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PHARMACOKINETICS AND DISPOSITION

Therapeutic dosage assessment based on population pharmacokinetics of a novel single-dose transdermal donepezil patch in healthy volunteers

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Abstract
Purpose We performed population pharmacokinetic (PK) analysis of a novel transdermal donepezil patch in healthy subjects who participated in a phase I trial. We also studied the optimal dosage regimen with repeated patch application for achieving a therapeutic range using a PK simulation model.
Methods This study used data from a randomized, single-dose escalation phase I clinical trial conducted in Korea. The population PK analysis was performed using NONMEM software, version 7.3. From the final PK model, we simulated repeat patch application results assuming various transdermal absorption rates.
Results Based on the clinical trial data, novel donepezil patches with doses of 43.75 mg/12.5 cm^2, 87.5 mg/25 cm^2, and 175 mg/50 cm^2 were placed on each subject. A linear one-compartment, first-order elimination with sequential zero- and first-order absorption model best described the donepezil plasma concentrations after patch application. Simulated results on the basis of the PK model showed that repeat application of the patches of 87.5 mg/25 cm^2 and 175 mg/50 cm^2 every 72 h would cover the therapeutic range of donepezil and reach steady-state faster with fewer fluctuations in concentration compared to typical oral administrations.
Conclusion A linear one-compartment with sequential zero- and first-order absorption model was effective for describing the PKs of donepezil after application of patch. Based on this analysis, 87.5 mg/25 cm^2 or 175 mg/50 cm^2 patch application every 72 h is expected to achieve the desired plasma concentration of donepezil.

Keywords Donepezil · Transdermal · Population pharmacokinetics · Patch

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Introduction

Donepezil is a well-known reversible noncompetitive acetylcholinesterase (AChE) inhibitor for the symptomatic treatment of Alzheimer's disease (AD). Animal model studies as well as positron emission tomography (PET) imaging studies in humans have demonstrated the therapeutic effects of donepezil via inhibition of AChE in the cortex [1–3]. Several clinical trials have shown that 5- or 10-mg donepezil treatment is associated with cognitive improvement compared to the placebo [4, 5]. Chronic administration of oral donepezil using a therapeutic dose (5 or 10 mg/day) resulted in plasma levels of 30 to 60 ng/mL, which is comparable to the results of a pharmacokinetic (PK) study showing a mean concentration at steady state ranging from 26.4 to 47.0 ng/mL [6, 7]. The overall PK profile of donepezil is not affected by food or oral formulation; even age and hepatic function changes do not alter the maximum concentration and clearance [8, 9]. Generally, donepezil is thought to be safe for patients. Gastrointestinal symptoms, such as nausea, vomiting, and diarrhea, due to a cholinergic reaction are reported as frequent adverse reactions, the occurrence of which is associated with the initial starting dose. A starting dose of 10 mg/day appears

to result in a higher incidence of adverse reactions than a starting dose of 5 mg/day used over several weeks and eventually increased to 10 mg/day [10]. Because these exposure-related side effects are common in the class of AChE inhibitors, the transdermal route is an attractive alternative approach to drug delivery for AD, as it overcomes the drawbacks of oral administration [11]. A good example is the approval of the rivastigmine transdermal patch. Rivastigmine has a similar mechanism of action to other drugs used for the treatment of AD, such as AChE inhibitors. The side effects (gastrointestinal symptoms) of rivastigmine are likely related to high maximum concentration and short time to maximum concentration, as well as to large fluctuations in concentration [12]. These side effects can be attenuated either by increasing the dosing frequency or by using an alternative transdermal approach. In fact, the therapeutic efficacy of the transdermal route was proven in a clinical trial (Investigation of transDermal Exelon in ALzheimer's disease trial (IDEAL)), with a lower incidence of adverse events compared to the oral administration [13]. The rivastigmine patch is currently used as an application every 24 h.

Similar to that, to reduce these cholinergic side effects and maintain continuous drug effects by reducing plasma concentration fluctuations, a new route of administration via a transdermal patch of donepezil (Codename: IPI-001, ICure Inc, Gyeonggi-do, Republic of Korea) has been developed [11].

Based on findings from in vitro study using human cadaver skin, the rate of skin penetration is approximately 8.5 μg/cm^2/h; that is, about 7.7 mg of donepezil can be absorbed by a single drug delivery layer patch of 43.75 mg/12.5 cm^2 applied every 72 h (IPI-001 investigator's brochure, version 01, 2012). In comparison, the oral administration of 5 mg/day donepezil for 72 h would result in a total absorption of 15 mg (the bioavailability of donepezil is close to 100 %). Based on these figures, a phase I clinical trial of donepezil patch single administration was conducted [14]. Because there are currently no population PK data of donepezil patch reported, we conducted a population PK analysis on the basis of the data from that phase I study [14]. Furthermore, we predicted the optimal dosage regimen of the donepezil patch by simulating in the situation of various transdermal absorption rates, using the results of the PK analysis.

Materials and methods

Study design

This population PK analysis was conducted by using data from a phase I randomized, single-dose escalation study at Asan Medical Center (Seoul, Republic of Korea) (ClinicalTrials #NCT0180625) [14]. We conducted a single-blind, placebo-controlled study that tested novel donepezil patch doses of 43.75 mg/12.5 cm^2, 87.5 mg/25 cm^2, and 175 mg/50 cm^2. In each dosing group, 12 medically proven healthy subjects by their medical history, physical examinations, vital sign, electrocardiograms, and clinical laboratory tests, with aged between 20 and 45 years, were included and received donepezil or placebo (allocation ratio 3:1); all subjects were given a single administration of the drug by attaching and maintaining the patch on the upper back for 72 h [14]. While wearing the patch, the status of patch adhesion was evaluated every 12 h by two different clinical doctors. After removal of the patch, the residual amount of drug in the patch from each subject was measured to calculate the amount of transdermal absorption. Among the 36 subjects, 27 were administered an active donepezil patch and therefore included in the population PK analysis.

For PK measurements, 7-mL blood samples were collected at the following times: pre-dose and at 4, 8, 12, 24, 48, 70, 72, 74, 76, 80, 96, 120, 144, 168, 216, 264, and 312 h after patch placement. Plasma samples were immediately frozen at or below −20 °C, then stored at or below −70 °C until analysis. Samples were assayed at Hubertbio (Gyeonggi-do, Republic of Korea) using a validated method based on liquid chromatography/mass spectrometry system (LC-MS/MS system, API 4000™, AB SCIEX, CA, USA) [14]. The lower limit of quantification was 0.1 ng/mL.

This study was conducted in accordance with the International Conference on Harmonization (ICH) guidelines for Good Clinical Practice (GCP) and the Declaration of Helsinki. The institutional review board approved the study protocol prior to the study, and all subjects provided written informed consent before participating.

Population PK modeling

Structural model

Plasma concentration-time data for donepezil were modeled using the nonlinear mixed effects approach with the NONMEM software version 7.3 (Icon Development Solutions, MD, USA). The first-order conditional estimation (FOCE) with interaction method was used in the estimation. Both one- and two-compartment(s) models with first-order elimination were tested. Also, zero- and first-order kinetics and combined (parallel first-order, parallel zero-order, mixture of first- and zero-order, or sequential zero- and first-order kinetics) absorption models with or without lag time were tested to describe the transdermal absorption process. All developing various compartment models used the ADVAN6 subroutines.

For each PK parameter, an exponential random effects model was used, assuming that the random effect would have a normal distribution with a mean of zero and a variance of ω^2. The residual error model was evaluated to be additive, proportional, or combined. The best structural model was assessed

on the basis of the statistical and graphical methods. Goodness-of-fit plots and visual predictive checks (VPC) by simulating 1000 replicates were used. Also, in the likelihood ratio test used, a p value of 0.05 was considered statistically significant that represented a decrease in objective function value (OFV) of 3.84 points (chi-square distribution, degree of freedom (df=1).

Covariate evaluation

The influence of the following covariates on PK parameters was evaluated: age, total body weight (BW), height, BMI, area of the patch, and estimated glomerular filtration rate (GFR) based on the Modification of Diet in Renal Disease (MDRD) formula. Several covariate-parameter relationships (linear, piece-wise linear, exponential, and/or power functions) were tested as shown below:

Linear relationship

$$\theta_i = \theta_{\mathrm{TV}} \cdot (1 + \theta_{\mathrm{COV}} \cdot (\mathrm{COV} - \mathrm{median}))$$

Linear relationship (categorical variable)

$$\theta_i = \theta_{\mathrm{TV}} \cdot (1 + \theta_{\mathrm{COV}})$$

Piece-wise linear relationship

$$\theta_i = \theta_{\mathrm{TV}} \cdot (1 + \theta_{\mathrm{COV1}} \cdot (\mathrm{COV} - \mathrm{median}) + \theta_{\mathrm{COV2}} \cdot (\mathrm{COV} - \mathrm{median}))$$

Exponential relationship

$$\theta_i = \theta_{\mathrm{TV}} \cdot e^{\theta_{\mathrm{COV}} \cdot (\mathrm{COV} - \mathrm{median})}$$

Power function

$$\theta_i = \theta_{\mathrm{TV}} \cdot \left(\frac{\mathrm{COV}}{\mathrm{median}} \right)^{\theta_{\mathrm{cov}}}$$

where θ_{TV} is the PK parameter for a subject with a typical value of covariate(s)), θ_{COV} is the influence factor, COV is the individual value of covariate(s), and θ_i is the PK parameter considering the covariate effect. Specific covariates on PK parameters were included in a stepwise manner (forward direction) if there was a p value <0.05 difference (df=1); when a full model was obtained, each covariate was retested (backward direction) to determine whether to retain or remove it based on a p value <0.01 difference (df=1).

Model evaluation

The final model was evaluated on the basis of goodness-of-fit plots, various diagnostic plots (including dependent variable (DV) versus population predicted values (PRED), DV versus individual predicted values (IPRED), conditional weighted residuals (CWRES) versus PRED, and CWRES versus time), VPC, and the likelihood ratio test. In addition, bootstrap validation was used to evaluate the robustness of the final model. Five hundred datasets were reconstructed by resampling the subjects from the original dataset. The mean and standard error of the parameter estimates from bootstrap results were compared with the final estimate values.

Simulation

The optimal dose and duration of patch attachment were examined based on the results of the Monte-Carlo simulation with the NONMEM software version 7.3. Simulated datasets of 300 replicates with different percent of absorption (from patch to body through skin attachment site) range between 15 and 25 % in 72 h. Simulations were performed to assess PK profiles of donepezil that maintain the therapeutic range, compared to the known steady-state average concentration of oral administration of donepezil:

Case 1. Five repeat doses of 87.5 mg/25 cm^2 donepezil patches every 72 h for subjects whose typical transdermal bioavailability was 20 %.
Case 2. Five repeat doses of 87.5 mg/25 cm^2 donepezil patches every 72 h for subjects whose typical transdermal bioavailability was 15 %.
Case 3. Five repeat doses of 87.5 mg/25 cm^2 donepezil patches every 72 h for subjects whose typical transdermal bioavailability was 25 %.
Case 4. Five repeat doses of 175 mg/50 cm^2 donepezil patches every 72 h for subjects whose typical transdermal bioavailability was 20 %.
Case 5. Five repeat doses of 175 mg/50 cm^2 donepezil patches every 72 h for subjects whose typical transdermal bioavailability was 15 %.
Case 6. Five repeat doses of 175 mg/50 cm^2 donepezil patches every 72 h for subjects whose typical transdermal bioavailability was 25 %.

Results

This population PK analysis was performed using data of 485 plasma concentrations collected from 27 subjects. Characteristics of the subjects according to dose group are presented in Table 1. The average amount of transdermal absorption calculated by the residual amount in the patch after removal was approximately 20 % regardless of dose group (Table 1). All subjects maintained patch adhesion for at least >75 % of the 72 h, except one subject (group 2) who experienced patch detachment after 61 h and 38 min. Almost all patches remained at least >90 % adhered until 60 h after administration. Most of the subjects showed minimal erythema immediately after patch removal (72 h from application), and all were returned to normal spontaneously. The longest follow-up until reporting no irritation was 192 h from patch removal [14]. Two local adverse events (AEs) were reported: papules (one case, in 43.75-mg dosing group) and skin discoloration (one case, in 87.5-mg dosing group); both were spontaneously resolved without sequelae. Also, all drug-related systemic AEs (bilirubin increased, headache, nausea, vomiting, abdominal discomfort; one case each, except two cases of abdominal discomfort) were of mild severity [14].

The PKs of the donepezil patch were well described by the one compartment with a sequential zero- and first-order absorption model, which included the interindividual variability (IIV) of all PK parameters. Residual variability was described as a combined error model. To explain the absorption process, a depot compartment was added and the absorption amount from the patch to depot compartment was first described by zero-order kinetics (D_1, duration of zero-order absorption [hour]), followed by modeling of first-order absorption from the depot to central compartment (Fig. 1). Duration of zero-order kinetics from the patch to depot was fixed at 72 h, with using exponential IIV. For searching covariates, no significant influence was detected in the forward selection. The final model parameter estimates are shown in Table 2.

The observed plasma concentrations versus predicted and individual predicted concentrations showed an overall good fit (Fig. 2). In addition, no significant distribution trends around zero were seen in the plots for time and in the model predicting concentration versus CWRES (Fig. 2). The results of the bootstrap results are shown in Table 2. The success rate was 98.6 %, and the average bootstrap results with 90 % confidence intervals were approximately consistent with the estimated values. The individual predicted concentration-time plots are shown in Fig. 3, and visual predictive check (VPC) plots according to each dosing group are shown in Fig. 4.

Simulations for determining the optimal dose in various clinical situations for adult patients are shown in Fig. 5. Overall, the concentration was expected to reach complete steady state after the application of the fourth patch, but near steady-state concentrations were actually met after application of the third patch. Considering that the average steady-state concentration after a 5-mg oral dosage regimen of donepezil is approximately 26 ng/mL [15], an 87.5-mg patch administered every 72 h would give similar concentrations to repeat oral donepezil administrations of 5 mg. Also, a 175-mg patch every 72 h would give similar concentrations to the steady-state average concentration reached by an oral donepezil administration of 10 mg (47 ng/mL). During repeat administration of an 87.5-mg patch, changes in transdermal absorption rate would not result in significant fluctuations in concentration; meanwhile, the transdermal absorption rate would be more important in the case of a 175-mg patch. Considering the relatively wide 95 % prediction interval, the initial first and second administrations of a 175-mg patch would cause abrupt increases in donepezil concentration, which may be amplified when the

Table 1 Characteristics of the study subjects

	Single-dose administration of the donepezil patch		
	43.75 mg/12.5 cm^2 (N=9)	87.5 mg/25 cm^2 (N=9)	175 mg/50 cm^2 (N=9)
Age (year)	27.89 (4.99)	28.33 (6.60)	24.89 (3.30)
Height (cm)	176.12 (6.73)	171.67 (4.87)	175.22 (6.76)
Weight (kg)	71.05 (9.60)	68.54 (5.06)	71.21 (8.01)
BMI (kg/m^2)	22.80 (1.79)	23.30 (2.10)	23.09 (1.46)
GFR	123.72 (9.89)	135.81 (8.76)	137.67 (6.83)
Amount of absorption (mg)[a]	8.27 (1.47)	17.12 (4.06)	37.72 (4.59)
%Amount of absorption[b]	18.9 (3.37)	19.6 (4.64)	21.6 (2.62)

Data are presented as mean (SD)

BMI body mass index

[a] Amount of absorption=(amount in patch before application)−(residual amount in patch after detachment)

[b] %Amount of absorption=(Amount of absorption)/(Amount in patch before application)

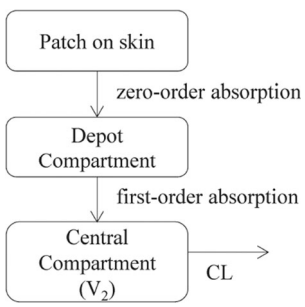

Fig. 1 Structure of the base model of the donepezil patch

Table 2 Population pharmacokinetic parameter estimates

Parameters	Estimates (RSE, %)	95 % CI	Bootstrap estimates (RSE, %)	Bootstrap 95 % CI
V_2 (L)	1140 (8.3 %)	954.58–1325.42	1142 (8.6 %)	987.08–1315.96
CL (L/h)	12.00 (7.3 %)	10.28–13.72	12.02 (7.6 %)	10.56–13.61
K_A (/h)	0.067 (8.5 %)	0.056–0.078	0.068 (9.6 %)	0.057–0.079
D_1	72.0 Fixed (–)	72.0 Fixed	72.0 Fixed (–)	72.0 Fixed
IIV of V_2	44.5 % (20.6 %)	0.108–0.254	0.173 (21.2 %)	0.115–0.234
IIV of CL	39.9 % (18.9 %)	0.093–0.203	0.142 (19.7 %)	0.096–0.188
IIV of K_A	41.8 % (39.1 %)	0.038–0.284	0.158 (45.3 %)	0.066–0.287
IIV of D_1	17.7 % (22.2 %)	0.017–0.044	0.030 (24.0 %)	0.019–0.042
ρ (V_2, CL)	38.8 % (20.3 %)	0.084–0.196	0.134 (21.2 %)	0.088–0.179
$\varepsilon 1$ (additive)	0.158 (15.3 %)	0.111–0.205	0.160 (16.2 %)	0.122–0.208
$\varepsilon 2$ (proportional)	0.083 (11.0 %)	0.065–0.100	0.082 (11.7 %)	0.067–0.098

IIVs were shown as coefficient of variation (CV (%), $\sqrt{(e^{\mathrm{OMEGA}}-1)} \times 100$). Residual random variabilities were modeled using combined error model, and interindividual variabilities were using a log-normal model

IIV interindividual variability, *RSE* relative standard error (SE/estimate × 100 %), *CI* confidence Interval, K_A absorption rate constant of the central compartment, V_2 central volume of distribution, *CL* total clearance of donepezil, D_1 duration of zero-order absorption into the depot compartment, ρ correlation of random effects

transdermal absorption rate is increased. Overall, continuous low transdermal absorption (about 15 % of bioavailability) would result in half of the average concentration profile compared to that of high absorption (about 25 % of bioavailability), regardless of the dose group.

Discussion

Our current study reports the results obtained from a population PK model of a single transdermal donepezil patch of various dosages in healthy male volunteers. The PKs of the donepezil patch were best described by a one-compartment model, first-order elimination with sequential zero- and first-order absorption. Our results are similar to those of a recent report of a population PK model for oral donepezil administration, also showing that a one-compartment model with first-order absorption and elimination best described the data [16]. Noetzli et al. reported an oral donepezil PK model on the basis of data from Caucasian patients and evaluated the effect of genotype as a covariate [16]. From their reported final model, gender and cytochrome P450 (CYP) *2D6* genotype were associated with the clearance of donepezil; women and CYP2D6 poor metabolizers were predicted to have decreasing clearance by −0.18 and −2.7 L/h, respectively, compared to the typical population. Meanwhile, CYP2D6 ultra-rapid metabolizers were estimated to have significantly higher clearance by 5.7 L/h. The estimated population mean of clearance was 8.6 L/h with IIV of 27 %. In contrast to those findings, our present study did not find any significant demographic covariates. This may be because our model included data on healthy male volunteers only, with relatively homogeneous features among subjects. Although we did not assess the *CYP2D6* genotype of each subject, the proportion of poor metabolizers of CYP2D6 among Koreans is generally low, compared to Caucasians [17]. Actually, when we applied mixture model on CL, there was no significant improvement ($p>0.05$). This difference may explain the slightly increased estimated value of clearance (population mean 12.0 L/h with IIV 19 %) in our study compared to previously reported values, but further genotype and ethnic factors should be evaluated.

Meanwhile, there have been few studies related to population PK models for patch drugs, fentanyl, or capsaicin patch cases [18, 19]. This might be partially due to the characteristics of the patch drugs itself; targeted drugs for transdermal application system almost have been focused on pain control (e.g., fentanyl, scopolamine) and/or compliance-related, to maximize the advantages of patch system. Because blood sampling would make additional discomfort and pain, relatively small PK samples would be obtained and measurement of pain-relief effect would be highlighted during pain control in clinical setting. In fact, these previously reported PK models for fentanyl and capsaicin used several fixed some parameters during estimation, because of the limited data during absorption process.

When we developed our PK model, the duration of zero-order absorption (D_1) from the patch to depot compartment was fixed at 72 h, because of facilitating to

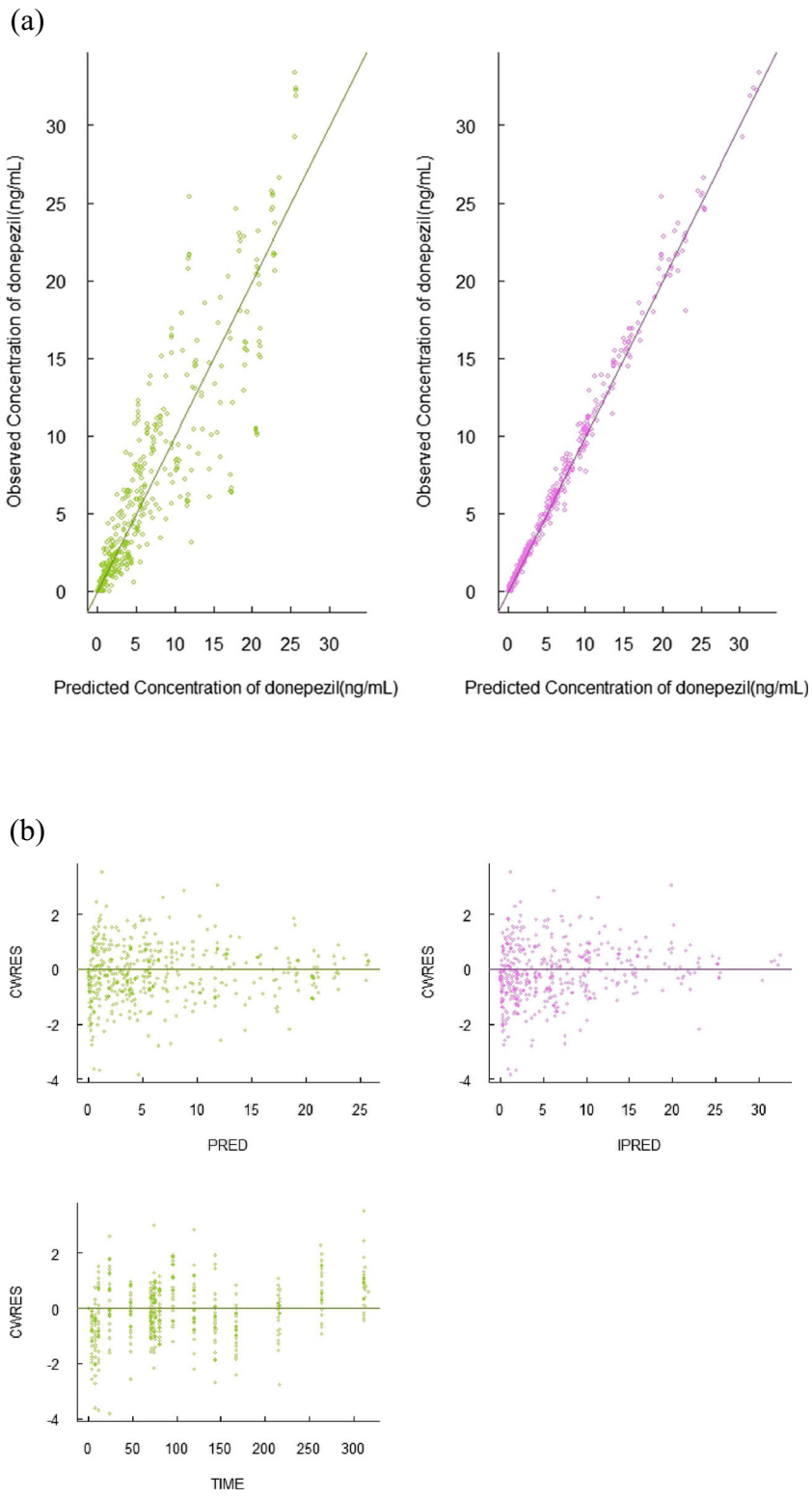

Fig. 2 Goodness-of-fit plots plots for the final population pharmacokinetic model of the donepezil patch. **a** Population predicted concentrations (PRED) versus the observed concentrations (*left*) and individual predicted concentrations (IPRED) versus the observed concentrations (*right*). **b** PRED versus conditional weighted residual (CWRES) (*upper left*), IPRED versus CWRES (*upper right*), and time versus CWRES (*lower left*)

apply the model to clinical setting when administration duration of patch is fixed. However, when we estimated D_1 as a parameter (theta), a statistically significantly lower OFV ($p<0.05$) than the OFV of model with fixed D_1 was observed, and the estimated parameter value was 60.6 h, with an IIV of 10 % in CV. This difference may be attributed to the time to maintain patch adhesion. From the clinical trial data used to develop this model, some subjects showed partial detachment of the patch (portion of attachment was about >75~>90 %, but

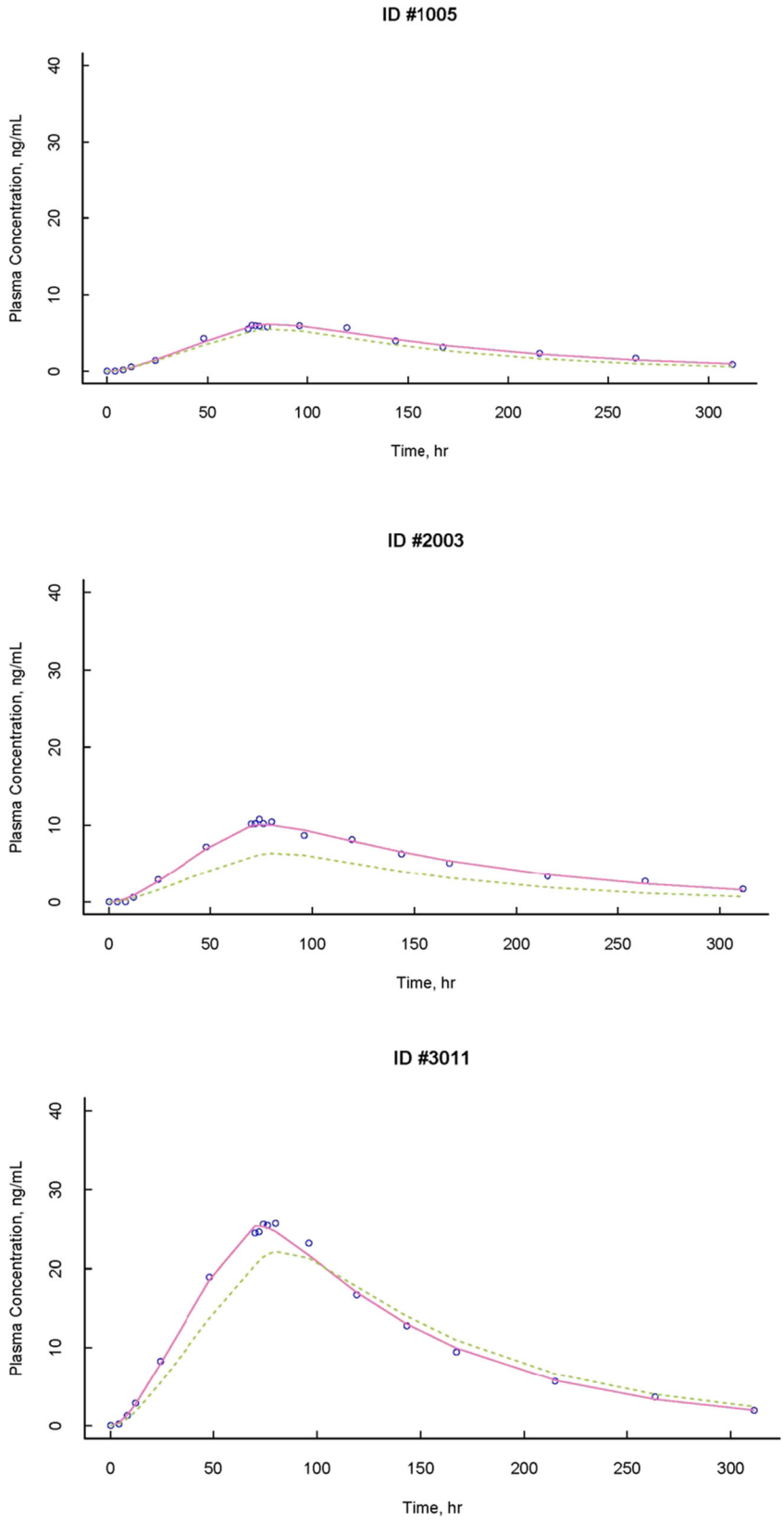

Fig. 3 Individual predicted (*solid line*) and observed (*open circle*) concentration-time plots. *Dashed line*: population predicted concentration-time values; each plot from *top* to *bottom* represents donepezil patch 43.75 mg/12.5 cm^2, 87.5 mg/25 cm^2, and 175 mg/50 cm^2 single-dose administrations, respectively

not 100 %) and partial detachment mostly occurred between 60 and 72 h. Furthermore, one subject experienced total detachment of the patch at 61 h from initial attachment. In future clinical settings, adhesion

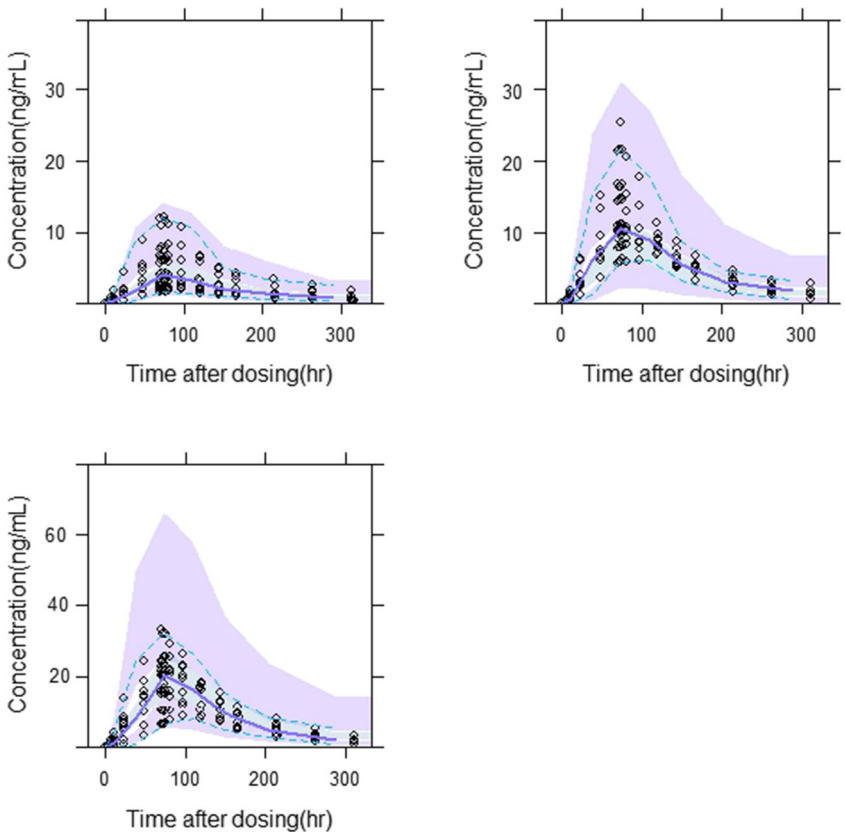

Fig. 4 Visual predictive checks of the final model of the donepezil patch by 1000 iterations (*solid line*: median of predicted values, *dashed line*: 5th and 95th percentiles of the predicted values, *open circle*: observed values, and *shaded area*: 5th and 95th percentiles of the confidence interval of the simulated concentration). *Upper left*: donepezil patch 43.75 mg/12.5 cm^2 dose group, *upper right*: 87.5 mg/25 cm^2 dose group, and *lower left:* 175 mg/50 cm^2 dose group

time could be made more stable by establishing a general dressing procedure for patch application, such as through the use of Tegaderm® medical dressing. In the phase I trial, the patch was placed on the subjects without covering dressings.

This novel donepezil transdermal patch is expected to have similar advantages to that of rivastigmine, such as maintaining concentrations within the therapeutic range with small fluctuations and decreasing the occurrence of cholinergic side effects. In addition, the longer dosing interval (72 h) compared to that of the oral administration could contribute to higher overall compliance [20–23]. In our current study, simulated results based on the final model showed that average concentrations would be similar to the steady-state concentration of oral administration of 5 to 10 mg/day. There is no defined therapeutic target range for donepezil, but recent published guidelines propose that 30~75 ng/mL [24] and patches of 87.5 mg/25 cm^2 and 175 mg/50 cm^2 would cover this range. Furthermore, target therapeutic concentrations would be reached in approximately 9 days, while 14 to 21 days are required to reach steady-state concentrations after oral administration, with known terminal disposition half-life of approximately 81 h [25, 26].

Although transdermal drug delivery could overcome the variability associated with gastrointestinal tract features, such as gastric pH, transit time, or food interference, characteristics of the drug molecule as well as certain patient factors may contribute to variations in drug levels. Local blood flow, metabolism by the CYP enzyme (e.g., CYP3A4) at the skin barrier [27, 28], and the lipophilicity of the molecule may affect the PKs of a drug delivered via transdermal administration. Following the patch application, the rate of donepezil absorption appeared to be relatively constant during a period starting 8–12 h after placement of the patch until removal at 72 h. After removal, concentration continued approximately 96 h and then declined, probably due to the continuous absorption from a cutaneous depot of drug at the site of application. This characteristic of delayed-onset and continuous absorption is similar to that of fentanyl transdermal application system [20, 21]. Fentanyl transdermal system application (duration to apply was 72 h) also showed steadily increasing its concentration starting at 8 h, and peak serum concentration reached up to 72 h after initial application [20, 22]. Similar to physiochemical properties of fentanyl [23], donepezil also has relatively low molecular weight (379.49) and high lipophilicity (LogP 3.6) (IPI-001

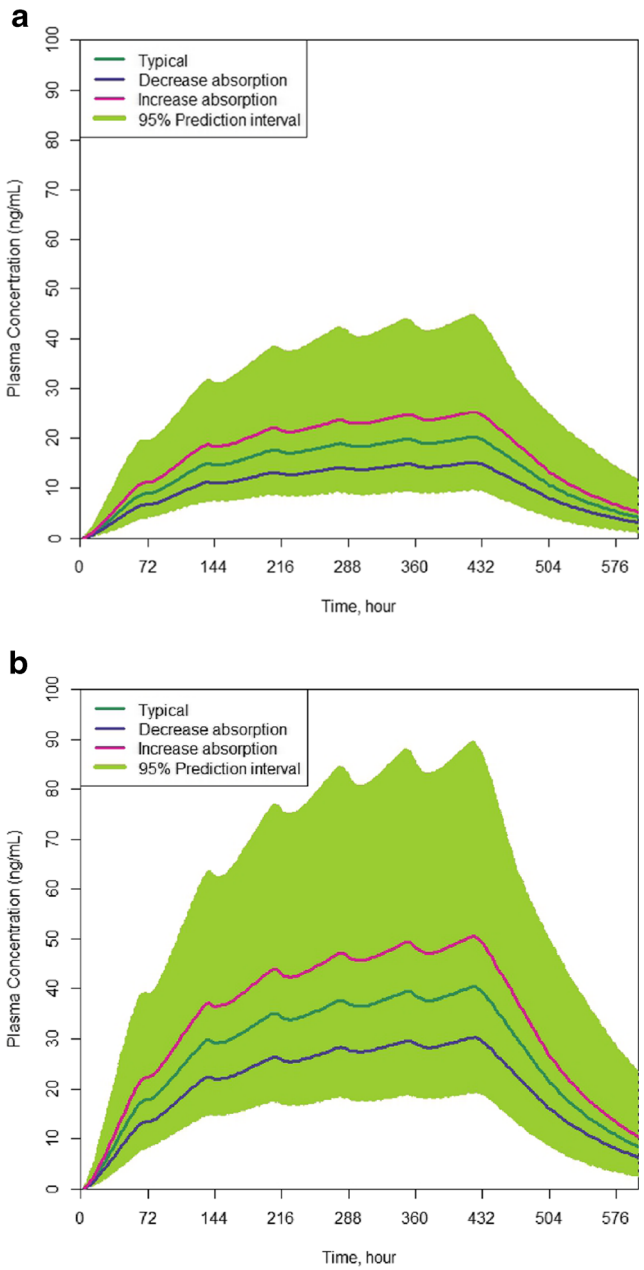

Fig. 5 The simulated plasma concentrations of donepezil in the study subjects, with 300 replications after repeat administrations of the patch every 72 h. **a** Donepezil patch 87.5 mg/25 cm^2 every 72 h. **b** Donepezil patch 175 mg/50 cm^2 every 72 h. The *green line* indicates the concentrations after 20 % of the patch drug quantity was absorbed through the transdermal route (typical). The *blue line* denotes simulated subjects who had a lower transdermal absorption (average 15 %). The *pink line* denotes cases with higher absorption (average 25 %). The *yellow-green-colored area* represents the 95 % prediction interval of the typical subjects

investigator's brochure, version 01, 2012). Although fentanyl has overall good characteristics to penetrate skin, the patch shows slow absorption because permeability constant was greatly lower than its removal by the regional blood supply [29]. Also, in a recent animal study using an electronic skin patch of donepezil, the time to reach peak concentration was at the time to removal (about 25 h) regardless of the strength of ionic current, which implied that the absorption of the drug might be limited by depot formation [30]. Although the patch used in our study was not same as that used in previous in vivo study, slow and continuous absorption during patch application might be explained by this phenomenon, considering the physiochemical characteristics of donepezil and complex local blood supply, similar to the fentanyl patch case. Relatively long half-life of donepezil might be also reflected this late and continuous absorption phenomenon.

Application site and skin irritation are also known to be important factors for the extent of absorption. In this study, the patch was applied on the upper back of all subjects, and no significant skin irritation and/or inflammation was detected [14]. Some drugs have been reported the PK characteristics independent of the application site, such as estradiol, norelgestromin, and fentanyl [29]. However, higher exposure was observed through the application on the chest, upper arm, and upper back compared to the thigh or abdomen from the rivastigmine case [31]. Therefore, evaluation of the extent of absorption of donepezil in the different application settings is also needed. However, no significant difference was observed in the drug exposure (maximum concentration or AUC) between elderly and adult populations after patch drug administrations in recent reports, although the aging process theoretically affects the integrity of skin barrier and drug penetration [29]. Similarly, there has been no definite evidence of a marked PK difference between men and women [32]. Meanwhile, no differences have been found in the range of concentrations between healthy subjects and patients after oral administration; a previous study reported that plasma levels of donepezil are approximately 30 to 60 ng/mL following oral donepezil administration in AD patients over a period of 12 to 24 months [6]. All things taken together, the results to date suggest that predicted drug concentrations could be expanded to elderly patients. However, since simulation results have been based on data from healthy subjects, further studies are needed in a wider range of patients.

In conclusion, the PKs of the novel donepezil patch are best fitted by a one-compartment model, first-order elimination with sequential zero- and first-order kinetics absorption. From the population PK model-based simulation, 87.5 mg/25 cm^2 or 175 mg/50 cm^2 patch application every 72 h is expected to achieve the desired plasma concentration of donepezil.

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