Pharmacokinetic modeling of Donepezil after transdermal administration in rat

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Objectives

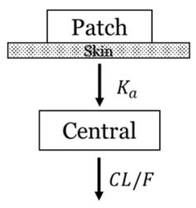
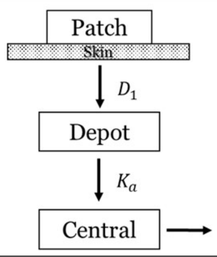
Donepezil (DPZ) is a widely used for treatment of Alzheimer's disease. But, most of patients were suffered from gastrointestinal symptoms such as nausea, vomiting, and diarrhea at a high start dose. Thus, transdermal administration is proposed to provide continuous drug delivery, leading to reducing side effects. The aim of this study was to develop a population pharmacokinetic (PK) model of transdermal DPZ patch in hairless rats to predict human first dose of DPZ.

Method

- **Study design**
  - The plasma concentration of donepezil was collected from the hairless rats during 0 to 168 hours after administration of transdermal patch at 6 dose-group
  - Two type of patch was used (circle shape and square shape) and each patch type with three different dose was administered.
  - Amount of DPZ in each group was controlled by the area of the patch

Group 1 (n=5)	Group 2 (n=5)	Group 3 (n=5)
Dose(average) = 2.4 mg	Dose(average) = 4.8 mg	Dose(average) = 7.9mg
		
Group 4 (n=4)	**Group 5 (n=4)**	**Group 6 (n=3)**
Dose(average) = 4.87 mg	Dose(average) = 10.13 mg	Dose(average) = 19.53 mg
		

- **Pharmacokinetic model**
  - Population PK analysis was performed using non-linear mixed effect modeling (NONMEM) software ver. 7.3.
  - When developing a compartment model with the patch data, it was difficult to construct an appropriate compartment model due to the delay of absorption of the patch.
  - We used plasma concentration data after intravenous injection of donepezil in rat data to set compartment model in this study.

1-compartment with first order absorption	1-compartment with zero- and first- order absorption
	

- **Model evaluation**
  - A combination of zero- or first-order absorption with or without lag time was tested to consider the drug disposition from skin to central compartment.
  - Inter-individual variability was evaluated using additive, proportional, and exponential model and residual error model was evaluated using additive, proportional and combined.
  - All parameter of final model was estimated using first-order conditional estimation with interaction method (FOCE + I).
  - Final model was selected considering the objective function value (OFV) , the goodness-of-fit and evaluated with visual predictive check (VPC, n=1,000) method

- **Simulation study**
  - To searching optimized first dose in human DPZ patch, simulation study was assessed using final PK model
  - Plasma concentration in rat after fivetimes multiple administration of DPZ patch was simulated using our final model with 6 group's dose.
  - Simulation data in steady state , The optimal dose was calculated by using the number of concentration values in a target range (20-40ng/mL)
  - Comparing the number of concentration values in a target range at each dose, the dose with the gratest values is the optimal dose in rat
  - Calculating the number of concentration values in a target range is followed below equation

$$\textit{The number of concentration values in a target range}(\%) = \frac{\textit{Number of value in Target range}}{\textit{Number of all value in steady state}}$$

  - To simulate the human data, we substitute human PK parameter studied at other reference with DPZ patch in our final pharmacokinetic model. At the same way with the rat simulation step, using the number of concentration values in a target range, we calculated the human optimal dose.

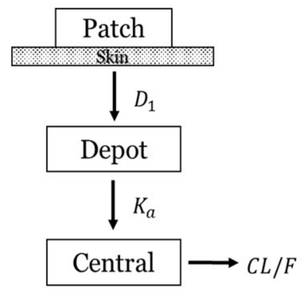
Used Parameter	Estimated value (% RSE)	IIV CV% (% RSE)
k_a (hr^{-1}) : first ordr absorption rate	0.067 (8.5%)	41.8% (19.5%)
V_c/F (L) : volume of distribution	1140 (8.3%)	44.5% (15.8 %)
CL/F (L/h) : clearance	12.00 (7.3%)	39.9% (8.8%)
D1 (hr) : duration of zero order absorption	72 Fixed (-)	17.7% (22.2%)
Residual variability (% RSE)		
Additive error	0.158 (15.3%)	
Proportional error	0.083(11.0%)	

  - Finally, we extrapolated the rat optimal dose to human dose for the body surface coefficient given in FDA guidance (Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Adult Healthy Volunteers) and got the ratio between extrapolated optimal dose and simulated human dose to evaluate our final pharmacokinetic model.
    - ➢ *Human optimal dose(mg/kg) * 6.2 (Inter-species scaling factor) = Rat optimal dose(mg/kg)*

Results

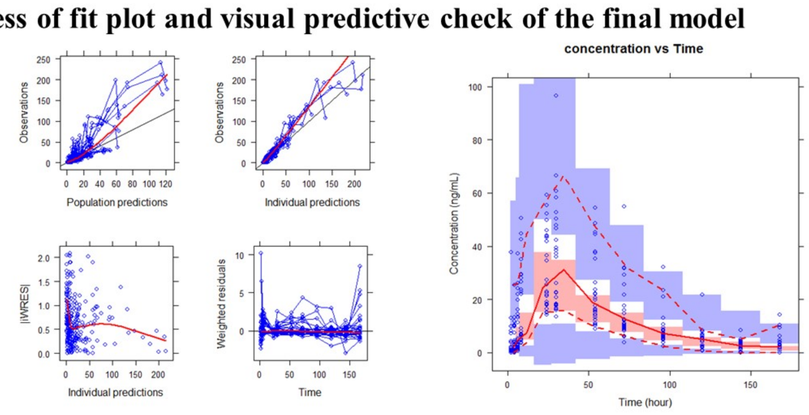
- **The final pharmacokinetic model**
  - From 332 plasma concentrations (n=34), the final model was developed using one-compartment model with sequential zero- and first-order absorption

Parameter	Estimated value (% RSE)	IIV CV% (% RSE)
k_a (hr^{-1}) : first order absorption rate	0.0213 (11%)	52.7% (19.5%)
V_c/F (L) : volume of distribution	17.3 (37%)	170.2% (15.8 %)
CL/F (L/h) : clearance	2.41 (11%)	49% (8.8%)
D1 (hr) : duration of zero order absorption	12.2 (22%)	-
Residual variability (% RSE)		
Proportional error	0.491 (7%)	



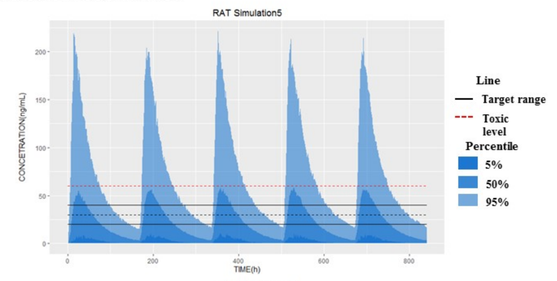
  - These estimated parameters were reasonable to reflect the physiologic feature of transdermal administration.

- **The goodness of fit plot and visual predictive check of the final model**

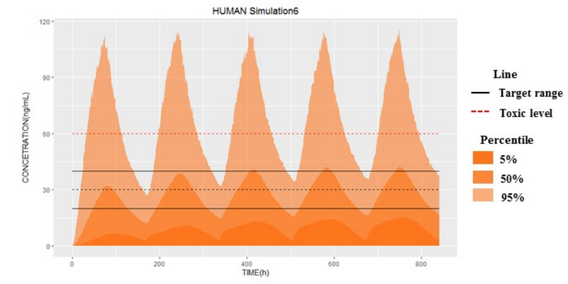


- **Simulation result**
  - The number of concentration in target range in each scenario.

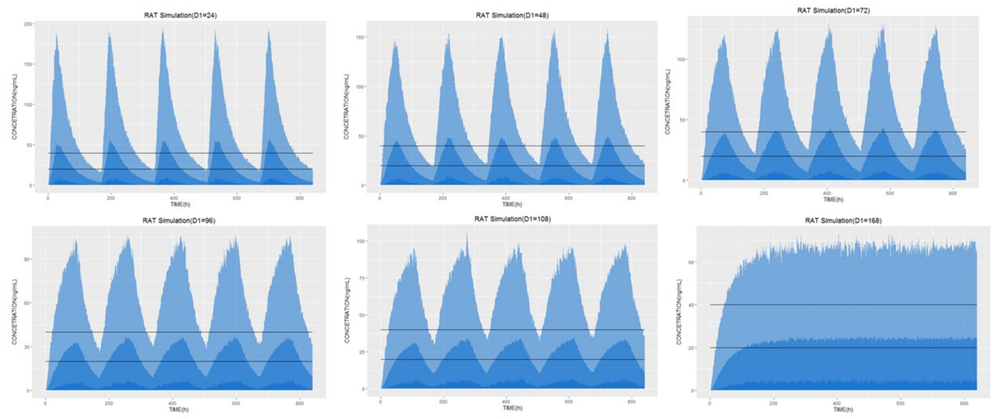
Rat scenario	Dose (μg)	Number of concentration in target range (%)	Number of concentration in toxic level (%)
1	2400	5.48	0.29
2	4400	13.4	2
3	4870	14.8	2.61
4	7900	20.07	8.05
5	10130	21.76	12.68
6	19530	20.58	30.13



Human Scenario	Dose (μg)	Number of concentration in target range (%)	Number of concentration in toxic level (%)
1	8270	0.41	0
2	17120	6.29	0.057
3	37720	32.27	2.36
4	40000	34.33	2.95
5	50000	41.26	6.24
6	60000	43.02	10.58



  - Simulation with changing of parameter D1(duration of zero-order absorption)



Comparing the optimal dose	Rat (280g)	Human (70kg)
Optimal dose(mg)	10.13mg, 36.17 mg/kg	60mg, 0.86 mg/kg
Converting to human dose	36.17 / 6.2 = 5.8 mg/kg	0.86 mg/kg
Ratio	5.8 / 0.86 = 6.74	

Discussion

- A transdermal absorption PK model was successfully developed using donepezil data and acceptable parameters were estimated.
- Especially, estimated parameters of absorption phase were reasonable to reflect the physiologic feature of transdermal administration.
- The optimal dosage in the rat model developed in this study is 6.74 times bigger than the optimal dose in humans.
- The best reason of occurring this difference should be the formulation of DPZ patch with our study and the other study(reference) used parameter in the human data simulation step
- The variabilities due to formulation in patch data, this difference can be acceptable.
- For the well-predicted the human first dose in DPZ patch, the accurate comparison of the optimal dose between human and another animal will be possible with the same formulation.

Reference

[1] P.J.Tiseo, S.L.Rogers & L.T.Friedhoff. (1998) Pharmacokinetic and pharmacodynamics profile of donepezil HCL following evening administration

[2]HY Choi, YH Kim, DH Hong, SS Kim, KS Bae, HS Lim. (2015) Therapeutic dosage assessment based on population pharmacokinetics of a novel single-dose transdermal donepezil patch in healthy volunteers

Acknowledgement

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