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The impact of paroxetine coadministration on stereospecific carvedilol pharmacokinetics

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Abstract

Study Objective—To assess the impact of paroxetine coadministration on the stereoselective pharmacokinetic (PK) properties of carvedilol.

Design—Prospective, randomized, 2 phase crossover.

Setting—The University of Michigan General Clinical Research Unit and Michigan Clinical Research Unit.

Participants—Twelve healthy volunteers age 18–45 years, male and female, receiving no treatment with prescription or nonprescription medications.

Interventions—Subjects received single dose oral carvedilol (12.5 mg) with and without coadministration of immediate release paroxetine (10 mg orally twice daily), in random order. Blood samples were collected at 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 4, 6, 8, 10, 12, and 24 hours post carvedilol dose for determination of R and S carvedilol plasma enantiomer concentrations by high pressure liquid chromatography.

Measurements and Main Results—Pharmacokinetic (PK) parameters were calculated for each enantiomer by noncompartmental methods and compared between study phases by analysis of variance (ANOVA) controlling for study phase order and subject, with Tukey's studentized range test post hoc. AUC increased significantly with paroxetine coadministration, approximately

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Location: This study was carried out at the University of Michigan Hospital.

CONFLICT OF INTEREST NOTIFICATION

SS, JN, MS, RB, KK: No real or potential conflicts of interests.

BB, LW: consultant and speaker's bureau, AstraZeneca.

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2.5 fold and 1.9 fold for the R and S enantiomers, respectively. R/S AUC ratio increased significantly, from approximately 2.3 to 3.0. Individual increases in enantiomeric AUCs with paroxetine coadministration ranged from 0% – 571% and changes in R/S ratio ranged from –8% – 108%. Heart rate, P-R interval, and blood pressure were monitored and no clinically significant changes in carvedilol effects were noted.

Conclusion—This study demonstrated a PK drug-drug interaction between paroxetine and carvedilol with considerable intersubject variability in carvedilol PK parameters and magnitude of drug interaction. Stereoselectivity of carvedilol metabolism is preserved with paroxetine coadministration and R/S AUC ratio generally widens. While this drug interaction could potentially increase adrenergic antagonism and have significant clinical effects in patients, these effects were not seen in our healthy volunteer subjects.

Keywords

Carvedilol; paroxetine; pharmacokinetics; cytochrome P-450 CYP2D6; drug interactions

INTRODUCTION

Carvedilol is a mixed β_1 , β_2 , and α_1 adrenergic antagonist widely prescribed in heart failure and hypertension. It is supplied as a racemic mixture of R (+) and S (–) enantiomers. The S enantiomer competitively inhibits β and α_1 adrenoceptors.¹ The R enantiomer has comparable α_1 adrenoceptor potency, with 100-fold weaker β inhibition.¹ Carvedilol is predominantly eliminated by hepatic metabolism, with more rapid elimination of the S enantiomer.² Cytochrome P450 2D6 (CYP2D6), CYP2C9, CYP2E1, CYP1A2, and CYP3A4 oxidize carvedilol to 4', 5', 8', and O-desmethyl metabolites.² Some carvedilol is directly glucuronidated.³ Previous studies have shown decreased clearance of carvedilol in CYP2D6 poor metabolizers (PMs) compared to extensive metabolizers (EMs), with approximate 2.4–2.6 fold greater area under the concentration-time curve (AUC) of the R enantiomer and 1.4–1.9 fold greater AUC of the S enantiomer.^{4,5}

Paroxetine is a selective serotonin reuptake inhibitor (SSRI) which inhibits CYP2D6 and thereby inhibits clearance of several known CYP2D6 substrates. Steady state dosing of fluoxetine 20 mg daily, another SSRI that inhibits CYP2D6, resulted in a significant 78% increase in R carvedilol area under the concentration time curve (AUC) with a nonsignificant 35% increase in S carvedilol AUC in heart failure patients.⁶ Some previous data indicate that paroxetine may be a more potent inhibitor of CYP2D6 than fluoxetine, and that the two drugs may differentially inhibit CYP2C9 and CYP3A4.^{7–9} This study was conducted to assess the impact of paroxetine coadministration on the stereoselective pharmacokinetic (PK) properties of carvedilol.

METHODS AND MATERIALS

Study Design

This was an open-label, randomized, crossover study. Subjects were assigned to receive carvedilol 12.5 mg (Coreg®) orally with and without paroxetine coadministration, in random order. The paroxetine regimen consisted of 10 mg immediate release paroxetine orally once daily for two days, then twice daily for five days, then twice daily on the day of carvedilol dosing, then daily for four days afterward (down titrated for safety reasons). On carvedilol dosing days, paroxetine 10 mg and carvedilol 12.5 mg were given orally concurrently in the morning, then the second dose of paroxetine 10 mg was given orally 12 hours later. All paroxetine doses were taken at home except on carvedilol dosing days, and dosing times were recorded in dosing diaries. Dosage regimens were chosen to yield

quantifiable carvedilol concentrations in blood and to minimize fluctuations in paroxetine exposure across the measurement period, while representing lower doses typical of clinical practice to minimize potential toxicity. There was a minimum 7 day washout period between carvedilol doses and between the last previous paroxetine dose and off-paroxetine carvedilol doses.

Subjects were healthy volunteers required to fast from 10 p.m. the night prior to each admission. Water was allowed ad lib except for 1 hour before and 2 hours after carvedilol dose. Carvedilol administration phases were carried out under the supervision of the General Clinical Research Center and Michigan Clinical Research Unit at The University of Michigan Hospital. Study medications were dispensed by the hospital pharmacy and given with 8 oz of water. Subjects received a standardized lunch and dinner prepared and monitored by the research center. The study protocol was approved by an Institutional Review Board of the University of Michigan Hospital.

Subjects

Prospective subjects were eligible for study inclusion if they were nonsmoking healthy adults, 18 – 45 years of age (inclusive), not regularly taking any medications (including natural products or supplements), willing to abstain from non-study medications during the study period, willing to adhere to dietary restrictions as required, willing to comply with the study requirements including documenting medication ingestion and adverse effects.

Potential subjects were excluded from the study if they had any clinically significant abnormal findings on history or physical exam including blood pressure less than 110/70 mmHg, resting heart rate less than 60 beats per minute, significantly abnormal findings on a screening electrocardiogram, and abnormal laboratory values at baseline or during follow-up laboratories. Other exclusion criteria included allergy or serious adverse reaction to any of the medications used in the study (including heparin), the presence of any condition that the investigator felt would interfere with successful completion of the study, and participation in any other study during the study period. Women who were breastfeeding, pregnant, or of childbearing potential and not on reliable contraception were excluded.

Sample Collection

Subjects had an intravenous catheter placed in an antecubital or forearm vein by 8:00 a.m. on carvedilol dosing days. Blood samples (7 mL/sample) were collected into tubes containing ethylene diaminetetracetic acid immediately prior to carvedilol administration (time 0), and at 0.25, 0.5, 0.75, 1, 1.5, 2, 4, 6, 8, 10, 12, and 24 hours after administration. The catheter was withdrawn after the 12 hour blood sample, and a final blood sample (7 mL) was drawn by venipuncture. Catheter patency was maintained with 3mL of heparin 10 units/mL solution. Three milliliters of blood were withdrawn from the catheter deadspace and discarded immediately prior to each blood sample. All blood samples were centrifuged at 4 °C and approximately 2800 rpm within one hour of collection. Plasma was then collected and stored at –70 °C until analysis. After each blood draw, heart rate and rhythm were measured by a 3-lead electrocardiogram. Next, a sitting blood pressure (BP) was measured with an automated blood pressure machine. Blood pressures were taken a minimum of three times per sample with no difference greater than 10 mmHg between systolic readings.

Bioanalytical Methods

Plasma carvedilol enantiomer concentrations were quantified at an independent outside laboratory (NSF International, Ann Arbor, MI). To summarize, 0.5 mL plasma was extracted with 6 mL diethyl ether then with 2 mL diethyl ether, after alkalization with Britton-Robinson buffer. The organic phase was evaporated and the residue reconstituted

with 1.0 mL 0.1% acetic acid. R and S enantiomers were then analyzed by a high pressure liquid chromatography system (Agilent Technologies, Santa Clara, California). The method employed a 4.0 mm chiral cellobiohydrolase column and a mobile phase consisting of 15% 2-propanol in 10 M sodium acetate buffer, pH 4.5, with 50 μ M disodium EDTA at a flow rate of 1.0 mL/min. A 100 μ L injection volume was used. Column effluent was measured using a fluorescence detector (Hitachi High-Technologies Corporation, Tokyo, Japan) using a 238 nm excitation wavelength and a 350 nm emission wavelength. The lower limit of quantification (LLOQ) was determined to be 0.5 ng/mL.

Data Analysis

PK Analysis—PK parameters for R and S carvedilol were calculated by noncompartmental methods with Winnonlin version 5.2.1 (Pharsight Corp, Mountain View, CA). Concentrations below the LLOQ were removed, including all pre-dose concentrations. PK variables evaluated included AUC from time 0 to infinity ($AUC_{0-\infty}$) calculated by the linear trapezoidal rule, maximum concentration (C_{max}), time to reach C_{max} (T_{max}), apparent oral clearance (Cl/F), and terminal elimination rate (λ_z). Area under the curve was extrapolated to infinity by dividing the last measureable concentration by λ_z .

Statistical Analysis—PK variables are reported as geometric mean $\pm$ standard deviation except for T_{max} which is reported as median (range). Demographic variables are reported as arithmetic mean $\pm$ standard deviation. Differences in PK and pharmacodynamic (PD) parameters between study phases were evaluated by analysis of variance (ANOVA) controlling for study phase order and subject, with post hoc analysis when appropriate by Tukey's studentized range test using R version 2.8.1 (Vienna, Austria). Ninety percent confidence intervals (CIs) around the carvedilol AUC geometric mean ratios (GMRs), with paroxetine/without paroxetine, are also given. A sample size of 12 subjects was calculated to detect a 20% increase in AUC with paroxetine coadministration with 80% power at a significance level of 0.05. A significance level of 0.05 was used in all statistical testing.

RESULTS

Twelve healthy volunteers gave their written informed consent and participated in the study. Carvedilol concentrations for one subject were not quantifiable due to assay interference, so this subject's data have been excluded from all analyses. The remaining 11 subjects, 7 males and 4 females, completed the study and are included in the PK analysis. At baseline, subjects were age 24 ± 4 years (range 19 – 30 years), weight 79.9 ± 18.9 kg (range 48.2 – 107.4 kg, N=10 measured), and height 175 ± 11 cm (range 156 – 190 cm, N=10 measured). Figures I and II show average plasma concentration versus time curves for R and S carvedilol.

Mean PK parameters are summarized in Table 1. Individual percent changes in AUC and R/S AUC ratio by subject are listed in Table 2. AUC increased significantly with paroxetine coadministration, approximately 2.5 fold (GMR 90% CI 2.1 – 3.1) and 1.9 fold (GMR 90% CI 1.5 – 2.3) for the R and S enantiomers, respectively. Total AUC increased in all subjects with paroxetine coadministration, and individual enantiomeric AUCs increased in all subjects except one who had no change in S enantiomer AUC (Figures III and IV). The R/S AUC ratio increased significantly with paroxetine coadministration, from approximately 2.3 to 3.0 (GMR 1.3, 90% CI 1.2 – 1.4). Individual changes in R/S AUC ratio ranged from an 8% decrease to a greater than doubling (Figure V). The percentage of R isomer $AUC_{0-\infty}$ extrapolated beyond the 24 hour time point averaged 5% (range 1 – 12%) without paroxetine and 4% (range 2 – 11%) with paroxetine. S isomer $AUC_{0-\infty}$ was extrapolated an

average of 13% (range 5 – 30%) without paroxetine and 9% (range 2 – 26%) with paroxetine.

Heart rate did not significantly change between baseline and R or S enantiomer $T_{\max}$. P-R interval increased significantly between baseline and S enantiomer $T_{\max}$ (146 ± 2 msec vs. 154 ± 3 msec, $p < 0.01$) but was unaffected by paroxetine. Systolic blood pressure decreased significantly between baseline and S and R enantiomer $T_{\max}$ (both 120 ± 16 mmHg vs. 110 ± 13 mmHg, $p < 0.01$) but was unaffected by paroxetine. Diastolic blood pressure decreased significantly between baseline and R and S enantiomer $T_{\max}$ and was significantly higher with paroxetine (carvedilol alone baseline 63 ± 10 mmHg, 59 ± 8 mmHg at $T_{\max}$ for both enantiomers; carvedilol with paroxetine baseline 67 ± 10 mmHg, 62 ± 8 mmHg at R enantiomer $T_{\max}$ and 63 ± 8 mmHg at S enantiomer $T_{\max}$).

Compliance with the paroxetine regimen was complete per subject dosing diaries except for one paroxetine dose that was missed three days prior to carvedilol dosing. Symptom diaries indicated tiredness, grogginess, jitteriness, mild dizziness, difficulty concentrating, stomachache, diarrhea, headache, and feelings of depression while taking paroxetine. None of these symptoms were severe or interfered with completion of the study.

DISCUSSION

Paroxetine coadministration significantly increased systemic exposure to R and S carvedilol. There was a high intersubject variability in the overall magnitude of effect and in the relative effects of paroxetine coadministration on carvedilol enantiomers. Stereoselective metabolism is preserved and the R/S AUC ratio generally widens with paroxetine coadministration. The 24 hour sampling period was sufficient to approximate the full magnitude of drug interaction, as indicated by low total AUC extrapolation.

In this study, carvedilol enantiomer clearances in the absence of paroxetine were similar to those seen in individuals expressing the CYP2D6 EM phenotype.⁵ Paroxetine coadministration resulted in clearances typical of the CYP2D6 PM phenotype.⁵ Increases in AUC with addition of paroxetine also mimicked a phenotypic shift from EM to a PM, with approximate 2.5 fold and 1.9 fold increases in the R and S enantiomer AUCs, respectively.^{4,5} These findings contrast somewhat with those of a previous study that employed fluoxetine in place of paroxetine and demonstrated AUC increases of roughly half this magnitude.⁶ This may be because paroxetine more potently inhibits CYP2D6 or other relevant enzymes such as CYP2C9 or CYP3A4. It also may be attributable in part or whole to differences in study design. The previous study examined heart failure patients rather than healthy subjects, used steady state carvedilol dosing rather than single dosing, and employed a 12 hour sample collection period rather than a 24 hour interval, all of which could impact results.

Increased carvedilol exposure as a result of paroxetine could enhance adrenergic antagonism, and a greater proportional rise in R enantiomer concentration could cause a shift toward greater α blockade. However, the pharmacodynamic effects of this and similar interactions in clinical studies to date have been mild,⁶ and there have been no published case reports to date of carvedilol toxicity related to paroxetine coadministration despite both being widely used agents. Although DBP was statistically significantly different between paroxetine phases in the present study, this is attributable to a higher baseline DBP during paroxetine dosing rather than a difference in carvedilol effect. Decreases in DBP with carvedilol were similar with and without paroxetine coadministration.

Limitations

One potential limitation of this study is the lack of enzyme specific genotype or phenotype data for subjects. CYP2D6 PM status, which has a known impact on carvedilol PK, occurs naturally in around 5–10% of Caucasians, 2–7% of African Americans, 2–7% of Hispanics, and approximately 1% of Eastern and Southeastern Asians.¹⁰ As previously discussed, however, carvedilol metabolism occurs via multiple pathways and its drug interaction with paroxetine may occur via multiple mechanisms. The relative importance of each potential mechanism and the ability of alternative pathways to compensate for lost function of others are poorly understood. Given the spectrum of responses seen in this study it is unlikely that specific genotype or phenotype data would provide additional insight. Subject 4, despite exhibiting virtually no change in carvedilol PK from one study phase to the next, was not outlying from the rest of the group in either study phase. This individual had the third lowest clearance of S and R carvedilol without paroxetine and the second (R) and sixth (S) highest enantiomer clearances with paroxetine.

CONCLUSION

This study demonstrated a PK drug-drug interaction between paroxetine and carvedilol. There was considerable intersubject variability in carvedilol PK parameters and the magnitude of drug interaction. This interaction may be of greater magnitude than the interaction between carvedilol and fluoxetine. While the drug interaction between paroxetine and carvedilol could theoretically increase adrenergic antagonism, evidence of a clinically significant effect is presently lacking.

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References

1. Ruffolo RR, Gellai M, Hieble JP, Willette RN, Nichols AJ. The pharmacology of carvedilol. *Eur J Clin Pharm* 1990;38:S82–S88.
2. Oldham HG, Clarke SE. *In vitro* identification of the human cytochrome P450 enzymes involved in the metabolism of R(+)- and S(–)-carvedilol. *Drug Metab Dispos* 1997;25(8):970–977. [PubMed: 9280405]
3. Neugebauer G, Akpan W, v Möllendorff E, Neubert P, Reiff K. Pharmacokinetics and disposition of carvedilol in humans. *J Cardiovasc Pharmacol* 1987;10(S11):S85–S88. [PubMed: 2454375]
4. Giessmann T, Modess C, Hecker U, et al. *CYP2D6* genotype and induction of intestinal transporters by rifampin predict presystemic clearance of carvedilol in healthy subjects. *Clin Pharmacol Ther* 2004;75(3):213–222. [PubMed: 15001973]
5. Zhou H, Wood AJ. Stereoselective disposition of carvedilol is determined by CYP2D6. *Clin Pharmacol Ther* 1995;57(5):518–524. [PubMed: 7768074]
6. Graff DW, Williamson KM, Pieper JA, et al. Effect of fluoxetine on carvedilol pharmacokinetics, CYP2D6 activity, and autonomic balance in heart failure patients. *J Clin Pharmacol* 2004;41:97–106. [PubMed: 11225566]
7. Jeppesen U, Gram LF, Vistlsen K, Loft S, Poulsen HE, Brøsen K. Dose-dependent inhibition of CYP1A2, CYP2C9, and CYP2D6 by citalopram, fluoxetine, fluvoxamine, and paroxetine. *Eur J Clin Pharm* 1996;51:73–78.
8. Lane RM. Pharmacokinetic drug interaction potential of selective serotonin reuptake inhibitors. *Int Clin Psychopharmacol* 1996;11(S5):31–61. [PubMed: 9032002]

9. Schmider J, Greenblatt DJ, von Moltke LL, Karsov D, Shader RI. Inhibition of CYP2C9 by selective serotonin reuptake inhibitors *in vitro*: studies of phenytoin *p*-hydroxylation. *Br J Clin Pharmacol* 1997;44:495–498. [PubMed: 9384467]
10. Zhou SF. Polymorphism of human cytochrome P450 2D6 and its clinical significance: Part I. *Clin Pharmacokinet* 2009;48:689–723. [PubMed: 19817501]

Figure I.

Average plasma concentration versus time curves for R carvedilol following a single 12.5 mg oral carvedilol dose. Error bars depict standard deviation. N=11.

▲: Carvedilol alone;■:Carvedilol + paroxetine

Figure II.

Average plasma concentration versus time curves for S carvedilol following a 12.5 mg oral carvedilol dose. Error bars depict standard deviation. N=11.

▲: Carvedilol alone; ■: Carvedilol + paroxetine

Figure III.

S carvedilol AUC following a 12.5 mg oral dose with and without paroxetine.

—: geometric mean AUC 25 ng*h/mL without paroxetine, 46 ng*h/mL with paroxetine

Figure IV.

R carvedilol AUC following a 12.5 mg oral dose with and without paroxetine.

—: geometric mean AUC 56 ng*h/mL without paroxetine, 139 ng*h/mL with paroxetine

Figure V.

Carvedilol R/S enantiomer AUC ratio following a 12.5 mg oral dose, with and without paroxetine.

—: geometric mean R/S ratio 2.3 without paroxetine, 3.0 with paroxetine.

Table 1

Stereospecific pharmacokinetic variables for carvedilol with and without paroxetine in healthy subjects (N=11).

Variable	Carvedilol Enantiomer	Carvedilol 12.5 mg Alone	Carvedilol 12.5 mg + Paroxetine
$AUC_{0-\infty}$ (ng* h/mL)	<i>R</i>	55.5±32.1	139.4±95.2 **
	<i>S</i>	24.6±14.4	46.4±30.3 **
<i>R/S AUC Ratio</i>	<i>R/S</i>	2.3±0.7	3.0±1.0 **
<i>C_{max}</i> (ng/mL)	<i>R</i>	17.8±11.3	32.3±19.4 *
	<i>S</i>	8.5±6.4	14.4±9.1 *
<i>T_{max}</i> (h)	<i>R</i>	0.8 (0.5–2)	1 (0.5–4)
	<i>S</i>	0.8 (0.5–1.5)	0.8 (0.5–2)
<i>CL/F</i> (L/h)	<i>R</i>	112.6±52.8	44.8±27.4 **
	<i>S</i>	254.2±118.1	134.8±91.1 **
λ_z (h ⁻¹)	<i>R</i>	0.30±0.10 ^a	0.18±0.05 ^b **
	<i>S</i>	0.21±0.10 ^c	0.18±0.07 ^b

Values are reported as geometric mean ± standard deviation except T_{max} which is reported as median (range). Terminal elimination rate constants λ_z correspond to terminal half-lives of:

^a 2.3 hr;

^b 3.9 hr;

^c 3.3 hr.

* $P < 0.05$;

** $P < 0.01$

Table 2

% change from baseline in $AUC_{0-\infty}$ and R/S carvedilol enantiomer AUC ratio with paroxetine coadministration in healthy subjects (N=11).

Subject	Carvedilol Enantiomer	$AUC_{0-\infty}$ (% change with paroxetine)	R/S AUC Ratio (% change with paroxetine)
1	R	55	41
	S	10	
2	R	121	108
	S	6	
3	R	31	3
	S	27	
4	R	18	18
	S	0	
5	R	217	87
	S	70	
6	R	162	24
	S	111	
7	R	269	-8
	S	303	
8	R	113	1
	S	111	
9	R	156	40
	S	83	
10	R	571	60
	S	319	
11	R	319	35
	S	210	