DOFETILIDE-PHENYTOIN INTERACTION STUDY

STUDY 115-006 **VOLUMES**: 1.31 **PAGES**: 1-352

INVESTIGATOR AND LOCATION: [

STUDY DATE: July 93 - April 94.

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

RATIONALE: Phenytoin is primarily an anti-convulsant drug used to treat partial and generalized seizures. It also has electrophysiological properties of a class 1B anti-arrhythmic drug and has been particularly useful in digoxin-induced arrhythmias. 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 interfere with the metabolism 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 dofetilide on the steady-state pharmacokinetics and pharmacodynamics of phenytoin.

DRUG FORMULATIONS:
Dofetilide capsules: 500mcg, FID# 0964, Lot No. 0964
Phenytoin sodium tablets: 100mg, FID# ED-O-122-593 Parke-Davis
Placebo capsules FID #748-17, Lot No. 0034

STUDY DESIGN: This was an observer-blind, placebo-controlled, parallel-group study of the interaction, under steady-state conditions, between phenytoin and dofetilide after multiple dosings. All subjects were to receive phenytoin sodium, 300 mg (equivalent to 274.8 mg phenytoin) od from Day 1 through Day 15. Plasma concentrations of phenytoin were then determined. Subjects with trough plasma concentrations between 8 and 20 μ/ml were entered into the next phase of the study. The dose in the remaining subjects was adjusted once only, either upwards or downwards to achieve a plasma phenytoin concentration of 8-20 μ/ml, and dosing at the adjusted dose was continued for 12 additional days after which time subjects with the desired plasma concentrations were randomized to the next phase. If plasma levels were again outside the 8 and 20 μ/ml range, the subject was discontinued from the study. One randomized group received phenytoin sodium od for 15 days and dofetilide bid for 16 days. The second randomized group received phenytoin sodium od for 15 days and placebo bid for

16 days. Complete pharmacokinetic and pharmacodynamic evaluations were done on Days 15(27) and 30(42) depending on initial duration of phenytoin sodium dosing. On days 15(27) and 30(42) plasma samples were collected from each subject at 0h (just prior to study drug administration), and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16 and 24 hours after dosing. Additional samples were collected at 36, 48, 72, and 96 hours after the last phenytoin sodium dose. To confirm steady-state concentrations of phenytoin, additional blood samples (Cmin) were collected on days 12-15 and 27-30(39-42) before the administration of the morning dose of the study drug. On Days 15(27) and 30(42), 0-24 h urine samples were collected and the volume measured. Ten mL aliquots of the pooled collection for each subject were frozen and stored at -20°C prior to analysis of total p-HPPH (5-(p-hydroxyphenyl)-5-phenylhydantoin), free and conjugated forms. Plasma samples were stored at -20°C until analyzed.

ASSAYS:

DATA ANALYSIS:
The pharmacokinetic parameters (Cmax, Tmax, AUC,) for phenytoin, total amount of the phenytoin metabolite, p-HPPH, excreted in the urine over the collection interval, and the ratio p-HPPH/AUCt during phenytoin sodium alone compared to phenytoin sodium + dofetilide 500mcg bid, and phenytoin sodium + placebo treatment arms were calculated. The area under the change from predose effect curve (AUECt), from predose to 24 hours postdose, was calculated by the linear trapezoidal rule for the QTc interval and PR intervals determined from the Expert Lead II ECG rhythm strips. Emax, the maximum increase in QTc and the maximum decrease in PR, was obtained directly from the data.

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

Table 1:

DOFETILIDE PROTOCOL 006
SUMMARY OF ANALYSIS OF DAY 30/42 VERSUS DAY 15/27 CHANGE IN EXPERT LEAD II QTC

Treatment			Day 15/27*	Day 30/42*		Within Treatment Comparison 95% Confidence Limits	Between Treatment Comparison (p-value)
Phenytoin Sodium +Dofetilide 500 mcg BID					Difference		
	AUCt (msec.h)	Mean	5.81	215.67	209.85	(-710.9,1130.0)	p = 0.7575
		S.D.	924.72	296.27	422.31		
		N	12	12	12		
	Cmax (msec)	Mean	20.17	35.50	15.33	(-21.4, 62.1)	p = 0.4627
		S.D.	15.76	14.85	21.43		
		N	12	12	12		
Phenytoin Sodium +Placebo					Difference		
	AUCt (msec.h)	Mean	61.95	211.02	149.07	(-970.7,1268.8)	
		S.D.	461.56	297.42	309.73		
		N	11	11	11		
	Cmax (msec)	Mean	17.91	26.55	8.64	(-30.6, 55.8)	
		S.D.	19.96	11.08	21.44		
		N	11	11	11		

Table 2:

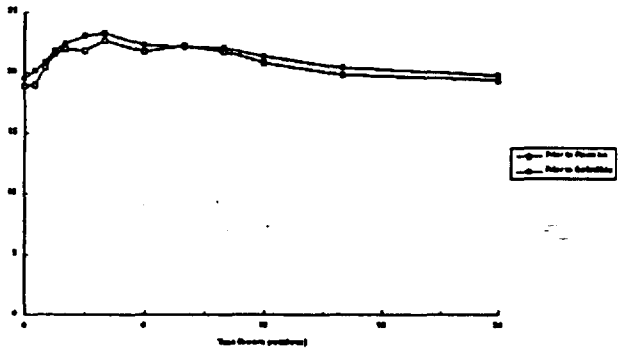
DOFETILIDE PROTOCOL 006
SUMMARY OF ANALYSIS OF DAY 30/42 VERSUS DAY 15/27 CHANGE IN PHENYTOIN PHARMACOKINETIC PARAMETERS

Treatment			Day 15/27*	Day 30/42*		Within Treatment Comparison 90% Confidence Limits	Between Treatment Comparison (p-value)
Phenytoin Sodium +Dofetilide 500 mcg BID					Ratio		
	AUCt (mcg.h/ml)	Mean	500.88	557.59	1.11	(89.4%, 138.6%)	p = 0.5807
		S.D.	98.86	154.62	0.14		
		N	12	12	12		
	Cmax (mcg/ml)	Mean	23.48	26.50	1.13	(91.2%, 139.8%)	p = 0.2496
		S.D.	4.19	6.73	0.14		
		N	12	12	12		
					Difference		
	Tmax (h)	Mean	3.54	4.17	0.63	(-5.7, 6.9)	p = 0.0369
		S.D.	2.29	2.47	3.53		
		N	12	12	12		
	Excretion Percentage	Mean	55.50	51.30	-4.20	(-51.5, 42.1)	p = 0.9642
		S.D.	19.67	12.34	26.08		
		N	10	10	10		
Phenytoin Sodium +Placebo					Ratio		
	AUCt (mcg.h/ml)	Mean	481.49	317.24	1.07	(77.9%, 148.1%)	
		S.D.	129.34	109.14	0.19		
		N	11	11	11		
	Cmax (mcg/ml)	Mean	23.16	24.33	1.05	(77.6%, 142.3%)	
		S.D.	6.04	8.26	0.18		
		N	11	11	11		
					Difference		
	Tmax (h)	Mean	6.27	3.86	-2.41	(-7.7, 2.9)	
		S.D.	2.28	2.78	2.94		
		N	11	11	11		
	Excretion Percentage	Mean	57.60	53.90	-3.50	(-78.0,71.0)	
		S.D.	28.04	17.38	41.08		
		N	10	10	10		

Table 3:

DOFETILIDE PROTOCOL 006
SUMMARY OF ANALYSIS OF DAY 30/42 VERSUS DAY 15/27 CHANGE IN EXPERT LEAD II PR

Treatment			Day 15/27*	Day 30/42*	Within Treatment Comparison 95% Confidence Limits	Between Treatment Comparison (p-value)
Phenytoin Sodium +Dofetilide 500 mcg BID				Difference		
	AUECt (msec.h)	Mean	-125.81	-92.10	103.71	(-130.2, 365.6)
		S.D.	101.99	87.99	120.22	
		N	12	12	12	
	Emax (msec)	Mean	-15.33	-13.58	1.75	(-10.7, 14.2) p = 0.8403
		S.D.	5.69	5.11	5.72	
		N	12	12	12	
Phenytoin Sodium +Placebo				Difference		
	AUECt (msec.h)	Mean	-18.00	-105.86	-87.86	(-444.2, 292.4)
		S.D.	143.64	124.67	172.79	
		N	11	11	11	
	Emax (msec)	Mean	-11.27	-15.64	-4.36	(-21.2, 12.5)
		S.D.	6.68	5.69	7.65	
		N	11	11	11	



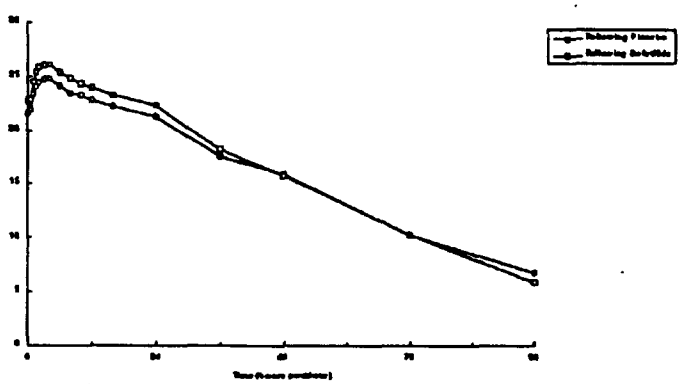


FIGURE 3
DOFETILIDE PROTOCOL 005
MEAN EXPERT LEAD II QTC CHANGES FROM PRE-DOSE ON DAYS 15/27 AND 30/42

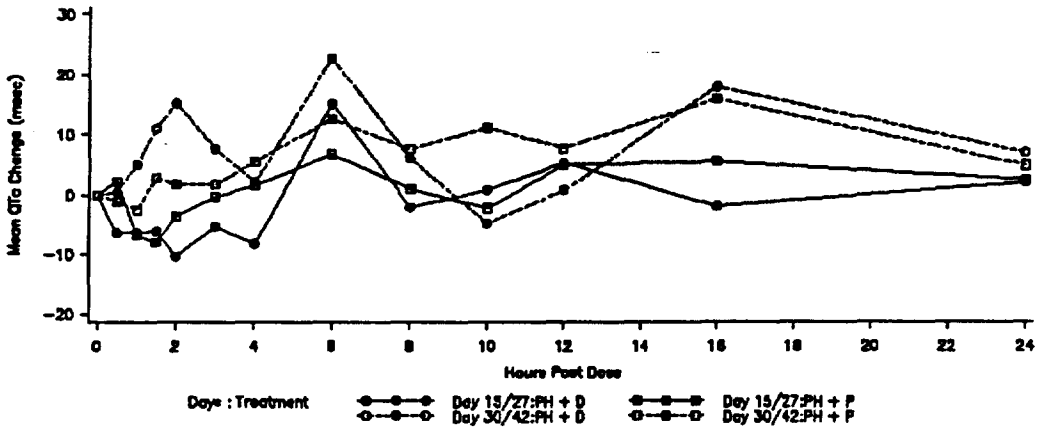
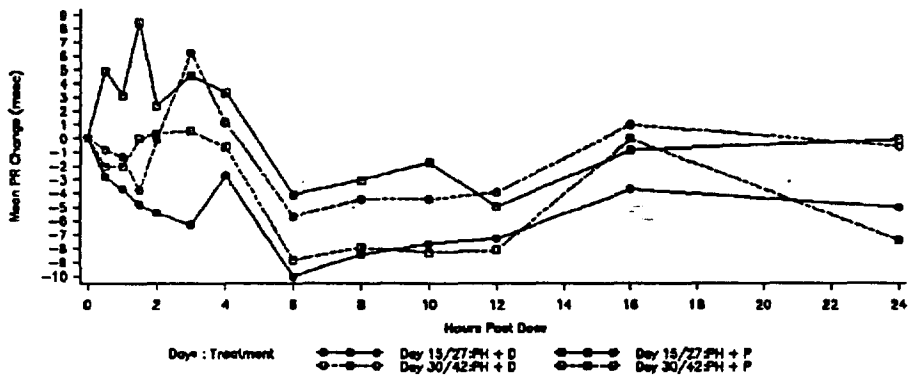


FIGURE 4
DOFETILIDE PROTOCOL 005
MEAN EXPERT LEAD II PR CHANGES FROM PRE-DOSE ON DAYS 15/27 AND 30/42



CONCLUSIONS: For the phenytoin sodium + dofetilide and the phenytoin sodium + placebo treatment groups, no statistically significant differences between Day 30(42) and Day 15(27) were found for the ratios of AUCt and Cmax, nor for the differences of Tmax or excretion percentage within treatment groups.

A comparison between Day 30(42) versus Day 15(27) ratios for AUCt and Cmax between the two treatment groups showed no statistically significant difference. No statistically significant difference was found for excretion percentage ($p=0.9642$), but there was a statistically significant difference found for Tmax ($p = 0.0369$) that was judged to be clinically unimportant.

For both QTc and PR, a comparison of the differences between Day 30(42) and Day 15(27)

values within each treatment group showed no statistically significant difference for either AUECt or Emax. Comparison of the difference in QTc changes between the two treatment groups also showed no statistically significant difference for either AUECt or Emax. The lack of statistical significance between the two groups for QTc may be due to the counteracting effect of phenytoin on dofetilide and/or to the large variability seen in these normal healthy volunteers. It should be noted that the steady state baseline QTc in the group treated with dofetilide was higher than in the group treated with placebo.
Comparison of the difference in PR changes between the two treatment groups showed a statistically significant difference for both AUECt and Emax.
In summary, dofetilide at a steady dose of 500mcg bid, had no clinically significant effect on the steady state pharmacokinetics or pharmacodynamics of phenytoin.

DOFETILIDE-CIMETIDINE/RANITIDINE INTERACTION STUDY

STUDY 115-253 **VOLUMES**: 1.39 - 1.40

INVESTIGATOR AND LOCATION: [

STUDY DATE: April - July 1995

RATIONALE: Cimetidine, a histamine H2-antagonist, has recently been shown to interact with dofetilide leading to an increase in plasma concentrations of the latter of approximately 50% (Pfizer study 115-004) presumably as a result of interference with the renal clearance of dofetilide. This is a potentially significant interaction as significant increases in dofetilide plasma concentrations would increase the risk of proarrhythmia due to excessive QT prolongation. Dofetilide clearance suggests involvement of both glomerular filtration and tubular secretion. Cimetidine competes for active tubular secretion and inhibits the cytochrome P450 oxidase system. Cimetidine has recently been approved as an over-the-counter medication at a lower dose (200mg daily) than is currently prescribed (800mg daily). One of the aims of this study is to investigate the effects of a lower dose of cimetidine (100mg bid) on the pharmacokinetics and pharmacodynamics (i.e. change in QTc) of dofetilide.
Ranitidine is another commonly prescribed histamine H2-antagonist which competes for active tubular secretion with cimetidine and hence may well interact with dofetilide. Ranitidine differs from cimetidine in that it has a greatly reduced effect on the cytochrome P450 oxidase system. Therefore, there was a need to characterise the effects of co-administration of ranitidine on the pharmacokinetics and pharmacodynamics of dofetilide in a young healthy population.

Study Objective: To determine the effects of cimetidine and ranitidine on the disposition of dofetilide; to evaluate the effect of any alteration of the pharmacokinetic profile of dofetilide on its pharmacodynamics as assessed from QTc intervals; to determine the effects of cimetidine and ranitidine on QTc intervals in the absence of dofetilide and to evaluate the safety and toleration of dofetilide whilst being given concurrently with cimetidine and ranitidine..

Drug Formulations:
Dofetilide 500mcg oral capsule (FID S00145AB, lot 2958-187)
Cimetidine 400mg oral tablet (lot 3713-099)
Cimetidine 100mg oral tablet (lot 3713-100)
Ranitidine 150 mg oral tablet (lot 3713-101)
Placebo oral tablet (FID 0766, lot 736-45X).

STUDY DESIGN:
This was an open, placebo controlled, randomised, four-way crossover study. Subjects received cimetidine (C) (100mg b.i.d. and 400mg b.i.d.), ranitidine (R) (150mg b.i.d.) or placebo during four treatment periods of four days each with a single dose of dofetilide (D)

(500mcg) on Day 2. Treatment periods were separated by an interval of one to two weeks. Dofetilide pharmacodynamics and pharmacokinetics were derived and compared between the treatment groups. Laboratory safety tests, electrocardiographic and haemodynamic measurements were repeated at intervals up to 48 hours after the completion of dosing. On Day 2 of each treatment period blood samples (4ml) were collected at time 0 (pre-dose) and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12 (immediately prior to evening dose), 16, 24, 36, 48 and 72 hours post dose. Urine samples were collected from -12-0, 0-12, 12-24, 24-36 and 36-48 hours post dofetilide dose. Urine and plasma samples were stored at -20°C until analyzed. On Day 1 of each treatment period duplicate 3-lead ECGs were performed at time 0 (pre-dose) and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12 and 16 hours post dose. Then on Day 2, duplicate 3-lead ECGs were performed at time 0 (prior to the dofetilide dose) and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, 48 and 72 hours post dose.

ASSAYS:

DATA ANALYSIS:

AUC, Cmax, Tmax, and Kel were computed. Renal clearance (CLr) of dofetilide was determined on Day 4 as Ae(0-12)/AUC(0-12) and on Day 10 as Ae(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. QTc interval values were computed for each subject from the recorded values of the QT interval and the RR interval using Bazett's formula. ANOVA was performed on the parameters.

RESULTS: Tables 1-2 and Figures 1-5 summarize the pharmacokinetic and pharmacodynamic data obtained from the study.

Table 1: Pharmacokinetic Results (Mean ± SD)

Mean Dofetilide Parameters:	*C100*	*C400*	*R150*	*Placebo*
Cmax (ng/ml)	2.27 ± 0.47	2.65 ± 0.66	2.09 ± 0.36	2.05 ± 0.30
Tmax (h)	1.3 ± 0.5	1.8 ± 0.9	1.9 ± 0.7	1.8 ± 0.8
AUC (ng.h/ml)	23.6 ± 2.4	31.5 ± 5.8	21.6 ± 2.7	21.3 ± 2.2
AUC(0-48) (ng.h/ml)	23.3 ± 2.9	29.9 ± 5.2	20.5 ± 2.6	20.6 ± 2.3
Total Oral Clearance (ml/min)	364.1 ± 48.2	287.0 ± 50.0	413.3 ± 51.6	409.4 ± 46.4
Renal Clearance (ml/min)	237.5 ± 35.0	184.3 ± 34.5	293.1 ± 56.1	273.7 ± 38.7
Non-renal Clearance (ml/min)	128.3 ± 28.6	102.7 ± 27.2	121.7 ± 52.7	135.3 ± 30.7
Kel (/h)	0.068 ± 0.010	0.062 ± 0.010	0.078 ± 0.012	0.078 ± 0.007

Ratio between means (90% C.I.s):	*Dofetilide/C100 - Dofetilide/Placebo*	*Dofetilide/C400 - Dofetilide/Placebo*	*Dofetilide/R150 - Dofetilide/Placebo*
Cmax	109.6% (101.8, 118.0)	126.8% (117.8, 136.6)	101.4% (94.2, 109.2)
AUC(0-48)	112.7% (108.7, 116.8)	143.9% (138.8, 149.2)	99.2% (95.7, 102.9)
Renal Clearance	87.7% (82.7, 92.8)	65.6% (60.7, 70.6)	106.7% (101.7, 111.7)
Non-renal Clearance	93.6% (83.7, 103.6)	75.6% (65.8, 85.4)	89.6% (79.9, 99.4)
Kel	86.9% (82.0, 91.7)	81.2% (76.0, 86.3)	101.1% (96.2, 106.1)

Table 2: Pharmacodynamics Results (Mean ± SD)

Max. change from baseline:				
QTc on Day 1 (msec)	11.7 ± 16.8	15.2 ± 15.2	10.3 ± 17.9	14.8 ±17.4
QTc on Day 2 (msec)	45.7 ± 13.4	49.8 ± 15.0	40.5 ± 14.9	37.4 ± 17.6
AUEC Change from baseline:				
on Day 1 (msec.h)	-73.4 ± 126.2	-33.7 ± 88.2	-80.9 ± 214.0	-33.0 ± 175.8
on Day 2 (msec.h)	265.4 ± 160.4	289.3 ± 150.1	224.5 ± 144.7	223.1 ± 168.9
Slope (msec/ng/ml)	18.53 ± 4.42	17.09 ± 4.47	19.27 ± 4.93	18.54 ± 3.79

Comparison: (adjusted means)	*Dofetilide/C100 - Dofetilide/Placebo*		*Dofetilide/C400 - Dofetilide/Placebo*		*Dofetilide/R150 - Dofetilide/Placebo*	
Diff. between means	Diff.	p-value	Diff.	p-value	Diff.	p-value
Max. change from baseline QTc on Day 2	8.3	0.0442	12.3	0.0034	3.0	0.4548
AUEC Change from baseline QTc on Day 2	42.3	0.2138	66.2	0.0541	1.4	0.9663

Figure 1:

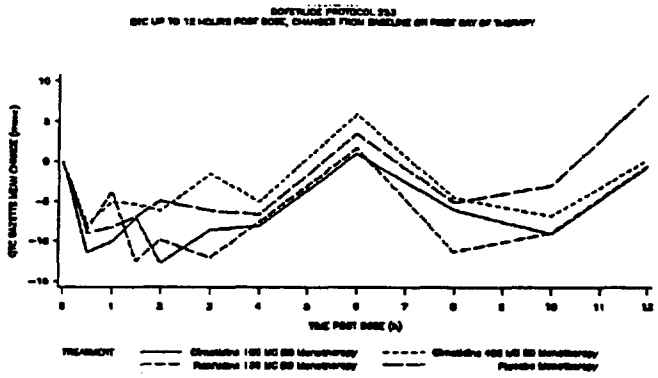


Figure 2:

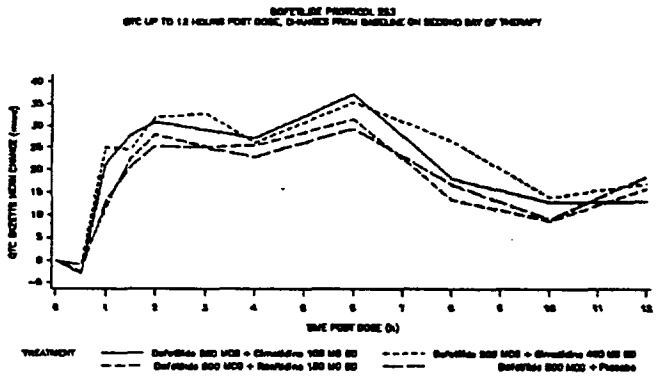


Figure 3:

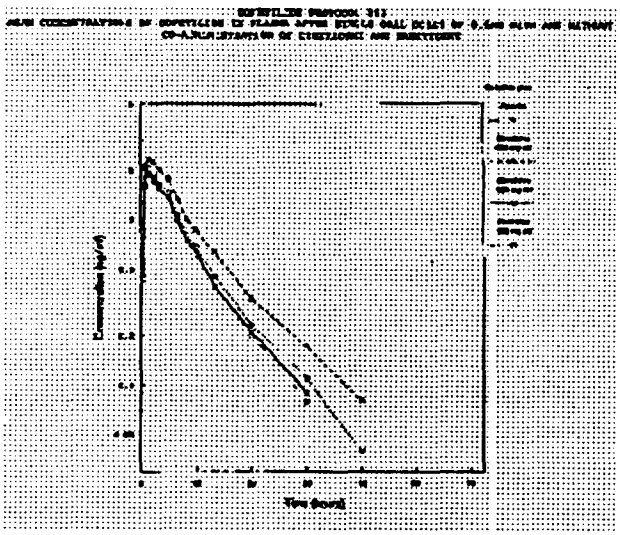


Figure 4:

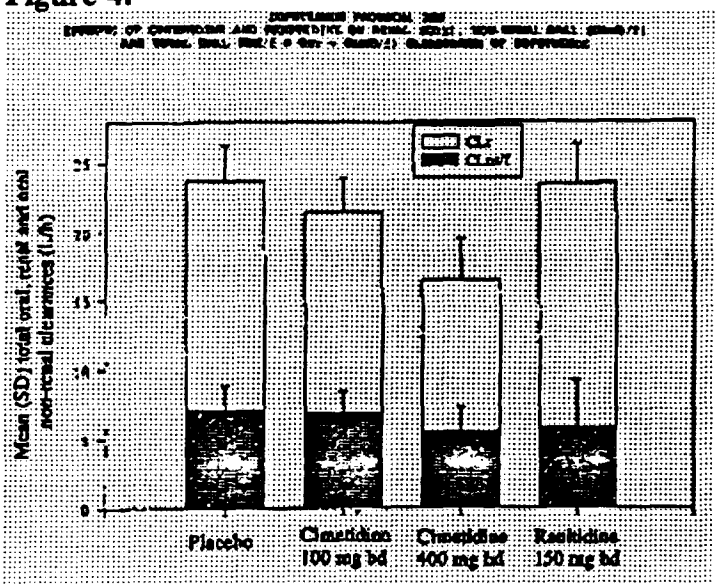
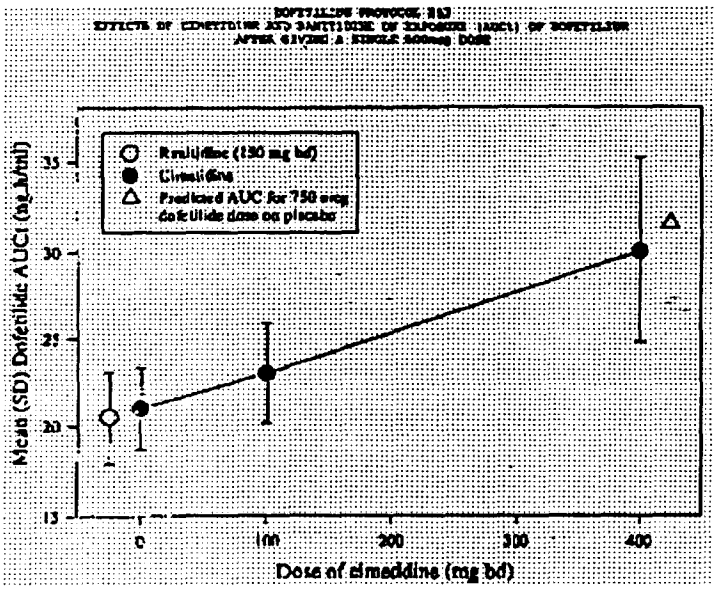


Figure 5:



Conclusions: Cimetidine 400mg caused a reduction in elimination arising from a statistically significant decrease in the renal clearance of dofetilide and a modest reduction in non-renal clearance. Thus exposure to dofetilide increased when dosed with cimetidine 400mg: mean AUC(0-48) was statistically significantly increased as well as mean Cmax. Cimetidine 100mg caused a much smaller reduction in elimination arising from a modest decrease in the renal clearance of dofetilide. No clinically or statistically significant differences in renal or non-renal clearance were observed with ranitidine 150mg when compared to placebo.

A single dose of ranitidine 150mg or cimetidine 100mg alone did not significantly affect QTc. Thereafter, when dofetilide was dosed, QTc increased in line with increases in dofetilide plasma concentration. The change in maximum QTc after cimetidine 400mg was statistically significantly larger than the change observed with placebo. After ranitidine 150mg the QTc response was similar to the response after placebo. Neither cimetidine nor ranitidine altered the sensitivity of QTc prolongation to dofetilide.

These results indicate that there would be no clinically significant interaction in the combination of ranitidine with dofetilide.

DOFETILIDE-AMLODIPINE INTERACTION STUDY

STUDY 115-255 **VOLUME**: 2.61 **PAGES**: 1-328

INVESTIGATOR AND LOCATION:

STUDY DATE: August - November 1996

RATIONALE: A significant proportion of patients who would benefit from treatment with dofetilide will already be receiving long term treatment with amlodipine, a widely prescribed calcium channel blocker used for the treatment of hypertension. Dofetilide is the compound with the narrower therapeutic window, compared to amlodipine, and it is important to assess the effect of multiple dose amlodipine on the pharmacokinetics and pharmacodynamics of dofetilide.

Study Objective: To investigate the effect of multiple dose amlodipine on the steady state pharmacokinetics and pharmacodynamics of dofetilide and to investigate the safety and toleration of co-administering the combination.

Drug Administration:
Dofetilide 250mcg capsules; FID No. S0011AB, Lot No. 4469-077
Amlodipine 10mg tablets; FID No. 0712, Lot No. 4503-077
Identical placebo tablets; FID No. 0766, Lot No. 4503-076

STUDY DESIGN:
This was a double-blind, randomised, placebo-controlled, two-period, parallel group study. In study period 1, all subjects received dofetilide twice daily for 4 days with a single dose on Day 5. In study period 2, 12 subjects received amlodipine for 12 days and 13 received placebo for 12 days. From Day 8, all the subjects were co-administered with dofetilide. Dofetilide pharmacokinetics were assessed at the end of each study period from plasma and urine samples. Dofetilide pharmacodynamics were assessed at the end of each study period by ECG evaluation.

ASSAYS:

DATA ANALYSIS:
AUC, Cmax, Tmax, CL/F, CLr and Kel were computed. The maximum change in QTc (Emax) and the area under the QTc versus time curve (AUEC) was calculated up to 12 hours post dose. ANOVA was performed on the parameters.

RESULTS: Tables 1-3 and Figures 1-6 summarize the pharmacokinetic and pharmacodynamic data obtained from the study.

Table 1: Pharmacokinetic Results

	Dofetilide 500mcg bid + Amlodipine		Dofetilide 500mcg bid + Placebo	
Mean ± SD	Period 1, Day 5*	Period 2, Day 12	Period 1, Day 5*	Period 2, Day 12
AUCtau[a] (ng.h/ml)	26.05 ± 3.63	26.41 ± 3.18	24.84 ± 3.61	24.69 ± 3.19
Cmax[a] (ng/ml)	3.46 ± 0.62	3.58 ± 0.49	3.13 ± 0.40	3.27 ± 0.57
Tmax[b] (h)	1.29 ± 0.33	1.50 ± 0.56	1.96 ± 0.50	1.67 ± 0.39
CL/F[b] (l/h)	19.37 ± 2.77	19.06 ± 2.32	20.33 ± 2.92	20.40 ± 2.62
CLr[b] (l/h)	8.83 ± 3.27	8.34 ± 2.29	8.86 ± 3.46	8.56 ± 4.07
CLnr/F[b] (l/h)	10.54 ± 4.44	10.72 ± 2.34	11.47 ± 4.19	11.84 ± 3.26

[a] geometric mean, [b] arithmetic mean * Dofetilide only

Table 2: Pharmacodynamic Results

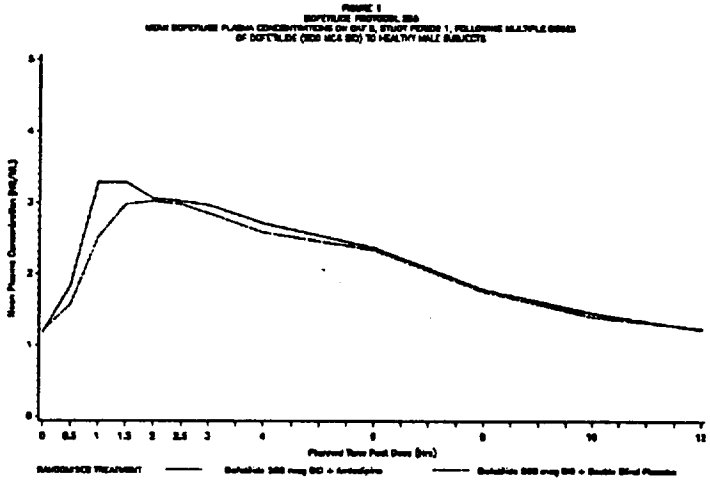
DOFETILIDE PROTOCOL 211
SUMMARY OF ANALYSIS OF DAY 12 VERSUS DAY 5 CHANGE IN DERIVED QTC

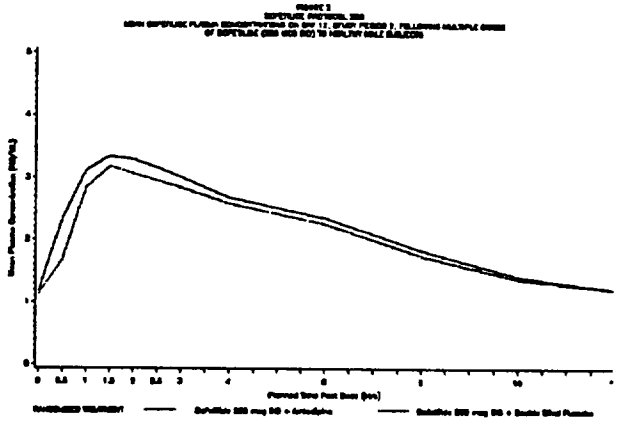
		Period 1 Day 5	Period 2 Day 12	Difference	Within Treatment Comparison 95% Confidence Limits	Within Treatment Comparison (p-value)
Dofetilide 500 mcg BID + Amlodipine						
AUECtau (msec.h)	Mean	92.5	202.8	110.4	(23.62 , 197.13)	p = 0.017
	S.D.	204.61	251.88	136.33		
	N	12	12	12		
Emax (msec)	Mean	40.0	43.9	3.9	(-6.65 , 14.49)	p = 0.432
	S.D.	15.13	21.23	16.64		
	N	12	12	12		
Dofetilide 500 mcg BID + Double Blind Placebo						
AUECtau (msec.h)	Mean	101.0	165.9	34.2	(-67.48 , 135.89)	p = 0.543
	S.D.	214.03	201.22	161.14		
	N	11	12	11		
Emax (msec)	Mean	25.6	27.5	1.9	(-12.29 , 16.11)	p = 0.771
	S.D.	26.36	20.39	22.23		
	N	12	12	12		

Table 3:

DOFETILIDE PROTOCOL 255
SUMMARY OF ANALYSIS OF CHANGE IN DIGITISED QTC

		Dofetilide 500mcg BID + Amlodipine	Dofetilide 500mcg BID + Double Blind Placebo	Difference	Between Treatment Comparison 95% Confidence Limits	Between Treatment Comparison (p-value)
Period 2, Day 12						
AUEC$_{tau}$ (msec.h)	Mean	202.8	165.9	36.9	(-156.09 , 230.73)	p = 0.697
	S.D.	252.80	202.22			
	N	12	12			
Emax (msec)	Mean	43.9	37.5	6.4	(-11.52 , 24.32)	p = 0.467
	S.D.	21.73	20.59			
	N	12	12			





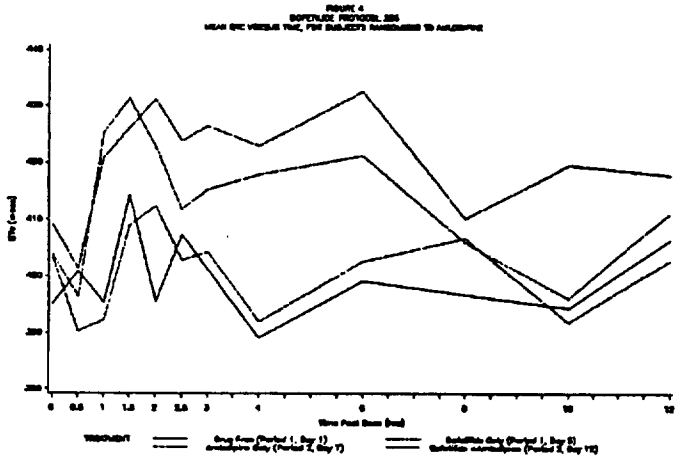
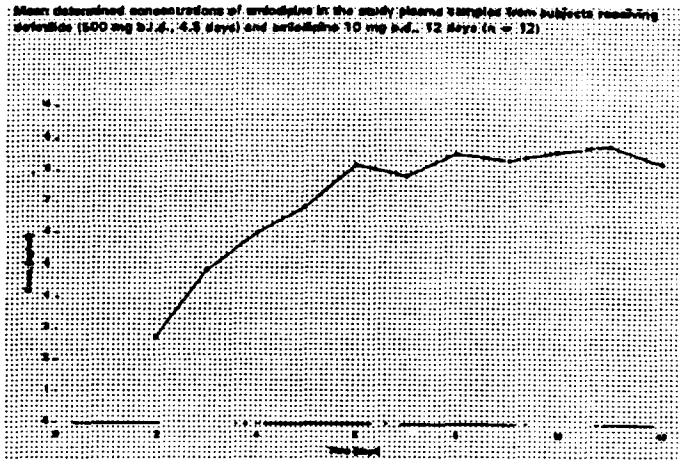


Figure 6:



CONCLUSIONS: Steady state dofetilide concentrations were achieved by the third day of dosing in each study period and steady state amlodipine concentrations were achieved by the sixth day of study period 2. The pharmacokinetic parameters for dofetilide measured on Day 5 of study period 1 were similar to those measured on Day 12 of study period 2 after co-administration with either amlodipine or placebo. Between treatment comparison of the ratio/difference of these pharmacokinetic parameters did not indicate statistical significance apart from the comparison of the difference in time of maximum plasma concentration ($p \_ 0.0001$). The difference between groups was minor, not clinically significant and unlikely to have arisen as a consequence of co-administration with amlodipine.

Changes in digitised QTc from baseline showed considerable variation between subjects. On Day 5 of study period 1 and Days 7 and 12 of study period 2, both groups of subjects had similar changes in AUECtau and Emax. On Day 12 of study period 2, none of the differences in AUECtau or Emax between groups that received either amlodipine or placebo co-administered with dofetilide were statistically significant.

In summary, co-administration of amlodipine with dofetilide has no clinically significant effect on dofetilide pharmacokinetics and pharmacodynamics

DOFETILIDE-THEOPHYLLINE INTERACTION STUDY

STUDY 115-009 **VOLUMES**: 1.34-1.35, 2.15

INVESTIGATOR AND LOCATION:

STUDY DATE: August - December 1993

RATIONALE: Theophylline is extensively metabolized in the liver, and like dofetilide, this process involves isozymes of the P450 mixed function oxidase system. For a large number of drugs including theophylline, and perhaps dofetilide, several isozymes appear to be involved in their metabolic elimination, thus permitting the possibility of differential cross-reaction, or overlapping substrate specificity. Theophylline may cause, or worsen cardiac arrhythmias. Chronic obstructive airway disease for which theophylline is often prescribed can be complicated with ventricular tachycardia or other types of arrhythmias for which dofetilide may be indicated. Thus, the potential for combined use of both agents in pharmacotherapy exists in clinical practice.

Study Objective: To examine the effects of administration of theophylline on the steady-state pharmacokinetics and pharmacodynamics of dofetilide in normal volunteers, and to assess safety and toleration during concurrent administration of the two drugs.

Drug Administration:
Dosage Forms Dofetilide capsules: 500mcg FID# 0964, Lot No. 503-20
Theophylline (Theo-Dur) tablets: 450mg Key Pharm, Lot No. ED-O-165-693
Placebo tablets: FID# G00085AA, Lot No. ED-G-089-392

STUDY DESIGN:
This was an observer-blind, randomized, placebo controlled, parallel group study. Dofetilide 500mcg was administered bid from Day 1 through the AM dose on Day 10. On Day 6 the subjects were randomly assigned to also receive either theophylline (as Theo-Dur) bid q 12h (Group A) or placebo bid (Group B) for 6 days. Pharmacokinetic and pharmacodynamic evaluations were performed following morning dofetilide administration on Days 5 and 10. To confirm steady-state concentrations of dofetilide and theophylline, blood samples (Cmin) were also collected on Days 3, 4, 5, 8, 9 and 10 before the administration of the morning dose.

ASSAYS:

DATA ANALYSIS:
AUC, Cmax, Tmax, CL/F, CLr and Kel were computed. The maximum change in QTc (Emax) and the area under the QTc versus time curve (AUEC) was calculated up to 12 hours post dose. ANOVA was performed on the parameters.

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

Table 1: Pharmacokinetic Results: Pharmacokinetic parameters (mean±SD)

	Group A		Group B	
	Dofetilide (Day 5)	Dof + Theo (Day 10)	Dofetilide (Day 5)	Dof + Placebo (Day 10)
AUC_τ (ng·h/mL)*	19.6±3.1	22.4±3.4	19.2±3.4	17.9±4.3
Cmax (ng/mL)*	2.41±0.42	2.55±0.43	2.36±0.40	2.15±0.58
Tmax (h)**	2.7±1.3	2.7±1.8	2.3±0.9	2.4±1.4
CLr (mL/min)**	332.6±51.6	278.0±57.0	339.2±86.1	395.5±136.2
Kel (h^{-1})**	--	0.0571±0.0058	–	0.0584±0.0083
T1/2 (h)**	--	12.1	–	11.9

* Geometric means
** Arithmetic means

Table 2: Analysis of Pharmacokinetics Data

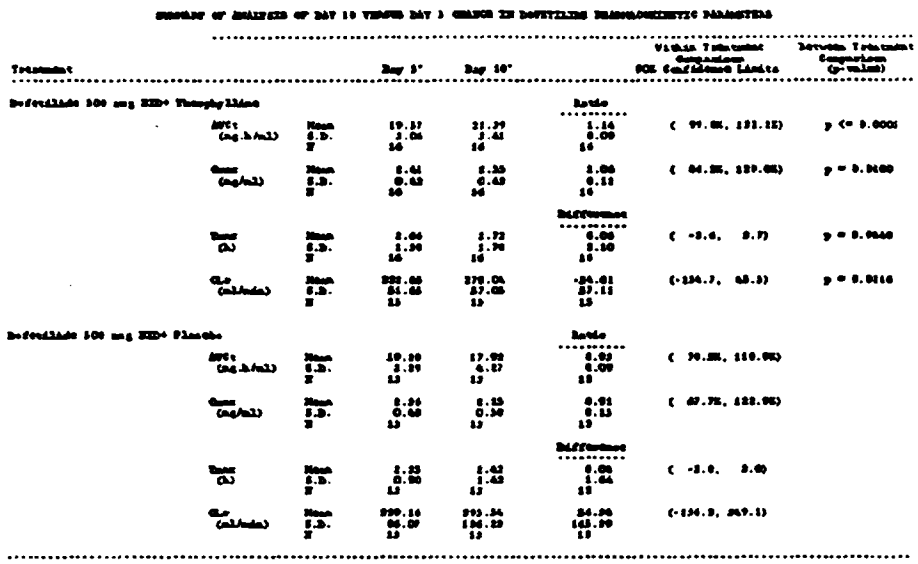


Table 3: Pharmacodynamic Results: PD parameters (mean±SD)

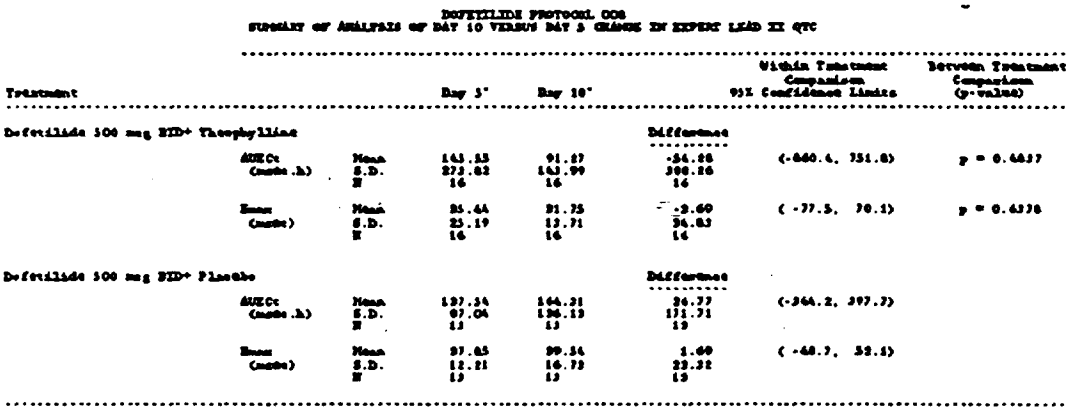
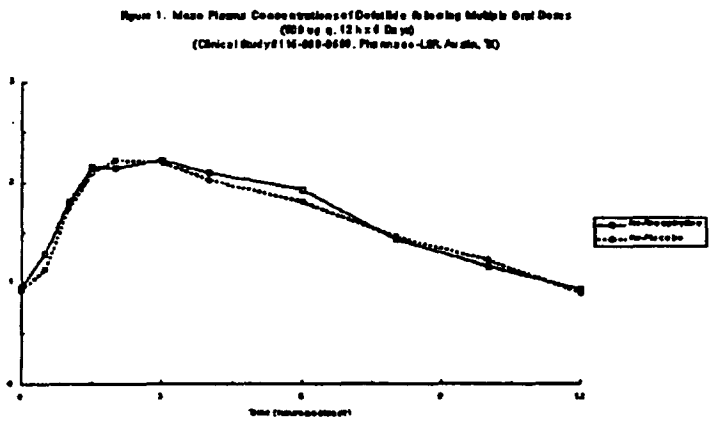


Table 4. Theophylline Predose Plasma Concentrations (Cmin)

	Theophylline Concentrations (μg/ml) on Days		
	8	9	10
Mean	11.6	11.7	12.6
SD	2.9	3.1	2.7
CV(%)	25	26	21



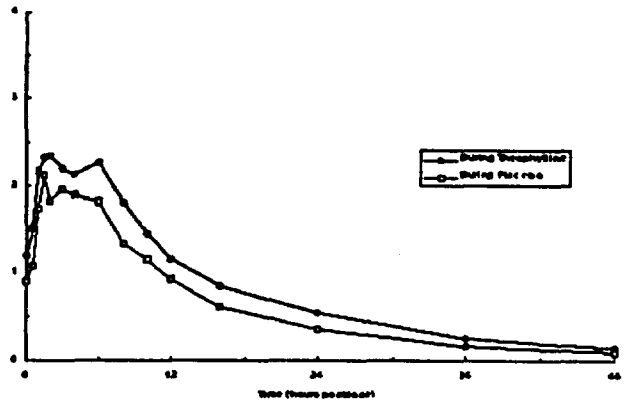
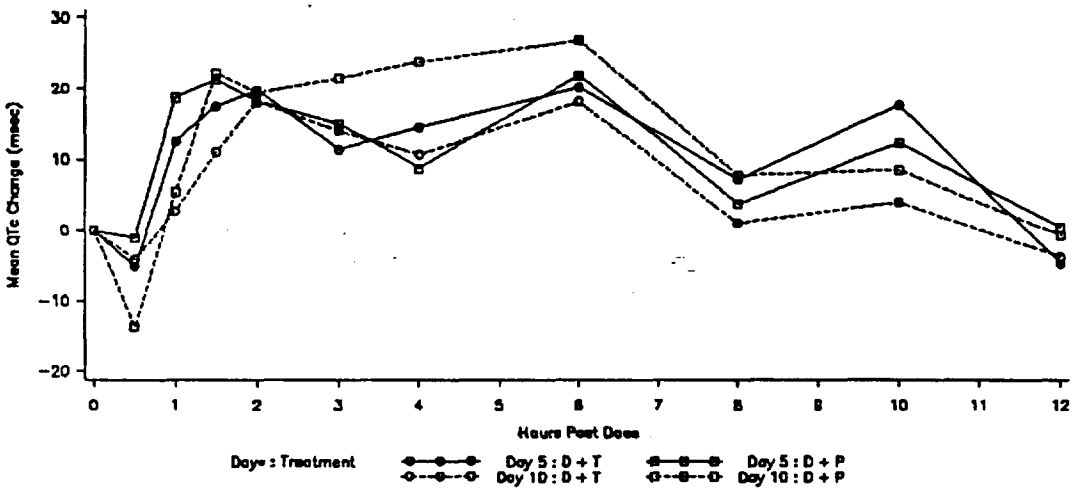


FIGURE 3
DOFETILIDE PROTOCOL 008
MEAN EXPERT LEAD II QTC CHANGES FROM PRE-DOSE ON DAYS 5 AND 10



CONCLUSIONS: The concomitant administration of theophylline and dofetilide resulted in increases in mean dofetilide AUCt and Cmax values of 14±9% and 6±12% (mean % change ± S.D.), respectively. For the placebo control group decreases in mean AUCt and Cmax of 7±9% and 9±15%, respectively, were observed. These within-group changes were not statistically significant (90% confidence intervals on the ratios include 100%). There were also no statistically significant within-group differences in CLr. In contrast, the between-group differences in Day 10/Day 5 ratios of AUCt and Cmax and in Day 10 minus Day 5 differences for CLr were statistically significant (p values were 0.0216 or less). Conversely, no statistically significant changes were observed for Tmax either within (90% confidence intervals on the differences include 0) or between (p=0.984) the treatment groups. Co-administration of theophylline was not shown to have a significant effect on the pharmacodynamics of dofetilide as assessed by QTc intervals. No statistically significant changes in AUECt or Emax between Day 10 and Day 5 either within or between the treatment groups were observed. However, the variability in QTc was high. Given that the study was not powered on QTc but on AUC, which has low variability, it is not surprising that no differences in QTc between treatment groups were observed. Also, in this study there was no apparent relationship between the pharmacodynamics (QTc) AUECt, Emax and AUC or Cmax, which might be explained by the high variability in QTc and that only one dose strength of dofetilide was given.

DOFETILIDE-THEOPHYLLINE INTERACTION STUDY

STUDY 115-009 **VOLUMES**: 1.36-1.37, 2.16

INVESTIGATOR AND LOCATION:

STUDY DATE: August - December 1993

RATIONALE: Theophylline is extensively metabolized in the liver, and like dofetilide, this process involves isozymes of the P450 mixed function oxidase system. For a large number of drugs including theophylline, and perhaps dofetilide, several isozymes appear to be involved in their metabolic elimination, thus permitting the possibility of differential cross-reaction, or overlapping substrate specificity. Theophylline may cause, or worsen cardiac arrhythmias. Chronic obstructive airway disease for which theophylline is often prescribed can be complicated with ventricular tachycardia or other types of arrhythmias for which dofetilide may be indicated. Thus, the potential for combined use of both agents in pharmacotherapy exists in clinical practice.

Study Objective: To examine the effects of concurrent administration of dofetilide to steady-state, on the steady-state pharmacokinetics and pharmacodynamics of theophylline in normal volunteers, and to assess the safety and toleration of the combination.

Drug Administration:
Theophylline (Theo-Dur) tablets: 450mg Key Pharm, Lot No. ED-O-165-693
Dofetilide capsules: 500mcg FID# 0964, Lot No. 503-20
Placebo capsules: FID# 0034, Lot No. 748-17

STUDY DESIGN:
This was an observer-blind, randomized, placebo-controlled, multi-dose, parallel group study. Theophylline (Theo-Dur) was administered bid q 12h from Day 1 through the AM dose of Day 10. On Day 6 the subjects were randomly assigned to receive in addition either dofetilide bid q 12h (group A) or placebo q 12h (group B) for 6 days (Days 6-11). Pharmacokinetic and pharmacodynamic measurements were taken following morning administration of theophylline on Days 5 and 10. Theophylline plasma concentrations were monitored on Days 5 and 10 at 0 (just prior to AM dosing), and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10 and 12 hours. Additional concentration measurements were obtained at 16, 24, 36, and 48 hours post Day 10 AM dosing. To confirm steady-state concentrations of theophylline and dofetilide, blood samples (Cmin) were also collected on Days 3, 4, 5, 8, 9, and 10 for theophylline, and on Days 8, 9, and 10 for dofetilide before the administration of the morning dose.

ASSAYS:

DATA ANALYSIS:
AUC, Cmax, Tmax, were computed for theophylline. The maximum change in QTc (Emax) and the area under the QTc versus time curve (AUEC) was calculated up to 12 hours post dose. ANOVA was performed on the parameters.

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

Table 1a. Dofetilide Predose Plasma Concentrations (Cmin)

	Dofetilide Concentrations (ng/ml) on Days		
	8	**9**	**10**
Mean	**1.15**	**1.05**	**1.10**
SD	**0.23**	**0.18**	**0.18**
CV(%)	**20**	**17**	**16**

Table 6.1 Summary of Theophylline Pharmacokinetic Parameters Following Multiple Oral Administration of 450 mg Theo-Dur q. 12 h Prior to (Day 5) and Following (Day 10) Multiple Doses of Dofetilide 500 µg q. 12 h or Placebo q. 12 h in Healthy Male Subjects
(Clinical Study #115-009-9599, Pharmaco-LSR, Austin, TX)

Day 5

Treatment	N		AUC(0-12)[c] (µg•h/ml)	Cmax[c] (µg/ml)	Tmax (h)
Theo + Dof[a]	17	Mean	176.0	16.90	5.2
		SD	49.8	5.65	1.6
		CV(%)	28	33	31
Theo + Pbo[b]	17	Mean	166.3	16.47	5.2
		SD	37.7	3.25	1.4
		CV(%)	23	20	28

Day 10

Treatment	N		AUC(0-12)[c] (µg•h/ml)	Cmax[c] (µg/ml)	Tmax (h)	Kel (h^{-1})	T1/2[d] (h)
Theo + Dof[a]	17	Mean	154.3	14.59	4.6	0.0966	7.2
		SD	40.0	3.96	2.2	0.0175	–
		CV(%)	26	27	47	18	–
Theo + Pbo[b]	17	Mean	157.0	15.23	5.0	0.0916	7.6
		SD	29.2	3.02	2.0	0.0134	–
		CV(%)	19	20	40	15	–

Table 2:

SUMMARY OF ANALYSIS OF DAY 10 VERSUS DAY 5 CHANGE IN THEOPHYLLINE PHARMACOKINETIC PARAMETERS

Treatment			Day 5*	Day 10*		Within Treatment Comparison 90% Confidence Limits	Between Treatment Comparison (p-value)
Theophylline +Dofetilide 500 mcg BID					Ratio		
	AUCt (mcg.h/ml)	Mean	175.96	156.28	0.88	(59.2%, 129.8%)	p = 0.2746
		S.D.	49.83	40.00	0.20		
		N	17	17	17		
	Cmax (mcg/ml)	Mean	16.90	14.59	0.86	(49.0%, 149.3%)	p = 0.4334
		S.D.	5.65	3.96	0.27		
		N	17	17	17		
					Difference		
	Tmax (h)	Mean	5.18	4.62	-0.56	(-4.9, 3.8)	p = 0.6851
		S.D.	1.59	2.16	2.52		
		N	17	17	17		
Theophylline +Placebo					Ratio		
	AUCt (mcg.h/ml)	Mean	166.27	156.96	0.94	(72.0%, 123.8%)	
		S.D.	37.70	29.19	0.13		
		N	17	17	17		
	Cmax (mcg/ml)	Mean	16.47	15.23	0.92	(69.1%, 123.8%)	
		S.D.	3.25	3.02	0.16		
		N	17	17	17		
					Difference		
	Tmax (h)	Mean	5.18	6.97	-0.21	(-4.6, 4.2)	
		S.D.	1.42	3.05	2.51		
		N	17	17	17		

SUMMARY OF ANALYSIS OF DAY 10 VERSUS DAY 5 CHANGE IN EXPERT LEAD II HEART RATE

Treatment			Day 5*	Day 10*		Within Treatment Comparisons 95% Confidence Limits	Between Treatment Comparisons (p-value)
Theophylline +Dofetilide 500 mcg BID					Difference		
	AUEC$_0^t$ (bpm.h)	Mean	23.16	79.57	56.41	(-137.0, 249.8)	p = 0.6009
		S.D.	91.89	54.64	101.36		
		N	17	17	17		
	Emax (bpm)	Mean	13.64	18.60	4.96	(-15.7, 25.6)	p = 0.9163
		S.D.	8.62	7.98	9.79		
		N	17	17	17		
Theophylline +Placebo					Difference		
	AUEC$_0^t$ (bpm.h)	Mean	41.22	66.10	25.98	(-100.2, 252.1)	
		S.D.	116.15	107.96	107.19		
		N	17	17	17		
	Emax (bpm)	Mean	16.91	21.31	4.39	(-22.6, 31.6)	
		S.D.	11.67	12.67	12.91		
		N	17	17	17		

Figure 1. Mean Theophylline Plasma Concentrations on Day 5 Following Multiple Oral Administration of 450 mg Theo-Dur q. 12 h Prior to Treatment with Dofetilide or Placebo in Healthy Male Subjects
(Clinical Study #115-009-9599, Pharmaco-LSR, Austin, TX)

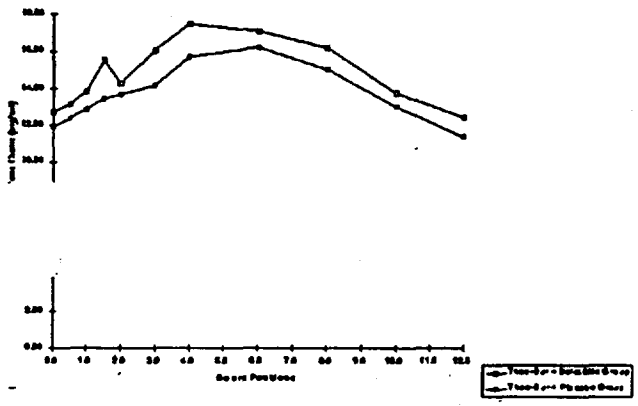


Figure 2. Mean Theophylline Plasma Concentrations on Day 10 Following Multiple Oral Administration of 450 mg Theo-Dur q. 12 h with Multiple Dose Dofetilide 500 mcg q. 12 h or Placebo q. 12 h in Healthy Male Subjects

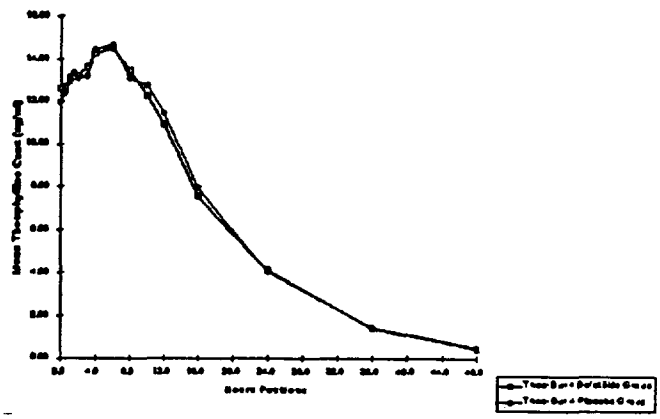
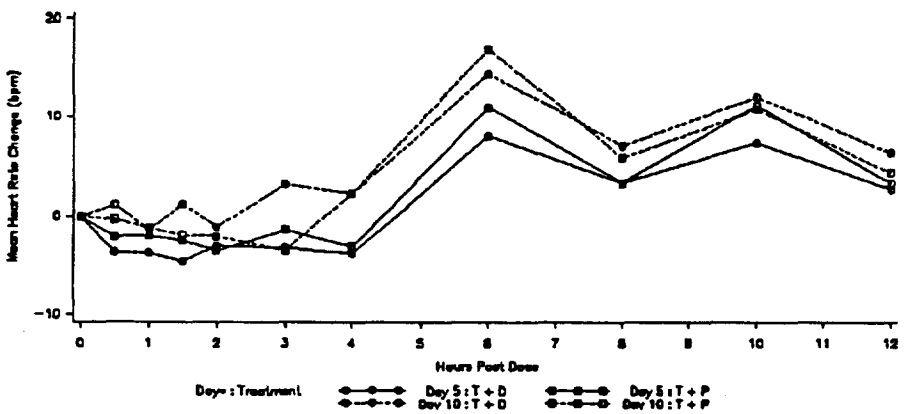


FIGURE 3
DOFETILIDE PROTOCOL 009
MEAN EXPERT LEAD II HEART RATE CHANGES FROM PRE-DOSE ON DAYS 5 AND 10



Conclusions: Systemic exposure to theophylline, as measured by AUCτ and Cmax, was not significantly affected by concurrent administration of dofetilide in healthy male subjects studied under steady state conditions. The mean Cmax and mean AUCτ decreased 16%, and 14%, respectively, in the group who received dofetilide, and 8% and 6%, respectively, in the group who received placebo. There were also no statistically significant differences for the Day 10/Day 5 ratios for AUCτ ($p=0.2746$) or Cmax ($p=0.4334$) between the two treatment groups.

The heart rate pharmacodynamics (AUECτ and Emax) of theophylline upon concomitant administration with dofetilide did not change significantly either within (the 95% confidence intervals on the differences include 0) or between the treatment groups ($p \geq 0.4009$).

DOFETILIDE-GLIBENCLAMIDE INTERACTION STUDY

STUDY 115-011 **VOLUMES**: 1.38 & 2.17

INVESTIGATOR AND LOCATION:

STUDY DATE: July - October 1994

RATIONALE: Glibenclamide (Glyburide) is a second generation, long-acting sulfonylurea. In addition to its hypoglycemic activity, glyburide has a modest diuretic effect in man. Recently, glyburide has been shown to possess a K-ATP channel blocking property, resulting in prolongation of the action potential duration. Concurrent administration of glyburide to patients receiving dofetilide could potentiate the pharmacodynamic action of dofetilide, resulting in increased incidence of proarrhythmia.
Glyburide is extensively metabolized in man, and is eliminated in equivalent amounts as inactive metabolites by both the liver and kidneys. Since renal elimination accounts for about 70% of the elimination of dofetilide, there is a potential for a pharmacokinetic interaction of dofetilide with glyburide. Such an interaction could also potentiate the pharmacodynamic effect of dofetilide.
It is conceivable that a diabetic receiving a sulfonylurea such as glyburide could suffer from an arrhythmia for which dofetilide is indicated. Consequently, it is necessary to characterize the effects of co-administration of glyburide on the steady-state pharmacokinetics and pharmacodynamics of dofetilide in a young healthy population.

Study Objective: To assess the effects of multiple doses of glibenclamide (glyburide) on the pharmacokinetics and pharmacodynamics of steady-state dofetilide in healthy young male volunteers. In addition, to evaluate the effect of any alteration of the pharmacokinetic profile of dofetilide on its pharmacodynamics assessed from QTc intervals.

Drug Administration:
Dofetilide capsules: 500mcg, FID 0964, Lot No. 503-20
Glyburide tablets: 5mg, FID Upjohn, Lot No. ED-O-210-694
Placebo capsules: FID 0034, Lot No. 748-45
Placebo tablets: FID G00434AA, Lot No. ED-G-006-194

Dosing Individual treatments were as follows:
(A) Dofetilide, 500mcg bid (q.12h, AM only on day 4) plus placebo tablet, AM only, for 4 days.
(B) Placebo capsule, bid (q.12h, AM only on day 4) plus glyburide, 5mg, AM only, for 4 days.
(C) Dofetilide, 500mcg bid (q.12h, AM only on day 4) plus glyburide, 5mg, AM only, for 4 days.

STUDY DESIGN:
This was an observer-blind, placebo-controlled, randomized, three period,

three treatment, six sequence, multi-dose crossover study. Study drugs were administered on days 1-4, 6-9, and 11-14. Only the AM dose of study drugs was administered on days 4, 9, and 14. No study drugs were administered on days 5 and 10. Measurements of dofetilide pharmacokinetics and pharmacodynamics were taken following morning administration of study drugs on days 4, 9, and 14. Dofetilide plasma concentrations were monitored on days 4, 9, and 14 at 0 (just prior to AM dosing), and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, and 48 hours after study drug administration. Urine dofetilide concentrations were obtained from all urine samples collected during the 24 hours following study drug administration on days 4, 9, and 14.

ASSAYS:

DATA ANALYSIS:
AUC, Cmax, Tmax, CLr and Kel were computed. The maximum change in QTc (Emax) and the area under the QTc versus time curve (AUEC) was calculated up to 12 hours post dose. ANOVA was performed on the parameters.

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

Table 1: Pharmacokinetic Results (Mean±SD)

PK Parameter	Dofetilide alone	Dofetilide + Glyburide
AUC(0-12) ng.h/ml	27.7±4.4	27.6±4.1
Cmax ng/ml	3.7±0.7	3.7±0.8
Tmax h	1.6±0.9	2.0±0.9
Kel h^{-1}	0.077±0.011	0.074±0.013
$T_{1/2}$ h	9.2±1.5	9.7±1.7
CLr ml/min	251.5±51.8	262.4±46

Table 2:

ANALYSIS OF DOFETILIDE PHARMACOKINETIC PARAMETERS SUMMARY

Pharmacokinetic Parameter	Comparison			90% Confidence Limits
		Adjusted Geometric Means	Ratio	
AUCt (ng.h/ml)	D + G vs. D + P	27.38 vs. 27.71	99.6%	(96.0%, 103.2%)
Cmax (ng/ml)	D + G vs. D + P	2.68 vs. 2.65	100.7%	(93.6%, 108.4%)
		Adjusted Arithmetic Means	Difference	
Tmax (h)	D + G vs. D + P	2.0 vs. 1.6	0.4	(-0.2, 0.9)
Kel (/h)	D + G vs. D + P	0.0739 vs. 0.0770	-0.0031	(-0.0062, 0.0000)
Clr (ml/min)	D + G vs. D + P	262.39 vs. 251.46	10.94	(-7.37, 29.25)

Table 3:

ANALYSIS OF PHARMACODYNAMIC PARAMETERS SUMMARY - EXPERT LEAD II QTC

Pharmacodynamic Parameter	Comparison			95% Confidence Limits
		Adjusted Arithmetic Means	Difference	
AUECt (msec.h)	D + G vs. D + P	202.39 vs. 157.21	45.18	(-67.90, 158.26)
	D + G vs. G + P	202.39 vs. 83.57	118.82	(5.74, 231.90)
Emax (msec)	D + G vs. D + P	42.89 vs. 42.50	1.29	(-7.84, 10.62)
	D + G vs. G + P	42.89 vs. 23.83	18.06	(8.03, 27.28)

Figure 1. Mean Plasma Concentrations of Dofetilide Following Oral Administration of 500 ug Twice Daily for Four Days With and Without 5 mg Glyburide Daily (Clinical Study #15-011-555, Dr. John Black, Austin, TX)

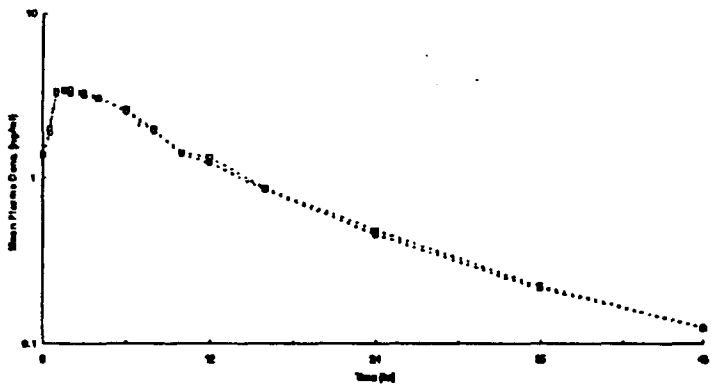


FIGURE 2
DOFETILIDE PROTOCOL 011
MEAN EXPERT LEAD II QTC CHANGES FROM PRE-DOSE FOR EACH TREATMENT

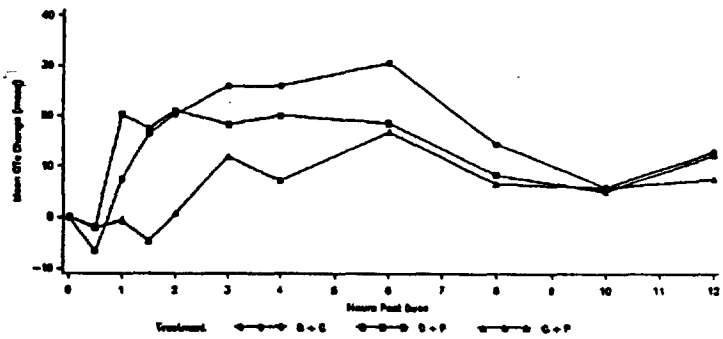


Figure 3:

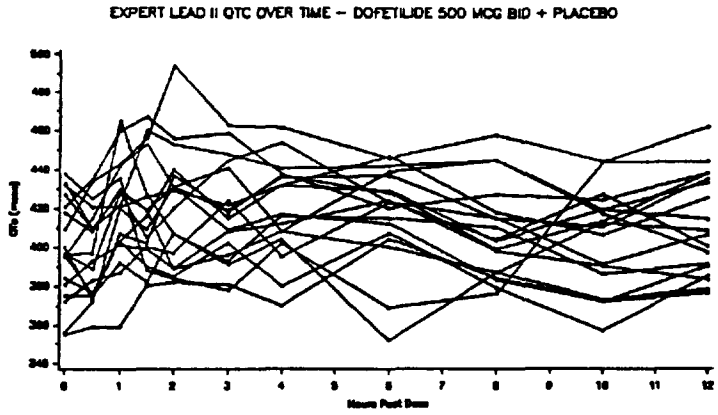
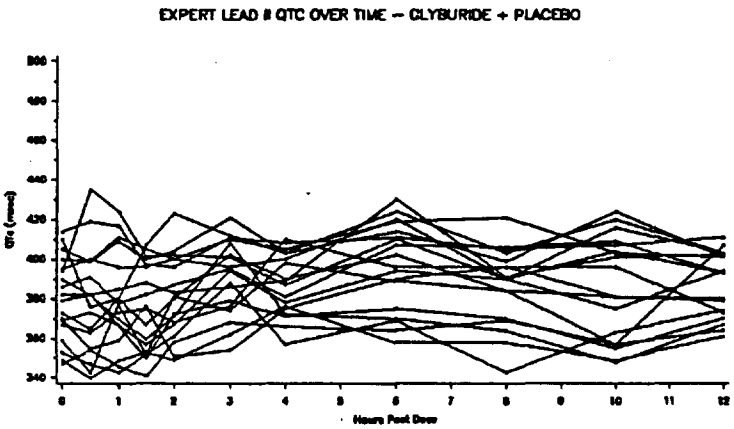


Figure 4:



CONCLUSIONS: The concomitant administration of glyburide had no effect on the pharmacokinetic parameters of dofetilide, including its renal excretion. In addition, no statistically significant differences were found in comparing the QTc intervals (by AUECτ and Emax) for dofetilide + glyburide versus dofetilide + placebo. A statistically significant increase in the QTc interval was found when comparing dofetilide + glyburide versus glyburide + placebo. Plasma concentrations of dofetilide appeared to be linearly related to QTc prolongation. Coadministration of glyburide and dofetilide did not result in a change in the dofetilide plasma concentration QTc relationship. In summary, concomitant administration of 5mg glyburide with 500mcg dofetilide did not affect the pharmacokinetics or pharmacodynamics of dofetilide.

RENAL IMPAIRMENT STUDY

STUDY 115-219 **VOLUME**: 1.28

INVESTIGATOR AND LOCATION:

STUDY DATE: September 1993 - April 1994

RATIONALE: The pharmacokinetics of dofetilide indicate that over 60% of the drug is excreted unchanged via the kidneys, but it is not known if there is a similar reduction in drug clearance with progressive renal impairment. This study was designed as a pilot investigation to assess the pharmacokinetics and pharmacodynamics in renally impaired patients in order to optimise the design of a more extensive study (115-400).

Study Objective: This pilot study was designed to assess the inter-subject variability in pharmacokinetics and pharmacodynamics of a single, oral dose (500mcg) of dofetilide in patients with impaired renal function and to examine safety and toleration in this population.

Drug Administration:
Dofetilide capsules: 500mcg, FID 0964, Lot No.842-49,

STUDY DESIGN:
This was an open, pilot study to evaluate the influence of renal impairment on the pharmacokinetics, pharmacodynamics and safety of a single, 500mcg oral dose of dofetilide in six subjects with severe renal impairment (CLcr < 20ml/min but no dialysis) and five with moderate impairment (CLcr 20-40ml/min). Blood samples (4ml) were collected before dosing, then at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 18, 24, 36, 48, 72 and 96 hours after dosing. Total urine output was collected during the periods 0-24, 24-48, 48-72, and 72-96
hours after dosing,

ASSAYS:

DATA ANALYSIS:

AUC, Cmax, Tmax, CL/F and Kel and QTc were computed. Data from this study were compared with those from Studies 244 and 229 which were conducted with normal, healthy subjects.

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

Table 1:

Mean (SD) pharmacokinetic parameters for dofetilide in normal male subjects (study 115-244) and subjects with moderate (CLcr 20-40 ml/min) and severe (CLcr <20 ml/min) renal impairment given a single oral 500 mcg dose of dofetilide.

Parameter	n	Normal	n	Moderate	n	Severe
Cmax (ng/ml)	18	1.97 (0.45)	5	2.69 (0.62)	6	3.11 (0.64)
Tmax (h)	18	3.1 (1.7)	5	3.3 (1.3)	6	4.5 (2.1)
AUC_t (ng.h/ml)	18	21.7 (3.5)	5	65.9 (14.8)	6	105.4 (19.6)
AUC (ng.h/ml)	15	23.5 (3.6)	5	69.5 (15.4)	5	116.7 (24.2)
Kel (h^{-1})	15	0.0708 (0.0132)	5	0.0320 (0.0067)	5	0.0220 (0.0026)
$t_{\frac{1}{2}}$ (h)	18	9.8	5	21.7	6	31.5
CL/f (L/h)	15	21.7 (3.2)	5	7.6 (1.7)	5	4.5 (1.3)
Vd/f (L)	15	311.8 (49.1)	5	251.1 (110.2)	6	205.2 (37.7)
CLcr (ml/min)	15	107.3 (21.6)	5	34.1 (4.0)	6	12.5 (3.3)
CLr (L/h)		-	5	2.0 (0.4)	6	0.8 (0.3)
Amount renally excreted (% dose)		-	5	26.4 (8.3)	6	17.0 (6.1)

Table 2:
Mean (SD) change from baseline QTc values in normal male subjects (study 115-229) and subjects with moderate (CLcr 20-40 ml/min) and severe (CLcr <20 ml/min) renal impairment given a single oral 500 mcg dose of dofetilide.

Parameter	n	Normal	n	Moderate	n	Severe
QTc max (msec)	6	50 (13)	5	57 (25)	6	52 (17)
QTc 12 hours (msec)	7	7 (14)	5	19 (23)	6	32 (18)
Slope (msec/ng/ml)	7	15.6 (2.4)	5	20.9 (12.5)	4	18.7 (3.3)

Table 3: Dofetilide free fraction in plasma from volunteers and renally impaired patients measured by equilibrium dialysis and ultrafiltration

Patient group	Ultrafiltration			Eqm Dialysis		
	Mean	SD	n	Mean	SD	n
Normal	0.197	0.030	7	0.337	0.021	7
Moderate renal failure	0.175	0.035	4	0.249	0.031	4
Severe renal failure	0.181	0.007	5	0.269	0.065	5

Table 4: Dofetilide free fraction in control human plasma with and without added alpha-1 -acid glycoprotein (AAG)

	Mean	SD	n
+ AAG	0.273	0.041	5
- AAG	0.259	0.033	5

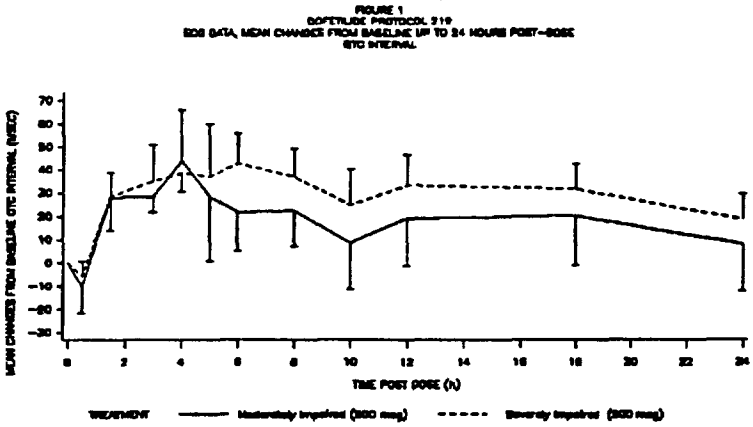


Figure 2:

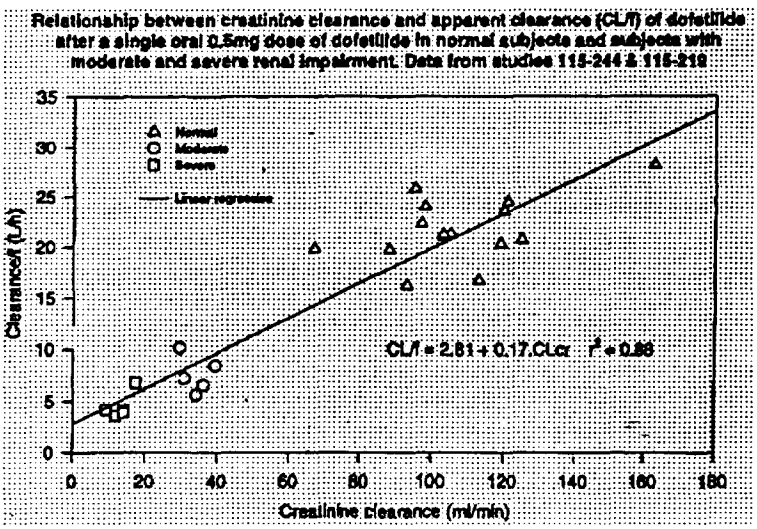


Figure 3:

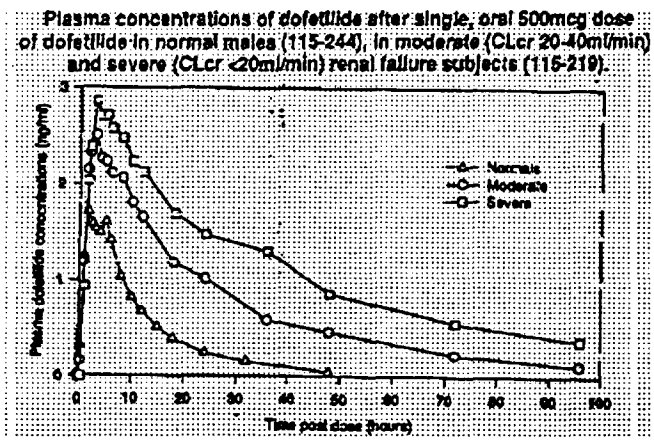
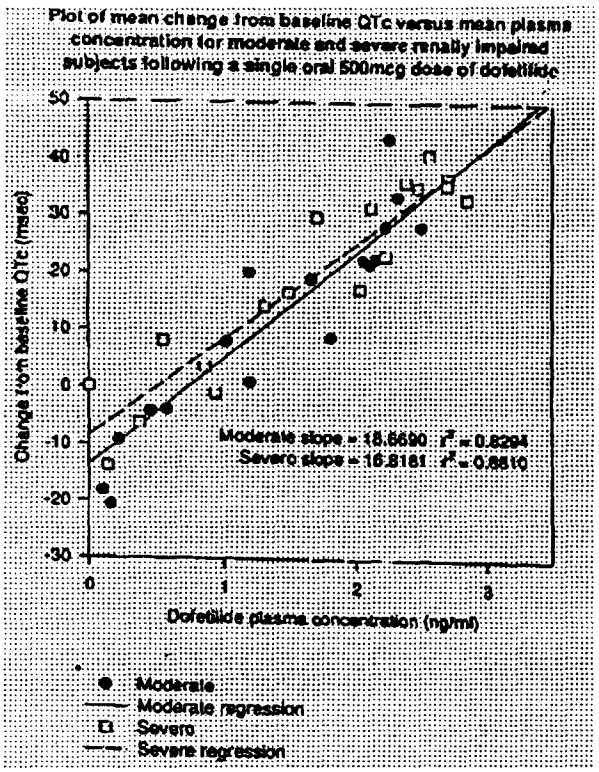


Figure 4:



Conclusions: Comparison of the pharmacokinetic data from this study with those from a normal population (Study 244) indicated that there was increased exposure to, and reduced apparent clearance of dofetilide in this patient population. The decrease in apparent clearance was greater than would be predicted and may have been due to a concomitant unexplained decrease in metabolic clearance. It was noted that the apparent clearance was proportional to creatinine clearance. Using these data, it was predicted that exposure would fall within normal limits by halving the dose or doubling the dose interval for those patients whose creatinine clearance fell within the range 20 - 40ml/min, with further, similar dosing changes for patients with lower clearance.
The maximum increase in QTc was not different between subjects with renal impairment and a normal population (Study 229), but the time to, and recovery from the maximum effect was extended in the patient population. Thus, the slope of increases from baseline in QTc with plasma concentrations of dofetilide were essentially similar to those of the normal population.
The increasing exposure to dofetilide with renal impairment was supported by the linear relationship between the apparent clearance of dofetilide and creatinine clearance (Figure 2). The apparent clearance of dofetilide gave a linear relationship with creatinine clearance (Figure 2), which fitted the equation:
$CL/f = 2.81 + 0.17.CLcr$, with $r^2 = 0.88$

In subjects with renal impairment it was expected that clearance would be reduced by approximately 60% of normal and not the 3- and 5-fold levels observed. The most likely reason for the magnitude of the reduction in clearance in the renally impaired subjects is that non-renal (metabolic) clearance is diminished along with renal clearance. Protein binding may be altered with renal impairment (elevated levels of alpha-1-acid glycoprotein), but dofetilide is only 65% protein bound so protein binding is unlikely to account for the effect and there is essentially no difference in the protein binding of dofetilide in normal and renally impaired patients (Table 3).

The pharmacodynamic activity of dofetilide in renally impaired subjects appeared to be similar to normal subjects. Although the maximum QTc was similar, the QTc at 12 hours post-dose was higher in the renally impaired patients than in the normals. The slope of the linear regression for each subject of the plasma concentration versus QTc relationship appeared to be similar for normal subjects and renally impaired subjects (in two subjects the slope was not well estimated). Thus, the increase in plasma concentrations of dofetilde in renally impaired patients would be expected to be mirrored by an increase in QTc. Therefore, on the basis of the pharmacokinetics, a reduction of dose and/or lengthening of dosing interval would be indicated in renally impaired subjects.

RENAL IMPAIRMENT STUDY

STUDY 115-400 Diamond RI **VOLUME: 2.72**

INVESTIGATOR AND LOCATION:

STUDY DATE: Jan 1995 to Jan 1996

RATIONALE: The pharmacokinetics of dofetilide indicate that over 60% of the drug is excreted unchanged via the kidneys, Study 219 had also indicated that decreased renal function alone did not account for the total decrease in drug clearance, implying that there was a concomitant decrease in non-renal clearance with renal impairment. Patients with heart failure and renal failure have been shown to have increased alpha-1-acid glycoprotein. A further increase in protein binding with this underlying disease could reduce the volume of distribution and may cause a decrease in non-renal clearance. DIAMOND RI provided the opportunity to examine protein binding in this population. Renal failure is intimately linked to cardiac disease and, based on these earlier studies with dofetilide, individual dosing in the DIAMOND studies was adjusted according to calculated values of creatinine clearance, on entry and during the study.

Study Objective: The primary objectives were to define the pharmacokinetics and protein binding of dofetilide in subjects with normal and impaired renal function, here defined by reduced CLcr, who were selected from the overall population recruited to the two main DIAMOND studies. The secondary objective was to evaluate whether any relationship between plasma concentrations of dofetilide and pharmacodynamic data, as indicated changes in QT/QTc could be identified.

Drug Administration:
Dosage Form Dofetilide, 250mcg oral capsules (FID S00114AB Lot 2833-130 and FID2958-069X, Lot 2833-183), and placebo as matching oral capsules (FID S00117AA, Lot 2833-122 and FID S00117AA, Lot 2968-078).

Dosing: 500mcg bid (normal function), 250mcg bid (mild impairment) 250mcg od (moderate impairment) unless adjusted for QTc intervals beyond prescribed limits or adverse events.
Duration One day within the duration of the primary studies.

STUDY DESIGN:
As part of the primary studies, subjects with normal renal function were randomised to dofetilide 500mcg bid or matched placebo capsules bid. Subjects with mild renal function had their dose adjusted to 250mcg bid and those with moderate renal failure received 250mcg od. Further dose adjustments were also made for subjects with AF/AFl, those with prolongation of QTc beyond recommended limits and those who experienced adverse or other events on their initial regimen which the investigator considered warranted a lower dose.

A sub-population from the primary studies of DIAMOND CHF and MI, who were taking randomised treatment for at least one month and whose renal function was defined by creatinine clearance (CLcr) levels as normal (CLcr > 60ml/min), mildly impaired (> 40- < 60ml/min) or moderately impaired (> 20- < 40ml/min) provided blood and urine samples across a dose interval to measure concentrations of dofetilide. QT/QTc intervals were measured throughout. On the assessment day, blood samples (4 ml) were collected at 0, (pre-dose) 1, 2, 3, 4, 5, 6, 8, 10 and 12 hours after dosing to measure concentrations of dofetilide. Subjects receiving the od regimen were also required to provide a further sample at 24h post dose. In addition, a second pre-dose blood sample was required to provide 3ml plasma to measure protein binding .Urine output was collected over 12 hourly periods across the dose interval.

ASSAYS:

DATA ANALYSIS:
AUC, Cmax, Tmax, CL/F and CLr and QTc were computed. Data from this study were compared with those from Studies 244 and 229 which were conducted with normal, healthy subjects.

RESULTS: Tables 1-10 and Figures 1-4 summarize the pharmacokinetic and pharmacodynamic data obtained from the study.

Table 1:

DOFETILIDE PROTOCOL 400 - DIAMOND RENAL IMPAIRMENT SUB-STUDY
DOSE ADJUSTMENT SUMMARY: EVALUABLE POPULATION

	DOFETILIDE MILD IMPAIRMENT	DOFETILIDE MODERATE IMPAIRMENT	DOFETILIDE NORMAL RENAL FUNCTION
Number of subjects:	11	11	10
0.50 bid	0	0	7 (70.0)
0.25 bid	9 (81.8)	0	3 (30.0)
0.25 od	2 (18.2)	11 (100.0)	0

Table 2:

DOFETILIDE PROTOCOL 400 - DIAMOND RENAL IMPAIRMENT SUB-STUDY
QTC SUMMARY: EVALUABLE POPULATION

DAY *		DOFETILIDE MILD IMPAIRMENT	DOFETILIDE MODERATE IMPAIRMENT	DOFETILIDE NORMAL RENAL FUNCTION
Day 1	Arithmetic Mean	402.1	415.7	421.2
	Std. Dev.	52.8	32.2	27.2
	N	8	6	6
	Range	301-448	375-459	387-460
	Missing	3	5	4
Day 1 ^	Arithmetic Mean	420.7	418.1	490.9
	Std. Dev.	54.8	39.0	72.1
	N	10	8	8
	Range	337-512	357-481	404-626
	Missing	1	3	2
Day 2 ^	Arithmetic Mean	433.8	425.5	437.1
	Std. Dev.	63.2	41.1	43.0
	N	9	8	7
	Range	346-529	366-493	386-515
	Missing	2	3	3
Day 4 ^	Arithmetic Mean	427.8	421.0	450.1
	Std. Dev.	68.5	40.9	30.6
	N	9	6	7
	Range	318-517	364-486	421-505
	Missing	2	5	3

* Day relative to start of study therapy (day 1)
^ ECG taken 2-4 hours post dose

Table 3:

Patients classified as having normal renal function (creatinine clearance >60 ml/minute)

A) 250 mcg bid

Parameter	Patient/Rekv. No./Centre number			Mean	sd
	689 2999 168	927 2949 172	3269 2935 172		
C_{max} (ng/ml)	1.77	1.38	2.24	1.80	0.43
T_{max} (hours)	10	12	3	8.3	4.7
AUC_t (ng.h/ml)	13.3	9.8	15.5	12.9	2.9
CL/F (L/h)	18.8	25.5	16.1	20.1	4.8
CL_r (L/h)	11.4	14.8'	7.5'	11.2	3.6

Table 4:

Patients classified as having normal renal function (creatinine clearance >60 ml/minute)

B) 500 mcg bid

Parameter	Patient/Rekv. No./Centre number							Mean	sd
	1014 2983 168	1018 2993 168	1435 9595 168	1439 9591 168	928 2957 172	932 2951 172	3267 2968 172		
C_{max} (ng/ml)	2.11	2.61	3.06	6.22	3.20	3.86	3.73	3.54	1.33
T_{max} (hours)	2	2	1	1	1	2	3	1.7	0.8
AUC_t (ng.h/ml)	17.0	21.0	19.6	34.6	25.5	29.6	32.5	25.7	6.8
CL/F (L/h)	29.4	23.8	25.5	14.5	19.6	16.9	15.4	20.7	5.7
CL_r (L/h)	18.4	16.4	12.9	8.7	12.8'	13.3'	9.8'	13.2	3.4

Table 5:

Patients classified as having mild renal impairment (creatinine clearance >40 - 60 ml/minute)

A) 250 mcg bid

Parameter	Patient/Rekv. No./Centre number									Mean	sd
	1009 2988 168	1013 2979 168	1205 2989 168	3453 2980 168	1136 2973 172	1235 9485 172	3402 6879 172	3574 6877 172	3575 2972 172		
C_{max} (ng/ml)	3.40	2.14	1.81	1.66	2.41	2.10	2.37	3.09	3.60	2.51	0.69
T_{max} (hours)	1	5	3	1	2	2	3	1	2	2.2	1.3
AUC, (ng.h/ml)	18.4	20.5	15.2	15.8	22.6	15.6	21.2	25.2	31.7	20.7	5.4
CL/F (L/h)	13.6	12.2	16.4	15.8	11.1	16.0	11.8	9.9	7.9	12.7	3.0
CL_r (L/h)	a	4.7	7.1	7.0	a	8.7[b]	7.6[b]	7.9[b]	4.5[b]	6.8	1.6

Table 6:

Pharmacokinetic parameters of dofetilide in patients with reduced systolic left ventricular function and congestive heart failure and/or recent myocardial infarction after repeated oral doses of 250 mcg od (τ = 24 hours)

Patients classified as having moderate renal impairment (creatinine clearance 20 - 40 ml/minute)

Parameter	Patient/Rekv. No./Centre number										Mean	sd
	1212 2981 168	3461 2986 168	1131 2966 172	1227 2967 172	1231 6881 172	1358 9416 172	2928 7376 172	3264 2950 172	3397 2954 172	3578 7379 172	3666 9489 172	
C_{max} (ng/ml)	3.13	1.88	2.34	2.31	3.23	1.64	1.64	1.77	2.11	1.82	1.87	2.16	0.56
T_{max} (hours)	2	4	2	2	1	3	4	6	1	2	3	2.7	1.5
AUC, (ng.h/ml)	a	28.7	35.0	26.3	31.8	23.3	30.8	25.3	32.7	27.8	26.4	28.7	3.6
CL/F (L/h)	b	8.7	7.1	9.5	7.9	10.7	8.3	9.9	7.6	9.0	9.5	8.8	1.1
CL_r (L/h)	b	2.8	4.4[c]	5.7[c]	4.1[c]	5.7	5.1	d	3.8[c]	4.5	4.1[c]	4.4	0.9

Table 7:

Concentrations and amounts of dofetilide excreted unchanged in urine of patients with reduced systolic left ventricular function and congestive heart failure and/or recent myocardial infarction during a dosage interval after repeated oral doses of either 250 or 500 mcg bid

Patients classified as having normal renal function (creatinine clearance >60 ml/minute)

A) 250 mcg bid

Dofetilide excreted in urine	Patient/Rekv. No./Centre number			Mean	sd
	689 2999 168	927 2949 172	3269 2955 172		
Concentration (ng/ml)	72.0	99.1	89.3	-	-
Amount (mcg)	151	145	116	137	19
Percent of dose (%)	60.4	58.0	46.4	54.9	7.5

Table 8:

Concentrations and amounts of dofetilide excreted unchanged in urine of patients with reduced systolic left ventricular function and congestive heart failure and/or recent myocardial infarction during a dosage interval after repeated oral doses of either 250 or 500 mcg bid

Patients classified as having normal renal function (creatinine clearance >60 ml/minute)

B) 500 mcg bid

Dofetilide excreted in urine	Patient/Relv. No./Centre number							Mean	sd
	1014 2983 168	1018 2993 168	1435 9595 168	1439 9591 168	928 2957 172	932 2951 172	3267 2968 172		
Concentration (ng/ml)	391.0	362.0	101.0	229.0	181.0	262.0	398.0	-	-
Amount (mcg)	313	344	253	300	326	393	318	321	45
Percent of dose (%)	62.6	68.8	50.6	60.0	65.2	78.6	63.6	64.2	8.5

Table 9:

Concentrations and amounts of dofetilide excreted unchanged in urine of patients with reduced systolic left ventricular function and congestive heart failure and/or recent myocardial infarction during a dosage interval after repeated oral doses of 250 mcg, either bid or od

Patients classified as having mild renal impairment (creatinine clearance >40 - 60 ml/minute)

A) 250 mcg bid

Dofetilide excreted in urine	Patient/Relv. No./Centre number									Mean	sd
	1009 2988 168	1013 2979 168	1205 2989 168	3453 2980 168	1136 2973 172	1235 9485 172	3402 6879 172	3574 6877 172	3575 2972 172		
Concentration (ng/ml)	106.0	78.4	132.0	163.0	62.1	88.0	80.5	154.0	131.0	-	-
Amount (mcg)	196[a]	96	108	110	155[a]	136	161	200	144	136	36
Percent of dose (%)	39.2	38.4	43.2	44.0	31.0	54.4	64.4	80.0	57.6	50.2	15.3

Table 10;

Concentrations and amounts of dofetilide excreted unchanged in urine of patients with reduced systolic left ventricular function and congestive heart failure and/or recent myocardial infarction during a dosage interval after repeated oral doses of 250 mcg od

Patients classified as having moderate renal impairment (creatinine clearance 20 - 40 ml/minute)

Dofetilide excreted in urine	Patient/Relv. No./Centre number										Mean	sd
	1212 2981 168	3461 2986 168	1131 2966 172	1227 2967 172	1231 6881 172	1358 9486 172	2928 7376 172	3264 2930 172	3397 2934 172	3578 7379 172	3666 9489 172		
Concentration (ng/ml)	162.0	24.3	54.0	71.5	72.1	41.4	90.1	75.1	37.4	38.7	46.5	-	-
Amount (mcg)	97[a]	80	154	150	130	132	153	23[b]	123	124	107	128	24
Percent of dose (%)	38.8[a]	32.0	61.6	60.0	52.0	52.8	61.2	9.2[b]	49.2	49.6	42.8	51.2	9.6

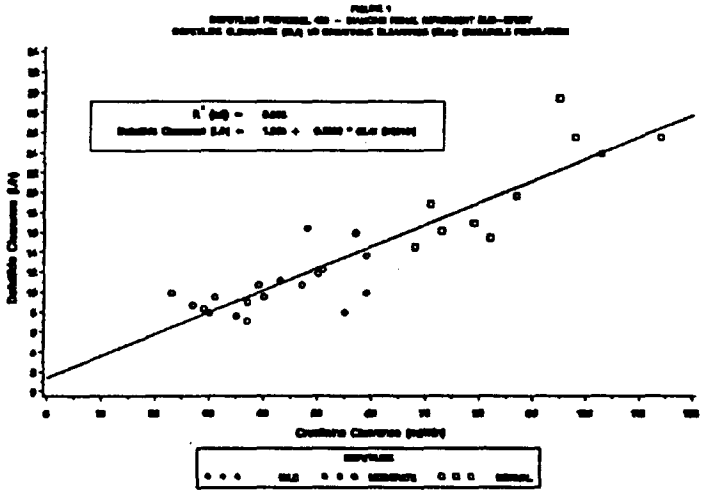


Figure 3:

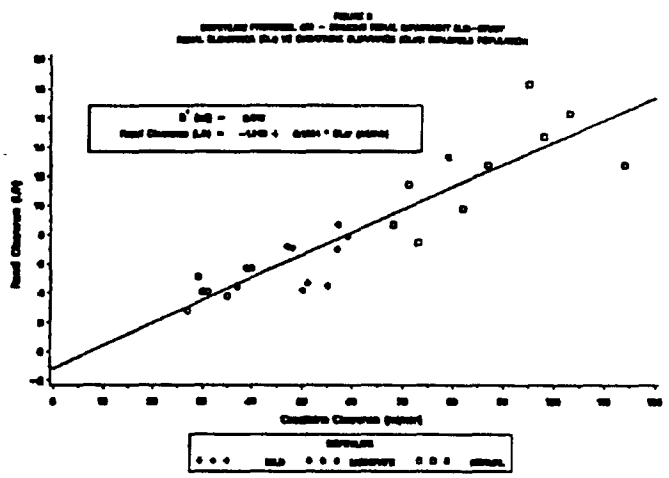
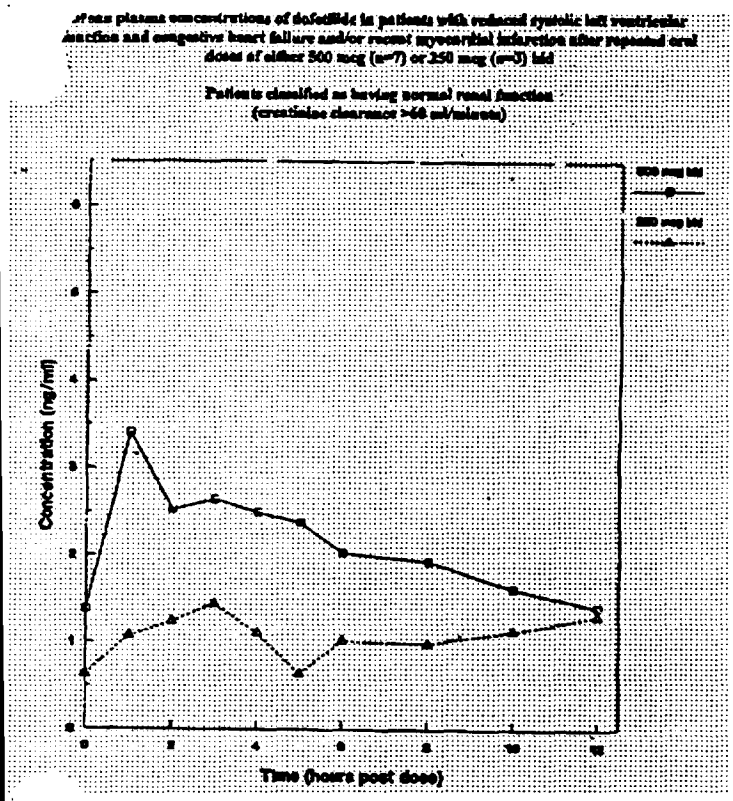
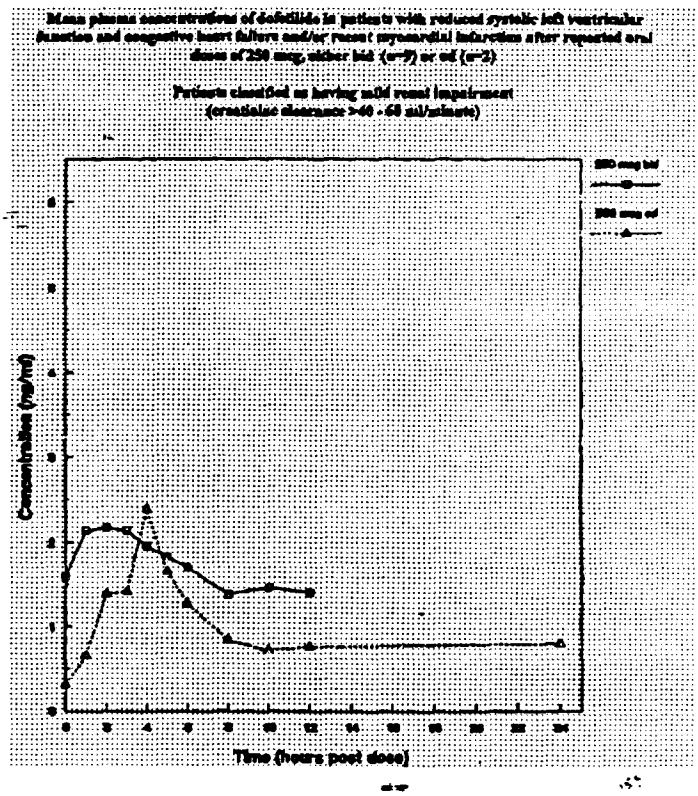


Figure 4:





CONCLUSIONS

There was a direct relationship between CLr and CLcr and between dofetilide clearance and CLcr. The ratio between dofetilide clearance and CLcr in this study (0.22x; Figure 1) was similar to that identified in Study 219 (0.17x) indicating that the relationship does not change with either chronic dosing or with a seriously ill population. Dose adjustments based on calculated levels of CLcr successfully reduced exposure to dofetilide in subjects from a population with mild and moderate renal impairment from what would be anticipated for a standard clinical dose.

As previously observed in Study 115-219, the protein binding of dofetilide in normal patients (62.9 ±5.9) is similar to that in mild renally impaired patients (65.0±13.1) or moderately renally impaired patients (68.0±8.1).

A cross-study comparison of Cmax and AUC in this population of patients with those in normal volunteers (Studies 115-004, 115-007, 115-011, 115-255) shows that dofetilide exposure is significantly higher in subjects with impaired renal function. Renal and oral clearance of dofetilide are also significantly reduced in this population of patients. Therefore, on the basis of the pharmacokinetics, a reduction of dose and/or lengthening of dosing interval would be indicated in renally impaired subjects.

HEPATIC IMPAIRMENT STUDY

STUDY 115-002 **VOLUME:** 1.27

INVESTIGATOR AND LOCATION:

STUDY DATE: June 1993 - October 1995

RATIONALE: Hepatic impairment may modify the pharmacokinetics and pharmacodynamics of drugs, especially those that undergo extensive metabolism. The absolute bioavailability of dofetilide is over 90%, suggesting limited presystemic metabolism. However, the apparent linear relationship between concentration and QTc prolongation, and between dose and concentration, that are seen in studies in healthy volunteers suggests that dofetilide's adverse effects, which are dose-dependent, may be concentration-related. In young, normal volunteers, approximately 30% of a given dose of dofetilide is excreted via non-renal routes after metabolism. Consequently, hepatic impairment could influence the disposition and pharmacodynamics of a drug with dofetilide's characteristics. It is therefore important to determine the pharmacokinetics and pharmacodynamics of dofetilide in a population of hepatically impaired patients following single and multiple doses.

Study Objective: To determine the pharmacokinetics and pharmacodynamics of dofetilide in patients with chronic stable hepatic impairment following single and multiple doses. In addition, to determine the effect of hepatic impairment on these parameters by comparison of the pharmacokinetic and pharmacodynamic profile of dofetilide in patients with chronic stable hepatic impairment with those of an age and sex-matched healthy group.

Drug Administration:
Dosage Form: Dofetilide capsules: 500mcg, FID# 0964, Lot No. 503-20
Dofetilide capsules: 250mcg, FID# 0963, Lot No. 842-33
Dosing: Single dose phase: Dofetilide, 500mcg on Day 1. Subjects in either group who tolerated this dose began the multiple dosing phase after a drug-free period of at least three days.
Multiple dosing phase: Dofetilide, 500mcg bid (q.12h) daily for 7 days (days 5 - 11). Only the AM dose was given on Day 11.
One subject was titrated downward to 250mcg dofetilide and restudied after a drug free interval of 20 days.

STUDY DESIGN:
This was an open, non-randomized, parallel group, single and multi-dose (7 days) study to compare dofetilide pharmacokinetics and pharmacodynamics in subjects with normal hepatic function, to subjects with chronic hepatic impairment. For the single dose phase of the study dofetilide was administered in the morning of day 1 and for the multi-dose phase of the study dofetilide was administered twice a day on days 5-10. Only the morning dose was administered on day 11. No study drug was administered on

days 2-4. Measurements of dofetilide pharmacokinetics and pharmacodynamics were taken following the morning administration of the study drug on day 1 and day 11. Dofetilide plasma concentrations were monitored on days 1 and 11 at 0 (just prior to dosing), and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, 48 and 72 hours after study drug administration. For the estimation of trough plasma concentrations, dofetilide plasma concentrations were also monitored on days 8, 9, and 10. Urine dofetilide concentrations were obtained from urine collected and pooled during the 24 hours following the morning administration of dofetilide on day 1 and day 11. Also on Days 1 and 11, Lead II ECG Rhythm Strips (analyzed by the investigator) were obtained at 0 (just prior to study drug administration), and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, and 24 hours after morning dosing.

ASSAYS:

DATA ANALYSIS:
AUC, Cmax, Tmax, Kel, T1/2, CLr and accumulation ratio R were calculated.

RESULTS: Tables 1-2 and Figures 1-5 summarize the pharmacokinetic and pharmacodynamic data obtained from the study.

Table 1:

ANALYSIS OF PHARMACOKINETIC PARAMETERS SUMMARY

Pharmacokinetic Parameter	Comparison				90% Confidence Limits
		Adjusted Geometric Means		Ratio	
Day 1					
AUCt (ng.h/ml)	HI (Class B) vs. HI (Class A)	12.65	vs. 16.50	87.2%	(71.5%, 106.6%)
	HI (All Subjects) vs. HE	19.54	vs. 16.07	96.2%	(78.0%, 120.7%)
Cmax (ng/ml)	HI (Class B) vs. HI (Class A)	1.79	vs. 1.93	92.8%	(73.2%, 115.6%)
	HI (All Subjects) vs. HE	1.87	vs. 1.86	100.5%	(72.0%, 140.2%)
		Adjusted Arithmetic Means		Difference	
Tmax (h)	HI (Class B) vs. HI (Class A)	2.10	vs. 2.94	0.16	(-1.31, 1.64)
	HI (All Subjects) vs. HE	2.02	vs. 2.38	0.64	(-1.44, 2.74)
Kel (/h)	HI (Class B) vs. HI (Class A)	0.0985	vs. 0.0802	0.0089	(-0.0119, 0.0293)
	HI (All Subjects) vs. HE	0.0843	vs. 0.0786	0.0057	(-0.0230, 0.0345)
Clr (ml/min)	HI (Class B) vs. HI (Class A)	169.83	vs. 217.95	51.88	(-38.80, 142.55)
	HI (All Subjects) vs. HE	243.89	vs. 226.13	17.76	(-112.59, 168.11)
Day 11					
AUCt (ng.h/ml)	HI (Class B) vs. HI (Class A)	20.11	vs. 24.89	80.8%	(45.1%, 145.0%)
	HI (All Subjects) vs. HE	22.37	vs. 20.33	110.6%	(68.7%, 251.1%)
Cmax (ng/ml)	HI (Class B) vs. HI (Class A)	2.56	vs. 2.10	81.7%	(44.9%, 152.7%)
	HI (All Subjects) vs. HE	2.82	vs. 2.67	105.9%	(44.6%, 248.8%)
		Adjusted Arithmetic Means		Difference	
Tmax (h)	HI (Class B) vs. HI (Class A)	1.63	vs. 1.94	-0.31	(-1.71, 1.09)
	HI (All Subjects) vs. HE	1.78	vs. 2.04	-0.26	(-2.19, 1.67)
Kel (/h)	HI (Class B) vs. HI (Class A)	0.0683	vs. 0.0731	-0.0048	(-0.0245, 0.0110)
	HI (All Subjects) vs. HE	0.0717	vs. 0.0631	0.0086	(-0.0159, 0.0330)
Clr (ml/min)	HI (Class B) vs. HI (Class A)	126.00	vs. 247.78	-123.78	(-200.25, -47.30)
	HI (Class B) vs. HE	126.00	vs. 219.20	-93.20	(-168.11, -22.29)
	HI (Class A) vs. HE	247.78	vs. 219.20	28.58	(-29.65, 86.60)
	HI (All Subjects) vs. HE	185.89	vs. 219.20	-33.31	(-160.66, 74.01)

Table 2:

ANALYSIS OF PHARMACODYNAMIC PARAMETERS SUMMARY - LEAD II QTC

Pharmacodynamic Parameter	Comparison			95% Confidence Limits
		Adjusted Arithmetic Means	Difference	
Day 1				
AUECt (msec.h)	HI (Class B) vs. HI (Class A)	262.43	vs. 247.14	-84.71	(-317.39, 157.98)
	HI (All Subjects) vs. HE	304.80	vs. 253.89	50.92	(-302.36, 404.17)
Emax (msec)	HI (Class B) vs. HI (Class A)	54.10	vs. 58.00	-3.88	(-27.43, 19.82)
	HI (All Subjects) vs. HE	54.10	vs. 52.17	3.83	(-30.57, 38.22)
Day 11					
AUECt (msec.h)	HI (Class B) vs. HI (Class A)	191.05	vs. 157.56	33.49	(-284.64, 291.61)
	HI (All Subjects) vs. HE	174.31	vs. 167.36	6.94	(-366.80, 382.68)
Emax (msec)	HI (Class B) vs. HI (Class A)	64.00	vs. 45.50	18.50	(-11.06, 48.06)
	HI (All Subjects) vs. HE	54.75	vs. 40.82	13.93	(-29.07, 54.94)

HI = Hepatically impaired

HE = Healthy Subjects