**Regular Article**

*Population Pharmacokinetics of an Angiotensin II Receptor Antagonist, Telmisartan, in Healthy Volunteers and Hypertensive Patients*

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**Summary:** Objective: To describe the factors affecting pharmacokinetics of telmisartan, an angiotensin II receptor antagonist, a population pharmacokinetic (PPK) model has been developed based upon the data collected from healthy volunteers and hypertensive patients.

Methods: A total of 1566 plasma samples were collected from 20 healthy volunteers and 129 hypertensive patients, together with the demographic background. The data were analyzed by the NONMEM program using two-compartment model with first-order absorption. The robustness of the obtained PPK model was validated by the bootstrapping resampling method.

Results: The oral clearance (CL/F) was found to be associated with age, dose and alcohol consumption, but neither related to serum creatinine nor smoking history. The volume of distribution for the central compartment was related to age and dose, and the volume of distribution for the peripheral compartment was related to body weight and gender. The absorption rate constant (Ka) and the absorption lag time were described as function of dose. The CL/F decreased with advanced age. The CL/F decreased and Ka increased with higher dose, reflecting the super-proportional increase in the plasma levels of telmisartan. The AUC and Cmax values predicted by the present PPK model were well consistent with the observed values. The means of parameter estimates obtained with 200 bootstrap replicates were within 95–111% of the final parameter estimates from the original data set.

Conclusion: A PPK model for telmisartan developed here well described the individual variability and exposure, and robustness of the model has been validated by the bootstrapping method.

**Key words:** telmisartan; population pharmacokinetics; modeling; covariate; NONMEM; model validation

**Introduction**

Telmisartan is a nonpeptide angiotensin II receptor antagonist,1,2) and is used for the treatment of hypertension.3,4) Because of its long elimination half-life, telmisartan shows sustained anti-hypertensive effect over the 24-hour dosing interval by once-daily dosing.3) Telmisartan is a lipophilic compound and extensively distributes to tissues. Telmisartan is highly bound to plasma proteins (99.5%)5) mainly albumin, and also bound to α1-acid glycoprotein, γ-globulin and lipoproteins. Telmisartan is metabolized to an inactive acylglucuronide conjugate, which is account for approximately 10% of the circulating drugs following a single 40 mg dose.6) Biliary-faecal excretion is the primary elimination route of telmisartan and its metabolite. Following a single oral or intravenous dose of 40 mg [14C] telmisartan to normal volunteers, more than 98% of total radioactivity was recovered in the faeces and <1% of radioactivity was recovered in urine.6)

Telmisartan shows a large interindividual variability in plasma concentration profile.5) The absolute bioavailability at 40 mg dose was 42% in fasting volunteers3) and it was reduced when administered after food intake. The absolute bioavailability was increased to 97.2% in patients with hepatic impairment, and the Cmax and AUC0–24h in hepatic impairment patients were approximately 3-fold greater than those in healthy subjects.7) The Cmax and AUC showed dose-proportionality after intravenous administration of 10 to 120 mg

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dose, whereas $C_{\text{max}}$ increased disproportionally with dose after oral administration for both single and multiple dosing, which indicates the saturable first-pass metabolism.

Recently, population pharmacokinetic (PPK) analysis has been applied to new drug development for a variety of drugs. The PPK analysis is helpful to identify factors that affect the pharmacokinetics of a drug, or to explain variability in a target population. To date, however, there is no report on the PPK of telmisartan although this drug is widely used as an antihypertensive agent. In the present article, we have developed a PPK model for telmisartan by analyzing the pooled data obtained in the course of clinical trials in Japan. Since telmisartan shows a large individual variability in pharmacokinetics, it is useful to develop a PPK model by integrating the currently available information for this agent. The obtained PPK model explains several factors that can cause the inter-individual variability in pharmacokinetics, and the model is capable to describe and predict the plasma concentration-time profiles for patients with various backgrounds.

### Methods

#### Subjects and studies:
A total of 1566 plasma concentration data were collected from 149 subjects (20 healthy volunteers, 129 hypertensive patients) participated in four clinical trials conducted in Japan (Table 1). Table 1 shows the plasma concentration-time data of telmisartan used for the present population pharmacokinetic analysis.

The study 1 was performed to collect the pharmacokinetic data for the population analysis in hypertensive patients. Ninety hypertensive patients were administered a single oral dose of 20, 40 or 80 mg of telmisartan after breakfast. Ten blood samples were drawn from the vein of each patient, immediately before dosing and 1, 2, 3, 4, 6, 8, 10, 12 and 24 hours after administration. The study 2 obtained the pharmacokinetic data after multiple oral dosing in hypertensive patients. Twenty essential hypertensive patients were given 40 or 80 mg telmisartan once daily for 14 days. The study 3 was a pharmacokinetic study performed in 19 hypertensive patients with renal dysfunction (Serum creatinine: 1.5 to 4.0 mg/100 mL) to evaluate the influence of renal impairment on the pharmacokinetics of telmisartan. A dose of 40 mg was orally given once daily for 7 days. The study 4 investigated the effect of food. Twenty healthy male subjects received 40 mg of telmisartan orally as a single dose. The 221 plasma concentrations obtained in the fed condition were included in the data set, because our purpose was to obtain the PPK model in a standard clinical situation and because the other three studies were all conducted in the fed condition.

#### Assay of telmisartan concentrations:
Plasma concentrations of telmisartan were determined by a validated reverse-phase high-performance liquid chromatographic method using a column-switching technique. All plasma samples collected in the four clinical studies were analyzed by the same procedure at the Department of Drug Metabolism and Pharmacokinetics, Kawanishi Pharma Research Institute, Nippon Boehringer Ingelheim Co., Ltd. In brief, telmisartan was extracted and concentrated on an enrichment column (LiChroprep RP-8, 20 × 4.0 mm, 25 – 40 μm) using a mixture of acetonitrile-water-piperidine (235:800:0.16 [vol/vol/vol]) as the mobile phase. Quantification was made based on the peak height ratio of telmisartan to the internal standard, 4-(4-methyl-6-(1-methyl-2-benzimidazolyl)-2-butyl-1-benimidazolyl)[methyli]-2-biphenyl carboxylic acid, detected by a fluorescence detector (excitation 300 nm, emission 385 nm). The lower limit of quantitation of the present assay was 0.5 ng/mL. Intra- and inter-day variation of assay precision was less than 5% and the average bias was within 8%.

#### Demographic background of the subject population:
Demographic background for the population participating in the present PPK analysis is summarized in Table 2. A total of 149 subjects (20 healthy volunteers

<table>
<thead>
<tr>
<th>Study Number</th>
<th>Study Objective</th>
<th>Dose (mg)</th>
<th>Number of subjects</th>
<th>Number of measurements</th>
<th>Average number of measurements</th>
<th>Ref. No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pharmacokinetic study in hypertensive patients</td>
<td>20, 40, 80</td>
<td>90</td>
<td>784</td>
<td>8.7/subject</td>
<td>10</td>
</tr>
<tr>
<td>2</td>
<td>Pharmacokinetics and pharmacodynamics in hypertensive patients</td>
<td>40, 80</td>
<td>20</td>
<td>298</td>
<td>14.9</td>
<td>11</td>
</tr>
<tr>
<td>3</td>
<td>Pharmacokinetics and pharmacodynamics in hypertensive patients with renal dysfunction</td>
<td>40</td>
<td>19</td>
<td>263</td>
<td>13.8</td>
<td>12</td>
</tr>
<tr>
<td>4</td>
<td>Effect of food on bioavailability in healthy male volunteers</td>
<td>40</td>
<td>20</td>
<td>221</td>
<td>11.1</td>
<td>15</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td>149</td>
<td>1566</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
and 129 hypertensive patients) were enrolled in the study. A total of 1566 drug concentration measurements were pooled and used for computation. The study population comprised 107 males and 42 females. The age ranged from 20 to 77 years old, body weight from 30.5 to 118.3 kg, and serum creatinine from 0.59 to 4.10 mg/100 mL. The subjects received 20, 40 or 80 mg telmisartan by single or once daily multiple dosing after meal.

**Non-compartmental analysis:** Before developing a PPK model, individual AUC values were calculated by a non-compartmental analysis with linear trapezoid rule (WinNonlin® professional software version 3.1).

**Model development:** The PPK modeling was performed using the NONMEM program (double precision, version V, level 1.0) with its library subroutines ADVAN4 and TRANS4. A two-compartment open
Table 2. Description of the population participating in the present study

<table>
<thead>
<tr>
<th>Description</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of subjects</td>
<td>149</td>
</tr>
<tr>
<td>Number of healthy volunteers</td>
<td>20</td>
</tr>
<tr>
<td>Number of hypertensive patients</td>
<td>129</td>
</tr>
<tr>
<td>Gender: Male</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>42</td>
</tr>
<tr>
<td>Male</td>
<td>107</td>
</tr>
<tr>
<td>Dose: 20 mg</td>
<td>31</td>
</tr>
<tr>
<td>40 mg</td>
<td>78</td>
</tr>
<tr>
<td>80 mg</td>
<td>40</td>
</tr>
<tr>
<td>Alcohol consumption: Non-drinker</td>
<td>57</td>
</tr>
<tr>
<td>Drinker</td>
<td>92</td>
</tr>
<tr>
<td>Smoking history: Non-smoker</td>
<td>65</td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>19</td>
</tr>
<tr>
<td>Smoker</td>
<td>67</td>
</tr>
<tr>
<td>Food condition: Fasting condition</td>
<td>0</td>
</tr>
<tr>
<td>Non-fasting condition</td>
<td>149</td>
</tr>
<tr>
<td>Renal function: Normal (Scr: &lt;1.5 mg/100 mL)</td>
<td>128</td>
</tr>
<tr>
<td>Moderate impairment (Scr: 1.5–3.0 mg/100 mL)</td>
<td>10</td>
</tr>
<tr>
<td>Severe impairment (Scr: 3.0–4.0 mg/100 mL)</td>
<td>11</td>
</tr>
<tr>
<td>Hepatic function: Glutamic-oxaloacetic transaminase ≤60U</td>
<td>147</td>
</tr>
<tr>
<td>Glutamic-oxaloacetic transaminase &gt;60U</td>
<td>4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Values</th>
<th>Min–Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>50.5 ± 16.0</td>
<td>[20–77] °</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>63.9 ± 13.0</td>
<td>[30.5–118.3]</td>
</tr>
<tr>
<td>Serum creatinine (mg/100 mL)</td>
<td>1.22 ± 0.74</td>
<td>[0.79–4.10]</td>
</tr>
<tr>
<td>Glutamic-oxaloacetic transaminase (U)</td>
<td>22.5 ± 12.9</td>
<td>[5–97]</td>
</tr>
</tbody>
</table>

a) Mean ± S.D.  b) Minimum–maximum values.

The minimum value of the NONMEM objective function (MOF) was used as a statistic to choose suitable models during the model-building process. Since the difference in MOF between one model and the other approximates a χ² distribution with freedom of the number of parameter differences, a difference in MOF of 3.84 for 1 degree of freedom (p < 0.05) was considered statistically significant in the model-building process.

Covariate model: Starting from a simple two-compartment model, a variety of covariates that could influence the pharmacokinetics of telmisartan were stepwise added to the basic model (forward selection method). Statistical significance for incorporation of each covariate was judged based upon the MOF. Covariates considered for inclusion in the model were subject demographic factors (body weight, age, gender), laboratory tests (renal dysfunction), telmisartan dose, smoking history and alcohol consumption. Once a full model was developed which incorporated all possible covariates, each covariate was in turn examined by removing one by one to confirm the statistical significance (backward selection) using more stringent criterion of MOF with 6.63 (p < 0.01). The final PPK model was reached by remaining the significant covariates.

Model validation: Bootstrap resampling method was used to evaluate the stability and robustness of the final PPK model. The final PPK model was fitted repeatedly to the 200 additional bootstrap datasets. The
means of parameter estimates calculated from the 200 bootstrap replications were compared with the final parameter estimates obtained from the original dataset. Each pharmacokinetic parameter was logarithmically transformed to calculate 95% symmetric confidence intervals.

Results

Model development: A two-compartment open model with first-order absorption was used as a basic structural model, and additional PK parameter such as absorption lag time, random variables for inter-individual variability and covariates were added stepwise to develop the population model for telmisartan pharmacokinetics. The absorption lag time (ALAG) was necessary in the model because its incorporation significantly improved the model fitting (ΔMOF = 184.19, p<0.001). Random variables on the inter-individual variability were needed for the parameters CL/F, V1/F, Q/F and V2/F, but not for Ka and ALAG.

Starting from a simple structural model, a variety of covariates that are likely to influence the pharmacokinetics of telmisartan were added one by one and tested for its statistical significance (forward selection method). The body weight was used as a size factor and incorporated into the parameters CL/F, V1/F and V2/F. For CL/F, further covariates such as age, gender, dose, serum creatinine, alcohol consumption and smoking history were tested.

For continuous variables, the covariate modeling was described according to a power function as described by the following example.

\[ CL/F = TVCL \cdot SCr^{\theta_1} \]

where SCr is the serum creatinine and \( \theta_1 \) is the influence factor to be estimated. TVCL reveals a typical value of clearance, which describes the CL/F value where SCr has no effect. If \( \theta_1 \) is significantly different from zero, it is leaded that SCr is associated with CL/F. For categorical variables, covariates were modeled as follows.

\[ CL/F = TVCL \cdot GENDER \]

where the variable GENDER takes 1 for female and a parameter \( \theta \) for male. If \( \theta \) is significantly different from unity, there exists some gender difference in CL/F.

Among the examined covariates, age, dose, alcohol consumption and smoking history were found to be associated with CL/F. The renal function was not picked up as a possible factor affecting CL/F. The influence of hepatic dysfunction was not examined because the number of hepatic impairment subjects was so small (Table 2). On the other hand, age showed a significant influence on CL/F (ΔMOF = 23.582). Age was also suggested to be a factor for the V1/F and V2/F.

Telmisartan dose was important factor for CL/F, V1/F, Ka and ALAG since this factor significantly improved the model fitting. There observed a gender difference in V2/F. By the above forward selection step, the following full PPK model was suggested, which was described by age, dose (DAMT), alcohol consumption (ETOH), smoking history (SMOK), gender and body weight (WTKG).

\[
\begin{align*}
CL/F &= \theta_1 \cdot WTKG^{\theta_2} \cdot AGE^{\theta_3} \cdot DAMT^{\theta_4} \cdot ETOH^{\theta_5} \cdot SMOK \cdot \exp (\eta_{CL/F}) \\
V1/F &= \theta_1 \cdot WTKG^{\theta_2} \cdot AGE^{\theta_3} \cdot DAMT^{\theta_4} \cdot \exp (\eta_{V1/F}) \\
Q/F &= \theta_2 \cdot \exp (\eta_{Q/F}) \\
V2/F &= \theta_1 \cdot WTKG^{\theta_2} \cdot GENDER \cdot AGE^{\theta_3} \cdot \exp (\eta_{V2/F}) \\
KA &= \theta_1 \cdot DAMT^{\theta_4} \\
ALAG &= \theta_1 \cdot DAMT^{\theta_4} 
\end{align*}
\]

where ETOH = 0, for drinker, 1 otherwise. SMOK = 1 for ex-smoker, 1 for smoker, 1 otherwise.

GENDER = 1 for male, 1 for female.

Model refinement was then made by the backward selection, in which statistically insignificant covariates were removed from the above full model (Table 3). Remaining only statistically significant factors (p < 0.01) leaded to the final PPK model. Through this process, the covariates body weight and smoking history on CL/F, body weight on V1/F, and age on V2/F were removed from the model. Therefore, the refined final PPK model is described as follows.

\[
\begin{align*}
CL/F &= \theta_1 \cdot AGE^{\theta_2} \cdot DAMT^{\theta_3} \cdot ETOH \cdot \exp (\eta_{CL/F}) \\
V1/F &= \theta_1 \cdot AGE^{\theta_2} \cdot DAMT^{\theta_3} \cdot \exp (\eta_{V1/F}) \\
Q/F &= \theta_2 \cdot \exp (\eta_{Q/F}) \\
V2/F &= \theta_1 \cdot WTKG^{\theta_2} \cdot GENDER \cdot \exp (\eta_{V2/F}) \\
KA &= \theta_1 \cdot DAMT^{\theta_4} \\
ALAG &= \theta_1 \cdot DAMT^{\theta_4} 
\end{align*}
\]

where ETOH = 0, for drinker, 1 otherwise. SMOK = 0 for ex-smoker, 1 for smoker, 1 otherwise.

GENDER = 1 for male, 1 for female.

The PPK parameter estimates for the final model are summarized in Table 4. Figure 2 also shows the comparison of individual Cmax values observed and calculated by the final PPK model. Figure 2 also shows the comparison of AUC’s computed by non-compartmental trapezoidal rule and calculated by the final PPK model. Both plots show a good agreement, indicating the present PPK model is capable for describing the observed concentrations even though those showed a large individual variability. Figure 3 and Table 5 represent how each covariate affects the plasma concentration profile and pharmacokinetic parameters of telmisartan. As described, age and dose could be an important factor for individual variability.
The CL/F was found to be associated with age, dose and alcohol consumption, but not related to serum creatinine, gender or smoking history. As the total urinary excretion of telmisartan is extremely low, it is reasonable that CL/F was not affected by renal function. This finding was also consistent with the result of a separate clinical study in subjects with mild to moderate renal dysfunction. On the other hand, considering that telmisartan is mainly excreted via bile, it will be important to examine the effect of hepatic impairment on telmisartan pharmacokinetics. A particular clinical study was performed in Germany in subjects with hepatic impairment. C_{max} and AUC were increased in hepatic impairment subjects compared with healthy volunteers after oral administration of 20 mg or 120 mg of telmisartan. The pharmacokinetic profile of telmisartan in the subjects with hepatic impairment was characterized by rapid absorption and a slow terminal elimination phase. Since the number of patients with hepatic impairment was only four in the present dataset and this number was thought insufficient for the analysis, the effect of hepatic impairment could not be examined in this analysis.

The volume of distribution for the central compartment was related to age and dose, and the volume of distribution for the peripheral compartment was related to body weight and gender. The CL/F decreased with advancing age. A typical AUC value in 70-year-old subject was 1.36-fold greater than that in 30-year-old subject. The AUC in non-drinkers was on average 1.22-fold greater than that in drinkers. The absorption rate constant (Ka) and the absorption lag time were described as a function of dose.

The CL/F and Ka tend to decrease and increase, respectively, with increasing dose. This reflects the super-proportional increase in the plasma levels of telmisartan.

Model validation: The final PPK model was fitted repeatedly to the 200 additional bootstrap re-sampled datasets. All 200 estimation steps were completed successfully and the results are summarized in Table 6. The geometric mean of 200 parameter estimates were, in most cases, within ±10% difference from the final PPK parameters obtained with the original data set.

Discussion

The PPK model of telmisartan in healthy volunteers and hypertensive patients has been developed based upon the pooled pharmacokinetic data obtained in the four pre-marketing clinical trials conducted in Japan.
Population Pharmacokinetic Analysis of Telmisartan

As previously reported, the AUC for 80 mg dose was 6.45-fold greater than that for 20 mg dose. We also tried a nonlinear pharmacokinetic model, which has a Michaelis-Menten type formula in the absorption phase. But due to the complexity of the model, the computation did not reach the convergence. Although the present PPK model might be a pragmatic expedient from a theoretical viewpoint, this simpler model possesses the advantage of easy clinical applications for describing the factors causing the inter-individual variability or further exposure-response analysis.

As for the estimation step of NONMEM, FO method was used in the present analysis to minimize the calculation time. However, first-order conditional estimation (FOCE) method might be also useful for the estimation. In the previous clinical studies, a large individual variability in pharmacokinetic profile of telmisartan was observed. The large CV(%) values of interindividual variability in the basic model without any covariates reflect this characteristic. After the inclusion of selected covariates as fixed effects in the model, all of interindividual variability and intraindividual variability in the final PPK model were smaller than those in the starting basic model. This indicates that the final PPK model describes the population profile and factors affecting the pharmacokinetics of this agent. However, the CV(%) of interindividual variability especially for CL/F and V/F were still large, suggesting to require further population PK analysis to find out the causes of the variability.

The biotransformation of telmisartan consists exclusively of a phase II reaction, that is, conjugation to glucuronic acid by UDP-glucuronosyltransferases, yielding an acylglucuronide of the compound, but no phase I oxidative metabolites have been identified. It was reported that there are polymorphisms in UDP-glucuronosyltransferase genes. At this moment, there is no available information whether the genetic variation of UDP-glucuronosyltransferases is associated with the large interindividual variability in the metabolism of telmisartan. In addition, it was reported that the Cmax and AUC increased more than proportionally with respect to the dose and it is considered that the super-proportional increase of exposure is a consequence of saturable intestinal first-pass metabolism and high-affinity but limited-capacity uptake of telmisartan by the liver. These complex features might be another factor causing large individual variability in telmisartan pharmacokinetics.

As shown in Fig. 2A, the values of Cmax predicted by the present PPK model were well consistent with the observed values. Furthermore, the values of AUC predicted by this PPK model were in good agreement with the values determined by the non-compartmental analysis, at a range of 2 orders (Fig. 2B). These results indicated that the present PPK model is capable of describing and predicting the individual exposure to telmisartan taking into account various patient backgrounds. Thus, this PPK model will be useful to further exposure-response analysis for antihypertensive effect of telmisartan.

![Fig. 2. Comparisons of individual exposure to telmisartan (A: Cmax, B: AUC) observed or calculated by non-compartment method versus predicted by the Bayesian estimation based upon the final population pharmacokinetic model. The solid line represents the unit line.](image-url)
Fig. 3. Typical plasma concentration–time profiles of telmisartan at steady state, simulated for various patient subgroups. (A) 30 versus 70 years old, (B) male versus female, (C) drinker versus non-drinker, (D) 20, 40 or 80 mg dose.

Table 5. Influences of covariates on pharmacokinetic parameters of telmisartan

<table>
<thead>
<tr>
<th>Covariates</th>
<th>Estimated parameters</th>
<th>Calculated exposures</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Model No. Gender</td>
<td>Weight (kg)</td>
</tr>
<tr>
<td>1</td>
<td>Male</td>
<td>60</td>
</tr>
<tr>
<td>2</td>
<td>Female</td>
<td>60</td>
</tr>
<tr>
<td>3</td>
<td>Male</td>
<td>60</td>
</tr>
<tr>
<td>4</td>
<td>Male</td>
<td>60</td>
</tr>
<tr>
<td>5</td>
<td>Male</td>
<td>60</td>
</tr>
<tr>
<td>6</td>
<td>Male</td>
<td>60</td>
</tr>
</tbody>
</table>

* The underline represents the covariate changed from model No. 1.

The reliability and robustness of the final PPK model was validated by the bootstrap resampling method (Table 6). The means of parameter estimates for 200 bootstrap replicates of datasets were almost within 10% difference from the final PPK parameters obtained from the original dataset. Furthermore, all 200 trials of computation completed successfully. These results indicate the stability of the final model and the reliability of the parameter estimates.

In conclusion, a PPK model for telmisartan has been
development based upon the data obtained in the pre-marketing clinical trials. Several covariates such as age, gender, body weight, dose and alcohol consumption have been found to be factors that affect the individual variability in pharmacokinetics of telmisartan. The present PPK model well described the individual exposure to telmisartan, and the model has been validated for reliability and robustness.

References


