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Effect of Fluoxetine on Carvedilol Pharmacokinetics, CYP2D6 Activity, and Autonomic Balance in Heart Failure Patients

Donald W. Graff, PharmD, Kristin M. Williamson, PharmD, John A. Pieper, PharmD, Stanley W. Carson, PharmD, Kirkwood F. Adams, Jr., MD, Wayne E. Cascio, MD, and J. Herbert Patterson, PharmD

The objective of this study was to examine the pharmacokinetic and pharmacodynamic consequences of concomitant administration of fluoxetine and carvedilol in heart failure patients. Fluoxetine (20 mg) or matching placebo was administered in a randomized, double-blind, two-period crossover study to 10 patients previously identified as extensive metabolizers of CYP2D6 substrates. Patients were maintained on a carvedilol dose of 25 or 50 mg bid and given fluoxetine/placebo for a minimum of 28 days. Plasma was collected over the 12-hour carvedilol dosing interval, and the concentrations of the R(+) and S(-) enantiomers of carvedilol were measured. CYP2D6 phenotype was assessed during each study period using dextromethorphan (30 mg). Changes in autonomic modulation between study periods were measured by heart rate variability in the time and frequency domains using ambulatory electrocardiographic monitoring. Compared to placebo, fluoxetine coadministration resulted

in a 77% increase in mean (\pm SD) R(+) enantiomer AUC_{0-12} (522 ± 413 vs. 927 ± 506 ng•h/mL, $p = 0.01$) and a nonsignificant increase in S(-) enantiomer AUC (244 ± 185 vs. 330 ± 179 ng•h/mL, $p = 0.17$). Mean apparent oral clearance for both enantiomers decreased significantly with fluoxetine administration (R(+): 10.3 ± 7.2 vs. 4.5 ± 2.2 mL/min/kg; S(-): 22.5 ± 12.3 vs. 12.6 ± 7.4 mL/min/kg; $p = 0.004$ and 0.03 , respectively). No differences in adverse effects, blood pressure, or heart rate were noted between treatment groups, and there were no consistent changes in heart rate variability parameters. In conclusion, fluoxetine administration resulted in a stereospecific inhibition of carvedilol metabolism, with the R(+) enantiomer increasing to a greater extent than the S(-) enantiomer. However, this interaction was of little clinical significance in our sample population.

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Beta-blockers are rapidly becoming a standard of practice for the treatment of heart failure in selected patient populations.¹ Meta-analysis of randomized clinical trials shows that beta-blockers reduce mortality in heart failure by 30% to 35% when added

to conventional therapy.²⁻⁴ These findings have recently been confirmed by two additional clinical trials, CIBIS II and MERIT-HF.^{5,6} Beta-blockers are thought to blunt the effects of long-term sympathetic nervous system activation such as beta-receptor down-regulation, renin-angiotensin system activation, and vasoconstriction.

Carvedilol (Coreg[®]) is currently the only beta-blocker approved by the Food and Drug Administration (FDA) as adjunctive therapy in the treatment of heart failure. It is administered orally as a racemic mixture (50:50 mixture of the R(+) and S(-) enantiomers) at a target dose of 25 mg twice daily (body weight \leq 85 kg) and is extensively metabolized in the liver by numerous cytochromes P450 (CYP) in a stereoselective manner.⁷ R(+) carvedilol is primarily metabolized by CYP2D6 and CYP2C9, while S(-) carvedilol is predom-

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inantly metabolized by CYP2C9 and, to a lesser extent, by CYP2D6.⁸ Other CYP isozymes involved in the metabolism of carvedilol include 1A2, 3A4, 2E1, and 2C19.⁸

Limited data have been published on the disposition of carvedilol in patients with heart failure. It has been reported in abstract form that the AUC of the R enantiomer is approximately 2 to 2.5 times the AUC of the S enantiomer in patients with New York Heart Association (NYHA) class III-IV heart failure.⁹ Consistent with these findings is the report that the oral clearance of the S enantiomer was found to be approximately twice that of the R enantiomer in a population pharmacokinetic study in patients with NYHA class II-IV heart failure.¹⁰ Understanding the pharmacokinetics of the enantiomers of carvedilol has potential clinical importance as carvedilol has a mixed adrenergic blocking profile and exhibits stereospecific pharmacodynamic properties. The enantiomers have equipotent α_1 -blocking activity, while the S(-) enantiomer alone possesses nonselective beta-blocking activity.¹¹ The vasodilating properties of carvedilol may enhance patient tolerability of the beta-blocking activity of the compound, especially in the early titration period of therapy. However, excessive blood pressure reductions may result in decreased tolerability and hypotensive events. Therefore, alterations in CYP2D6 and/or CYP2C9 activity by genetic polymorphisms or coadministered medications may alter the balance of the stereoselective pharmacodynamic response to carvedilol, thereby potentially compromising efficacy and patient safety.

Since there is a high incidence of depression in patients with cardiovascular disease, it is likely that carvedilol will be coadministered with antidepressant agents. Specifically, the selective serotonin reuptake inhibitors (SSRIs) are likely to be prescribed due to their favorable cardiovascular side effect profile in comparison to the tricyclic antidepressants.¹²⁻¹⁴ Fluoxetine (Prozac[®]) is currently one of the most widely dispensed SSRIs in the United States. When administered in daily doses of 20 to 60 mg, fluoxetine has been shown to effectively treat depression and a variety of other psychopathological conditions.¹⁵ Fluoxetine and its active metabolite, norfluoxetine, are potent inhibitors of CYP2D6 ($k_i = 0.6-1.4$ and $0.4-1.5$, respectively) and have inhibitory effects on CYP2C9 as well.¹⁶ There is added clinical relevance to this potential treatment based on studies showing that depression carries with it an elevated relative risk of cardiovascular death in patients with both depression and cardiovascular disease.¹⁷ Therefore, concomitant administration of these two agents should be examined in patients.

Largely due to its noninvasive nature, heart rate variability (HRV) is a widely used tool to assess autonomic regulation of heart rate.¹⁸ Through various methods of analysis, it is possible to determine sympathetic and parasympathetic influences to the sinus node. High-frequency variations are reflective of parasympathetic activity, while low-frequency variations are reflective of sympathetic and parasympathetic activity. The quantification of these variations may contribute to the understanding of the pathophysiology of heart failure and lead to the development of new therapies. Depressed HRV has been confirmed as a strong and independent predictor of mortality after myocardial infarction and has been associated with a poor prognosis in patients with heart failure.¹⁹⁻²² In addition, the use of beta-blockers in previous studies has been demonstrated to partially restore HRV in patients with heart failure and in post-MI patients.²³⁻²⁵

This study was performed to address the implications of changes in CYP450 isozyme activity by fluoxetine on the pharmacokinetics and the resulting pharmacodynamic effects of carvedilol. We assessed changes in the pharmacokinetic profile of R(+) and S(-) carvedilol, CYP2D6 phenotype, and pharmacodynamic effects (autonomic modulation as assessed by heart rate variability measurements and blood pressure) of carvedilol when coadministered with fluoxetine or placebo.

METHODS

Study Subjects

Patients were recruited from the University of North Carolina Heart Failure Program for this study. Study entry requirements included stable heart failure, defined as no recent (within 3 months) deterioration of heart failure status (hospitalizations or significant worsening of symptoms); on a stable carvedilol dose for at least 3 months; no recent changes in heart failure treatment; and CYP2D6 extensive metabolizer phenotype (identified in a previous study using dextromethorphan as the metabolic probe). Patients were excluded if they were receiving CYP2D6 substrates or inhibitors, were being treated for depression, or were allergic or intolerant to any of the study medications. Women of childbearing potential were also excluded from the study. Consumption of alcohol within 72 hours or caffeine within 24 hours of phenotyping procedures was prohibited. All heart failure medications and doses were held constant throughout the study.

Study Protocol

This was a randomized, double-blind, placebo-controlled, two-period crossover study, approved by the Committee on the Protection of the Rights of Human Subjects of the University of North Carolina School of Medicine. Patients were screened in the General Clinical Research Center (GCRC) of the University of North Carolina School of Medicine for potential inclusion into the study. At this screening visit, the nature of the study was explained, and informed consent was obtained. A brief history and physical exam were performed to assess baseline symptoms, and the first dose of study medication (fluoxetine 20 mg once daily or matching placebo) was given. Following study medication administration, patients remained in the GCRC for 2 hours for safety purposes. During this time, blood pressure and heart rate were monitored every 30 minutes, and the patients were observed for signs of hypersensitivity to the study medication. On discharge from the GCRC, patients were given a supply of study medication with instructions for standardization of medication administration times (7 a.m. for fluoxetine/placebo, 7 a.m. and 7 p.m. for carvedilol). These procedures were performed prior to each study period.

During study period 1, the patients received study medication for a minimum of 28 days (range: 28-33 days) in addition to their standard daily medication regimen. Study period 1 was followed by a washout period of at least 28 days (range: 28-84 days). Patients then entered study period 2, in which they received the other study medication for a minimum of 28 days (range: 28-37 days).

Following each study period, patients were admitted to the GCRC on the evening prior to pharmacokinetic sampling (study day 1). On admission, a brief history and physical exam were performed to assess for changes in symptoms of heart failure, and a holter monitor was placed at 7 p.m. for 24-hour continuous electrocardiographic data. To assess CYP2D6 phenotype, the patients emptied their bladder, were administered 30 mg dextromethorphan (Robitussin Maximum Strength[®] cough syrup), and started a 24-hour urine collection. Patients were administered their evening dose of carvedilol at 7 p.m. and fasted after midnight except for water and medications until 11 a.m. on study day 2.

On the morning of study day 2, an intravenous catheter was placed for venous blood sampling. At 7 a.m., a blood sample was drawn and medications were administered. Blood sampling continued throughout study day 2 at 0.5, 1, 2, 4, 6, 8, 10, and 12 hours

following study medication and carvedilol administration. Plasma was separated and stored at -70°C until assayed. At 7 p.m. on study day 2, the patients emptied their bladder to complete the 24-hour urine collection, the holter monitor was removed, and the patient was discharged. Urine volume was recorded and aliquots were stored at -70°C until assayed. These procedures were followed during both study periods 1 and 2.

Analytical Procedures

Carvedilol assay. R(+) and S(-) carvedilol, as well as the internal standard, naftopidil, were supplied by Smith-Kline Beecham Pharmaceuticals. All chemicals used were analytical grade. Plasma concentrations of R(+) and S(-) carvedilol were quantified in a GLP analytical facility at the University of North Carolina School of Pharmacy with modifications of earlier methods.²⁶⁻²⁷ Plasma and the internal standard, naftopidil, were extracted with 8 M guanidine HCl using a solid-phase extraction technique. C₁₈ SFE cartridges (Analytichem International) were treated with elution solvent (3% triethylamine, 80% acetonitrile in water) and washed with wash solvent (35% acetonitrile in water). The sample was then applied to the columns and washed with wash solvent. Each column was treated with two aliquots of elution solvent, which were subsequently collected. Triethylamine and the derivatizing agent (2,3,4,6-tetra-Oacetyl- β -D-glucopyranosyl isothiocyanate in acetonitrile) were then added to each tube, and the derivatizing reaction was allowed to proceed for 30 minutes. An aliquot was injected onto a 4.6 \times 250 mm Econex Sil 5 C₁₈ 5 μm column (Phenomenex) using a mobile phase consisting of 67% methanol, 3% ethanol, and 30% (NH₄)₂HPO₄. Fluorescence emission was measured at 355 nm (excitation at 285 nm). The retention times for R(+) and S(-) carvedilol and naftopidil were approximately 9.7, 11.3, and 17.3 minutes, respectively. The lower limit of quantitation was 1 ng/mL for each enantiomer. The assay was specific for the carvedilol enantiomers, and there were no interferences observed when fluoxetine, norfluoxetine, or common cardiovascular agents were added to blank plasma. No interference was observed with any patient samples. Standards and samples were stable at -70°C for at least 1 year.

Dextromethorphan/dextrorphan assay. The urinary concentrations of dextromethorphan and its metabolite, dextrorphan, were quantified using HPLC with modifications of earlier methods.²⁸ Urine samples (0.5 mL) were incubated at 37 $^{\circ}\text{C}$ with 50 μl of a 10 mg/mL

solution of 6- β -glucuronidase for 18 hours. Internal standard (hydrocodone) and 2 N sodium hydroxide were then added to each sample. Samples were extracted with 10% N-butyl alcohol in chloroform, vortexed, and centrifuged. The organic phase was removed, allowed to evaporate under nitrogen at 37°C, and reconstituted with an acetate buffer. An aliquot was injected onto a 4.6 \times 250 mm Hypersil Silica 3 μ column (Keystone Scientific) with a Hypersil ODS C₁₈ guard column (Keystone Scientific) and eluted with a gradient mobile phase composed of 5% to 25% acetonitrile in a phosphate buffer, tetrabutyl ammonium hydrogen sulfate, and triethylamine. Fluorescence emission was measured at 330 nm (excitation at 225 nm) for detection of dextromethorphan, while ultraviolet absorbance (225 nm) was used to detect dextropropranolol and the internal standard. The retention times for dextromethorphan, dextropropranolol, and internal standard were approximately 28, 19, and 30 minutes, respectively. The lower limits of quantitation were 2.5 ng/mL for dextromethorphan and 100 ng/mL for dextropropranolol.

Fluoxetine/norfluoxetine assay. Plasma concentrations of fluoxetine and its metabolite, norfluoxetine, were quantified using HPLC with modifications of earlier methods.^{29,30} Internal standard (desipramine) and ammonium hydroxide were added to 250 μ L of plasma. Samples were extracted with 1 mL 10% isoamyl alcohol in hexane, vortexed, and centrifuged. The organic layer was separated and evaporated under a nitrogen bath at 37°C and reconstituted with mobile phase. An aliquot was injected onto a 4.6 \times 250 mm Hypersil Silica 3 μ column (Keystone Scientific). The mobile phase consisted of 0.5% ammonium hydroxide in acetonitrile. Ultraviolet absorbance (225 nm) was used to detect all compounds. The retention times for norfluoxetine, fluoxetine, and desipramine were approximately 6, 10, and 18 minutes, respectively. The lower limit of quantitation for fluoxetine and norfluoxetine was 20 ng/mL. The assay was specific for fluoxetine and norfluoxetine, and no interferences with the carvedilol enantiomers were found.

Heart rate variability assessment. For all subjects, 24-hour electrocardiograms were obtained with a Cardionostics holter monitor during moderately restricted, in-hospital activity. The recordings were analyzed on a Zymed holter system, which performed initial QRS labeling and editing by standard Zymed algorithms. An investigator blinded to the treatment randomization then reedited the electrocardiogram to ensure proper labeling of each QRS complex. Prema-

ture atrial and ventricular beats were labeled as abnormal and excluded, as were segments containing interfering noise. The remaining normal-to-normal (N-N) QRS intervals were then transferred to a second software program that downloaded the N-N files to a floppy disk for further analysis. Excluded intervals were replaced using an interpolation method. Recordings with > 15% ectopic beats or noise during the intervals of interest were excluded from analysis.

Standard time and frequency domain measures were calculated and reported as measures of autonomic balance. Time domain parameters included the standard deviation of all N-N intervals, the standard deviation of the averages of N-N intervals of all 5-minute intervals, and the square root of the mean of the sum of the squares of differences between adjacent N-N intervals. Frequency domain analysis was limited to 5-minute epochs at the carvedilol trough and peak times for each patient. Low, high, and total frequency bands were defined as 0.04 to 0.15, 0.15 to 0.4, and 0 to 0.5 Hz, respectively.

Pharmacokinetic analysis. Pharmacokinetic analysis was conducted using WinNonlin 1.1 software (Pharsight Corp.). AUC for each enantiomer was determined over the dosing interval at steady state using the log-linear trapezoidal method. Clearance for each patient was determined by dividing the dose of each enantiomer administered by the AUC of each enantiomer and then normalized to each patient's actual body weight (kg). The elimination rate constant was determined by regression analysis of the line of best fit of the terminal elimination phase. Half-life ($t_{1/2}$) was calculated as the natural log of 2 divided by the elimination rate constant.

Statistical analysis. SAS JMP, Version 6.0 (Cary, NC), was used for all statistical purposes. All comparisons between treatment phases (placebo vs. fluoxetine) were made using a two-tailed Student's *t*-test for parametric data and the Wilcoxon signed-rank test for nonparametric data. Significance was set at a *p*-value of less than 0.05.

The power analysis was based on the findings of a study by Zhou and Wood in which the investigators compared R(+) AUC_{0- ∞} data between CYP2D6 extensive metabolizers and poor metabolizers (159 \pm 38 and 409 \pm 72 ng \cdot h/mL, respectively).³¹ Because R(+) carvedilol is the enantiomer most likely to be affected by a change in CYP2D6 phenotype, and assuming that fluoxetine would reduce the R(+) AUC_{0- ∞} close to that observed in patients with the poor metabolizer phenotype, the coefficient of variation of the AUC_{0- ∞} for the R(+) enantiomer (23.9%) was used to assess the number of subjects

Table I Patient Demographics

Patient	Age	Gender	Race	NYHA Class	Ejection Fraction (%)	Carvedilol Dose (mg bid)
1	52	F	AA	II	35	25
2	56	M	C	II	25	50
3	59	M	C	I	32	50
4	75	F	AA	III	37	25
5	49	F	AA	II	48	25
6	48	M	AA	I	20	50
7	46	M	AA	I	33	25
8	42	M	AA	I	67	50
9	58	F	AA	II	74	25
10	64	M	AA	I	46	50

NYHA, New York Heart Association; AA, African American; C, Caucasian.

required for statistical significance. We anticipated that 9 patients in each group (fluoxetine and placebo) would provide sufficient power to detect a difference in R(+) carvedilol AUC. We also anticipated that the variability would be greater in heart failure patients than in healthy volunteers, which would be minimized by using a crossover design and paired measurements.

RESULTS

Demographics. Demographic data are shown in Table I. Ten patients (6 males, 4 females) were recruited into this study. Eight were African American, and 2 were Caucasian. Patient ages ranged from 42 to 75 years, with a mean age of 55 years. Five patients were receiving carvedilol doses of 25 mg twice daily, while the other 5 were receiving 50 mg twice daily. New York Heart Association class ranged from I to III. Patient weight ranged from 42 to 135 kg and did not significantly differ between treatment periods. In addition to carvedilol, all patients were receiving an ACE inhibitor and a diuretic, while 9 patients were receiving digoxin (Table II). None of the patients had been diagnosed with clinical depression at the time of entry into the study. However, 1 patient elected to continue fluoxetine therapy at the conclusion of the trial.

CYP2D6 metabolic ratio. Fluoxetine administration resulted in a significant increase in mean (\pm SD) dextromethorphan to dextroprphan metabolic ratio compared to placebo (0.089 ± 0.082 vs. 0.015 ± 0.036 , $p = 0.002$); however, only 1 patient converted to the slow metabolizer phenotype (defined as a metabolic ratio > 0.3). Figure 1 illustrates the individual changes in metabolic ratio for each patient. Accordingly, the mean

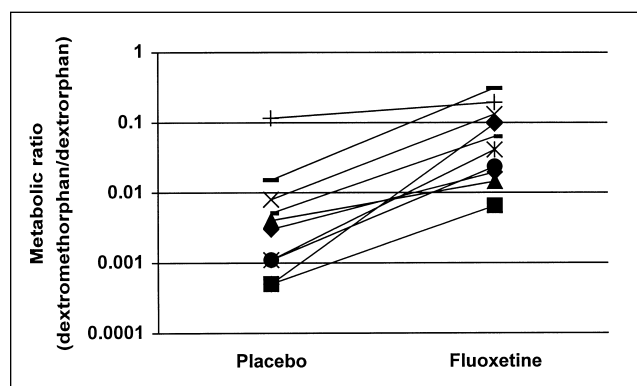


Figure 1. Individual changes in CYP2D6 metabolic ratio.

(\pm SD) amount of dextromethorphan excreted in the 24-hour urine collection when compared to placebo was significantly increased during fluoxetine administration (0.15 ± 0.26 mg vs. 0.69 ± 0.59 mg, $p = 0.01$), while the amount of dextroprphan excreted significantly decreased during fluoxetine administration (19.4 ± 6.8 mg vs. 10.7 ± 7.6 mg, $p = 0.02$), demonstrating significant CYP2D6 inhibition by fluoxetine. Mean trough concentrations of fluoxetine and norfluoxetine were 86 ± 47 and 202 ± 98 ng/mL, respectively, with corresponding micromolar concentrations of 0.28 for fluoxetine and 0.68 for norfluoxetine.

Carvedilol pharmacokinetics. Figure 2 illustrates the changes seen in the mean concentration-time curves for R(+) and S(-) carvedilol in the presence and absence of concomitant fluoxetine administration. The changes in AUC_{0-12} , Cl_{oral} , half-life, and R:S AUC ratio between study phases for R(+) and S(-) carvedilol are listed in Table III. Concomitant fluoxetine adminis-

Table II Concomitant Medications

Patient	1	2	3	4	5	6	7	8	9	10
ACEI	Enalapril	Enalapril	Enalapril	Enalapril	Enalapril	Enalapril	Enalapril	Enalapril	Lisinopril	Enalapril
Digoxin	Digoxin	Digoxin	Digoxin	Digoxin	Digoxin	Digoxin	Digoxin	Digoxin	Digoxin	Digoxin
Diuretic	Furosemide	Furosemide	Furosemide	Furosemide	Furosemide	Furosemide	Furosemide	Furosemide	Furosemide	Furosemide
Other	KCl Warfarin Insulin	KCl Warfarin Isosorbide Dinitrate Lovastatin Allopurinol	Warfarin	KCl Felodipine Isosorbide Dinitrate	KCl Felodipine Isosorbide Dinitrate Troglitazone Glimeperide Glyburide Insulin Prempro	KCl Warfarin Isosorbide Dinitrate Lovastatin Glucophage Acarbose Glipizide Allopurinol Nizatidine Isomiazid	KCl Glyburide Allopurinol Pentoxifyphylline	KCl Felodipine	KCl	KCl

Table III Mean (\pm SD) Carvedilol Pharmacokinetic Parameters

	R(+) Carvedilol			S(-) Carvedilol			R:S Ratio		
	Placebo	Fluoxetine	<i>p</i>	Placebo	Fluoxetine	<i>p</i>	Placebo	Fluoxetine	<i>p</i>
AUC ₀₋₁₂ (ng•h/mL)	522 (413)	927 (526)	0.01	244 (185)	330 (179)	0.17	2.2	2.9	0.008
Cl _{oral} (mL/min/kg)	10.3 (7.3)	4.5 (2.2)	0.004	19.9 (11.3)	13.2 (6.9)	0.03			
t _{1/2} (h)	3.4 (0.7)	4.2 (0.9)	0.04	4.3 (1.2)	4.7 (1.2)	0.37			

tration significantly decreased the weight-normalized oral clearance of the R(+) enantiomer by 56% ($p = 0.004$) and decreased the weight-normalized oral clearance of the S(-) enantiomer by 34% ($p = 0.03$), with a corresponding 77% increase in the AUC₀₋₁₂ of R(+) carvedilol ($p = 0.01$) and a 35% increase in the AUC₀₋₁₂ of S(-) carvedilol ($p = 0.17$). Results were similar when clearance values unadjusted for weight were analyzed. A statistically significant increase was also seen in R(+) carvedilol t_{1/2} ($p = 0.04$) and in the R:S AUC ratio ($p = 0.008$) after fluoxetine administration as compared to placebo.

Pharmacodynamic measurements. No significant differences between placebo and fluoxetine treatment periods were seen in mean (\pm SD) systolic blood pressure (121 \pm 24 vs. 141 \pm 34 mmHg, $p = 0.08$), diastolic blood pressure (68 \pm 15 vs. 75 \pm 8 mmHg, $p = 0.08$), or heart rate (71 \pm 11 vs. 73 \pm 11 bpm, $p = 0.76$). Moreover, no difference between treatment periods was seen in any of the heart rate variability parameters assessed (Table IV). Two patients' electrocardiographic data were excluded from analysis due to unsatisfactory recordings, and another was excluded for atrial fibrillation.

DISCUSSION

To our knowledge, this is the first study evaluating potential interactions between carvedilol and fluoxetine in heart failure patients. The administration of fluoxetine, a potent CYP2D6 inhibitor, resulted in a stereospecific inhibition in carvedilol metabolism without exhibiting significant effects on blood pressure, heart rate, or heart rate variability. The stereospecific pharmacokinetic changes seen in our study are similar to those found in a study of normal volunteers reported by Zhou and Wood in which the pharmacokinetics of R(+) carvedilol were shown to be influenced by CYP2D6 activity.³¹ These authors found the clearance of R(+) carvedilol to be 66% lower in CYP2D6 poor metabolizers ($n = 7$) compared to exten-

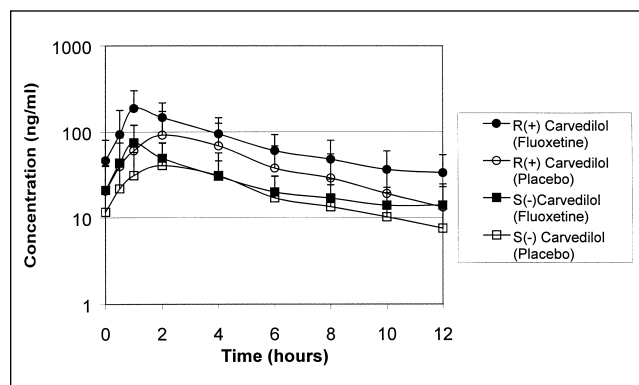


Figure 2. R(+) and S(-) carvedilol mean concentration-time curves.

sive metabolizers ($n = 12$), whereas there was no statistically significant effect on the clearance of S(-) carvedilol. Poor metabolizers had a corresponding 156% higher R(+) carvedilol AUC_{0-∞} than extensive metabolizers, but there was not a significant difference in S(-) carvedilol AUC_{0-∞} between phenotypes.

Administration of fluoxetine 20 mg for a minimum of 28 days converted only 1 patient from the extensive metabolizer phenotype to the poor metabolizer phenotype in our study. The plasma concentrations of fluoxetine and norfluoxetine achieved in our study are comparable to those found in previous studies of similar doses.³²⁻³⁴ Despite the lack of phenotype conversion, we did see significant inhibition of CYP2D6 activity, as shown by the significant change in dextromethorphan metabolic ratio between treatment phases. These data are supported by the significant increase in the amount of dextromethorphan and significant decrease in the amount of dextrophan excreted in urine during fluoxetine administration.

Our findings are in contrast to a study by Vandel et al, in which a similar fluoxetine dose converted 6 of 12 patients from the extensive metabolizer phenotype to the poor metabolizer phenotype.³⁵ Mean fluoxetine and norfluoxetine concentrations attained in that study

Table IV Mean (\pm SD) Heart Rate Variability Parameters

	Placebo		Fluoxetine		<i>p</i>
Time domain (ms)					
SDNN	117	(23)	109	(35)	0.48
SDANN	87	(19)	72	(20)	0.14
RMSSD	86	(53)	76	(74)	0.42
Frequency domain (ms ²):					
trough carvedilol concentration					
Low _{trough}	2281	(3105)	434	(187)	0.11
High _{trough}	929	(995)	995	(1492)	0.58
Total _{trough}	6857	(5902)	4013	(4272)	0.33
Frequency domain (ms ²):					
peak carvedilol concentration					
Low _{peak}	1455	(1565)	3947	(8572)	0.81
High _{peak}	1932	(1793)	2197	(3041)	0.86
Total _{peak}	7782	(6467)	7290	(11,989)	0.58

SDNN, standard deviation of all normal-to-normal (N-N) intervals (estimate of overall heart rate variability [HRV]); SDANN, standard deviation of the averages on N-N intervals of all 5-minute intervals (estimate of long-term components of HRV); RMSSD, square root of the mean of the sum of the squares of differences between adjacent N-N intervals (estimate of short-term components of HRV). Low frequency = 0.04 to 0.15 Hz. High frequency = 0.15 to 0.4 Hz. Total frequency = 0 to 0.5 Hz.

were 128 ± 206 ng/mL and 57 ± 23 ng/mL, respectively. In comparison to the patients in the Vandell study, our patients appeared to have greater CYP2D6 activity at baseline, as evidenced by the lower mean metabolic ratio in our population (0.015 vs. 0.13). However, the patients in the Vandell study were receiving a variety of tricyclic antidepressants prior to initiation of fluoxetine therapy. The tricyclic antidepressants are known to inhibit CYP2D6 to varying degrees, and therefore their baseline values may not be reflective of their drug-free phenotype. This previous tricyclic antidepressant therapy is also the most likely reason we saw a greater increase in mean metabolic ratio (493% vs. 107%). In addition, their patients only received fluoxetine for 10 days. This was not an adequate time for the patients to reach steady-state plasma concentrations of norfluoxetine, which accounts for the disparity between norfluoxetine concentrations achieved in the two studies.

The baseline clearance and AUC values for R(+) and S(-) carvedilol in our study are similar to those found in other studies published previously. In a dose escalation study of 20 male patients with NYHA class III-IV heart failure, Tenero et al found steady-state AUC₀₋₁₂ R:S ratios of 2.14 and 1.94 following twice-daily dosing of 25 and 50 mg, respectively, for 7 days.⁹ Another study of 13 patients with moderate essential hypertension and normal renal function but no heart failure found a mean R:S ratio of 2.44 following a 25 mg daily dose of carvedilol for 7 days.³⁶ Though no information

on phenotype is given in either of these studies, their ratios are comparable to the mean R:S ratio of 2.2 found in our study. In addition, Miller et al studied the population pharmacokinetics of R(+) and S(-) carvedilol in patients with NYHA class II-IV heart failure.¹⁰ These investigators found an R:S clearance ratio of 0.49 for patients 60 years old classified as extensive metabolizers. In the present study, we demonstrated a mean R:S clearance ratio of 0.53 at baseline.

We found a significant difference in clearance between study treatments for both enantiomers. However, we saw a significant difference in AUC between study treatments only for the R(+) enantiomer. When we examined the coefficient of variation (CV, standard deviation/mean) of the AUC, non-weight-adjusted clearance, and weight-adjusted clearance, we observed the CV to be smaller for the clearance parameters as compared to the AUC values. This smaller CV for the clearance of the S(+) enantiomer is reflected in statistical differences that are not apparent with the AUC values.

Due to the clinical instability of heart failure patients, changes in the balance of alpha- and beta-blockade with a drug such as carvedilol may have significant consequences. Selective inhibition of the metabolism of the R(+) enantiomer to a greater extent than the S(-) enantiomer could result in greater alpha-blockade and therefore a greater degree of vasodilatation. A greater relative degree of vasodilatation could potentially result in hypotensive episodes and

decreased patient tolerability, thereby compromising efficacy and safety. There was no clinical evidence of this in our patient population as no changes in symptoms, blood pressure, or heart rate were seen. However, our patients had been receiving carvedilol chronically and may have been less sensitive than carvedilol-naïve patients to hemodynamic changes resulting from an increase in carvedilol plasma concentrations. A study in patients being up-titrated on carvedilol may yield different results when patient tolerance to alpha- and beta-blockade is a more significant issue.

Heart failure patients are known to have decreased HRV when compared to subjects with normal cardiac function.^{37,38} This decrease reflects enhanced sympathetic activity, which is often seen in this patient population. Our patients did have decreased time domain measures when compared to patients with normal heart function. However, our values were greater than those found in treatment-naïve patients, most likely attributable to the long-standing treatment the patients had been receiving prior to entry into the study. Despite the increase in R(+) carvedilol plasma concentrations (and presumably alpha₁-blockade), no change in any of the HRV parameters was noted between treatment phases. The lack of statistical significance is not surprising and is due to the large degree of variability in the HRV parameters assessed in this study. Conditions for reducing variability due to measurement technique in HRV include controlling for room temperature and brightness, body posture, degree of ambulation, and respiratory rate during 5- to 7-minute periods of measurement. We were unable to consistently maintain these conditions during the study. However, our study results were similar to those found in a study by Sander-son et al.³⁹ Using 24-hour ambulatory electrocardiographic monitoring, the authors compared various HRV measurements in heart failure patients at baseline and following 12 weeks of either metoprolol or carvedilol treatment. In their study, they found no significant changes in any of the measurements assessed.

Drug interactions involving the CYP450 system are an important source of drug misadventures. We have shown that two potentially coadministered drugs, carvedilol and fluoxetine, can be safely given together in heart failure patients stabilized on carvedilol. However, care should be taken when administering any enzyme inhibitors or inducers in this fragile patient population.

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