Dose proportionality and pharmacokinetics of carvedilol sustained-release formulation: a single dose-ascending 10-sequence incomplete block study

Yo Han Kim
Hee Youn Choi
Yook-Hwan Noh
Shi Hyang Lee
Hyeong-Seok Lim
Chin Kim
Kyun-Seop Bae

Department of Clinical Pharmacology and Therapeutics, College of Medicine, University of Ulsan, Asan Medical Center, Chong Kun Dang Clinical Research and Clinical Epidemiology and Medical Information, CKD Pharmaceuticals, Seoul, Republic of Korea

Background: Carvedilol is a third-generation β-blocker indicated for congestive heart failure and high blood pressure. The aim of this study was to investigate the dose proportionality of the carvedilol sustained-release (SR) formulation in healthy male subjects.

Methods: An open-label, single dose-ascending, 10-sequence, 3-period balanced incomplete block study was performed using healthy male subjects. In varying sequences, each subject received three of five carvedilol SR formulations (8, 16, 32, 64, or 128 mg once). The treatment periods were separated by a washout period of 7 days. Serial blood samples were collected up to 48 h after dosing. The plasma concentrations of carvedilol were determined by using validated liquid chromatography–tandem mass spectrometry. Pharmacokinetic parameters including the area under the plasma concentration–time curve (AUC) from time 0 to the last measurable time (AUC_{last}), AUC extrapolated to infinity (AUC_{inf}), and the measured peak plasma concentration (C_{max}) were obtained by noncompartmental analysis. Dose proportionality was evaluated if the ln–ln plots of AUC_{last} AUC_{inf} and C_{max} versus dose were linear and the 90% confidence intervals (CIs) of the slopes were within 0.9195 and 1.0805. Tolerability was assessed by vital signs, electrocardiogram, clinical laboratory tests, and monitoring of adverse events (AEs) throughout the study.

Results: A total of 31 subjects were enrolled, and 30 completed the study. The assessment of dose proportionality meets the statistical criteria; the point estimates of slope were 1.0104 (90% CI: 0.9524–1.0277) for AUC_{last}, 1.0003 (90% CI: 0.9748–1.0258) for AUC_{inf}, and 0.9901 (90% CI: 0.9524–1.0277) for C_{max}, respectively. All AEs were mild, and none of the subjects dropped out due to AEs.

Conclusion: In this study, exposure to carvedilol was proportional over the therapeutic dose range of 8–128 mg. The carvedilol SR formulation was well tolerated.

Keywords: dose linearity, carvedilol, sustained release, healthy subjects

Introduction

Carvedilol is a third-generation β-blocker indicated in the treatment of congestive heart failure and high blood pressure. In addition to its β-blocking properties, it has blocking effect at α₁-adrenergic receptor, and exhibits low levels of intrinsic sympathomimetic activity (ISA). The lack of ISA reduces side effects and makes carvedilol better tolerated than the other β-blockers.

Carvedilol was developed as an immediate-release (IR) formulation in 1995. It is rapidly absorbed with time to maximum concentration (t_{max}) at 1–2 h, and then declines with a terminal half-life of approximately 7–10 h; thus, twice-daily dosing is recommended. It is extensively metabolized primarily by CYP2D6, and greater
than 98% of the drug is bound to plasma proteins, primarily albumin.\textsuperscript{7,8}

A new sustained-release (SR) formulation of carvedilol was approved in 2006 by the Food and Drug Administration (FDA) for all of the same indications as twice-daily carvedilol based on several clinical trials.\textsuperscript{9,10} The $t_{\text{max}}$ of carvedilol SR formulation was reached approximately 4–6 h after drug administration, and the maximum concentration ($C_{\text{max}}$) and area under the plasma concentration–time curve (AUC) did not differ for the IR and SR formulations in patients.\textsuperscript{11,12} In a previous report, drug-taking compliance with carvedilol SR was comparable to carvedilol IR formulations, and there were no differences in adverse events (AEs) among patients switching from carvedilol IR to SR formulations.\textsuperscript{13}

In Korea, the SR formulation of carvedilol was also developed by Chong Kun Dang Pharmaceutical Corp. (Seodaemun-gu, Seoul, Republic of Korea). From a study to compare the pharmacokinetics between carvedilol IR 25 mg twice daily and SR 64 mg once daily, the $C_{\text{max}}$ and AUC were found equivalent.\textsuperscript{14} As a drug label, the therapeutic dose range of IR carvedilol was 3.125–50 mg twice daily,\textsuperscript{14} but the therapeutic dose range of SR formulations is expected to be 8–128 mg once daily.

The aim of this study was to investigate the pharmacokinetics and dose proportionality of the carvedilol SR formulation across the dose range of 8–128 mg in healthy male subjects.

Materials and methods

Subjects

Healthy male volunteers aged 20–55 years and having a body mass index (BMI) of 19–26 kg/m\textsuperscript{2} were eligible for this study. Volunteers were considered to be in good health based on medical history, physical examinations, vital signs (systolic blood pressure [SBP], diastolic blood pressure [DBP], heart rate [HR], and body temperature), 12-lead electrocardiogram (ECG), clinical laboratory tests (hematology, blood chemistry, and urinalysis), serology (human immunodeficiency virus antibody, hepatitis B surface antigen, hepatitis C virus, and syphilis high quality reagin test), and urine drug screening (amphetamine, cocaine, opiate, barbiturates, benzodiazepine, tetrahydrocannabinol, and methadone) within 4 weeks of the first administration of the study drug. Volunteers with a sitting SBP $\geq 140$ or $< 90$ mmHg, DBP $\geq 90$ or $< 60$ mmHg, or HR of $> 95$ or $< 55$ beats per minute were excluded. Volunteers with known allergy or hypersensitivity to carvedilol, or with a history of drug abuse were also excluded from the study.

The study protocol was approved by the Korean Food and Drug Administration (KFDA) and the institutional review board of Asan Medical Center (AMC), Seoul, Republic of Korea. All volunteers provided written informed consent prior to screening tests. This trial was registered with the identifier number NCT01369472 at ClinicalTrials.gov.

Study design

This study was designed as an open-label, single dose-ascending, 10-sequence, 3-period balanced incomplete block study (Figure 1). Subjects were randomly assigned to one of ten sequences and received three of five carvedilol SR formulations (8, 16, 32, 64, or 128 mg once). All treatments were given after consuming a standardized meal. The study drug was administered 30 min after the start of the meal.
Dose proportionality of carvedilol SR formulation

Pharmacokinetic assessment and statistical analysis

The plasma concentration–time profiles of carvedilol of each subject were analyzed by a noncompartmental method using WinNonlin® 6.1 (Pharsight Corporation, Mountain View, CA, USA). All analyses were made using actual times of sampling. The peak plasma concentration (Cmax) and time at Cmax (tmax) were determined from the observed values. The terminal elimination rate constant (λz) was estimated by linear regression of the terminal log-linear portion of the plasma concentration–time curves. The area under the time–concentration curve (AUC) from time 0 to the last measurable time (AUClast) was calculated by the trapezoidal rule, and the AUC extrapolated to infinity (AUCinf) was obtained as:

$\text{AUC}_{\text{last}} + C_{\text{last}}/\lambda_z$ (Clast: the last quantifiable concentration).

The t1/2 was calculated for each participant as ln(2)/λz.

All statistical analyses were performed using SAS® 9.3 (SAS Korea, Gangnam-gu, Seoul, Republic of Korea) and WinNonlin® 6.1 (Pharsight Corporation, Mountain View, CA, USA). Descriptive data and pharmacokinetic parameters were summarized using descriptive statistics.

The dose proportionality of carvedilol over the dose range 8–128 mg was assessed by fitting a power model. The power model assumes a linear relationship between natural log-transformed pharmacokinetic exposure parameter (AUClast, AUCint, and Cmax) and natural log-transformed dose; ln(PK) = β0 + β1 ln(dose). The proportionality constant (β1) and its corresponding 90% confidence interval (CI) were compared with the modified acceptance range; lower limit as 1+ln(0.8)/ln(r) and upper limit as 1+ln(1.25)/ln(r), where r was the maximal dose ratio for the study.15–17 In this study, the maximal dose ratio was 16 (128/8), so the acceptance range was 0.9195–1.0805.

In addition to the power model, analysis of variance (ANOVA) model with factors for sequence, subject within sequence, period, and treatment were used to investigate the natural log-transformed, dose-normalized pharmacokinetic parameters including AUClast, AUCint, and Cmax.18 P-values <0.05 were deemed to indicate statistical significance.

Results

Study participants

A total of 31 healthy Korean volunteers were enrolled, and 30 subjects completed the study. One subject was dropped by the principal investigator for taking concomitant medication without notice. The mean (standard deviation) age of study participants was 25.06 ± 3.55 years, the mean weight was 68.67 ± 7.64 kg, and the mean height was 174.57 ± 6.23 cm.
Pharmacokinetic analysis

Thirty subjects, who completed the study, were included for pharmacokinetic analysis. The mean plasma carvedilol concentration–time profile is presented in Figure 2. The geometric mean $C_{max}$ increased from 6.93 to 77.04 ng/mL, and the geometric mean $AUC_{int}$ increased from 60.84 to 703.29 ng⋅h/mL with an increase in the carvedilol dose from 8 mg to 128 mg (Table 1). Regarding the carvedilol dose, the median $t_{max}$ was about 6.0 h, and the geometric mean half-life ranged from 6.73 to 7.67 h at each dose level.

Carvedilol $AUC_{last}$, $AUC_{inf}$, and $C_{max}$ were proportional to dose. The plots of the function fitted for the power model with 90% CIs were presented for $AUC_{last}$, $AUC_{inf}$, and $C_{max}$ in Figure 3. The estimate of the proportionality constant (90% CI) for $AUC_{last}$, $AUC_{inf}$, and $C_{max}$ were 1.0104 (0.9849–1.0359), 1.0003 (0.9748–1.0258), and 0.9901 (0.9524, 1.0277), respectively. The estimates and 90% CIs all fell within the prespecified range (0.9195–1.0805). When analyzed using the ANOVA model, the dose-adjusted $AUC_{last}$, $AUC_{inf}$, and $C_{max}$ were not statistically different among all treatments (Tables 2 and 3). Thus, carvedilol systemic exposure was concluded to be dose proportional over the therapeutic dose range of 8–128 mg.

Tolerability

Overall, carvedilol was well tolerated. Twelve subjects experienced a total of 13 AEs, among which 11 events in 11 subjects were considered “possibly related” to the study drug (Table 4). All AEs were of mild severity, and resolved without sequelae. No death or serious AE occurred during the entire course.

![Figure 2](https://www.dovepress.com/)

**Figure 2** Mean (SD) plasma concentration–time curves of carvedilol SR formulations: (A) linear; (B) log-linear.

**Abbreviations:** SD, standard deviation; SR, sustained release.
Table 1 Pharmacokinetic parameters of carvedilol SR by each dose group

<table>
<thead>
<tr>
<th>Parameter</th>
<th>AUC_{last} (ng h/mL)</th>
<th>AUC_{inf} (ng h/mL)</th>
<th>C_{max} (ng/mL)</th>
<th>t_{1/2} (h)</th>
<th>t_{max} (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>8 mg</td>
<td>58.29 (66.83)</td>
<td>60.84 (65.11)</td>
<td>6.93 (63.19)</td>
<td>6.73 (42.75)</td>
<td>5.98 (4.0, 8.0)</td>
</tr>
<tr>
<td>16 mg</td>
<td>100.3 (69.92)</td>
<td>104.16 (68.85)</td>
<td>12.26 (53.52)</td>
<td>6.96 (39.41)</td>
<td>6.0 (5.0, 8.0)</td>
</tr>
<tr>
<td>32 mg</td>
<td>184.11 (62.74)</td>
<td>188.78 (62.95)</td>
<td>22.6 (65.83)</td>
<td>7.38 (41.33)</td>
<td>6.0 (5.0, 15.98)</td>
</tr>
<tr>
<td>64 mg</td>
<td>413.51 (62.76)</td>
<td>423.02 (62.95)</td>
<td>46.31 (64.04)</td>
<td>7.74 (47.67)</td>
<td>6.02 (5.0, 8.02)</td>
</tr>
<tr>
<td>128 mg</td>
<td>689.35 (62.76)</td>
<td>703.29 (63.95)</td>
<td>77.04 (66.99)</td>
<td>7.67 (41.93)</td>
<td>6.02 (5.0, 11.98)</td>
</tr>
</tbody>
</table>

Notes: n=18. *Data presented as geometric mean cV, except for t_{max}, for which median (min, max) is shown.

Abbreviations: AUC_{last}, area under the plasma concentration–time curve from time 0 to last measurable time point; AUC_{inf}, area under the plasma concentration–time curve from time 0 to infinity; C_{max}, measured peak plasma concentration; CV, coefficient of variation; t_{1/2}, terminal half-life; t_{max}, time to reach peak concentration; SR, sustained release.

of the study. Likewise, there were no clinically significant abnormalities in physical examinations, or ECGs.

Decreases in mean systolic and diastolic blood pressure were observed 4–12 h after the study drug administration compared with baseline (Figure 4); however, the changes were not clinically significant. The lowest mean SBP values were 106.1 mmHg at 8 mg and 97.6 mmHg at 128 mg group, which were measured 8 h after administration, respectively. The lowest mean DBP values were 62.8 mmHg at 8 mg and 56.3 mmHg at 128 mg group, which were measured 8 h after administration, respectively.

Discussion

The current study was designed to evaluate the dose proportionality and pharmacokinetics of single-dose carvedilol SR formulations in healthy male subjects. Carvedilol systemic exposure was dose proportional over the dose range of 8–128 mg. The pharmacokinetic parameters are consistent with former reports. These results demonstrate that there is a predictable and consistent dose–response relationship among the five different dose levels of carvedilol SR formulations.

A comparison of three or more formulations of a study drug shows that a balanced incomplete block design has
**Table 2** Summary of analysis of variance for dose-normalized pharmacokinetic parameters of carvedilol

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Source</th>
<th>Degree of freedom</th>
<th>Sum of squares</th>
<th>Mean square</th>
<th>F value</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AUC_{\text{last}}/dose</strong></td>
<td>Sequence</td>
<td>9</td>
<td>5.166555</td>
<td>0.574062</td>
<td>0.6</td>
<td>0.7818</td>
</tr>
<tr>
<td></td>
<td>Subject (sequence)</td>
<td>20</td>
<td>22.15506</td>
<td>1.107753</td>
<td>62.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>Period</td>
<td>2</td>
<td>0.017512</td>
<td>0.008756</td>
<td>0.49</td>
<td>0.6138</td>
</tr>
<tr>
<td></td>
<td>Dose</td>
<td>4</td>
<td>0.022278</td>
<td>0.005557</td>
<td>0.31</td>
<td>0.8679</td>
</tr>
<tr>
<td></td>
<td>Error</td>
<td>54</td>
<td>0.960124</td>
<td>0.017778</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>AUC_{\text{inf}}/dose</strong></td>
<td>Sequence</td>
<td>9</td>
<td>5.254612</td>
<td>0.583846</td>
<td>0.62</td>
<td>0.7679</td>
</tr>
<tr>
<td></td>
<td>Subject (sequence)</td>
<td>20</td>
<td>21.89227</td>
<td>1.094613</td>
<td>61.41</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>Period</td>
<td>2</td>
<td>0.015427</td>
<td>0.007714</td>
<td>0.43</td>
<td>0.6509</td>
</tr>
<tr>
<td></td>
<td>Dose</td>
<td>4</td>
<td>0.025575</td>
<td>0.006394</td>
<td>0.36</td>
<td>0.8368</td>
</tr>
<tr>
<td></td>
<td>Error</td>
<td>54</td>
<td>0.962456</td>
<td>0.017823</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>C_{\text{max}}/dose</strong></td>
<td>Sequence</td>
<td>9</td>
<td>3.48442</td>
<td>0.387158</td>
<td>0.46</td>
<td>0.8864</td>
</tr>
<tr>
<td></td>
<td>Subject (sequence)</td>
<td>20</td>
<td>19.564</td>
<td>0.9782</td>
<td>25.29</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>Period</td>
<td>2</td>
<td>0.000868</td>
<td>0.000434</td>
<td>0.01</td>
<td>0.9889</td>
</tr>
<tr>
<td></td>
<td>Dose</td>
<td>4</td>
<td>0.071528</td>
<td>0.017882</td>
<td>0.46</td>
<td>0.7631</td>
</tr>
<tr>
<td></td>
<td>Error</td>
<td>54</td>
<td>2.088889</td>
<td>0.038683</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: AUC_{last}, area under the plasma concentration–time curve from time 0 to last measurable time point; AUC_{inf}, area under the plasma concentration–time curve from time 0 to infinity; C_{max}, measured peak plasma concentration.

**Table 3** Summary of geometric mean ratio for dose-normalized pharmacokinetic parameters of carvedilol

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Dose (mg)</th>
<th>AUC_{\text{last}}/dose</th>
<th>AUC_{\text{inf}}/dose</th>
<th>C_{\text{max}}/dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>GMR</td>
<td>P-value</td>
<td>GMR</td>
<td>P-value</td>
</tr>
<tr>
<td>16 vs 8</td>
<td>0.9388</td>
<td>0.3220</td>
<td>0.9329</td>
<td>0.2771</td>
</tr>
<tr>
<td>16 vs 32</td>
<td>0.9804</td>
<td>0.7387</td>
<td>0.9853</td>
<td>0.8035</td>
</tr>
<tr>
<td>16 vs 64</td>
<td>1.0109</td>
<td>0.8946</td>
<td>1.0234</td>
<td>0.7779</td>
</tr>
<tr>
<td>32 vs 8</td>
<td>0.9576</td>
<td>0.6219</td>
<td>0.9468</td>
<td>0.5346</td>
</tr>
<tr>
<td>32 vs 64</td>
<td>1.0312</td>
<td>0.6061</td>
<td>1.0387</td>
<td>0.5245</td>
</tr>
<tr>
<td>64 vs 8</td>
<td>0.9287</td>
<td>0.5114</td>
<td>0.9116</td>
<td>0.4124</td>
</tr>
<tr>
<td>128 vs 8</td>
<td>0.9127</td>
<td>0.5153</td>
<td>0.9004</td>
<td>0.4558</td>
</tr>
<tr>
<td>128 vs 16</td>
<td>0.9722</td>
<td>0.8022</td>
<td>0.9652</td>
<td>0.7531</td>
</tr>
<tr>
<td>128 vs 32</td>
<td>0.9531</td>
<td>0.5845</td>
<td>0.9510</td>
<td>0.5678</td>
</tr>
<tr>
<td>128 vs 64</td>
<td>0.9828</td>
<td>0.7848</td>
<td>0.9878</td>
<td>0.8466</td>
</tr>
</tbody>
</table>

Abbreviations: AUC_{last}, area under the plasma concentration–time curve from time 0 to last measurable time point; AUC_{inf}, area under the plasma concentration–time curve from time 0 to infinity; C_{max}, measured peak plasma concentration; GMR, geometric mean ratio; vs, versus.

**Table 4** Summary of adverse events

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>8 mg (n=18)</th>
<th>16 mg (n=19)</th>
<th>32 mg (n=18)</th>
<th>64 mg (n=18)</th>
<th>128 mg (n=18)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dizziness</td>
<td>0 (0)</td>
<td>1 (1)</td>
<td>0 (0)</td>
<td>1 (1)</td>
<td>4 (4)</td>
<td>6 (6)</td>
</tr>
<tr>
<td>Headache</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Light-headedness</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (1)</td>
<td>0 (0)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (1)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Bilirubin total increased</td>
<td>1 (1)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Blepharospasm</td>
<td>0 (0)</td>
<td>1 (1)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (1)</td>
</tr>
</tbody>
</table>

Notes: *Data presented as number of subjects (number of events); †drug-related adverse events.
some advantages over a complete crossover design. First, the subject is less likely to drop out. Second, the trial execution timeline is reduced. Third, the total blood sampling volume of the subject is also decreased. Fourth, statistical analysis is simple such that the balance is preserved.\textsuperscript{19,20}

Carvedilol is a racemic mixture of two enantiomers, $R(+)$-carvedilol and $S(-)$-carvedilol.\textsuperscript{21} Both enantiomers have $\alpha_1$-blocking activity, but $S(-)$-carvedilol primarily has a $\beta$-adrenoreceptor blocking activity.\textsuperscript{22} The $S(-)$-carvedilol is metabolized faster than the $R(+)$-carvedilol in human cytochrome P450 enzymes.\textsuperscript{23} Thus, the $C_{\text{max}}$ and AUC for the $R(+)$-carvedilol were shown to be two to three times larger than those of $S(-)$-carvedilol in healthy subjects.\textsuperscript{24}

In this study, we additionally measured the concentration of $R(+)$-carvedilol and $S(-)$-carvedilol, respectively. The pharmacokinetic parameters of $R(+)$-carvedilol and $S(-)$-carvedilol were presented at Table 5. In $S(-)$-carvedilol, the data for the 8 mg dose group were not presented because the concentration–time profiles were not consistently well described. The estimates of the proportionality constant (90% CI) for $\text{AUC}_{\text{last}}$ and $C_{\text{max}}$ of $R(+)$-carvedilol 8–128 mg were 1.0861 (1.0439–1.1283), and 1.0493 (0.9913, 1.1074), respectively. The estimates of the proportionality constant (90% CI) for $\text{AUC}_{\text{last}}$ and $C_{\text{max}}$ of $S(-)$-carvedilol 16–128 mg were 1.0956 (1.0023–1.1889), and 1.0103 (0.9000, 1.1206), respectively. Although the data for the lowest-dose group (8 mg) of $S(-)$-carvedilol were excluded because of insufficient data to obtain pharmacokinetic parameters, the racemic mixtures of carvedilol were also proportional to dose.

The most common AEs were dizziness and headache, which were likely due to the pharmacologic effects of lowering blood pressure in healthy volunteers. These AEs were similar and consistent with the known safety profile of carvedilol.\textsuperscript{25} Moreover, all AEs were mild and resolved without treatment, and the decreased blood pressures also resolved within 24 h without any clinically related symptoms.

Because all of the subjects in the current study were male, sex differences in the pharmacokinetics of carvedilol were not investigated. As a recent report, bioavailability of carvedilol in female subjects was slightly higher than that

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{Figure4.png}
\caption{Mean (SD) (A) systolic and (B) diastolic blood pressure after administration of carvedilol SR formulation in healthy male volunteers. Abbreviations: SD, standard deviation; SR, sustained release.}
\end{figure}

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|c|}
\hline
Parameter\textsuperscript{a} & $R(+)$-carvedilol & & $S(-)$-carvedilol\textsuperscript{b} & \\
\hline
 & $\text{AUC}_{\text{last}}$ (ng h/mL) & $C_{\text{max}}$ (ng/mL) & $t_{\text{max}}$ (h)\textsuperscript{c} & $\text{AUC}_{\text{last}}$ (ng h/mL) & $C_{\text{max}}$ (ng/mL) & $t_{\text{max}}$ (h)\textsuperscript{c} \\
\hline
8 mg & 43.81 (94.11) & 6.31 (81.52) & 5.95 (4.00, 8.00) & 34.7 (106.35) & 4.96 (100.56) & 6.00 (4.95, 8.02) \\
16 mg & 88.09 (80.93) & 12.44 (68.91) & 5.98 (4.00, 8.02) & 71.15 (84.18) & 9.52 (84.55) & 5.99 (4.00, 15.97) \\
32 mg & 189.28 (84.52) & 25.84 (95.34) & 5.98 (4.00, 15.97) & 160.28 (78.34) & 18.0 (78.59) & 6.05 (5.98, 8.00) \\
64 mg & 367.22 (92.24) & 44.73 (88.5) & 6.04 (5.00, 12.00) & 272.9 (66.12) & 31.8 (71.17) & 7.99 (5.00, 12.00) \\
128 mg & 606.98 (81.75) & 76.1 (88.85) & 6.01 (5.00, 12.00) & \textbf{Note}: n=18. \textsuperscript{a}The 8 mg dose group of $S(-)$-carvedilol was not presented due to insufficient data. \textsuperscript{b}Data presented as geometric mean and CV, except for $t_{\text{max}}$, for which median (min, max) is shown. \textsuperscript{c}Abbreviations: $\text{AUC}_{\text{last}}$, area under the plasma concentration–time curve from time 0 to last measurable time point; $C_{\text{max}}$, measured peak plasma concentration; CV, coefficient of variation; $t_{\text{max}}$, time to reach peak concentration.
\end{tabular}
\caption{Pharmacokinetic parameters of $R(+)$- and $S(-)$-carvedilol by each dose group}
\end{table}
in male subjects, but these differences could be explained by the lower body weight of females. On the other hand, as drug label, there were no age- or gender-related differences in response to carvedilol. Thus, dose adjustment based on clinical status of patients would be helpful.

**Conclusion**

In conclusion, exposure to carvedilol was proportional over the therapeutic dose range of 8–128 mg in this study. Based on the results, a predictable and linear increase in systemic exposure of carvedilol can be expected. The carvedilol SR formulation was well tolerated.

**Acknowledgment**

The study was funded by Chong Kun Dang Pharmaceutical Corp. (Seoul, Republic of Korea).

**Disclosure**

Chin Kim is an employee of Chong Kun Dang Pharmaceutical Corp. The other authors report no conflicts of interest in this work.

**References**