.12	9.30
	S.E.	0.65	2.69	3.93
	N	6	3	3
THALP	MEAN*	0.15	0.08	0.07

D: 24FEB93 - 15AUG95
 T: 15AUG95 (13:08)

Source: Appendix IIIC

* Mean half life calculated as $\ln(2) / \text{mean}(Ke0)$

Figure 1. QTc Changes from baseline

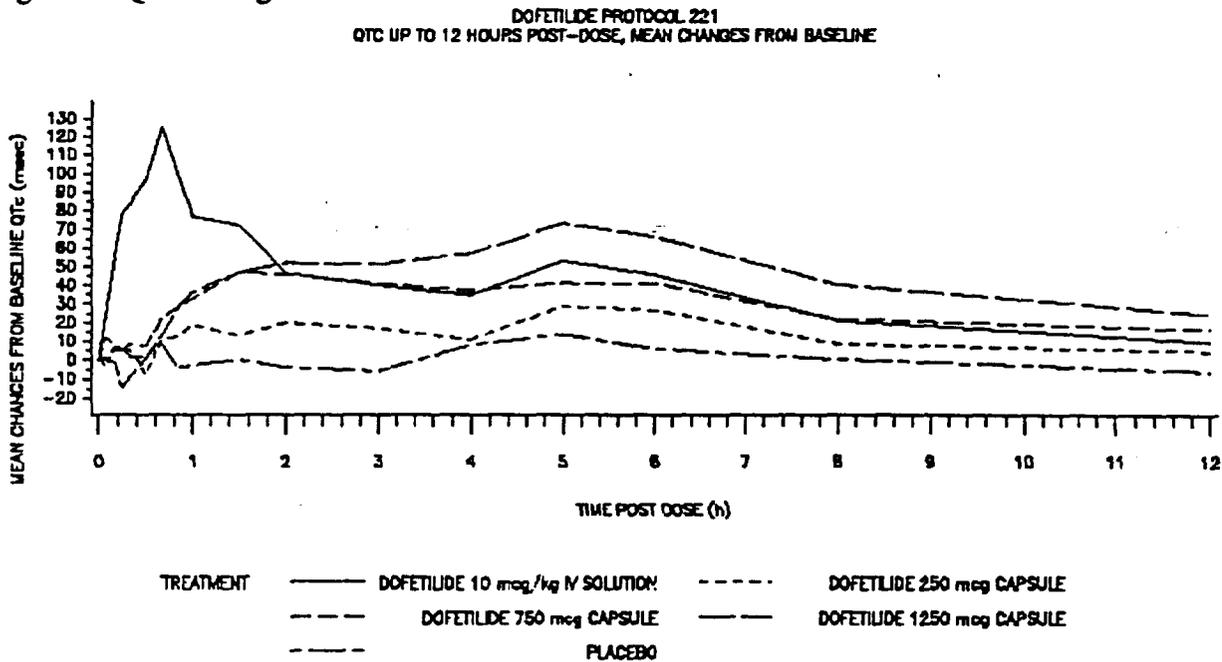
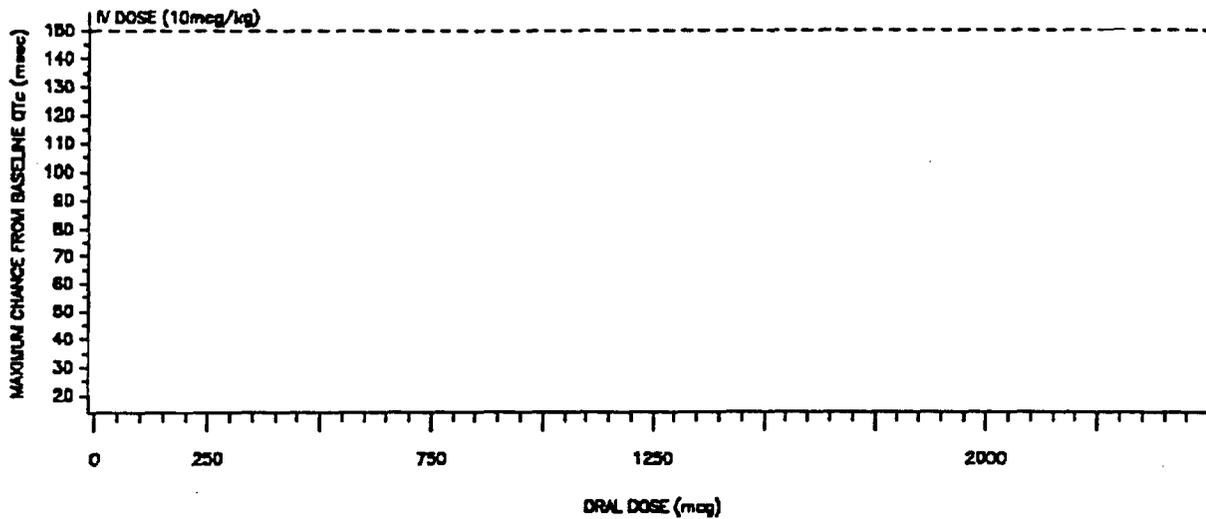


Figure 2. Dose-Response Relationship for QTc

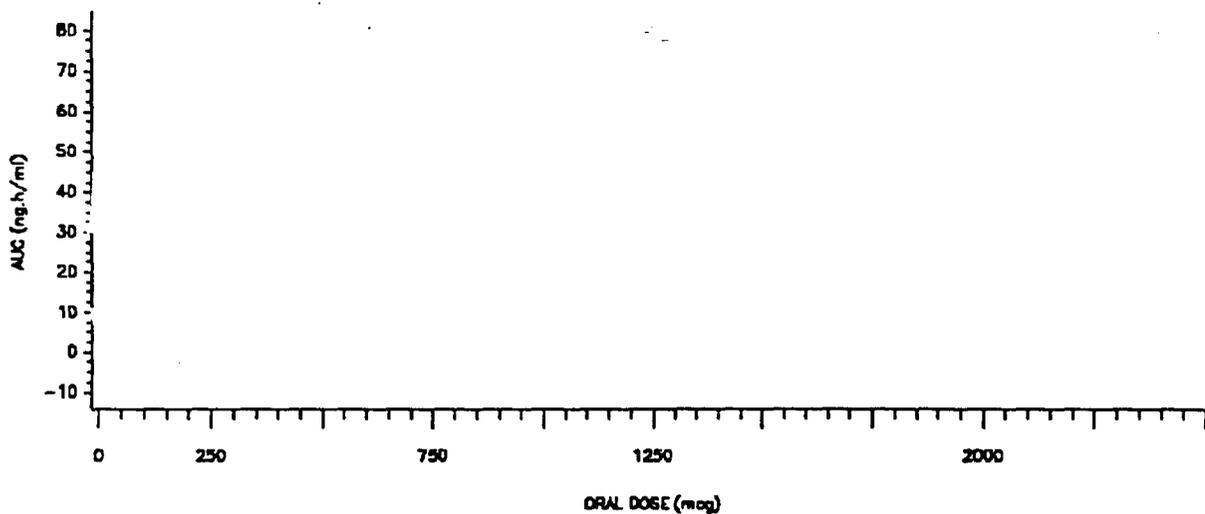
DOFETILIDE PROTOCOL 221
DOSE RESPONSE RELATIONSHIP FOR MAXIMUM CHANGE FROM BASELINE QTc



LINEAR DOSE RESPONSE EQUATION: MAXIMUM CHANGE FROM BASELINE QTc (msec) = 0.05 x (ORAL DOSE (mg)) + 27.1

Figure 3. Dose-Response Relationship for QTc

DOFETILIDE PROTOCOL 221
DOSE RESPONSE RELATIONSHIP FOR AUC DOFETILIDE PLASMA CONCENTRATION



LINEAR DOSE RESPONSE EQUATION: AUC (ng.h/ml) = 0.05 x (ORAL DOSE (mg)) - 0.41

Figure 4. Mean Plasma Concentration and Change in QTc after I.V. Administration

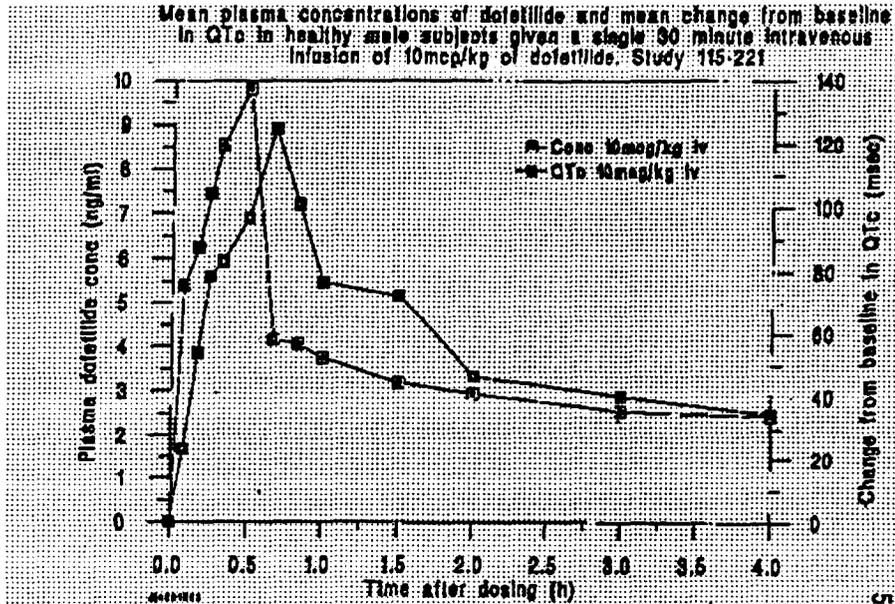


Figure 5. Mean Plasma Dofetilide Profiles

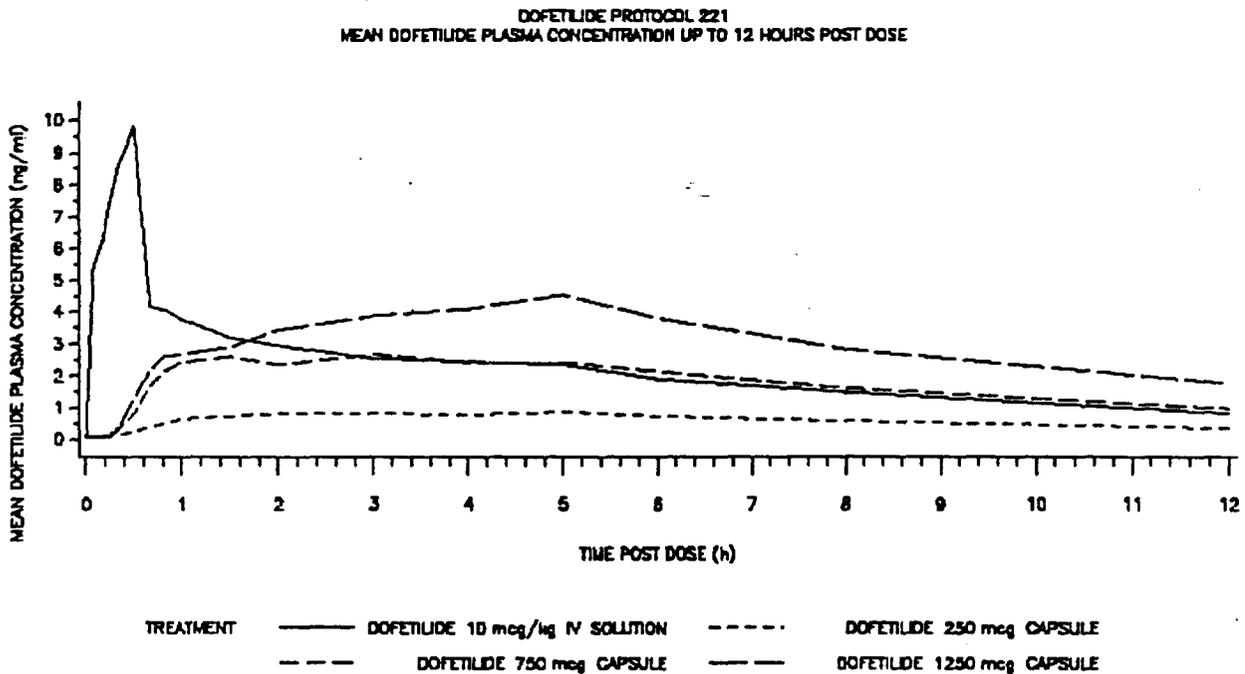
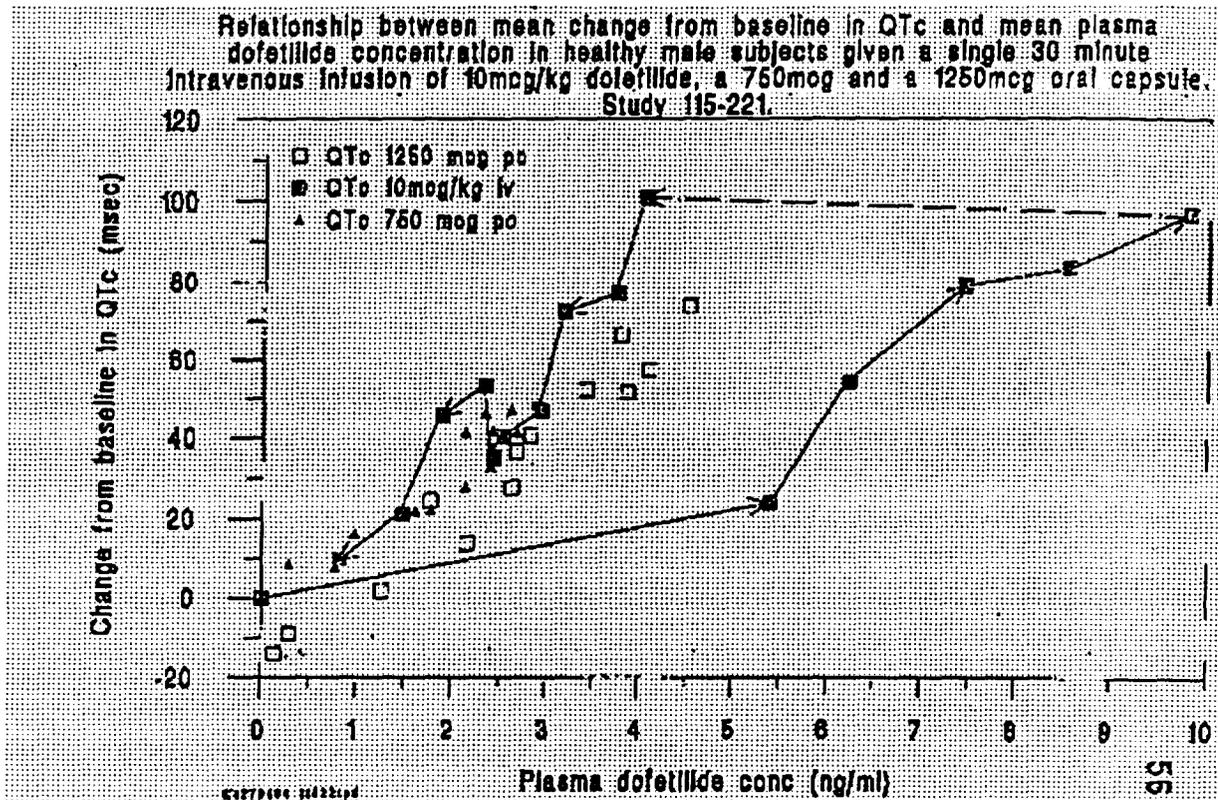


Figure 6. Observed Hysterisis After Administration of Dofetilide



CONCLUSIONS:

Linear dose response relationships were shown for AUC, Cmax, maximum change from baseline in QTc and AUECt after oral dofetilide. After iv administration there was a temporal displacement between peak plasma concentrations and maximum change in QTc, such that the plot of QTc versus concentration showed an anticlockwise hysteresis. Collapse of this hysteresis using an effect compartment model gave a KeO value of 4-9/h (KeO t1/2 range of 4-9 minutes), a linear relationship between change from baseline in QTc and either plasma concentration or effect compartment concentration and a similar slope (15-20msec/ng/ml) after oral and iv dosing.

DOFETILIDE-WARFARIN INTERACTION STUDY

STUDY 115-213

VOLUME: 2.34

PAGES: 1-219

INVESTIGATOR AND LOCATION: [

STUDY DATE: May to July 1989.

STUDY OBJECTIVES: To evaluate the effects of orally administered dofetilide on warfarin-induced increment in prothrombin time and to assess the safety and toleration of the combination.

Drug Administration:

Test Product: Dofetilide, 250mcg capsules: FID 0963, Lot 772-04

Reference Therapy: Matched placebo capsules: FID 0034, Lot 748-06

Interactant: Warfarin, 4 x 5mg tablets, commercially available.

Duration: Dofetilide or matching placebo given b.i.d. one hour before a meal for two sets of 7 days, 1 dose on Day 8 separated by a washout period; warfarin was given 2 hours as a single dose after the morning dose on Day 5 of each period.

STUDY DESIGN:

This was a randomised double-blind, placebo-controlled, two period crossover study. The study was conducted over two 8-day periods with a washout period of not less than 2 weeks between. Subjects received dofetilide, 250mcg, or placebo twice daily for 7 days with 1 dose on Day 8, with 20mg warfarin given two hours after treatment on the fifth day of both periods. Warfarin pharmacodynamics were assessed by evaluation of prothrombin times before and up to 96 hours after warfarin (prior to dosing with study compound on the first, third and fifth day of dosing, then 12, 24, 36, 48, 72 and 96 hours after dosing with warfarin on the fifth day). Plasma concentrations of dofetilide were monitored throughout Day 1 and four hours after the morning dose on Days 2 - 8. (immediately before and 1, 2, 4, 8, 12 and 24 hours after the morning dose on the first day, then 4 hours after the morning dose on all subsequent study days).

ASSAYS:

DATA ANALYSIS:

The average of the three prothrombin times measured on Days 1, 3 and before warfarin treatment on Day 5 of each study period was used as a baseline for that period. The area

under the prothrombin time/time curve up to 96 hours post-dose (AUECt) was calculated for both treatment groups using the linear trapezoidal rule, to the last sampling time. The difference between areas for the two treatments was analysed using an analysis of variance appropriate for the 2-way crossover design, containing the effect Sequence + Subject + Period + Treatment, and summarised via the statistical package SAS.

RESULTS: Tables 1-5 and Figures 1-3 summarize the data obtained from the study.

DOFETILIDE PROTOCOL 213
AREA UNDER PROTHROMBIN TIME CURVE, SUMMARY

Area Under Prothrombin Time Curve (sec.h)				
SUBJECT ID	SEQUENCE*	Dofetilide 250 mg bd	Double Blind Placebo	Dofetilide - Placebo
00050001	1	1042.60	1028.60	34.20
00050002	1	1007.80	1042.60	45.80
00050003	2	1146.80	1288.80	-110.00
00050004	2	1090.20	1164.00	-73.80
00050005	1	1161.60	1047.60	94.00
00050006	2	1172.80	1227.20	-34.40
00050007	2	1188.80	1336.00	-147.20
00050008	1	1271.60	1274.80	96.00
00050009	2	1248.00	1474.60	-126.60
00050010	2	1083.00	1159.20	-76.20
00050012	1	1196.60	1120.20	76.40
00050013	2	1240.80	1330.00	-89.20
00050014	1	1146.80	1098.60	76.40
00050015	1	1444.80	1187.20	177.60
00050016	2	1323.00	1367.60	-44.60

MEAN		1209.81	1219.39	-8.77
S.E.		30.90	34.79	15.79

D: 29OCT94				
T: 29OCT94(12:15)				

Source: Appendix XIII Table 4

Sequence 1: Dofetilide 250 mg bd -> Double Blind Placebo
Sequence 2: Double Blind Placebo -> Dofetilide 250 mg bd

Table 2. Analysis of Area Under the Prothrombin-Time Curve

DOFETILIDE PROTOCOL 213
ANALYSIS OF AREA UNDER PROTHROMBIN TIME CURVE, SUMMARY

COMPARISON: Dofetilide 250 mg bd - Double Blind Placebo

AREA UNDER PROTHROMBIN TIME CURVE (sec.h)	DIFFERENCE BETWEEN ADJUSTED MEANS	95% CONFIDENCE LIMITS ON DIFFERENCE BETWEEN MEANS		P-VALUE
		LOWER	UPPER	
AREA UNDER PROTHROMBIN TIME CURVE (sec.h)	-2.84	-26.07	20.34 (-2%, 2%)	0.7999

D: 29OCT94				
T: 29OCT94(12:47)				

Source: Table 6.1, Appendix XIII Table 1

Note: the values in parentheses are the confidence limits expressed as a percentage of the placebo when

Table 3. Mean Changes in QTc from First Day

DOFETILIDE PROTOCOL 213
QTc INTERVAL, MEAN CHANGES FROM BASELINE ON FIRST DAY OF THERAPY

QTc INTERVAL BASELINES (msec)

TREATMENT		BASE-LINE	TIME POST-DOSE (h)				
			1	2	4	8	12
DOFETILIDE 250 mcg BD	MEAN	370.07	4.40	16.60	21.97	0.43	10.07
	S.E.	3.37	3.17	3.29	4.42	3.46	3.20
	N	15	15	15	15	15	15
DOUBLE BLIND PLACEBO	MEAN	369.27	-7.07	-8.22	4.34	-1.36	-4.43
	S.E.	4.58	2.19	2.69	2.54	3.04	3.39
	N	15	15	15	15	15	15

D: 13JUL94 - 27OCT94
T: 17OCT94(11:18)

Table 4. Mean Changes in Prothrombin Time from Baseline

DOFETILIDE PROTOCOL 213
PROTHROMBIN TIME, MEAN CHANGES FROM BASELINE

PROTHROMBIN TIME (sec)

TREATMENT		BASE-LINE	TIME POST-DOSE (h)					
			12	24	36	48	72	96
DOFETILIDE 250 mcg BD	MEAN	10.37	0.39	3.17	4.39	3.32	2.02	0.69
	S.E.	0.04	0.07	0.33	0.60	0.48	0.32	0.20
	N	15	15	15	15	15	15	15
DOUBLE BLIND PLACEBO	MEAN	10.34	0.38	3.17	4.06	3.63	2.00	0.83
	S.E.	0.04	0.09	0.34	0.66	0.61	0.32	0.29
	N	15	15	15	15	15	15	15

D: 13JUL94 - 28OCT94
T: 28OCT94(11:43)

Table 5. Mean Changes in QTc from Baseline

DOFETILIDE PROTOCOL 213
QTc INTERVAL, MEAN CHANGES FROM BASELINE & HOURS POST-DOSE

QTc INTERVAL BASELINES (msec)

TREATMENT		BASE-LINE	TIME POST-DOSE (h)							
			DAY 1				DAY 2			
			1	2	3	4	5	6	7	8
DOFETILIDE 250 mcg BD	MEAN	370.07	21.97	14.49	18.80	10.83	10.06	15.09	14.92	18.16
	S.E.	3.37	4.42	3.14	2.85	3.70	2.97	3.23	4.54	4.58
	N	15	15	15	15	15	15	15	15	15
DOUBLE BLIND PLACEBO	MEAN	369.27	4.34	-3.07	-5.04	1.53	-1.22	-3.77	-0.70	0.02
	S.E.	4.58	2.54	3.06	4.34	4.90	4.21	3.47	3.07	4.42
	N	15	15	15	15	15	15	15	15	15

D: 13JUL94 - 27OCT94
T: 17OCT94(11:13)

Figure 1. Mean Changes in Prothrombin Time From Baseline

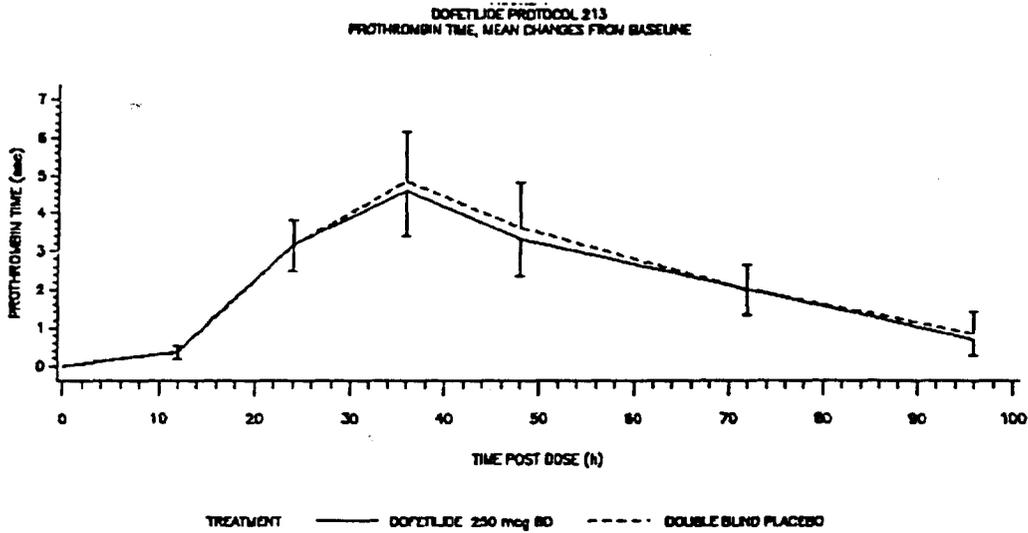


Figure 2. Mean Changes in QTc From Baseline

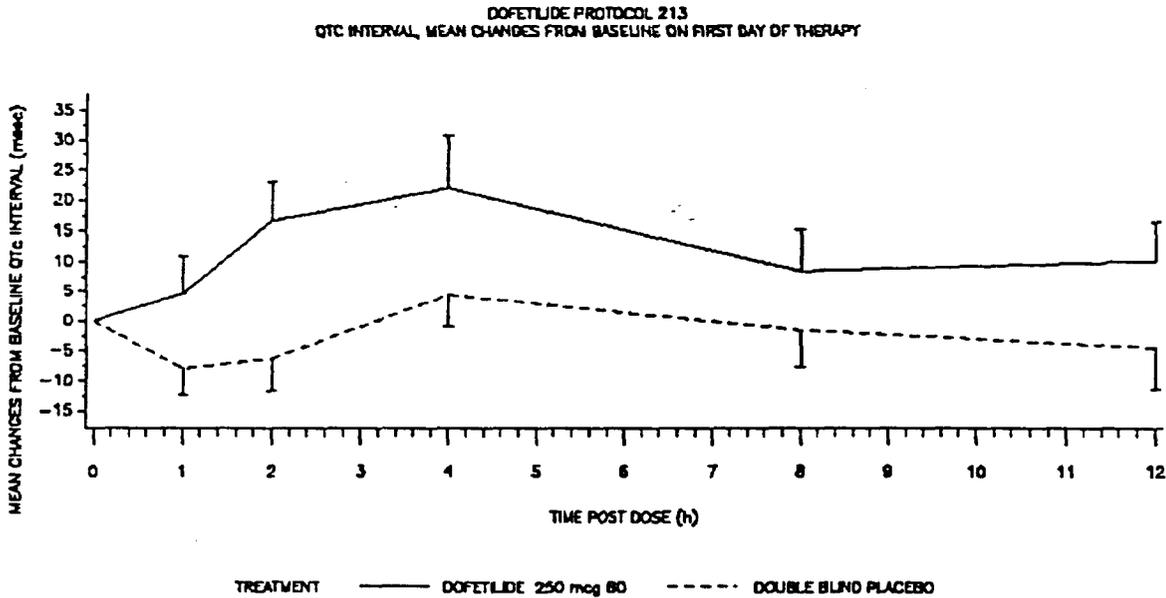
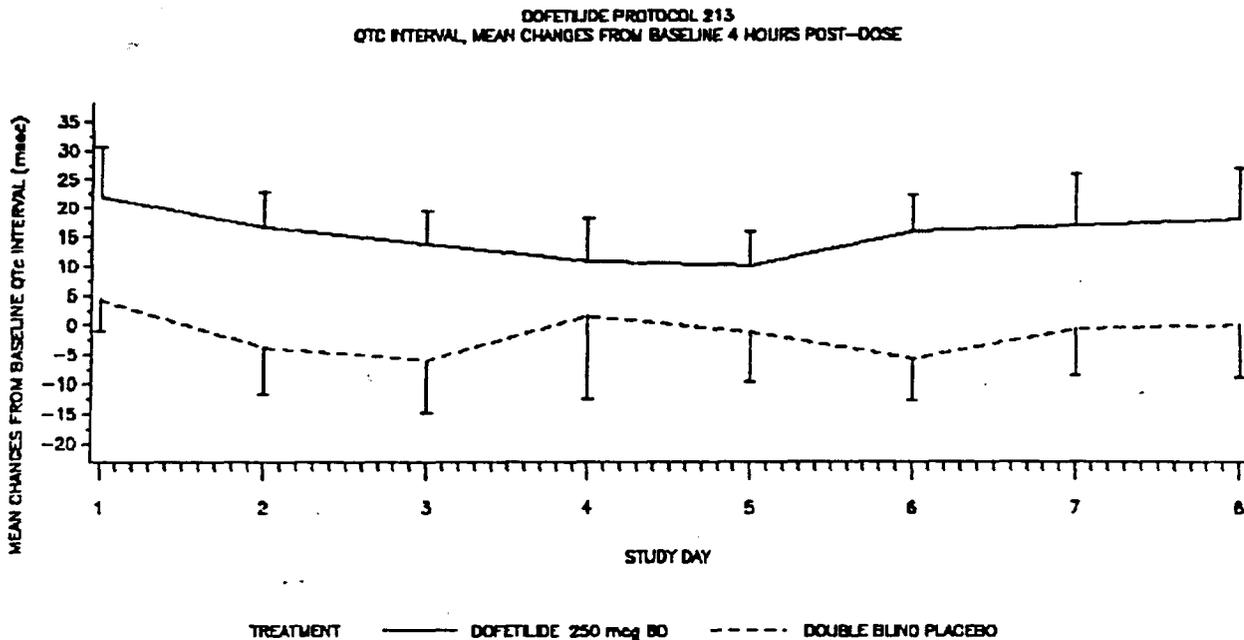


Figure 3. Mean Changes in QTc From Baseline at 4 hours Post-Dose



CONCLUSIONS: Dofetilide, 250mcg, given b.i.d. as oral capsules for eight days did not affect warfarin-induced mean increments in prothrombin time. Concomitant treatment with warfarin did not appear to affect plasma concentrations of dofetilide or mean QTc increments four hours after dofetilide. However, the increases in prothrombin time observed indicate that the dose of warfarin used in this study was probably clinically marginal; the study has subsequently been repeated with a higher dose of warfarin (Protocol 242).

DOFETILIDE-WARFARIN INTERACTION STUDY

STUDY 115-242 **VOLUME: 2.54** **PAGES: 1-297**

INVESTIGATOR AND LOCATION: ⌈

STUDY DATE: September 1992 - December 1992. ⌋

STUDY OBJECTIVES: To determine whether steady state dofetilide treatment alters warfarin pharmacodynamics.

DRUG FORMULATIONS:

Test Product: Dofetilide, 3 x 250mcg capsules: FID 0963, Lot 503-15

Reference Therapy: Matched placebo capsules: FID 0034, Lot 748-16

Interactant: Warfarin, 8 x 5mg tablets, commercially available.

STUDY DESIGN:

This was a randomised, double-blind, placebo-controlled, two period crossover study in healthy male volunteers. The study was conducted over two 8-day periods with a washout period of not less than 1 week between. Subjects received dofetilide, 750mcg, or placebo twice daily on each of seven days with a single dose on the eighth day. On the fifth day of both treatment periods 40mg warfarin was given as a single dose two hours after dofetilide/placebo. Warfarin pharmacodynamics were assessed by evaluation of prothrombin times before and up to 96 hours after warfarin (prior to dosing with study compound on the first, third, fourth and fifth day of dosing, then 6, 12, 24, 36, 48, 72 and 96 hours after dosing with warfarin on the fifth day). An additional sample was to be taken 2 hours post-dose on Day 4 with a final sample to be taken at the follow-up visit, two weeks after the end of the second treatment period. Blood samples were collected for estimation of plasma levels of dofetilide at the following times during each study period: pre-dose on Days 1 - 8 inclusive and at 1, 2, 3, 4, 6, 8 and 12 hours after the morning dose on Days 4 and 5 only.

ASSAYS: ⌈

DATA ANALYSIS:

AUC, Cmax, Tmax and AUECt (areas under the prothrombin time/time curves) were calculated. The differences between AUECt for the two treatments and the differences between changes from baseline to 2 hours post-dose on Day 4 for the two treatments were compared using an analysis of variance technique appropriate for the 2-way crossover design. QTc intervals were computed from the QT interval and heart rate. ⌋

RESULTS: Tables 1-5 and Figures 1-3 summarize the data obtained from the study.

Table 1: AUECt

DOFETILIDE PROTOCOL 242
AREA UNDER PROTHROMBIN TIME CURVE, SUMMARY

Area Under Prothrombin Time Curve (sec.h)				
SUBJECT ID	SEQUENCE*	Defetilide 750 mg bid	Double Blind Placebo	Defetilide - Placebo
00790001	1	1695.54	1644.12	51.42
00790003	1	2645.36	2310.78	334.58
00790004	1	2197.52	2024.40	172.92
00790005	2	1595.74	1614.88	-21.12
00790007	1	2095.14	2002.08	92.18
00790008	2	2019.60	2114.28	-94.68
00790009	2	2169.42	2177.10	-7.68
00790010	2	2019.84	2054.70	-34.86
00790011	1	2545.94	2325.92	220.02
00790012	1	2001.00	2342.82	-341.82
00790013	1	2185.44	1975.14	210.30
00790014	2	1940.02	1950.14	-110.22
MEAN		2152.55	2128.21	24.34
S.E.		112.57	108.71	43.86

Table 2:

DOFETILIDE PROTOCOL 242
PROTHROMBIN TIME, MEAN CHANGES FROM BASELINE ON DAY 3

PROTHROMBIN TIME (sec)		TIME POST-DOSE (h)							
		BASE-LINE	6	12	24	36	48	72	96
DOFETILIDE 750 mg bid	MEAN	14.67	-0.16	0.57	7.09	14.03	12.84	8.54	4.25
	S.E.	0.19	0.12	0.23	0.48	1.25	1.61	1.79	1.17
	N	12	12	12	12	12	11	12	12
DOUBLE BLIND PLACEBO	MEAN	14.34	0.06	0.78	7.12	13.57	13.08	7.77	4.61
	S.E.	0.10	0.18	0.23	0.45	1.23	2.13	1.49	1.15
	N	12	12	12	12	12	12	12	12

Table 3:

DOFETILIDE PROTOCOL 242
ANALYSIS OF AREA UNDER PROTHROMBIN TIME CURVE, SUMMARY

COMPARISON: Defetilide 750 mg bid - Double Blind Placebo

AREA UNDER PROTHROMBIN TIME CURVE (sec.h)	DIFFERENCE BETWEEN ADJUSTED MEANS	95% CONFIDENCE LIMITS ON DIFFERENCE BETWEEN MEANS		P-VALUE
		LOWER	UPPER	
	13.13	-88.57	114.63 (-4%, 5%)	0.7790

Table 4:

DOFETILIDE PROTOCOL 242
PROTHROMBIN TIME, MEAN CHANGES FROM BASELINE ON DAY 4

TREATMENT		TIME POST-DOSE (h)	
		BASE-LINE	2
DOFETILIDE 750 mcg BD	MEAN	14.43	0.37
	S.E.	0.19	0.09
	N	12	12
DOUBLE BLIND PLACEBO	MEAN	14.41	0.29
	S.E.	0.17	0.08
	N	12	12

Table 5:

DOFETILIDE PROTOCOL 242
ANALYSIS OF CHANGE FROM BASELINE PROTHROMBIN TIMES ON DAY 4, SUMMARY

COMPARISON: Dofetilide 750 mcg bd - Double Blind Placebo

CHANGE FROM BASELINE PROTHROMBIN TIME ON DAY 4 (sec)	DIFFERENCE BETWEEN ADJUSTED MEANS	95% CONFIDENCE LIMITS ON DIFFERENCE BETWEEN MEANS		P-VALUE
		LOWER	UPPER	
	0.04	-0.20	0.29 (-64%, 93%)	0.6910

Table 6:

DOFETILIDE PROTOCOL 242
QTC INTERVAL, MEAN CHANGES FROM BASELINE ON DAYS 4 AND 5

QTC INTERVAL VALUES (sec)

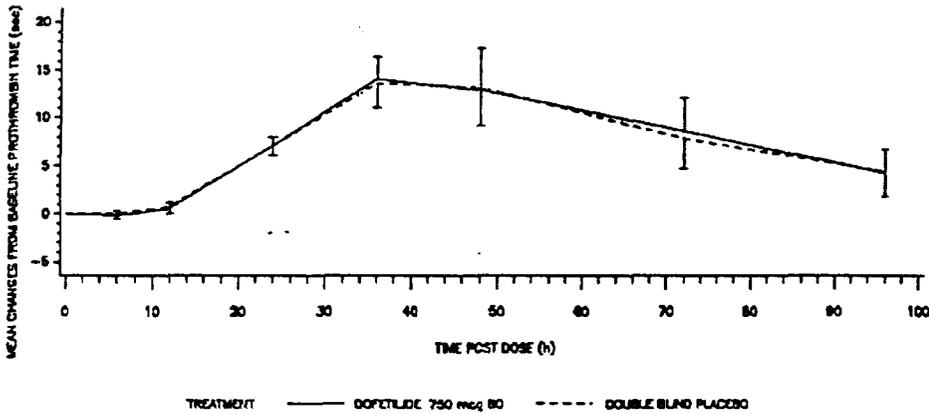
TREATMENT	TIME POST-DOSE (h)	DAY												
		BASE-LINE	4						5					
			1	2	3	4	6	8	1	2	3	4	6	8
DOFETILIDE 750 mcg BD	MEAN	349.40	40.90	49.89	53.61	37.28	40.68	29.48	31.30	73.96	62.47	44.71	49.69	32.59
	S.E.	3.83	7.19	6.98	6.85	5.30	5.46	5.58	7.91	8.05	5.19	7.08	6.14	5.89
	N	12	12	12	12	12	12	12	12	12	12	12	12	12
DOUBLE BLIND PLACEBO	MEAN	372.09	-1.09	12.65	1.20	-5.94	9.91	2.61	-3.99	6.50	4.28	2.63	1.49	1.05
	S.E.	4.64	5.78	6.99	5.08	4.40	4.55	4.83	4.63	4.87	4.44	5.28	4.64	4.33
	N	12	12	12	12	12	12	12	12	12	12	12	12	12

Table 7:

Mean (\pm STD) pharmacokinetic parameters of dofetilide on day 4 (pre-warfarin dosing) and day 5 (after a single 40 mg warfarin dose) in 12 healthy subjects dosed with dofetilide 750 mcg bid for 8 days.

Parameters	Day 4	Day 5
C_{max} (ng/ml)	3.74 ± 1.09	3.94 ± 0.85
T_{max} (h)	2.08 ± 0.79	2.17 ± 0.58
AUC_{12} (ng.h/ml)	25.9 ± 6.56	25.8 ± 7.59

FIGURE 1
DOFETILIDE PROTOCOL 342
PROTHROMBIN TIME, MEAN CHANGES FROM BASELINE ON DAY 8



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FIGURE 2
DOFETILIDE PROTOCOL 242
QTc INTERVAL, MEAN CHANGES FROM BASELINE ON DAYS 4 AND 5
TREATMENT=DOFETILIDE 750 mcg QD

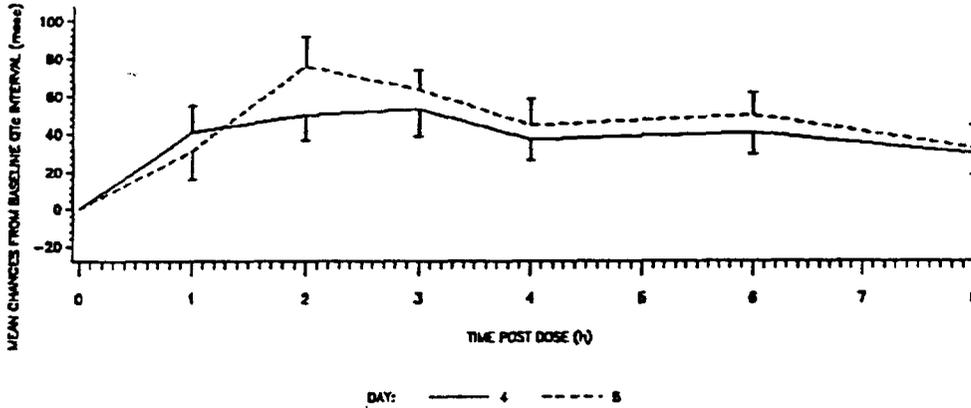
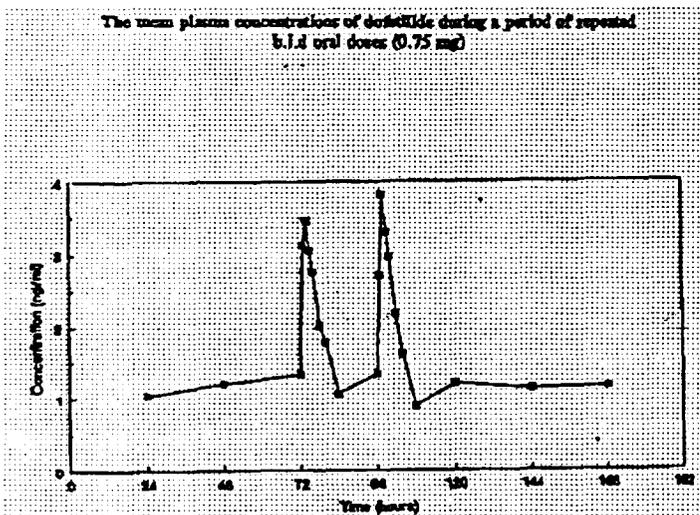


Figure 3:



CONCLUSIONS:

Dofetilide, 750mcg, given b.i.d. as oral capsules for eight days did not affect warfarin-induced mean increments in prothrombin time. There were no statistically significant differences between the treatment groups in the mean changes of prothrombin time from baseline to 2 hours post-dose on Day 4.

There was a consistent increase in QTc after treatment with dofetilide compared to baseline or placebo treatment. The mean increases from baseline over 8 hours after dosing for the dofetilide group ranged between 8 and 14% on Day 4 and between 8 and 21% on Day 5. Administration of a single dose of warfarin had no apparent effect on the pharmacokinetics of dofetilide.

DOFETILIDE-DIGOXIN INTERACTION STUDY

STUDY 115-214 **VOLUME: 2.35** **PAGES: 1-203**

INVESTIGATOR AND LOCATION: [

STUDY DATE: June 1989 - July 1989.

STUDY OBJECTIVES: To investigate the effects of oral dofetilide, 250mcg b.i.d. for 5 days, on the pharmacokinetics of steady-state digoxin and to evaluate the safety and toleration of the combination.

DRUG FORMULATIONS:

Test Product: Dofetilide, 250mcg capsules: FID 0963 Lot No. 772-04

Interactant: Digoxin (Lanoxin), 250mcg tablets, purchased locally

Reference: Identical placebo capsules: FID 0034 Lot No. 748-06

STUDY DESIGN:

This was a double-blind, placebo-controlled, randomized parallel group study. Subjects received digoxin 1mg on Day 1, 500mcg on Day 2 and 250mcg on Days 3 to 12 and dofetilide 250mcg b.i.d. or matching placebo given at the same time as the morning dose of digoxin and 12 hours later on Days 8 to 12 inclusive. Digoxin plasma concentrations were monitored on a daily basis with full pharmacokinetic evaluations from plasma and urine samples measured over 24 hours on Days 7 and 12 (samples were taken 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 16 and 24 hours after the morning dose). Trough plasma concentrations of dofetilide were measured from Day 8 to Day 12. All urine and plasma samples were stored at -20°C until analyzed.

ASSAYS: (

DATA ANALYSIS:

The pharmacokinetic parameters (C_{max}, T_{max}, AUC, renal clearance (CL_r) and trough plasma digoxin concentrations) for digoxin were compared within groups on study Days 7 and 12 using a t-test.

RESULTS: Tables 1-4 and Figures 1-3 summarize the data obtained from the study.

Table 1. Digoxin Pharmacokinetics

	Active treatment group mean \pm SD	Placebo treatment group mean \pm SD
DAY 7		
AUC 0-24 (nmol.h/l)	20.71 \pm 3.17	22.01 \pm 3.03
C _{max} (nmol/l)	2.08 \pm 0.53	2.01 \pm 0.37
T _{max} (hour)	1.3 \pm 0.5	0.8 \pm 0.4
Cl urine (ml/min)	149 \pm 34	136 \pm 57
DAY 12		
AUC 0-24 (nmol.h/l)	17.04 \pm 3.40	17.97 \pm 2.60
C _{max} (nmol/l)	1.97 \pm 0.40	1.92 \pm 0.45
T _{max} (hour)	0.9 \pm 0.6	1.1 \pm 0.2
Cl urine (ml/min)	144 \pm 17	155 \pm 30

Table 2.

DOFETILIDE PROTOCOL 214
SUMMARY OF TROUGH DIGOXIN LEVELS

DIGOXIN PLASMA CONCENTRATION C _{min} (L/L)		TREATMENT	
		Digoxin + DoFetilide 250 mg bid	Digoxin + DoFetilide Placebo
DAY 7	MEAN	0.77	0.70
	S.E.	0.03	0.04
	N	6	5
DAY 12	MEAN	0.60	0.63
	S.E.	0.03	0.04
	N	6	5
DAY 12 - DAY 7	MEAN	-0.17	-0.10
	S.E.	0.03	0.04
	N	6	5

Table 3:

DOFETILIDE PROTOCOL 214
SUMMARY OF PLASMA CONCENTRATIONS OF DOFETILIDE

DOFETILIDE PLASMA CONCENTRATIONS (ng/ml)		STUDY DAY / TIME POST-DOSE (h)					
		8	9	10	11	12	
TREATMENT		0	4	0	0	0	0
Digoxin+ Dofetilide 250 mcg bd	MEAN	BQL	0.60	0.36	0.39	0.41	0.46
	S.E.	0.00	0.03	0.02	0.02	0.02	0.02
	N	8	8	8	8	8	8

Table 4:

DOFETILIDE PROTOCOL 214
MEAN QTc CHANGES FROM BASELINE ON DAY 12

QTc INTERVAL BASELINS (msec)		TIME POST-DOSE (h)						
		BASELINE	1	2	4	6	12	16
Digoxin+ Dofetilide 150 mcg bd	MEAN	253.83	-2.58	11.26	21.96	14.47	14.94	22.61
	S.E.	3.32	4.43	5.04	5.42	4.26	9.72	3.91
	N	8	6	8	8	8	8	8
Digoxin+ Double Blind Placebo	MEAN	247.77	-11.26	-8.04	14.09	11.65	9.03	4.94
	S.E.	9.36	1.64	7.94	3.80	4.75	4.66	4.94
	N	5	5	5	5	5	5	5

Figure 1. Mean Plasma Digoxin Concentrations

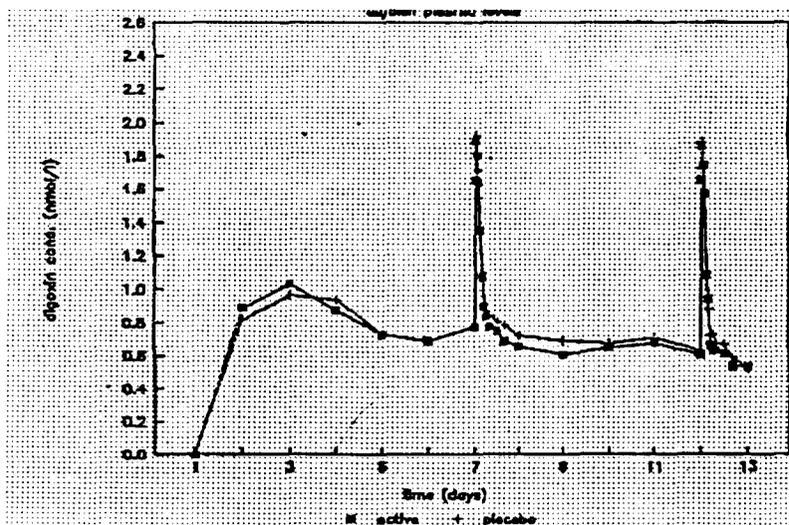


Figure 2:

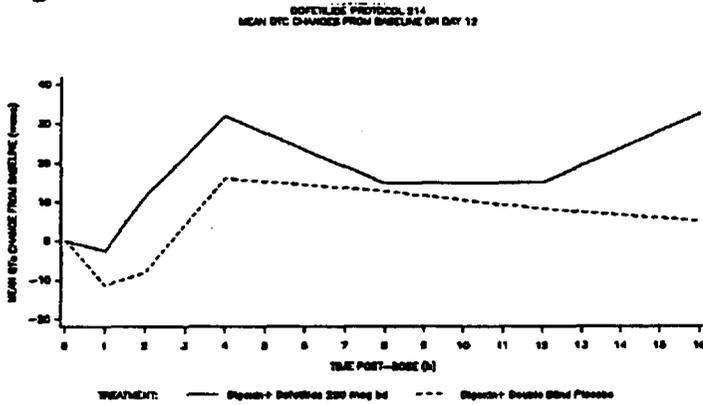
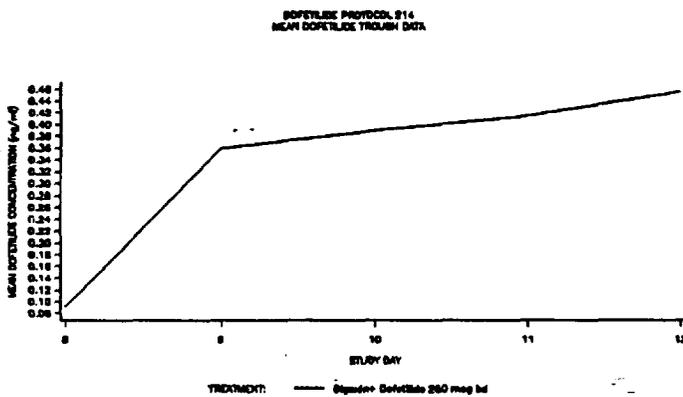


Figure 3:



CONCLUSIONS:

The data from this study suggest that concomitant treatment with dofetilide did not affect digoxin pharmacokinetics. Trough plasma concentrations of dofetilide gradually increased to steady state by Day 12 consistent with an 8-hour half-life and b.i.d. dosing. Although the mean increase in QT interval was greater after treatment with dofetilide than placebo, the difference was not reflected in the increases in QTc, which were approximately 9% and 5% respectively from baseline over the first four hours after treatment.

DOFETILIDE-PHENYTOIN INTERACTION STUDY

STUDY 115-007

VOLUME: 1.32-1.33

INVESTIGATOR AND LOCATION: (

STUDY DATE: Jan - Mar 94.

STUDY OBJECTIVES: To assess the effects of concurrent administration of phenytoin on the steady-state pharmacokinetics and pharmacodynamics of dofetilide in normal volunteers and to assess the safety and toleration of this combination.

RATIONALE: Phenytoin is metabolized in the liver and excreted in the urine by tubular secretion. This process of tubular secretion could compete with the renal elimination of drugs similarly excreted. Dofetilide is a relatively basic drug (pKa 7) and its clearance suggests involvement of both glomerular filtration and tubular secretion. Since renal excretion accounts for about 70% of dofetilide elimination, there is a potential for competition between phenytoin and dofetilide for tubular secretion. Phenytoin is a potent inducer of the cytochrome P450 microsomal enzyme system and is a substrate for this system. Since dofetilide is partially metabolized by this system, its metabolism could be altered by the presence of phenytoin. Phenytoin also has the electrophysiologic effect of shortening the QTc interval while dofetilide prolongs the same parameter. Consequently, there is a need to characterize the effects of co-administration of phenytoin on the steady-state pharmacokinetics and pharmacodynamics of dofetilide.

DRUG FORMULATIONS:

Dofetilide capsules: 500mcg, FID# 0964, Lot No. 0964

Phenytoin sodium capsules: 100mg, FID# ED-O-430-Z93, Parke-Davis.

Placebo capsules: FID#0034, Lot No. 748-17

STUDY DESIGN:

This was an observer-blind, placebo controlled, multi-dose, parallel group study of the pharmacokinetic and pharmacodynamic interaction between dofetilide and phenytoin. Dofetilide 500mcg was administered bid on Days 1-5. On Day 5 following the morning dose of dofetilide, a pharmacokinetic and pharmacodynamic evaluation was performed over the following 12 hours. On Day 6 the subjects were randomized into two subgroups. One subgroup received dofetilide 500mcg bid q12h for 15 days, with only the morning dose of dofetilide given on Day 15, and phenytoin sodium 300mg od for 16 days. The second sub-group was dosed with dofetilide 500mcg bid q12h for 15 days, with only the morning dose of dofetilide given on Day 15, and with placebo od for 16 days. A complete pharmacokinetic and pharmacodynamic evaluation was done on Day 20 after morning dosing of study drug. Phenytoin/placebo dosing continued through Day 21. Plasma samples were collected at hour 0 (baseline just before dosing), and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12 hours on Days 5 and 20. On Day 20, additional blood samples were to be collected

at 16, 24, 36 and 48 hours. To confirm steady-state concentrations of dofetilide and phenytoin, additional plasma samples (Cmin) were collected on Days 3, 4, 5, 17, 18, 19 and 20 before the administration of the morning dose of the study drug. Total urine voided between the time of drug administration and 12 hours later were collected on Days 5 and 20. Plasma and urine samples were stored at -20°C until analyzed.

ASSAYS:

DATA ANALYSIS:

The pharmacokinetic parameters (Cmax, Tmax, AUC, renal clearance (CLr), QTc (Emax) and the area under the QTc versus time curve (AUEC_t) were calculated .

RESULTS: Tables 1-3 and Figures 1-5 summarize the data obtained from the study.

Table 3:

DOFETILIDE PROTOCOL 007
 SUMMARY OF ANALYSIS OF DAY 10 VERSUS DAY 5 CHANGE IN EXCRETED LEAD II QTC

Treatment		Day 5*	Day 10*	Difference	Within Treatment Comparison 95% Confidence Limits	Between Treatment Comparison (p-value)
Doferilide 300 mg BID+ Phenytoin Sodium						
	AUC₀₋₂₄ (nmoles .h)	Mean 14.07	109.41	95.34	(-709.6, 900.3)	p = 0.6730
		S.D. 248.16	199.63	345.71		
		N 11	11	11		
	Mean (nmoles)	Mean 21.27	21.45	0.18	(-67.9, 68.2)	p = 0.2592
		S.D. 22.84	18.97	20.90		
		N 11	11	11		
Doferilide 300 mg BID+ Placebo						
	AUC₀₋₂₄ (nmoles .h)	Mean 127.42	173.90	49.48	(-254.4, 351.3)	
		S.D. 186.84	99.84	160.19		
		N 13	13	13		
	Mean (nmoles)	Mean 34.08	44.62	12.34	(-33.2, 58.2)	
		S.D. 22.82	18.71	21.13		
		N 13	13	13		

Figure 1. Mean Doferilide Plasma Concentrations on Day 6 Following Multiple Dose Administration (100 mg BID) Prior to Phenytoin/Placebo Treatment in Healthy Male Subjects (Clinical Study #146-007-0001, Dr. T. Hunt, Austin, TX)

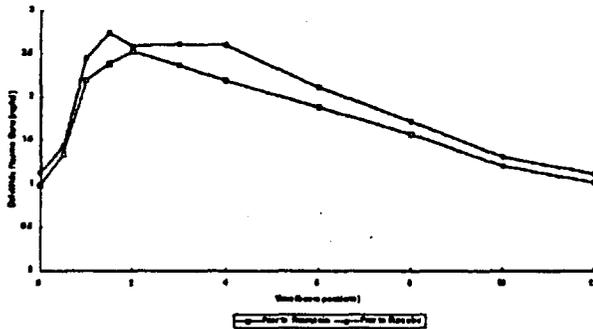


Figure 2. Mean Doferilide Plasma Concentrations on Day 20 Following Multiple Dose Administration (100 mg BID) With Phenytoin/Placebo Treatment in Healthy Male Subjects (Clinical Study #146-007-0001, Dr. T. Hunt, Austin, TX)

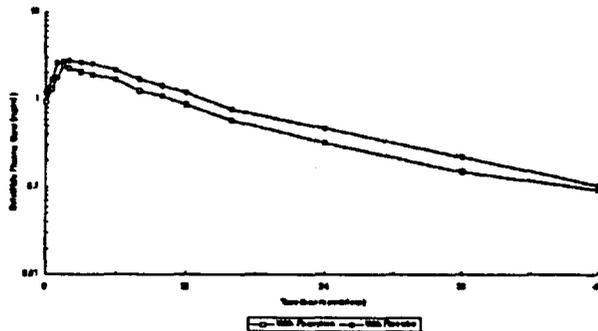


FIGURE 3
DOFETILIDE PROTOCOL 007
MEAN EXPERT LEAD II QTC CHANGES FROM PRE-DOSE ON DAYS 5 AND 20

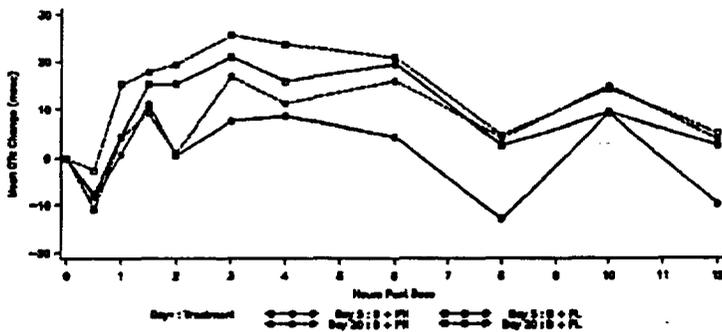


FIGURE 4
DOFETILIDE PROTOCOL 007
EXPERT LEAD II QTC EMAX VS AUC_T

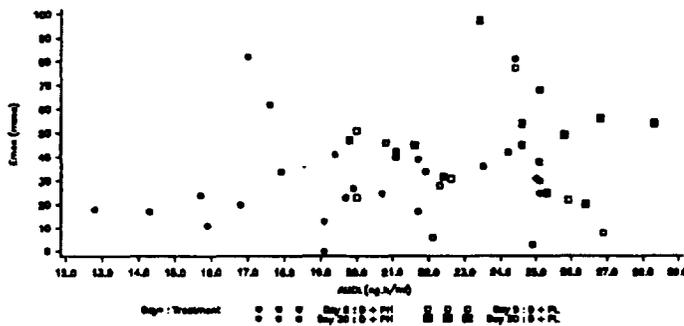
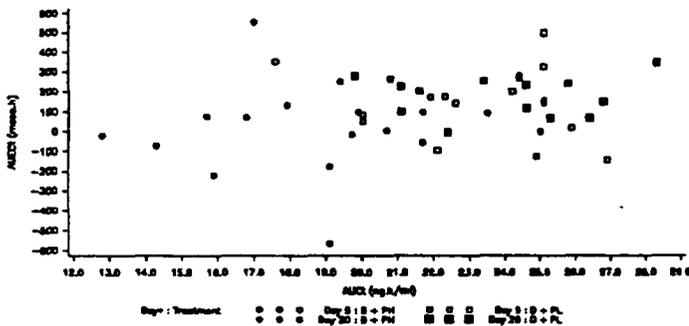


FIGURE 5
DOFETILIDE PROTOCOL 007
EXPERT LEAD II QTC AUECT VS AUC_T



CONCLUSIONS: There were no statistically significant differences within treatment groups comparing Day 20 versus Day 5 values for the ratios of AUC_T and C_{max}, nor for the Day 20 versus Day 5 differences of T_{max} and CL_r. A comparison between Day 20/Day-5 ratios for the two treatment groups showed a statistically significant difference for AUC_T ($p < 0.0001$) possibly due to an increase in hepatic clearance caused by induction of catabolism by phenytoin. The AUC_T ratio for the phenytoin sodium treated group showed a 13% decrease,

while the ratio for the placebo group showed a 2% increase. No significant differences were found between the treatment groups for the ratio for Cmax or for the differences for Tmax and CLr. No statistically significant differences for AUEC τ or Emax occurred within each treatment group when comparing Day 20 to Day 5. In addition, no significant differences were found when comparing the Day 20 minus Day 5 differences in AUEC τ or Emax between the two treatment groups. Neither AUEC or Emax changed significantly within the subject groups treated concomitantly with phenytoin or placebo. However, the variability in QTc was very high. Also, in this study there was no apparent linear relationship between the pharmacodynamic (QTc) and the AUC(0-12) parameters which might be explained by the high variability in QTc and the fact that only one dose strength of dofetilide was given. Concomitant administration of 300mg of phenytoin sodium with dofetilide at a dose of 500mcg BID (q12h) at steady state had no clinically significant effects on dofetilide pharmacokinetics or pharmacodynamics.

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