Population Pharmacokinetic Analysis of Daikenchuto, a Traditional Japanese Medicine (Kampo) in Japanese and US Health Volunteers

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Running title: Population Pharmacokinetics of daikenchuto constituents

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Number of text pages: 15

Number of Tables: 3

Number of Figures: 9

Number of References: 19

Number of Words:
  Abstract: 225
  Introduction: 502
  Results: 6820
  Discussion: 899

Abbreviations: DKT, daikenchuto; HAS, hydroxy-α-sanshool; HBS, hydroxy-β-sanshool; 6S, [6]-shogaol; 10S, [10]-shogaol; GRB1, ginsenoside Rb1; LC-MS/MS, liquid chromatography-tandem mass spectrometry; PK, pharmacokinetic; CL1/F, oral clearance of the central compartment; V1/F, volume of distribution for the central compartment; CL2/F, inter-compartmental clearance; V2/F, volume of distribution for the peripheral compartment; Ka, first-order absorption rate constant; BQL, below the quantification limit
ABSTRACT

We constructed population pharmacokinetic (PK) models for the five constituents of daikenchuto (DKT), a traditional Japanese herbal medicine. Data were collected from two randomized PK studies conducted in Japan and the US. Participants received single oral doses of 2.5 g, 5 g, and 10 g of DKT. The plasma concentrations of five DKT constituents, hydroxy-α-sanshool (HAS), hydroxyl-β-sanshool (HBS), 6-shogaol(6S), 10-shogaol(10S), and ginsenoside Rb1(GRB1) were determined by LC-MS/MS. A total of 1859 samples from 55 participants (US, n = 36; Japanese, n = 19) were included in the analysis. Population PK models of HAS, HBS, 6S, and 10S were best described by a one or two-compartment model with a bolus input. On the other hand, the model of GRB1 was best described by a one-compartment model with non-linear extra vascular input. Among the covariates evaluated, BMI and age were found to influence oral clearance (CL/F) and volume of distribution (Vd/F) for HAS and HBS, respectively. The influence of body weight on CL/F and Vd/F for 6S was demonstrated. Marked differences were observed in mean plasma concentrations of HAS and HBS between Japanese and US participants. However, the simulation results indicated that the difference in plasma concentrations may be attributed to the difference in demographic factors such as BMI, body weight, and age, whereas ethnic difference between the Japanese and US participants was considered minimal.
INTRODUCTION

Daikenchuto (DKT) is a traditional Japanese herbal medicine which consists of extracted three botanical raw materials, Japanese pepper, processed ginger, and ginseng radix (Kono et al., 2009). Ever since its approval as a prescription drug in 1986 by the Japanese Ministry of Health, Labour and Welfare, DKT has been widely used by gastroenterologists and surgeons for the treatment of various gastrointestinal disorders such as postoperative ileus and obstructive bowel disease (Itoh et al., 2002; Ohya et al., 2003; Kono et al., 2009). Consequently, the gastrointestinal effects of DKT have become a vibrant area of clinical and basic research in recent years. Several animal studies have reported that the ameliorating effects of DKT on laparotomy- or chemically-induced intestinal dysmotility and postoperative intestinal adhesion were abrogated by atropine, a 5-HT4 antagonist (Tokita et al., 2007), and a TRP-channel antagonist (Tokita et al., 2011), respectively, suggesting that the pro-motility and anti-adhesion effects of DKT likely occur via the activation of 5-HT4 receptors and TRP channel. Further, recent studies have addressed the possibility that DKT increases intestinal blood flow and ameliorate colitis via CGRP and/or adrenomedullin (Murata et al., 2002; Kono et al., 2008; Kono et al., 2010; Kono et al., 2011). The wide range of medicinal actions of DKT has been attributed to its multiple active constituents such as sanshools, shogaols, and ginsenosides. On the basis of a number of reports indicating the ameliorating effect of DKT in various animal GI disease models, several double-blind, placebo-controlled, randomized trials in patients with postoperative paralytic ileus, refractory functional constipation, irritable bowel syndrome, and Crohn’s disease are currently being conducted in Japan (JFMC39-0902, JFMC40-1001 and JFMC42-1002 funded by the Japanese Foundation For Multidisciplinary Treatment of Cancer) and in the United States (NCT00871325, NCT01139216, NCT01388933, and NCT01348152) with the U.S. FDA approval of DKT as an investigational...
new drug. Among these studies, one recent study reported that DKT has a prokinetic effect in healthy volunteers (Manabe et al., 2010).

Despite widespread use in clinical practice, the pharmacokinetic (PK) knowledge of DKT is limited. Recently, Iwabu et al. (2010) reported that 44 compounds derived from DKT were detected in the plasma and urine after oral administration of DKT by using the liquid chromatography-tandem mass spectrometry (LC-MS/MS). Moreover, Munekage et al. (2011) reported that the plasma concentration profiles of six pharmacologically active constituents of DKT, hydroxy-α-sanshool (HAS), hydroxyl-β-sanshool (HBS), 6-shogaol (6S), 10-shogaol (10S), ginsenoside Rb₁ (GRB1), and ginsenoside Rg₁ in Japanese healthy volunteers.

In recent years, the population PK approach has been used for the development of various pharmaceuticals (Williams and Ette, 2000). This approach can identify the measurable factors that cause changes in the dose-concentration relationship and the extent of these changes (FDA Guidance for Industry, Population Pharmacokinetics, 1999). In this study, we first sought to develop the population PK models for the five constituents of DKT using the plasma concentration data obtained from healthy volunteers participating in the Japanese or US study. We then determined whether potential inter-ethnic differences in the pharmacokinetics of DKT existed between the study populations.
Materials and Methods

Clinical Trials and Data Collection. Data were collected from two randomized, open label, three-arm, three-period crossover studies in Japan and the US. Participants received single oral doses of 2.5 g, 5 g, and 10 g of DKT after fasting for 12 hours at each period. A washout period of greater than one month followed Period I and Period II, preceding administration of the next dose of study drug. All foods and drinks (including spices) containing ginseng, Japanese pepper, and ginger were strictly prohibited from 3 days prior to dispensing the study medication until completion of each treatment phase. Overall study design is summarized in Figure 1.

In the Japanese study, 19 healthy volunteers enrolled and 18 completed the study, and a total of 560 observations at 0.25, 0.5, 1, 2, 3, 4, 8, 12, 24, and 48 hours after dosing were used for the population PK analysis. There were three participants who did not meet the eligibility criteria of the study. The effects of these data were evaluated by final population models as sensitivity analysis.

In the US study, 36 healthy volunteers enrolled and 30 completed the study, and a total of 1299 observation at 0.25, 0.5, 1, 2, 3, 4, 8, 12, 24, 48, 72, 96, and 168 hours after dosing were collected. Data from one subject were excluded from the dataset for the model building of GRB1 because the concentration-time profile showed a pharmacokinetically unreliable pattern. However, the entire dataset was re-evaluated using final population models.

Disposition and demographics of the participants are summarized in Table 1. Content of each DKT constituent in the study medication was comparable between the two studies (Table 2).

Determination of plasma concentration of DKT constituents. The concentrations of five DKT constituents, HAS, HBS, 6S, 10S, and GRB1 were determined by a validated LC-MS/MS
method as reported by Munekage et al. (2011). The limits of the quantification were 0.01 ng/mL for HAS, HBS and GRB1, and 0.02 ng/mL for 6S and 10S.

**Population Pharmacokinetic Model Building.** Population pharmacokinetic analysis was performed using the Phoenix NLME (Ver 1.3, Certara L.P., St. Louis, Missouri USA) by the Laplacian method.

One- or Two- compartment models with or without extra vascular input was examined for exploration of the mean structure of the modeling. The basic PK parameters used in this study were oral clearance of the central compartment (CL1/F), volume of distribution for the central compartment (V1/F), inter-compartmental clearance (CL2/F), volume of distribution for the peripheral compartment (V2/F), and first-order absorption rate constant (Ka). Non-linear absorption coefficient (b) was introduced for GRB1 population PK modeling as a power of dose (see supplement).

The interoccasion variability and the interindividual variability were modeled by lognormal distribution using Eq. 1;

\[ P_{ikj} = tvP_{ik} \cdot \exp (\eta_{ioc_{ikj}} + \eta_{ik}) \quad \text{Eq. 1} \]

where \( P_{ikj} \) is the \( k \)th pharmacokinetic parameter for the \( i \)th individual during the \( j \)th period, \( tvP_{ik} \) is the covariate adjusted typical value of the \( k \)th parameter. \( \eta_{ioc_{ikj}} \) is an interoccasion variability and \( \eta_{ik} \) is an interindividual variability. \( \eta_{ik} \) is Gaussian random deviate for the \( i \)th individual in the \( k \)th parameter with mean 0 and standard deviation \( \omega_k \). \( \eta_{ioc_{ikj}} \) is an independent Gaussian random deviate for the \( i \)th individual in the \( k \)th parameter during the \( j \)th period with mean 0 and standard deviation \( \omega_{ioc} \).

The residual variability was described by the proportional error model (Eq. 2) or combined...
proportional and additive model (Eq. 3).

The proportional error model;

\[ C_{\text{obs,ijt}} = C_{ijt} \cdot (1 + Eps_{ijt}) \]  

Eq. 2

where \( C_{\text{obs,ijt}} \) is the plasma concentration observed in the \( i_{th} \) individual, at time \( t \) after the drug administration during the \( j_{th} \) period. \( C_{ijt} \) is the predicted plasma concentration, and \( Eps_{ijt} \) is a random variable which is normally distributed with mean 0 and standard deviation \( \sigma \).

The combined proportional and additive model;

\[ C_{\text{obs,ijt}} = C_{ijt} + Eps_{ijt}(1 + C_{ijt} \cdot CMixRatio) \]  

Eq. 3

where proportional error component is obtained as the product of \( Eps_{ijt} \) and \( CMixRatio \).

Once the basic model was selected, the influences of covariates were evaluated by a stepwise procedure based on the likelihood ratio test using \( P < 0.05 \) as entry criterion. The covariate evaluated were the individual’s age, body weight, BMI, gender, and participation in the Japanese or US study (inter-study difference).

The influences of continuous covariates (age, body weight, and BMI) onto the \( k_{th} \) parameter were described as a power model as shown in Eq. 4;

\[ tvP_k = tvR_k \cdot \left( \frac{\text{Age}_{i}}{\text{median Age}} \right)^{dP_k\text{dAge}} \cdot \left( \frac{\text{WT}_{i}}{\text{median WT}} \right)^{dP_k\text{dWT}} \cdot \left( \frac{\text{BMI}_{i}}{\text{median BMI}} \right)^{dP_k\text{dBMI}} \]  

Eq. 4

where \( tvP_k \) is a typical value of \( k_{th} \) parameter, WT is the body weight, and \( dP_k\text{dAge} \), \( dP_k\text{dWT} \), \( dP_k\text{dBMI} \), are the fixed effect parameters for the age, body weight and BMI.

The influences of categorical covariate (gender and study identifier) were described as Eq. 5;

\[ tvP_k = tvR_k \cdot \exp(dP_k\text{dGender} \cdot G_{\text{female}}) \cdot \exp(dP_k\text{dStudy} \cdot S_{US}) \]  

Eq. 5

where \( G_{\text{female}} \) is a dummy variable which took on a value of 1 if the gender of the subject was female and 0 otherwise. Likewise \( S_{US} \) is a dummy variable which took on a value of 1 if the study was conducted in the US, and 0 otherwise.
BQL (below the quantification limit) values were treated as the left censored data and used in the model fitting procedure via the maximum likelihood method (Beal, 2001).

**Model validation.** Bootstrap re-sampling method (Ette, 1997) and visual predictive check method (Post et al., 2008) were used to evaluate the accuracy and robustness of our models. A total of 1000 re-sampling was executed for the bootstrap method, and a total of 1000 replicates of the original dataset were simulated for the predictive check method in order to generate the predicted concentration values and the 95% prediction interval.
Results

Demographics and disposition of the study participants are summarized in Table 1. A total 1859 samples from 55 participants were included in the population PK analysis. There were marked differences in subject demographics.

Figure 2 and 3 demonstrates observed (mean +/- SD, presented as dots) and the model predicted (population mean values, presented as solid lines) plasma concentration-time profiles of the five DKT constituents, HAS, HBS, 6S, 10S, and GRB1 after a single oral dose of DKT in healthy Japanese and US adults. Noticeable differences were observed in the mean plasma concentrations of HAS and HBS between the Japanese and US participants.

Final population PK parameters are summarized in Table 3

Population PK model of HAS was best described by a two-compartment model with a bolus input (see model equation in supplement). Interoccasion variability and interindividual variability were estimated for V1/F, CL1/F, and V2/F. The interindividual variation of PK parameters showed a positive correlation. A combined proportional and additive model was selected to describe the residual variability. BMI and age were the covariates affecting V1/F, V2/F and CL1/F. The relative standard error of estimation (RSE%) for the fixed effect parameters stayed within the range from 2.7% to 32.7% and the RSE% of random effect parameters ranged from 7.8% to 45.5% (Table S1-1 in supplement). Goodness-of-fit plot for the final population PK model showed no remarkable biases (Figure 4). The visual predictive check plots indicated that the predictive concentrations displayed a good fit with the observed concentrations (Figure S1-1 in supplement). All of the re-sampling successfully converged in the
bootstrap evaluation and the estimated parameters from bootstrap were similar to the parameters obtained from the final model (Table S1-1 in supplement).

The model for HBS, 6S, and 10S was best described by a one-compartment population PK model with a bolus input. Interindividual variability was estimated for V1/F and CL1/F. Regarding the interindividual variation of these two parameters, a positive correlation emerged for all constituents. Interoccasion variability was only calculated for HBS. A combined proportional and additive model was selected to describe the residual variability. For HBS, BMI and age affected V1/F and CL1/F as covariate. Similarly, body weight was incorporated into V1/F and CL1/F for the 6S model. However, the model for 10S retained no significant covariates. The RSE% for the parameters stayed within the range of 2.7% to 33.2% (Table S2-1, S3-1, and S4-1 in supplement). Goodness-of-fit plot for the final population PK model of HBS (Figure 5) and 6S (Figure 6) indicated no remarkable biases. The plots of the 10S model implied that the model contained a slight asymmetry at high concentrations (Figure 7). The visual predictive check plots indicated that there were good agreements between the predicted and observed concentrations (Figure S2-1, S3-1, and S4-1 in supplement). The re-sampling successfully converged in the bootstrap evaluation and the estimated parameters from bootstrap were similar to the parameters obtained from the final model (Table S2-1, S3-1 and S4-1 in supplement).

Population PK model of GRB1 was best described by a one-compartment model with non-linear extra vascular input. Interindividual variability was estimated for V1/F, Ka, and CL/F. The interoccasion variability was calculated for V1/F. No statistically significant covariate was incorporated into the model. For all estimated parameters, RSE% was considered acceptable.
within the range of 2.6% to 30.0%), except for the covariance between Ka and CL1/F, which showed greater RSE% due to the mean value nearly zero. (Table S5-1 in supplement) Residuals of population prediction and the observed value showed log-normal distribution. On the other hand, individual post-hoc estimation and observed value showed no remarkable biases (Figure 8). The visual predictive check plots indicated that the predictive concentrations were well fitted to the observed concentrations (Figure S5-1 in supplement). All of the re-sampling successfully converged in the bootstrap evaluation and the estimated parameters from bootstrap were similar to the parameters obtained from final model (Table S5-1 in supplement).

Figure 9 indicates that the influence of covariates on the calculated AUCs of DKT constituents, HAS, HBS and 6S. BMI showed a pronounced influence on the AUCs of HAS and HBS.
Discussion

We analyzed six pharmacologically active constituents of daikenchuto (DKT), hydroxy-α-sanshool (HAS), hydroxyl-β-sanshool (HBS), 6-shogaol (6S), 10-shogaol (10S), ginsenoside Rb₁ (GRB1), and ginsenoside Rg₁ (GRG1) in respective Japanese and US PK studies. Population PK models were constructed for the five constituents, but not for GRG1 because most of the GRG1 concentrations fell below detection limit.

When the first-order absorption model and the bolus input model were evaluated as population PK models for HAS, HBS, 6S, and 10S, the bolus input model was found to best describe the PK of these constituents. This was because the t_{max} was observed in many subjects at the first sampling point, which occurred at an early time point of 15 minutes. Wade et al. (1993) reported that when no data are present in the absorption phase, then the misspecification of the rate of drug absorption and/or the model used to describe drug absorption has little consequence on the estimation of the remaining population parameters. On the other hand, the goodness-of-fit plot of the model for 10S indicated that the predicted plasma concentrations overestimated the observed plasma concentrations at the highest predicted plasma concentration, i.e., the first sampling point. This was based on participants who were actually observed during the absorption phase. Without incorporating the absorption phase into the model, the plasma level in the proximity of C_{max} was unpredictable. Although the modeling is limited to an elimination phase, the model is considered still applicable to the pharmacokinetic characterization of the compound with a short absorption phase.

As reported previously in Japanese PK study (Munekage et al. 2011), nonlinearity was observed
in AUC of GRB1 but dose-dependence in half-life was not; therefore, non-linear absorption
model was assumed for the GRB1 analysis. As the result, nonlinear parameter (b) showed a
significant value, and AIC value indicated better fit as compared to the model not assuming the
nonlinear parameter. Estimated b value below 1 suggested the convex dose-concentration
relationship.

The BQL data included in the dataset were used for the analysis. Although useful information is
included in the BQL data, there are concerns regarding the possible bias caused by the
mishandling of BQL data. (Hing et al., 2001, Byon et al., 2008). Beal (2001) reported an
overview of ways to fit a PK model in the presence of BQL data. The method applied conditional
likelihood estimation to the observations above BQL and the likelihood for the data being above
BQL were maximized with respect to the model parameters. Phoenix NLME, which was the
analysis software used in this study, implemented this method. We therefore treated BQL data as
left censored data and used them in the model fitting procedure via the maximum likelihood
method.

Among the covariates evaluated, BMI, age or body weight were found to affect CL/F and Vd/F
for HAS, HBS, and 6S. The 3D plot (Figure 9) of the covariate relationship with AUC indicated
that BMI was the most important covariate to explain the AUC variability of HAS and HBS
because the AUCs decreased by two-fold when the BMI increased by two-fold from 18 to 30.
The package insert of DKT in Japan describes that the dosage may be adjusted according to the
patient’s age, body weight, and symptoms and our findings support this statement. However, it is
necessary to judge in consideration of clinical meaning about the necessity for dosage adjustment.
Remarkable differences were observed in mean plasma concentrations of HAS and HBS between the Japanese and US participants (Figure 2 and 3). However, inter-study difference has not been selected for the final models of all constituents of DKT. On the other hand, the simulated plasma concentrations at the median value of covariates in each study could reproduce the study difference observed. These results suggest that the difference in the plasma levels between the study populations could be explained by the difference in terms of demographic factors such as BMI and age, rather than the inter-ethnic difference between the Japanese and the US habitants.

The likelihood ratio test is frequently used as the criteria for the selection of covariates. The possibility of type 1 error inflation in the likelihood ratio test has been cautioned (Wählby et al., 2001). Therefore, a very low p value such as p < 0.001 is often used as the significance level. Nevertheless, as the first exploratory analysis of DKT via population modeling, we set a criterion of p value at 0.05 to increase the probability of detecting a greater number of covariates which might influence pharmacokinetic parameters. In order to protect against the inclusion of false covariates, more evaluations are needed.

Pharmacokinetic information is very useful to characterize a medication, and is indispensable to determine the proper use of the medication. However, the clinical effects of herbal medicines are complex due to the presence of numerous constituents. We therefore constructed PK models for five constituents of a single formulation that simultaneously contains constituents with very different PK properties, as seen from constituents with a short half-life such as shogaols and...
sanshools versus those with a long half-life such as ginsenosides. In order to effectively extrapolate our findings to a wider population, further investigation of the relationship between PK and efficacy is warranted.

The results from this study are useful and are a preliminary step towards a more comprehensive PK/PD study in patients.
Acknowledgments

We thank Masaru Kaneko, M.D., Ph.D (SNBL-CPC, Baltimore, MD, USA) for conducting the clinical trial in the US.
Authorship Contributions

Participated in research design: Munekage, Ichikawa, Kitagawa, Kono, Hanazaki

Conducted experiments: Munekage, Ichikawa, Kitagawa, Hanazaki

Performed data analysis: Ishihara, Uehara, Watanabe

Contributed to the writing of the manuscript: Munekage, Ichikawa, Kitagawa, Ishihara, Uehara, Watanabe, Kono, Hanazaki
References


channel in postoperative adhesive obstruction and its prevention by a kampo

the absorption process on subsequent parameter estimation in population analysis. J


Williams PJ and Ette EI (2000) The role of population pharmacokinetics in drug
development in light of the Food and Drug Administration's 'Guidance for Industry:
Footnotes

This study was supported by a grant from TSUMURA & CO., Tokyo, Japan.
Figure Legends

Figure 1. Study design chart

*) Japanese study; Pre-dose, 0.25, 0.5, 1, 2, 3, 4, 8, 12, 24, and 48 hours, US study; Pre-dose, 0.25, 0.5, 1, 2, 3, 4, 8, 12, 24, 48, 72, 96, and 168 hours

Figure 2. Mean plasma concentration of five DKT constituents in Japanese healthy volunteers.
A; HAS, B; HBS, C; 6S, D; 10S and E; GRB1
Each symbol represents mean ± SD of observed concentration.
Solid line indicated the model predicted concentration using the median values as covariate.

Figure 3. Mean plasma concentration of five DKT constituents in US healthy volunteers.
A; HAS, B; HBS, C; 6S, D; 10S and E; GRB1
Each symbol represents mean ± SD of observed concentration.
Solid line indicated the model predicted concentration using the median values as covariate.

Figure 4. Goodness of fit plot for HAS
A; Observations plotted against population predicted concentrations.
B; Observations plotted against individual predicted concentrations.

Figure 5. Goodness of fit plot for HBS
A; Observations plotted against population predicted concentrations.
B; Observations plotted against individual predicted concentrations.
Figure 6. Goodness of fit plot for 6S
A; Observations plotted against population predicted concentrations.
B; Observations plotted against individual predicted concentrations.

Figure 7. Goodness of fit plot for 10S
A; Observations plotted against population predicted concentrations.
B; Observations plotted against individual predicted concentrations.

Figure 8. Goodness of fit plot for GRB1
A; Observations plotted against population predicted concentrations.
B; Observations plotted against individual predicted concentrations.

Figure 9. Influence of covariates on calculated AUCs of DKT constituents.
A; HAS, B; HBS and C; 6S
Table 1 Disposition and demographics of the study participants.

<table>
<thead>
<tr>
<th>Type of subject</th>
<th>Japanese Study (TJ-100-4-2)</th>
<th>US Study (TU100CPT4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subject</td>
<td>Healthy volunteer</td>
<td>Healthy volunteer</td>
</tr>
<tr>
<td>Total</td>
<td>19</td>
<td>36</td>
</tr>
<tr>
<td>2.5 g</td>
<td>18</td>
<td>33</td>
</tr>
<tr>
<td>5 g</td>
<td>19</td>
<td>34</td>
</tr>
<tr>
<td>10 g</td>
<td>19</td>
<td>33</td>
</tr>
</tbody>
</table>

Participant demographics

<table>
<thead>
<tr>
<th>Gender (Male/Female)</th>
<th>14/5</th>
<th>28/8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (^{a)}\ (Year)</td>
<td>22 (20, 37)</td>
<td>42 (21, 56)</td>
</tr>
<tr>
<td>Body Weight (^{a)}\ (kg)</td>
<td>58 (44.5, 72.5)</td>
<td>81.1 (50.0, 97.8)</td>
</tr>
<tr>
<td>BMI (^{a)}\ (kg/m)</td>
<td>20.9 (18.5, 24.1)</td>
<td>26.9 (19.1, 29.9)</td>
</tr>
</tbody>
</table>

\(^{a)}\); Each data represents median (minimum, maximum).
Table 2 Content of each constituent in study medication (μg/g)

<table>
<thead>
<tr>
<th></th>
<th>Japanese Study (TJ-100-4-2)</th>
<th>US Study (TU100CPT4)</th>
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</thead>
<tbody>
<tr>
<td>HAS</td>
<td>591 ± 7</td>
<td>534 ± 6</td>
</tr>
<tr>
<td>HBS</td>
<td>100 ± 1</td>
<td>114 ± 2</td>
</tr>
<tr>
<td>6S</td>
<td>162 ± 1</td>
<td>167 ± 3</td>
</tr>
<tr>
<td>10S</td>
<td>43.3 ± 0.6</td>
<td>42.9 ± 2.1</td>
</tr>
<tr>
<td>GRB1</td>
<td>128 ± 2</td>
<td>155 ± 2</td>
</tr>
</tbody>
</table>

Each data represents mean ± S.D.
Table 3  Summary of Final population PK parameter for five constituents of DKT

<table>
<thead>
<tr>
<th>Pharmacokinetic model</th>
<th>HAS</th>
<th>HBS</th>
<th>6S</th>
<th>10S</th>
<th>GRB1</th>
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<tbody>
<tr>
<td></td>
<td>2-Compartment (bolus input)</td>
<td>1-Compartment (bolus input)</td>
<td>1-Compartment (bolus input)</td>
<td>1-Compartment (bolus input)</td>
<td>1-Compartment (non-linear extra vascular input)</td>
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<tr>
<td>Population Mean Parameter</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>V1/F [L]</td>
<td>13.2 \cdot (BMI^{1.90}) \cdot (AGE^{0.402})</td>
<td>14.4 \cdot (BMI^{2.19}) \cdot (AGE^{0.560})</td>
<td>4259 \cdot (WT^{0.933})</td>
<td>309</td>
<td>4384</td>
</tr>
<tr>
<td>CL1/F [L/hr]</td>
<td>7.69 \cdot (BMI^{1.66}) \cdot (AGE^{0.322})</td>
<td>6.95 \cdot (BMI^{1.37}) \cdot (AGE^{0.389})</td>
<td>8451 \cdot (WT^{0.041})</td>
<td>279</td>
<td>66.2</td>
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<tr>
<td>V2/F [L]</td>
<td>0.281 \cdot (BMI^{0.628}) \cdot (AGE^{0.509})</td>
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<td>CL2/F [L/hr]</td>
<td>0.0343</td>
<td></td>
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<td></td>
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<tr>
<td>Ka [h^{-1}]</td>
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<td></td>
<td>0.719</td>
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<td>b</td>
<td></td>
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<td>0.862</td>
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<td>Interoccasion Variability (CV [%])</td>
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<td>36.3</td>
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<tr>
<td>\omega_{iocV1/F}</td>
<td>13.9</td>
<td>24.1</td>
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<td>\omega_{iocCL1/F}</td>
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<td>28.6</td>
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<td>\omega_{iocV2/F}</td>
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<td>Interindivial Variability (CV [%])</td>
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<td>\omega_{V1/F}</td>
<td>16.2</td>
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<td>30.7</td>
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<td>\omega_{CL1/F}</td>
<td>23.0</td>
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<td>26.7</td>
<td>46.8</td>
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<td>\omega_{V2/F}</td>
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<td>\omega_{Ka}</td>
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<td>Correlation Coefficient</td>
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<td>V1/F vs CL1/F</td>
<td>0.982</td>
<td>0.994</td>
<td>0.789</td>
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<tr>
<td>V2/F vs CL1/F</td>
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<td>V1/F vs Ka</td>
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<td>0.792</td>
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<td>CL1/F vs Ka</td>
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<td>Residual error (S.D. [ng/mL] for additive, CV [%] for proportional)</td>
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<td>0.0162</td>
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<td>\sigma_{additive}</td>
<td>0.00481</td>
<td>0.0125</td>
<td>0.00558</td>
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<td>\sigma_{proportional}</td>
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<td>21.1</td>
<td>35.7</td>
<td>54.1</td>
<td>32.0</td>
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--; Not estimated
Figure 1

Screening

Randomization

Dosing

10 g

Dosing

10 g

Dosing

10 g

Sampling period*

2.5 g

2.5 g

2.5 g

Sampling period*

5 g

5 g

5 g

Sampling period*

Washout

≥30 days

Washout

≥30 days

Washout

≥30 days
Figure 2

A. HAS, Japanese Study

B. HBS, Japanese Study

C. 6S, Japanese Study

D. 10S, Japanese Study

E. GRB1, Japanese Study

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DMD Fast Forward. Published on April 1, 2013 as DOI: 10.1124/dmd.112.050112

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Figure 4

A

Observed Concentration (ng/mL) vs. Population Predicted Concentration (ng/mL)

B

Observed Concentration (ng/mL) vs. Individual Predicted Concentration (ng/mL)
Figure 5

A

Population Predicted Concentration (ng/mL) vs. Observed Concentration (ng/mL)

B

Individual Predicted Concentration (ng/mL) vs. Observed Concentration (ng/mL)
Figure 6

A

Observed Concentration (ng/mL) vs. Population Predicted Concentration (ng/mL)

B

Observed Concentration (ng/mL) vs. Individual Predicted Concentration (ng/mL)
Figure 8

A

Observed Concentration (ng/mL)

Population Predicted Concentration (ng/mL)

B

Observed Concentration (ng/mL)

Individual Predicted Concentration (ng/mL)