Pharmacokinetic/Pharmacodynamic Modeling and Simulation of Rosuvastatin Using an Extension of the Indirect Response Model by Incorporating a Circadian Rhythm

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Pharmacokinetic/pharmacodynamic (PK/PD) modeling and simulation enable the prediction of the effect of a medication in various situations in clinical practice. The aims of this study were to define the PK/PD model of rosuvastatin in various situations in clinical practice. The effective dosage regimen for acetaminophen in chronic pain patients was suggested by PK/PD modeling and simulation. The plasma rosuvastatin and MVA concentrations reported by Martin et al. were used as the source of PK/PD modeling data. For each simulation, a summary parameter, the area under the plasma MVA concentration–time curves for 24 h in the steady state (AUEC24), was used to characterize the time course of each endpoint. To estimate the influence of PK parameters on rosuvastatin effects, the AUEC24 reduction ratio of baseline levels was simulated from the 0.33–3.0-fold value of each PK parameter estimate. The PK/PD model of rosuvastatin was used to determine the effective rosuvastatin dosage regimen.

Key words rosuvastatin; pharmacokinetic-pharmacodynamic modeling; circadian rhythm

In 2004, the United States Food and Drug Administration issued a “critical path” document for characterizing model-based drug development as the development and application of pharmacostatistical models of drug efficacy and safety from preclinical and clinical data to improve drug development knowledge management and decision making. Pharmacokinetic/pharmacodynamic (PK/PD) modeling and simulation also enable the prediction of the effects of a medicine in various situations in clinical practice. The effective dosage regimen for acetaminophen in chronic pain patients was suggested by PK/PD modeling and simulation. The development of a safe, effective dosage regimen for sotalol was based on population PK/PD modeling and simulation. The PK/PD analysis of sotalol suggested a dosage regimen based on age and body weight. Thus PK/PD modeling and simulation provide a useful tool that is applicable in clinical practice.

Rosuvastatin is a highly effective inhibitor of hydroxymethylglutaryl-CoA (HMG-CoA) reductase. HMG-CoA reductase converts HMG-CoA to mevalonic acid (MVA). The inhibition of HMG-CoA reductase, which catalyzes the rate-limiting step of cholesterol biosynthesis in the liver, causes a decrease in the concentration of low-density lipoprotein cholesterol (LDL-C). The reduction in intracellular cholesterol concentration induces a subsequent upregulation of LDL-C receptors on the surface of hepatocytes, which results in an enhanced extraction of LDL-C from the blood and a decreased concentration of circulating LDL-C. MVA that is produced by the action of HMG-CoA reductase on HMG-CoA is the precursor of cholesterol. Plasma MVA concentration has been shown to be a good index of the in vivo rate of cholesterol synthesis. Despite the importance of HMG-CoA reductase inhibitors in the management of dyslipidemia, the relationship between drug exposure and the extent of HMG-CoA inhibition has not been elucidated. In general, peak cholesterol biosynthesis occurs at night, suggesting that the hypocholesterolemic effects of HMG-CoA reductase inhibitors are stronger after evening administration than after morning administration. However, robust trials are necessary to determine the best administration time to achieve optimal LDL-C lowering for rosuvastatin. PK/PD modeling and simulation provide information on the relationship of the dosage regimen and the response to rosuvastatin. However, there are as yet no reports on a PK/PD model of rosuvastatin.

The aims of this study were to define the PK/PD model of rosuvastatin and to predict the response to rosuvastatin using simulated plasma MVA concentration in various dosage regimens such as poor compliance, and morning and evening dosage of rosuvastatin. Moreover, to clarify the PK parameter affecting the response to rosuvastatin, useful information was provided in clinical practice.

MATERIALS AND METHODS

Data Source The plasma rosuvastatin and MVA concentrations reported by Martin et al. were used as the source of PK/PD modeling data. Graphs of concentration–time data were scanned, and all of the graphed data points were extracted using the software program UN-SCAN-IT (Silk Scientific, Inc., Orem, UT, U.S.A.). Table 1 provides a summary of the study. The study design was an open-label, random-
ized, two-way crossover trial comprising two 14-d treatment periods separated by a 4-week washout period. Eligible volunteers were randomized to receive a single oral dose of rosuvastatin (10 mg) each morning (approximately 07:00) or evening (approximately 18:00) for 14 d. After the washout period, the volunteers received an alternative (morning or evening) treatment regimen for an additional 14 d. The blood samples for the determination of rosuvastatin concentration were collected 0.5 h predose and at fixed intervals (0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 18, 24, 48, 72 h) after the administration of rosuvastatin on treatment day 14. The plasma rosuvastatin concentration was measured using an LC/MS/MS system. During each treatment period, the plasma MVA concentration was measured using an LC/MS/MS system at baseline, on treatment days 1 and 14, and at follow-up (day 1 posttreatment).

**PK/PD Modeling** For PK/PD modeling, the study design was converted into a one-way trial comprising two 14-d treatment periods separated by a 2-week washout period. Rosuvastatin (10 mg) was administered at 07:00 for the first treatment period and at 18:00 for the second treatment period. The reported mean plasma rosuvastatin concentrations after the morning and evening administrations were used as those at 14 d for the first and second treatment periods, respectively. The reported mean plasma MVA concentrations for the morning pre- and postdoses were used as those on day −1, treatment day 1, treatment day 14, and day 1 posttreatment for the first treatment period. The reported mean plasma MVA concentrations for the evening pre- and postdoses were used as those on day −1, treatment day 1, treatment day 14, and day 1 posttreatment for the second treatment period.

The PK model was estimated using a first-order absorption two-compartment model. The PK model was parameterized in terms of absorption rate constant (\( k_{in} \)), volume of the central compartment (\( V_c \)), clearance (\( CL/F \)), volume of the peripheral compartment (\( V_p/F \)), and intercompartmental clearance (\( Q/F \)) after oral administration. PD modeling was performed with a sequential approach where the rosuvastatin clearance was estimated using the PK model was used to drive the PD modeling. The PK/PD model consisted of the PK model and the indirect response model with input inhibition, as shown in Fig. 1. Additionally, the extension of the indirect response model by incorporating a time-dependent periodic function for a zero-order rate constant for the increase in plasma MVA concentration takes into account the chronopharmacologic rhythm.\(^9\) Assumining that the mechanism of the inhibition of MVA formation by rosuvastatin is mediated through HMG-CoA reductase inhibition, the rate of change in the plasma MVA concentration over time is described by an extended physiologic indirect response model\(^{1,10}\) according to

\[
\frac{dR}{dt} = k_{in} \cdot \left[ 1 - \frac{C_p^p}{IC_{50} + C_p^p} \right] - k_{out} \cdot R
\]

where \( R \) is the response variable, \( k_{in} \) is a zero-order rate constant for the increase in plasma MVA concentration, \( C_p \) is the plasma rosuvastatin concentration, \( IC_{50} \) is the plasma rosuvastatin concentration that decreases \( k_{in} \) by 50\%, \( k_{out} \) is a first-order rate constant for the decrease in plasma MVA concentrations, and \( \gamma \) is a sigmoidicity parameter. \( k_{in} \) is redefined as follows for circadian rhythm:

\[
k_{in} = k_{m} + k_{amp} \cdot \cos(2 \cdot \pi(t - tz)/24)
\]

where \( k_{m} \) is the mean MVA synthesis rate, \( k_{amp} \) is the amplitude of the MVA synthesis rate, and \( tz \) is the acrophase time signifying the maximum synthesis rate (at \( t = tz \), \( \cos 0 = 1 \), \( k_{in} = k_{m} + k_{amp} \); at \( t = tz \pm 12 \), \( \cos \pi = -1 \), \( k_{in} = k_{m} - k_{amp} \)). The parameter \( k_{in} \) represents the following function reported by Krzyzanski et al.\(^{1,11}\):

\[
k_{in} = k_{m} \cdot IC - \frac{k_{amp} \cdot k_{in}^2}{k_{in}^2 + (2 \pi / 24)^2} \left[ \cos \left( \frac{2 \pi}{24} \cdot tz \right) - \frac{2 \pi}{24} \cdot k_{in} \cdot \sin \left( \frac{2 \pi}{24} \cdot tz \right) \right]
\]

where IC is the initial condition plasma MVA concentration. This method assumes that \( tz \) is less than 24 and \( k_{amp} \) is less than \( k_{m} \). The initial condition for Eq. 3 was fixed at the measured mean plasma MVA concentration at 06:00 (4.32 ng/ml). The parameters were estimated by the naive averaged data method. All the datasets were estimated using the computer software package NONMEM, ver. 6 (Icon Development Solutions, Ellicott City, MD, U.S.A.), in conjunction with Intel Visual Fortran Compiler, ver. 10, and Wings for NONMEM.\(^{1,12}\)

**Simulation Using PK/PD Parameter Estimates** Using PK/PD parameter estimates, simulations were performed to predict the time course of rosuvastatin effects for an oral dose of 10 mg with various dosage regimens using NONMEM, ver. 6 (Icon Development Solutions). For each simulation, a summary parameter, the area under the plasma MVA concentration–time curves for 24 h in the steady state

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects (m/f)</td>
<td>24 (22/2)</td>
</tr>
<tr>
<td>Age (y)</td>
<td>38.6 (19—61)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>76.9 (57—100)</td>
</tr>
<tr>
<td>Fasting serum LDL-C for all subjects</td>
<td>&lt;4.14 mmol/L</td>
</tr>
<tr>
<td>Fasting serum TG for all subjects</td>
<td>≤3.39 mmol/L</td>
</tr>
<tr>
<td>Rosuvastatin dose (mg)</td>
<td>10</td>
</tr>
</tbody>
</table>

**Table 1. Summary of Pharmacokinetic/Pharmacodynamic Study of Rosuvastatin**

![Fig. 1. PK/PD Model for Rosuvastatin](image)

- \( k_{in} \) absorption rate constant; \( V_c/F \) volume of the central compartment; \( CL/F \) clearance; \( V_p/F \) volume of the peripheral compartment; \( Q/F \) intercompartmental clearance; \( C_p \) plasma rosuvastatin concentration; MVA, mevalonic acid; \( k_{out} \) circadian production of mevalonic acid; \( k_{in} \) first-order rate of mevalonic acid removal.
(AUEC<sub>24</sub>), was used to characterize the time course of each endpoint after rosuvastatin administration. AUEC<sub>24</sub> was determined with the use of “dummy” compartments with mass transport described by

\[
\frac{d\text{AUEC}}{dt} = C_t
\]

(4)

where AUEC represents the AUEC from 0 to time \( t \) of MVA, and \( C_t \) is the concentration of MVA at time \( t \). The AUEC<sub>24</sub> reduction ratio (%) of the baseline was calculated for each simulation.

To estimate the influence of PK parameters on the AUEC<sub>24</sub> reduction ratio, the AUEC<sub>24</sub> reduction ratio was simulated from the 0.33—3.0-fold value of the PK parameter estimates (\( k_a, CL/F, V_c/F, V_p/F, Q/F \)). The simulation was performed by systematically varying one PK parameter estimate for rosuvastatin 10 mg administration at 07:00 or 18:00, while maintaining the remaining PK parameter estimates at their fitted values for rosuvastatin PK data. The influence of all PK parameters was visually shown by plotting their values on a graph.

RESULTS

PK/PD Modeling

The PK profile for rosuvastatin was described by a first-order absorption two-compartment model and served as a suitable driving function for the PD model. The time courses of the observed and predicted plasma rosuvastatin and MVA concentrations are shown in Fig. 2. A good agreement was demonstrated between the observed and predicted effects of rosuvastatin after the morning and evening doses, respectively. The PK/PD parameter estimates with their standard error are summarized in Table 2.

Simulation Using PK/PD Parameter Estimates

The PK/PD model was used to simulate steady-state rosuvastatin effects for once-daily dosing schedules. The relationships between changes in the PK parameter estimates and the AUEC<sub>24</sub> reduction ratio are shown in Fig. 3. Each bar represents the influence of a PK parameter on the AUEC<sub>24</sub> reduction ratio. The vertical lines represent the AUEC<sub>24</sub> reduction ratio simulated using the PK parameter estimates shown in Table 2. The AUEC<sub>24</sub> reduction ratio after 07:00 administration was 7.7% lower than that after 18:00 administration. The AUEC<sub>24</sub> reduction ratio was more sensitive to changes in the PK parameters after 07:00 administration compared with that after 18:00 administration.

To predict the MVA concentration profile in the poor-compliance case, the PK/PD model was used to simulate rosuvastatin effects for the following dosage regimens: A, missing a dose in the steady state for once-daily 10-mg administration at 07:00; B, missing a dose in the steady state for once-daily 10-mg administration at 07:00, and 10-mg administration at 12:00 after the missing dose; C, missing a dose in the steady state for once-daily 10-mg administration at 07:00, and 10-mg administration at 20:00 after the missing dose; D, missing a dose in the steady state for once-daily 10-mg administration at 18:00; E, missing a dose in the steady state for once-daily 10-mg administration at 18:00, and 10-mg administration at 23:00; and F, missing a dose in the steady state for once-daily 10-mg administration at 18:00, and 10-mg administration at 07:00 on the day after the missing dose. The simulated MVA curves are shown in Fig. 4. The MVA concentrations almost reached their baseline level after the missing-drug administration. The simulated MVA concentration–time curves when rosuvastatin was taken 5 h after a patient forgot to take rosuvastatin were similar to those when rosuvastatin was taken in the morning or evening. The simulated MVA concentration–time curve when rosuvastatin was taken at 07:00 1 d after a patient forgot to take rosuvastatin at 18:00 was similar to the baseline levels during nighttime; lower values were observed at about 12:00.
In this study, a PK/PD model for describing the plasma rosuvastatin concentration and MVA concentration profiles was developed. Rosuvastatin is widely used for decreasing LDL-C concentration in dyslipidemia therapy. However, there is no PK/PD model of the MVA concentration–time relationship of rosuvastatin. Modeling the PK/PD of rosuvastatin is thought to be useful for determining drug dosage regimens in clinical practice. Using this PK/PD model, we explored the effective dosage regimens and systemic exposures for evaluating the effects of these two factors on plasma MVA concentration.

Physiologic functions do not remain constant within 24 h. The effect of circadian rhythm on drug PK has been observed for a number of drugs, such as ketorolac, bupivacaine, 5-fluorouracil, and atorvastatin. However, the PK model in this study was not considered to take into account the circadian rhythm since the plasma rosuvastatin concentration data used in this study were very similar after the morning and evening administrations, as shown in Fig. 2. The circadian rhythm of plasma MVA concentration has been reported in humans. The pattern of plasma MVA concentration over the course of one day is asymmetric and it is therefore necessary to convert the observed time pattern, e.g., single cosine, into the input rate. Because the circadian rhythm of the plasma MVA concentration has already been observed, and rosuvastatin inhibits HMG-CoA reductase, which catalyzes MVA synthesis, we used a first-order absorption two-compartment model with an extended indirect response model by incorporating a time-dependent periodic function for $k_{in}$ taking into account chronopharmacologic rhythms. The population PK analysis of rosuvastatin has been described using a two-compartment model with linear...
elimination and simultaneous first- and zero-order absorptions with respective lag times. The CL/F (264 l/h) in this study was nearly the typical value of CL/F (257 l/h) in the population analysis. The turnover of labeled MVA that is injected into the plasma compartment is characterized by a half-life of 1 h in the elimination phase. In this study, the plasma MVA concentration half-life (1.04 h) is in agreement with that in the literature. The IC_{50} value of 1.97 ng/ml in this study was close to that of 5.4 ng/ml in the study of the activity of rosuvastatin inhibiting HMG-CoA reductase using a purified human catalytic domain. The derived model adequately describes the plasma rosuvastatin concentration and MVA concentration profiles after the morning and evening administrations of rosuvastatin.

PK/PD modeling and simulation are valuable in decision making in all stages of drug development. PK/PD modeling and simulation are thought to be valuable in planning the dosage regimen in clinical practice. In this study, we simulated the MVA concentration–time curves in once-daily administration. Furthermore, the MVA concentration–time curves in the case when the patient forgot to take rosuvastatin were simulated. Patients often forget to take medications, but there is little information on dealing with such a situation. Figure 3 provides graphic evidence that the AUEC_{24} reduction ratio after morning administration was 7.7% lower than that after evening administration and that the changes in the PK parameters more prominently affected the AUEC_{24} reduction ratio after morning administration than that after evening administration. This result might be explained by the relationship between the IC_{50} value and the plasma rosuvastatin concentration from 15:30 to 03:30. k_{in} was higher than k_{out} from 15:30 to 03:30 because t_{1/2} was estimated to be 15.5 h. The plasma MVA concentration profile was strongly affected by changes in the inhibitory effect from 15:30 to 03:30. The simulated plasma rosuvastatin concentration was nearly equal to IC_{50} after morning administration and it was higher than IC_{50} after evening administration from 15:30 to 03:30. Thus the changes in the PK parameters more prominently affected the AUEC_{24} reduction ratio after morning administration than after evening administration. The effects of lovastatin and simvastatin on the diurnal periodicity of plasma MVA concentrations was reported. The 24-h mean plasma MVA concentration, total cholesterol, and LDL-C after the administration of simvastatin were 6.9%, 14%, and 16.3% lower than those of lovastatin, respectively. The effects on total cholesterol and LDL-C after morning administration of rosuvastatin may be lower than those after evening administration because the AUEC_{24} reduction ratio after morning administration was 7.7% lower than that after evening administration. As shown in Figs. 4A and D, the simulated MVA concentrations returned to baseline levels on the day a patient forgot to take a 10-mg dose of rosuvastatin in the morning and evening, respectively. The simulated MVA concentration–time curves when rosuvastatin was taken 5 h after a patient forgot to take rosuvastatin were similar to those when rosuvastatin was taken in the morning or evening (Figs. 4B, E). The simulated MVA concentration–time curve when rosuvastatin was taken at 07:00 1 d after a patient forgot to take rosuvastatin at 18:00 was similar to the baseline levels during nighttime; lower values were observed at about 12:00 (Fig. 4F). These results suggest that the evening dose of rosuvastatin is useful in clinical practice, although caution should be exercised in patients with poor compliance.

One limitation of this study is the use of mean PK/PD data. Mean data provide no information on intersubject variability. Therefore the PK/PD parameter estimates must be interpreted carefully in view of this fact. The other limitation is the use of the plasma rosuvastatin concentration and plasma MVA concentration data obtained from the administration of only 10 mg of rosuvastatin. Rosuvastatin inhibits HMG-CoA reductase in the liver and reduces plasma MVA concentration. In this study, k_{in} was inhibited by the plasma rosuvastatin concentration. For example, from the nonlinear relationship between the plasma rosuvastatin concentration and liver rosuvastatin concentration, the simulation of plasma MVA concentration in the case of other dosages may have low reliability. Recently, concentration-dependent rosuvastatin uptake via organic anion-transporting peptides has been described by assuming one saturable component and one nonsaturable component in vitro. However, the Michaelis constant value for each transporter was much higher than the plasma rosuvastatin concentration in clinical practice. It was thought that the simulation of the other dosages could be extrapolated by the results obtained using this rosuvastatin 10 mg administration data.

In conclusion, we characterized the plasma rosuvastatin concentration and plasma MVA concentration profiles using the PK/PD model incorporating a time-dependent periodic function. The AUEC_{24} reduction ratio was lower after morning administration than that after evening administration. The changes in the PK parameters affected the AUEC_{24} reduction ratio after morning administration compared with that after evening administration. The MVA concentration–time curves when rosuvastatin was taken 5 h after a patient forgot to take rosuvastatin were considered similar to those when rosuvastatin was taken in the morning or evening. The evening dose of rosuvastatin is useful in clinical practice, although caution should be exercised in patients with poor compliance. Knowledge of the PK/PD parameters for rosuvastatin will allow for an effective dosage plan.

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REFERENCES AND NOTES