Population Pharmacokinetics of R- and S-Carvedilol in Japanese Patients with Chronic Heart Failure

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Received January 20, 2010; accepted May 25, 2010; published online May 27, 2010

Carvedilol is a β-adrenoceptor antagonist used for treating chronic heart failure (CHF). Two clinical studies were conducted to evaluate the population pharmacokinetics and pharmacodynamics of R- and S-carvedilol, and associated covariates, in patients with CHF. Fifty-eight patients (male=45, female=13) with New York Heart Association class I—IV CHF were enrolled in two clinical studies. R- and S-carvedilol concentrations were measured using HPLC at steady-state after oral administration of carvedilol at 1.25—20 mg o.d. or b.i.d. The data from both studies were used to estimate the population pharmacokinetic parameters and covariates using the nonlinear mixed effects model program. For 40 patients evaluated in one clinical study, the cytochrome P450 (CYP)2D6 *1, *10, and *5 genotypes were determined using allele-specific primer PCR, and individual patients’ oral clearance (CL/F) of both enantiomers was estimated by the empirical Bayes method. A one-compartment model with a first-order absorption rate was established, in which body weight and α,-acid glycoprotein were significant covariates. Individual CL/F values for carvedilol were significantly lower in Japanese CHF patients with the CYP2D6 *1/*5, *5/*10 and *1/*10 genotypes. Estimation of the population pharmacokinetic parameters and their covariates for each enantiomer in Japanese patients with CHF showed that the CL/F values for R- and S-carvedilol were dependent on body weight, α,-acid glycoprotein, and CYP2D6 genotype. Prediction of exposure to free plasma carvedilol is important for dosage adjustment of β-blocker therapy in patients with CHF.

Key words carvedilol enantiomer; population pharmacokinetic; cytochrome P450 2D6 genotype; adverse event; chronic heart failure

Carvedilol is an β1, β2 and α1 adrenergic receptor antagonist, clinically administered as a racemic mixture of the R(+) - and S(−)-enantiomers. Beta-blockers have been reported to prolong life and reduce the risk of disease progression in patients with chronic heart failure (CHF).1–3) However, these drugs have a risk of causing symptomatic hypotension and/or worsening heart failure during the dose titration step. As tolerance to treatment with carvedilol varies widely among individuals, careful titration and treatment initiation are necessary in daily practice. The pharmacokinetics of carvedilol and its covariates in patients with CHF have been investigated,4,5) but the relationship between pharmacokinetics and tolerability, and the cause of this wide inter-individual variability, are still unclear.

The R- and the S-enantiomers of carvedilol exhibit different pharmacological effects, i.e., the β-receptor blocking activity of S-carvedilol is about 200 times higher than that of R-carvedilol, whereas both enantiomers are equipotent α-blockers.6) Also, the enantiomers exhibit differences in pharmacokinetic behavior in humans.7,8) Carvedilol is metabolized to various derivatives by both oxidation and conjugation in the liver, and the main oxidative isoenzyme is cytochrome P450 (CYP) 2D6.9) Absolute bioavailability upon oral administration is 31.1% and 15.1% for the R- and S-enantiomers, respectively, and the difference in metabolic stability is attributed mainly to CYP2D6.10,11) Carvedilol shows high plasma protein binding (98—99%),12) and is known to bind to α1-acid glycoprotein with high affinity.13)

The COMMET study reported that serious adverse and CHF-related events in patients switching from metoprolol (a β1-selective agent) to carvedilol (a nonselective agent) were lower than in patients switching from carvedilol to metoprolol.14) It is considered that the vasodilation effect through α1 blockade and its potency might be a key factor in β-blocker tolerability. Therefore, it is very important to assess the characteristics of enantioselective pharmacokinetics, and clarify the factors that influence clinical response.

In this study, we investigated the population pharmacokinetic parameters of R- and S-carvedilol and its covariates in Japanese patients with CHF, and evaluated the effect of CYP2D6 genotypes on individual oral clearance (CL/F) values. Relationships between adverse events and drug exposure level were also assessed by exploratory analysis.

MATERIALS AND METHODS

Study Patients Fifty-eight Japanese CHF patients (13 females and 45 males) were enrolled in two studies (studies I and II) between August 2001 and December 2003. This study was performed according to the Helsinki Declaration of 1964 (revised in 2004) and the Japanese government’s “Ethical Standards for Human Genome and Genetic Analysis Research.” These protocols were approved by the institutional review board of Sakakibara Heart Institute. Written informed consent for participation in the study was obtained from all patients. Studies I and II had the same inclusion and exclusion criteria. The main demographic characteristics are presented in Table 1. The patients ranged in age from 31 to 87 years (mean: 65 years), with a body weight of between 33.8 and 94.0 kg (mean: 58.5 kg).
macokinetic parameters were estimated with the NONMEM post-hoc option.

Relationship Tolerability of Carvedilol and the Drug Exposure Level Any adverse effects probably related to carvedilol tolerability were picked out by the investigator, and then the relationship between adverse events and drug exposure level were assessed by exploratory analysis.

Study Procedure All patients received a low initial dose (1.25—2.5 mg once daily (o.d.) or twice daily (b.i.d.)) of carvedilol tablets (Artist® tablet; Daiichi Pharmaceutical Co., Ltd., Tokyo, Japan) in addition to their usual medication. Patients who were able to tolerate the initial dose received an increased dose every 7 d aiming for the maximum daily dose (20 mg) on the basis of symptoms. After dose adjustment, the patients were followed up for an additional 6—12 months. If the dose was not tolerable, the daily dose was reduced temporarily. Blood samples were collected at steady-state after the initiation of individual treatment. During this period, the patients’ other concomitant therapies were kept constant, unless adverse events occurred that were thought to be related to either the study drug or others.

Assay of Carvedilol in Plasma Blood samples were collected in EDTA-2K tubes. After centrifugation, the plasma supernatant was added to a labeled polystyrene tube, which was immediately frozen and stored at below −20 °C until analysis. R- and S-carvedilol concentrations were measured by a HPLC method. The lower limits of quantification for R- and S-carvedilol enantiomers were both 0.5 ng/mL. Intra- and inter-day variability was less than 5.9%.

Genotyping of CYP2D6 In study II, CYP2D6 variants were genotyped in 40 patients after obtaining written informed consent. In this study, the CYP2D6*5 and *10 mutants, which have been reported to have high frequencies in the Japanese population, were selected. The CYP2D6*2 allele was not investigated in this study, because the phenotypic effect of this allele is known to be about the same as that of the wild type. Blood samples were collected in EDTA-2K tubes. Genomic DNA was isolated from the peripheral blood with a QIAamp®DNA Mini Kit (Qiagen, Tokyo, Japan), and stored at −80 °C. The CYP2D6*5 and *10 mutants were determined using a SNP Typing Kit (Toyobo Co., Ltd., Osaka, Japan) for the allele-specific primer PCR method.

Assay of α1-Acid Glycoprotein (AGP) Serum AGP concentrations were determined using a radical immunodiffusion plate (Kent Laboratories Inc., WA, U.S.A.).

Population Pharmacokinetic Model Population pharmacokinetic parameters were estimated with the NONMEM Version VI software package employing the first-order conditional estimation (FOCE) method. All statistics and graphics were analyzed with SAS (Version 6, SAS Institute, NC, U.S.A.) and S-Plus (6.2 for Windows, Insightful, WA, U.S.A.).

Oral clearance (CL/F), the apparent volume of distribution (V/F), and the absorption rate constant (K) were estimated by the one-compartment model with a first-order absorption rate in the NONMEM-PREDPP library subroutines, ADVAN2 and TRANS2. After the base model had been defined, the effects of the following demographics and clinical laboratory data on pharmacokinetic parameters were tested: body weight (BW), age (AGE), gender (SEX), α1-acid glycoprotein (AGP), and left ventricular ejection fraction (LVEF). The stepwise forward procedure was tested to select the population pharmacokinetic model including covariates using the likelihood ratio test at the p<0.05 level. The interaction between covariates and the magnitude of the selected covariate effects were also investigated.

Model robustness was assessed by a bootstrap resampling technique. The final model from the original dataset was fitted to each of the 300 bootstrap datasets. For bootstrap estimates, the arithmetic mean, standard error (S.E.) and 95% confidence interval (2.5th to 97.5th percentiles) were calculated, and compared with the original parameter estimates. The adequacy of the final model was also evaluated by a visual predictive check (VPC). To perform a visual predictive check, 1000 datasets were simulated for carvedilol 10 mg o.d. From the simulation data, plots of median and 95% prediction intervals (2.5th to 97.5th percentiles) with observations were generated.

The pharmacokinetic parameters in individual subjects were estimated according to empirical Bayes analysis using the NONMEM post-hoc option.

Study of the Relationship Between Carvedilol Tolerability and Drug Exposure Level Any adverse effects probably related to carvedilol tolerability were picked out by the investigator, and then the relationship between adverse events and drug exposure level were assessed by exploratory analysis.

### Table 1. Demographic Data of Patients Enrolled in the Study

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>Study I</th>
<th>Study II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>58 (13/45)</td>
<td>10 (2/8)</td>
<td>48 (11/37)</td>
</tr>
<tr>
<td>Underlying disease of CHF</td>
<td>Dilated cardiomyopathy 19</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Idiopathic cardiomyopathy 16</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hypertensive heart disease 7</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Others 16</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NYHA classification</td>
<td>6/23/28/1</td>
<td>1/4/5/0</td>
<td>5/19/23/1</td>
</tr>
<tr>
<td>LVDd (mm)</td>
<td>61.9±9.1 (36—80)</td>
<td>63.2±9.1</td>
<td>61.6±9.2</td>
</tr>
<tr>
<td>LVDs (mm)</td>
<td>53.2±10.0 (22—69)</td>
<td>55.5±7.3</td>
<td>52.6±10.5</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>29.4±12.9 (13—69)</td>
<td>26.2±8.1</td>
<td>30.2±13.8</td>
</tr>
<tr>
<td>Age (years)</td>
<td>65±11 (31—87)</td>
<td>66±7</td>
<td>64±12</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>58.5±12.8 (33.8—94.0)</td>
<td>57.6±10.1</td>
<td>58.7±13.4</td>
</tr>
<tr>
<td>α1-Acid glycoprotein (mg/dl)</td>
<td>77.8±20.3 (42.8—121.9)</td>
<td>61.4±7.8</td>
<td>81.2±20.5</td>
</tr>
<tr>
<td>Sampling points</td>
<td>Total 192 points</td>
<td>3—8 points/patient</td>
<td>1—3 points/patient</td>
</tr>
<tr>
<td></td>
<td>Total 92 points</td>
<td>(pre-dose: 10 points)</td>
<td>Total 100 points</td>
</tr>
</tbody>
</table>

R-Carvedilol 151 points
S-Carvedilol 155 points
L VDd: left ventricular dimension diastolic, L VDs: left ventricular dimension systolic, L VEF: left ventricular ejection fraction.

Mean±S.D. (min–max).
RESULTS

Population Pharmacokinetic Analysis of Carvedilol Enantiomers A total of 151 (R-carvedilol) or 155 (S-carvedilol) concentration data from the two studies, involving 58 patients, were included in the analysis. The plasma concentration of R-carvedilol was about double that of S-carvedilol.

A one-compartment model with a first-order absorption rate was selected for describing the pharmacokinetic profile of carvedilol, considering the distribution of the collected plasma samples. Inter-individual variability was modeled as being log-proportional, and residual variability was modeled as being a combination of additive and proportional because of the objective function value (OFV) and goodness-of-fit plots. Covariate adjustments were investigated using the stepwise forward procedure. A run record for demographic covariate model building is summarized in Table 2. At the first step, the covariate models including BW, AGE, AGP and SEX were statistically significant. However, as BW showed a strong correlation with AGE and SEX, the models including AGP with BW, AGP with AGE, AGP with SEX, and AGP with SEX were assessed in the next step. On the basis of the results, BW and AGP were adopted as covariates for the CL/F of both enantiomers in the final model in view of the OFV and goodness-of-fit plots. V/F was also investigated as a covariate; however, no covariate was included in the final model. The final population pharmacokinetic model and its precision estimates are given in Eqs. 1—4 and Table 3. The goodness-of-fit of the final population pharmacokinetic model is shown in Figs. 1 and 2, and the correlations between the individual CL/F estimated by empirical Bayes analysis in the basic model and demographics (BW, AGP, and LVEF) are presented in Fig. 3.

R-Carvedilol

\[
CL/F (l/h) = 1.29 \times BW (kg) \times (1 - 0.00685 \times AGP (mg/dl))
\]

(1)

\[
V/F (l) = 259
\]

(2)

S-Carvedilol

\[
CL/F (l/h) = 2.30 \times BW (kg) \times (1 - 0.00680 \times AGP (mg/dl))
\]

(3)

\[
V/F (l) = 1050
\]

(4)

The CL/F values of R- and S-carvedilol were estimated to be 0.58 l/h/kg and 1.05 l/h/kg (when the AGP concentration was 80 mg/dl), respectively. BW was estimated to increase the CL/F proportionally, while AGP decreased the CL/F of R- and S-carvedilol by approximately −0.7% per AGP (mg/dl). The V/F values of R- and S-carvedilol were estimated to be 2591 and 10501, respectively. The residual variability was high for each enantiomer.

Validation of this model and the population parameter estimates were carried out using the bootstrap method, and the

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Table 2. Run Record of Demographic Covariate Model Building for CL/F of Carvedilol

<table>
<thead>
<tr>
<th>Model</th>
<th>Comparison model</th>
<th>OFV</th>
<th>(\Delta OFV)</th>
<th>p-Value</th>
<th>OFV</th>
<th>(\Delta OFV)</th>
<th>p-Value</th>
<th>Equation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base</td>
<td>—</td>
<td>573.579</td>
<td>—</td>
<td>316.733</td>
<td>—</td>
<td>296.591</td>
<td>20.142</td>
<td>CL/F = θ1</td>
</tr>
<tr>
<td>1-1</td>
<td>Base</td>
<td>555.354</td>
<td>18.225</td>
<td>296.591</td>
<td>20.142</td>
<td>—</td>
<td>—</td>
<td>CL/F = BW × θ1</td>
</tr>
<tr>
<td>1-2</td>
<td>Base</td>
<td>569.836</td>
<td>3.743</td>
<td>314.769</td>
<td>1.964</td>
<td>0.0530</td>
<td>311.524</td>
<td>CL/F = θ1 × (1 + LVEF × θ4)</td>
</tr>
<tr>
<td>1-3</td>
<td>Base</td>
<td>570.189</td>
<td>3.390</td>
<td>311.524</td>
<td>5.209</td>
<td>0.0033</td>
<td>273.956</td>
<td>CL/F = θ1 × (1 + AGP × θ4)</td>
</tr>
<tr>
<td>1-4</td>
<td>Base</td>
<td>560.431</td>
<td>13.148</td>
<td>295.714</td>
<td>21.619</td>
<td>&lt;0.0001</td>
<td>286.759</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>1-5</td>
<td>Base</td>
<td>561.605</td>
<td>9.213</td>
<td>308.227</td>
<td>8.506</td>
<td>0.0035</td>
<td>286.059</td>
<td>CL/F = θ1 × (1 + SEX × θ4)</td>
</tr>
<tr>
<td>1-4</td>
<td>1-1</td>
<td>542.172</td>
<td>13.182</td>
<td>273.956</td>
<td>22.635</td>
<td>&lt;0.0001</td>
<td>259.878</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>1-4</td>
<td>1-4</td>
<td>551.218</td>
<td>9.213</td>
<td>286.059</td>
<td>9.655</td>
<td>0.0019</td>
<td>286.059</td>
<td>CL/F = θ1 × (1 + AGP × θ4)</td>
</tr>
<tr>
<td>1-4</td>
<td>1-5</td>
<td>542.172</td>
<td>13.182</td>
<td>273.956</td>
<td>22.635</td>
<td>&lt;0.0001</td>
<td>259.878</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

a) Final model.

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Table 3. Population Pharmacokinetic Parameters of R- and S-Carvedilol in Japanese CHF Patients

<table>
<thead>
<tr>
<th>Parameter</th>
<th>R-Carvedilol</th>
<th>S-Carvedilol</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean %RSE</td>
<td>95% CI</td>
</tr>
<tr>
<td>CL/F (l/h/kg)</td>
<td>1.29 20.9% (0.763—1.82)</td>
<td>2.30 9.0% (1.89—2.71)</td>
</tr>
<tr>
<td>V/F (l)</td>
<td>259 35.4% (79.5—439)</td>
<td>1050 14.2% (758—1340)</td>
</tr>
<tr>
<td>(K_e (h^{-1}))</td>
<td>0.594 50.0% (0.0119—1.18)</td>
<td>1.08 38.6% (0.263—1.90)</td>
</tr>
<tr>
<td>Impact of AGP</td>
<td>−0.00685 11.1% (−0.00833—0.00537)</td>
<td>−0.00680 5.5% (−0.00753—0.00607)</td>
</tr>
<tr>
<td>Inter Individual variability</td>
<td>(\eta_{CL/F}) 51.1% 34.0%</td>
<td>38.6% 32.2%</td>
</tr>
<tr>
<td></td>
<td>(\eta_{V/F}) 49.4% 58.6%</td>
<td>44.4% 44.0%</td>
</tr>
<tr>
<td></td>
<td>(\eta_{K_e/F}) 179% 70.1%</td>
<td>149% 40.4%</td>
</tr>
<tr>
<td>Residual variability</td>
<td>(e_{prop}) 33.3% 35.5%</td>
<td>29.4% 20.8%</td>
</tr>
<tr>
<td></td>
<td>(e_{abs}) 0.538 44.6%</td>
<td>0.116 187%</td>
</tr>
</tbody>
</table>

%RSE: relative standard error, \(e_{prop}\): proportional error, \(e_{abs}\): absolute error.
results were shown in Table 4. The distribution of the bootstrap estimates for each parameter was comparable with the estimates of the final model. The VPC plots for carvedilol 10 mg o.d. were also generated for the final model (Fig. 4). In general, the observations were with in the 95% predictive intervals (PIs).

**Relationship between CYP2D6 Genotype and Oral Clearance of Carvedilol**

In study II, CYP2D6 variants were genotyped, and the genotypes *1/*1, *1/*10, *10/*10, *1/*5, *5/*10, and *5/*5 were found to have frequencies of 12 (30%), 19 (48%), 5 (13%), 1 (3%), 3 (8%), and 0 (0%), respectively. The frequencies of the CYP2D6*5 and *10 alleles were 5% and 10%, respectively (Table 5).

Figure 5 shows the effects of the CYP2D6 genotypes on the individual (CL/F)/BW values estimated by empirical Bayes analysis. The (CL/F)/BW values for R- and S-carvedilol in patients with the *10/*10, *1/*5, and *5/*10 genotypes trended to be lower than the patients with the *1/*1 and *1/*10 genotypes.

**Relationship between Adverse Events and Pharmacokinetics of Carvedilol**

The adverse effects judged as “probably related” to carvedilol tolerability were bradycardia (n=7), dizziness (n=5), weight gain (n=3), pleural effusion (n=3), grade I AV block (n=1), and hyperkalemia (n=1) throughout the two studies. We were unable to find any definite tendency as a whole between adverse events and drug exposure level as a result of this retrospective assessment. However, in some cases, adverse effects of initial high exposure to carvedilol were suspected. One patient (BW: 58 kg, AGP: 87 mg/dl) who appeared to be hyperkalemic showed a high plasma drug concentration (R-carvedilol: 18.3 ng/ml, S-carvedilol: 7.4 ng/ml at 3 h after administration of 5 mg o.d.), and the daily dose of carvedilol was reduced. Another patient (BW: 69 kg, AGP: 85 mg/dl) who appeared to have bradycardia (prolonged RR interval of 3 s or more) showed a high trough plasma concentration (R-carvedilol: 2.0 ng/ml, S-carvedilol: 1.1 ng/ml at 23.5 h after administration of 2.5 mg o.d.), and a stepwise increase in the daily dose of carvedilol was not possible. CYP2D6 genotyping showed that these two cases had a *5/*10 genotype.

**DISCUSSION**

In this study, the population pharmacokinetics of carvedilol were investigated in Japanese patients with CHF. The population means of the CL/F for R- and S-carvedilol were similar to those reported in pharmacokinetic studies of patients with CHF. Carvedilol clearance in CHF patients is about half that in healthy subjects. This is likely because of decreased hepatic blood flow in a background of impaired cardiac function. In addition, it is speculated that a decrease in blood flow causes damage to hepatic parenchymal cells.

The covariates that were identified to have a significant influence on CL/F were BW and AGP. On the other hand, LVEF as a parameter of cardiac function did not affect CL/F. In general, CL/F is determined by plasma protein binding,
Fig. 2. Goodness-of-Fit of the Final Population Pharmacokinetic Model for S-Carvedilol in Patients with CHF

Fig. 3. Diagram Correlation between Individual CL/F Estimated by Empirical Bayes Analysis in the Basic Model and Demographics (BW, AGP, and LVEF)
intrinsic clearance and absorption rate. The effect of AGP is supported for the reason that carvedilol has high plasma protein binding (90%), and is known to bind to AGP with high affinity. As the mean level of AGP in CHF patients was almost the same as that in healthy persons, the main reason for the low clearance in CHF patients is thought to be the result of cardiac dysfunction. Furthermore, the oral clearance and distribution volume of the free drug are not theoretically influenced by the variability of AGP, because the main elimination pathway of carvedilol is hepatic metabolism and the distribution volume is larger than total body fluids. Therefore, the variability of AGP will not influence the free drug concentration, and prediction of the changes in hepatic intrinsic clearance corrected by the level of AGP is important in clinical practice.

Inter-individual variability in the clearance of R- and S-carvedilol was large, even after considering the effects of two covariates. One of the reasons for the large pharmacokinetic variability may have been the underlying cardiac disease. On the other hand, carvedilol is metabolized by both glucuronide conjugation and oxidation. The effect of genetic polymorphism of human UDP-glucuronosyltransferase (UGT2B7) and CYP2D6 on the pharmacokinetics of carvedilol has been reported in Japanese. Therefore, it is suspected that one reason for the large variability is genetic polymorphism of these enzymes.

In the present study, the CYP2D6*5 and *10 alleles were determined, and their effect on individual CL/F was investigated. The accuracy of individual pharmacokinetic parameters estimated by Bayes analysis is dependent on dose regimen, sampling time, and differences in prior means and individual true parameter values. According to their simulation study, most of the blood samples in this study were collected at the nadir after a steady state had been reached, and therefore the estimated individual CL/F values were probably reasonable, whereas Vd/F might have been invalid.

Genotyping showed that the frequencies of the CYP2D6*5 and *10 alleles were similar to those in the Japanese population reported previously, and the (CL/F)/BW values for R- and S-carvedilol in patients with the *10/*10, *1/*5, and *5/*5 genotypes tended to be lower than the patients with the *1/*1 and *1/*10 genotypes. Zhou and Wood reported that the concentrations of R-carvedilol in poor metabolizers of debrisoquin were substantially higher than those in extensive metabolizers. In a Japanese study, Honda et al. investig-
gated the effect of the CYP2D6 allele on stereoselective carvedilol pharmacokinetics in healthy subjects.\textsuperscript{19} They showed that the mean (CL/F)/BW value of R-carvedilol in CYP2D6*10*10 subjects was 51.3% lower than that in subjects lacking the CYP2D6*10 allele. On the other hand, the mean (CL/F)/BW value of S-carvedilol in subjects with CYP2D6*10/*10 was only 30.8% lower than that in subjects with CYP2D6*1/*1, *1/*2, or *2/*2. The present findings are in line with those reports, and reflects the fact that CYP2D6 plays a predominant role in the metabolism of R-carvedilol.\textsuperscript{19}

Horiiuchi et al.\textsuperscript{4} reported the effect of CYP2D6 and UGT2B7 polymorphism in patients with HF.\textsuperscript{3} They showed that the mean CL/F values for R- and S-carvedilol in patients with HF were 0.89 l/h/kg and 1.52 l/h/kg, respectively, similar to the values obtained in the present study. However, according to their report, there were no significant effects of CYP2D6 and UGT2B7 polymorphism on CL/F in patients with HF.\textsuperscript{5} On the other hand, Honda et al.\textsuperscript{19} and Takekuma et al.\textsuperscript{4} reported that UGT2B7*3 decreased the CL/F value of carvedilol in healthy subjects and patients with HF (CHF and angina pectoris), respectively. Study design and/or population may be a crucial factor when investigating the effect of CYP2D6 and UGT2B7 polymorphism on the pharmacokinetics of carvedilol. It will be necessary to clarify the effects of CYP2D6 and UGT2B7 polymorphism in patients with CHF by quantitative model analysis.

We were unable to find any definite tendency as a whole between adverse events and the exposure level of R- and S-carvedilol using this retrospective assessment because CHF patients show great intra- and inter-individual variations in physiological function due to the disorder's characteristics. Although the degree of impact on clinical efficacy and safety is still unclear because of the small population examined, the results of this population pharmacokinetic evaluation and the effect of the CYP2D6 allele may help when considering future appropriate clinical treatment. Further studies are needed to clarify the factors influencing the clinical response.

In conclusion, the population pharmacokinetic parameters and their covariates in Japanese patients with CHF were estimated for each enantiomer of carvedilol. The CL/F values of R- and S-carvedilol depend on BW, AGP, and CYP2D6 genotype. Prediction of exposure to free plasma carvedilol is important for adjusting the dosage of beta-blockade therapy in patients with CHF.

Acknowledgements This work was supported in part by a grant from the Welcome Trust and a research grant for Open Research Center Projects from the Ministry of Education, Culture, Sports, Science and Technology of Japan.

None of the authors has any conflict of interest.

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