Population Analysis of the Dose-Dependent Pharmacokinetics of Zonisamide in Epileptic Patients

Yukiya Hashimoto, Atsuko Odani, Yusuke Tanigawara, Masato Yasuhara, Takehiko Okuno, and Ryohoi Hori

Department of Pharmacy and Department of Pediatrics, Kyoto University Hospital, Faculty of Medicine, Kyoto University, Sakyo-ku, Kyoto 606, Japan. Received August 4, 1993; accepted October 1, 1993

The pharmacokinetics of zonisamide was studied using routine therapeutic drug monitoring data from 68 epileptic patients. The 266 serum concentration data at steady-state after repetitive oral administration were analyzed using the nonlinear mixed effects model (NONMEM) program designed for estimation of population pharmacokinetic parameters. A one-compartment model with dose-dependent clearance was used for the pharmacokinetic analysis of zonisamide. The volume of distribution (V) was estimated to be 1.27 l/kg in a typical 33-kg patient, assuming that the bioavailability of orally administered zonisamide is 100%. The maximal daily dose to be cleared (V_max) and the concentration giving half maximal clearance (a Michaelis-Menten constant) was 27.6 mg/kg and 45.9 µg/ml, respectively. The parameter of a power function of weight to adjust V and V_max was estimated to be 0.741. In addition, V_max for zonisamide appears to be 13% increased in patients receiving carbamazepine concurrently. The population pharmacokinetic parameters of zonisamide will be useful for designing dosage regimens in epileptic patients.

Keywords zonisamide; population pharmacokinetics; dose-dependent kinetics; carbamazepine; drug interaction; NONMEM

Zonisamide (1,2-benzisoxazole-3-methanesulfonamide), a newly developed antiepileptic drug, has an anticonvulsant effect in experimental animals, and shows clinical efficacy for various types of epilepsy, especially refractory seizures.2,3 The best response to zonisamide is suggested to be attained at plasma levels of 20—30 µg/ml in the adult epileptic patients. However, because of the complex and nonlinear pharmacokinetics of zonisamide, it is difficult to design the dosage regimen.4-6 The pharmacokinetics of zonisamide after single oral administration can be analyzed by the simple linear compartment model, whereas the steady-state plasma levels are approximately three times higher than those predicted from a single dose study.4-6 Wagner et al.4,5 therefore, proposed a Michaelis-Menten kinetic model for the elimination of zonisamide, of which clearance is partially saturated at the doses used to treat epilepsy in the adult patient. However, the information about the pharmacokinetics of this drug is limited, especially in the pediatric patient.7

Another important therapeutic implication for the treatment of epilepsy is the drug interaction in pharmacokinetics, because many epileptic patients are often treated with multiple antiepileptic drugs which have a narrow margin of safety between effective and toxic levels. Sackellares et al.5 suggested the possibility that zonisamide induces the rise in concentration of concomitantly administered antiepileptic drugs. They also reported that the single-dose pharmacokinetic parameters of zonisamide in epileptic patients were different from those in normal human volunteers, and suggested that coadministered antiepileptic drugs may affect the pharmacokinetics of zonisamide: a time to reach peak concentration of 2.8 h and a mean elimination half-life of 28.4 h in patients vs. a time to reach peak concentration of 5.3 h and a mean elimination half-life of 62.9 h in normal volunteers.5,8

In the present study, we collected the routine therapeutic drug monitoring data of zonisamide from both pediatric and adult patients. The concentration data at steady-state after repetitive oral administration were analyzed with a dose-dependent clearance model using the nonlinear mixed effects model (NONMEM) program, which was designed for the estimation of population pharmacokinetic parameters.9,10 We also analyzed the effect of concomitantly administered carbamazepine on the disposition of zonisamide.

MATERIALS AND METHODS

Patients and Data Description Data were collected from 68 epileptic patients, who were treated with oral administration of zonisamide (Excergan tablet/powder, Dainippon Pharmaceutical Co., Osaka, Japan) at Kyoto University Hospital between November 1989 and July 1992. Table I depicts the characteristics of the 68 patients. Thirty patients were under 10 years old, and 5 patients were over 20 years old. Other antiepileptic drugs were also administered concurrently with zonisamide to most of the patients. The mean daily dose of zonisamide was 135 mg. Twenty-six patients were treated with only one level of zonisamide dose, whereas 17 patients received more than 3 dose levels. Two hundred sixty-six serum samples at steady-state after repetitive dosing (for more than one month) were collected for the pharmacokinetic analysis. Zonisamide was administered orally at 12 h intervals to 62 patients. The 208 serum samples were obtained for the measurement of approximate peak levels at 2 to 6 h after the dosing, and the 33 samples were obtained for the measurement of trough levels at 12 h after the dosing.

Assay of Zonisamide The serum concentration of zonisamide was measured by high performance liquid chromatography (HPLC).11 A 40 µl solution of N,N-dimethyl-zonisamide (an internal standard; Dainippon Pharmaceutical Co., Osaka, Japan) was added to the 0.1 ml
Table 1. Description of Patient Data Used in Population Analysis of Zonisamide Kinetics in the Epileptic Patient

<table>
<thead>
<tr>
<th>Description</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>68</td>
</tr>
<tr>
<td>Number of outpatients</td>
<td>60</td>
</tr>
<tr>
<td>Number of females</td>
<td>31</td>
</tr>
<tr>
<td>Age (years)</td>
<td>11.2 ± 6.4</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>33.4 ± 17.7</td>
</tr>
<tr>
<td>Number of patients taking zonisamide alone</td>
<td>2</td>
</tr>
<tr>
<td>Number of patients taking other anticonvulsants</td>
<td>2</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>37</td>
</tr>
<tr>
<td>Valproic acid</td>
<td>32</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>27</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>5</td>
</tr>
<tr>
<td>Daily dose of zonisamide (mg)</td>
<td>135 ± 104</td>
</tr>
<tr>
<td>Number of measurements</td>
<td>266</td>
</tr>
</tbody>
</table>

Mean ± S.D.

serum sample, and zonisamide was extracted into 5.5 ml of a chloroform–ethanol mixture (10:1). The organic layer was evaporated to dryness, and the residue was dissolved with ethanol. A 20 μl aliquot was injected into the HPLC system, which consisted of a solvent delivery pump (Tirrotor-III, Jasco, Tokyo, Japan) and a reversed-phase column (Chemcosorb 5-ODS-UH, 4.6 × 150 mm, Chemco Co., Osaka, Japan). The mobile phase consisted of an 80:11:10 mixture of 1% acetic acid, isopropyl alcohol, and acetonitrile, and the eluted zonisamide was detected at a wavelength of 235 nm (UVIDEC-100-III, Jasco, Tokyo, Japan).

Pharmacostatistical Model: Most of the serum samples were obtained to measure the peak and/or trough zonisamide levels for routine therapeutic drug monitoring purposes. Therefore, no significant absorption phase was observed in the serum zonisamide concentration data following oral administration. We used the one-compartment model following regular repetitive (bolus) dosing. Assuming that the elimination half-life of zonisamide is long enough as compared with the dosing interval, and that the clearance of the drug is constant in the inter-dose interval at steady-state after repetitive dosing, the serum drug concentration is described by the following equation:

\[
\text{SZC}_{ij}^d = D_{ij}V_i^d(e^{−CL_i^d\tau_{ij}}−e^{−CL_i^d\tau_{ij}/(1−e^{−CL_i^d\tau_{ij}})}
\]

where \( \text{SZC}_{ij}^d \) is the predicted \( j \)th serum zonisamide concentration in the \( i \)th individual, \( \tau_{ij} \) is the time after dosing associated with \( \text{SZC}_{ij}^d \), and \( D_{ij} \) is the dose given at the dosing interval, \( V_i \) is the volume of distribution and clearance in the \( i \)th subject, respectively.

The influence of body weight on volume of distribution of zonisamide was modeled using the following equations:

\[
\text{SIZE}_i = 33\cdot(WT_i/33)^{0.45}
\]

\[
V_i = V_{max} \cdot \text{SIZE}_i
\]

where \( \text{SIZE}_i \) is the hypothetical body size to adjust \( V_i \) in the \( i \)th individual, \( WT_i \) is the individual body weight in kg, and \( \theta_i \) is the model parameter to be estimated. \( V \) is the predicted population mean of volume of distribution. Modeling body size in this way allows the data to determine the optimal power function of weight to be used to adjust \( V_i \). Note that when \( \theta_i = 1 \), \( \text{SIZE}_i \) is simply linearly proportional to weight, and when \( \theta_i = 0 \), \( \text{SIZE}_i \) is independent of weight.

We assumed that the clearance of zonisamide is dose-dependent, and that carbamazepine influences its clearance. By rearranging the usual Michaelis–Menten model which is used to analyze the relationship between steady-state concentration and dose rate of phenytoin, we get the equation representing the relationship between clearance \( (CL_i) \) and dose rate \( (D_{ij}/\tau_{ij}) \) of zonisamide:

\[
CL_i = (V_{max} \cdot \text{SIZE}_i \cdot \theta_i^{m_{CE}} - D_{ij}/\tau_{ij})/K_m(1 + \eta_{CL_i})
\]

where \( V_{max} \) and \( K_m \) is the maximal daily dose to be cleared and the Michaelis–Menten constant (concentration giving half maximal clearance), respectively. We introduced \( \text{SIZE}_i \) to adjust the maximal dose rate \( (V_{max}) \) for the power function of weight, and modeled the effect of carbamazepine on the \( V_{max} \) value. \( \theta_i \) is the parameter to estimate the effect of concurrently administered carbamazepine on the clearance of zonisamide: that is, \( CBZ = 1 \) in case of the coadministration of carbamazepine, and otherwise \( CBZ = 0 \). In addition, for the interindividual variation, we assumed that the \( CL_i \) value is randomly and normally distributed from the predicted value. \( \eta_{CL_i} \) is a random variable to be distributed with zero mean and variance equal to \( \sigma_{CL_i}^2 \). This model postulates the dose-dependent clearance of zonisamide; however, it also enables us to explore another extreme condition. That is, if the \( K_m \) value is estimated to be the infinite (very large) value, the clearance of zonisamide is assumed to be independent of the dose rate.

Finally, the \( j \)th observed zonisamide concentration in the \( i \)th subject \( (\text{SZC}_{ij}^o) \) was assumed to be normally and normally distributed from the predicted value \( (\text{SZC}_{ij}^o) \):

\[
\text{SZC}_{ij}^o = \text{SZC}_{ij}^d \cdot (1 + \varepsilon_{ij})
\]

where \( \varepsilon_{ij} \) is a random variable describing intraindividual variability with mean zero and variance \( \sigma^2 \).

Data Analysis: Data analysis was performed with the NONMEM software (double precision NONMEM Version IV Level 1.1 and NM-TRAN Version II Level 1.1) on a FACOM M-1800 running under a MXP/M UNIX clone at the Kyoto University Data Processing Center. NONMEM allows us to estimate the population mean parameters, \( V \), \( V_{max} \), \( K_m \), \( \theta_1 \), \( \theta_2 \), and the interindividual variability, \( \sigma_{CL_i}^2 \), and also the intraindividual variability, \( \sigma^2 \). NONMEM provides estimates of the standard error for all the parameters, and standard error can be used to define confidence intervals for true parameter values. Statistical significance of the parameters was evaluated by the likelihood ratio test using the minimum value of the objective function \((-2 \log likelihood)\) produced by NONMEM. A \( p \) value less than 0.05 was considered to be statistically significant.

RESULTS AND DISCUSSION

The present study was designed to analyze the relationship between the daily dose of zonisamide and the steady-state serum concentration after repetitive oral administration. Prior to the parameter estimation using NONMEM, we preliminarily analyzed the pharmacoki-
natics of zonisamide, and explored the covariates influenci-
ing it. That is, we temporarily ignored the time-related
decreases of serum zonisamide concentration in the
inter-dose interval, and analyzed the relationship between
the daily dose of zonisamide \( D_i / \tau_{ij} \) and the serum
concentration at steady-state \( (SZC_{ij}) \) using the usual
Michaelis–Menten model\(^1\)–\(^3\):

\[
(D_i / \tau_{ij}) / SIZE_i = \frac{V_{\text{max},i} \cdot SZC_{ij} / (K_m + SZC_{ij})}{
}
\] (6)

where \( SIZE_i, V_{\text{max},i} \) and \( K_m \) have the same meanings as
those in Eqs. 1–4.

Figure 1 shows the relationship between daily dose and
serum concentration of zonisamide, and also the least
squares fit by Eq. 6. When the daily dose was corrected
by body weight (i.e., \( \theta_1 = 1.0 \) in Eq. 2), the daily dose–
concentration relationship in the younger patient was
significantly different from that in the older patient.
Grasela et al.\(^1\)–\(^3\) used the power function of weight
to adjust pharmacokinetic parameters of phenytoin and
procainamide, and found that the best power is 0.625 for
\( V_{\text{max}} \) of phenytoin and 0.78 for the volume of distribution
and clearance of procainamide. In the preliminary
analysis, we therefore used a hypothetical value, \( \theta_1 = 0.7, \)
for the power function of weight to adjust the daily dose
of zonisamide. Figure 2 shows the relationship between
the size-corrected daily dose vs. serum zonisamide concen-
tration in the younger and older patients. The least squares
fits by Eq. 6 were identical between the two groups, which
suggested that the age-effect on the pharmacokinetics of
zonisamide may be adjusted by use of a power function
of body weight.

Figure 3 shows the effect of the concomitantly ad-
ministered carbamazepine on the relationship between
size-corrected dose and serum concentration of zonisam-
ide. A slight but significant increase in \( V_{\text{max}} \) (not in \( K_m \))
was observed in the patients receiving carbamazepine,
suggesting a drug interaction between zonisamide and
carbamazepine. On the other hand, valproic acid and
phenytoin did not significantly affect the relationship
between the size-corrected dose and serum zonisamide
concentration (data not shown). In addition, it was difficult

![Fig. 1. Weight-Corrected Dose vs. Serum Concentration of Zonisamide in Younger (Less than and Equal to 10-Years Old, Closed Circles) and Older Patients (over 10-Years Old, Open Circles)](image1)

The solid (younger) and dotted (older) lines represent the least-squares fits using Eq. 6.

![Fig. 2. Size-Corrected Dose vs. Serum Concentration of Zonisamide in Younger (Less than and Equal to 10-Years Old, Closed Circles) and Older Patients (over 10-Years Old, Open Circles)](image2)

The solid (younger) and dotted (older) lines represent the least-squares fits using Eq. 6.

![Fig. 3. Size-Corrected Dose vs. Serum Concentration of Zonisamide in Patients Taking Zonisamide with (Open Circles) or without (Closed Circles) Coadministration of Carbamazepine](image3)

The dotted (with carbamazepine) and solid (without carbamazepine) lines represent the least-squares fits using Eq. 6.

### Table II. Final Estimates of Population Pharmacokinetic Parameters of Zonisamide

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>95% Confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>( V ) (l/kg)</td>
<td>1.27</td>
<td>0.38–2.16</td>
</tr>
<tr>
<td>( V_{\text{max}} ) (mg/d/kg)</td>
<td>27.6</td>
<td>22.6–32.6</td>
</tr>
<tr>
<td>( K_m ) (( \mu )g/ml)</td>
<td>45.9</td>
<td>34.9–56.9</td>
</tr>
<tr>
<td>( \theta_1 )</td>
<td>0.74</td>
<td>0.665–0.817</td>
</tr>
<tr>
<td>( \theta_2 )</td>
<td>1.13</td>
<td>1.02–1.24</td>
</tr>
<tr>
<td>( \alpha_{EI} ) (%)</td>
<td>29.7</td>
<td>25.2–33.6</td>
</tr>
<tr>
<td>( \sigma ) (%)</td>
<td>17.8</td>
<td>14.5–20.7</td>
</tr>
</tbody>
</table>

### Table III. Hypothesis Testing for Pharmacokinetic Parameters of Zonisamide

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Fixed value</th>
<th>l.d.(^a)</th>
<th>( p ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>( K_m )</td>
<td>10(^5)</td>
<td>111</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>( \theta_1 )</td>
<td>0</td>
<td>226</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>( \theta_2 )</td>
<td>1</td>
<td>39.5</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>( \theta_3 )</td>
<td>1</td>
<td>7.61</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

\( a\) = \(-2\log \text{likelihood difference between two models allowing the parameters of interest freely estimated versus fixed to a hypothetical value.} \)
to see the effect of phenobarbital on the pharmacokinetics of zonisamide, since only 5 of 68 patients received the drug concurrently with zonisamide.

Based on the preliminary investigations, we estimated the population pharmacokinetic parameters in Eqs. 1—5 using NONMEM. Table II lists the final estimates of the parameter and its 95% confidence interval. Table III lists the null hypothesis value for $K_m$, $\theta_1$, $\theta_2$, the $-2$ log likelihood difference associated with the null hypothesis, and the associated $p$ value. $V$ was estimated to be 1.27 l/kg in a typical 33-kg patient; however, the 95% confidence interval was large. All of the steady-state concentration of zonisamide may contribute to the estimation of $V_{\text{max}}$ and $K_m$ as suggested by Eq. 6, whereas $V$ should be deduced from a clearance value and an elimination half-life. In the present study, 78% of all serum samples were collected to measure approximate peak levels, and only 12% of samples were obtained for the measurement of trough levels. Thus, probably due to the limited information on an elimination half-life of zonisamide, it was not possible to obtain a very precise estimate of $V$. On the other hand, the 95% confidence intervals of $V_{\text{max}}$ and $K_m$ were small (Table II). When the $K_m$ value was set to the nearly infinite value (10$^5$), the objective function ($-2$ log likelihood) value was significantly increased (Table III). These results indicated that the estimated $K_m$ value (49.5 $\mu$g/ml) is significant, and that the pharmacokinetics of zonisamide is dose-dependent in the epileptic patient. The estimated $\theta_1$ value, in conjunction with the result of hypothesis testing, suggested that weight has a significant influence on $V$ and $V_{\text{max}}$ and that the optimum adjustment of these parameters should use weight to the power 0.741 ($\neq 1$). In addition, the effect of carbamazepine on $V_{\text{max}}$ ($\beta_1 = 1.13$) was statistically significant (Table III), and the clearance was suggested to be 13% increased in patients receiving carbamazepine. Finally, the interindividual variability of $CL_i$ ($\omega_{CL}$) was estimated to be 29.7%, and the intridual variability random error ($\sigma$) was $17.8\%$. Since all patients received only oral therapy, the extent of bioavailability could not be estimated and was assumed to be 100%. The effect of patient noncompliance may be included in the estimates of $\omega_{CL}$ and/or $\sigma$, and possibly the mean parameter estimates.

Figure 4 shows the simulated serum zonisamide concentration based on the population pharmacokinetic parameters for typical patients with body weight of 33 kg (a) and 10 kg (b). Three important therapeutic implications follow from the present results. Firstly, the elimination half-life of zonisamide is longer than the frequently used dosing intervals (12 h), which is consistent with the previous reports.$^{4,6}$ Secondly, the serum concentration of zonisamide shows a greater difference between the 10-kg and 30-kg patient, when the doses are corrected by body weight (not by body size). The results suggested that the correction of dose by weight may result in a considerable misconception for predicting zonisamide levels, particularly in the pediatric patient. Lastly, the $K_m$ value is relatively higher than the concentration achieved at the given doses to treat epilepsy (ca. 10 mg/d/kg), which is in contrast to the case of phenytoin.$^{13}$

In conclusion, we demonstrated the dose-dependent pharmacokinetics of zonisamide, and estimated the population pharmacokinetic parameters using drug concentration data obtained in routine clinical procedure. These findings will be useful for designing dosage regimens of zonisamide in epileptic patients.

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REFERENCES AND NOTES

1) Present address: Pharmaceutical Research and Technology Institute, Kinki University, Kowakae, Higashi-Osaka 577, Japan.