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Pharmacokinetic Modeling to Simulate the Concentration-Time Profiles After Dermal Application of Rivastigmine Patch

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ABSTRACT

Rivastigmine is an inhibitor of acetylcholinesterases and butyrylcholinesterases for symptomatic treatment of Alzheimer disease and is available as oral and transdermal patch formulations. A dermal absorption pharmacokinetic (PK) model was developed to simulate the plasma concentration-time profile of rivastigmine to answer questions relative to the efficacy and safety risks after misuse of the patch (e.g., longer application than 24 h, multiple patches applied at the same time, and so forth). The model comprised 2 compartments which was a combination of mechanistic dermal absorption model and a basic 1-compartment model. The initial values for the model were determined based on the physicochemical characteristics of rivastigmine and PK parameters after intravenous administration. The model was fitted to the clinical PK profiles after single application of rivastigmine patch to obtain model parameters. The final model was validated by confirming that the simulated concentration-time curves and PK parameters (C_{max} and area under the drug plasma concentration-time curve) conformed to the observed values and then was used to simulate the PK profiles of rivastigmine. This work demonstrated that the mechanistic dermal PK model fitted the clinical data well and was able to simulate the PK profile after patch misuse.

Introduction

Rivastigmine is a slowly reversible (pseudo-irreversible), centrally selective dual inhibitor of acetylcholinesterase and butyrylcholinesterase, which increases the available acetylcholine levels and improves neurotransmission. It has established efficacy in the symptomatic treatment of Alzheimer disease[1-3] and Parkinson disease dementia (PDD)[4] and was shown to improve activities of daily living, cognition, behavior, and global function.[2,5-8] Studies of dose–response relationships for cholinesterase inhibitors support greater enzyme inhibition, in turn leading to higher efficacy and long-term benefits with higher drug doses.[9]

Rivastigmine has been developed for oral twice daily administration as capsule (3, 6, 9, and 12 mg/d) and as solution (2 mg/mL) and for transdermal daily administration as patch (5 cm^2 [4.6 mg/24 h], 10 cm^2 [9.5 mg/24 h], 15 cm^2 [13.3 mg/24 h] and 20 cm^2 [17.4 mg/24 h]; of note: the 20-cm^2 patch has not been launched to market to date). Transdermal patch is an optimal way to deliver rivastigmine and provides many benefits over conventional oral treatments, allowing patients easier access to optimal therapeutic doses.[10] Treatment with rivastigmine patch is initiated with the 5-cm^2 (4.6 mg/24 h) patch, which when well tolerated, is uptitrated to the 10-cm^2 (9.5 mg/24 h) patch and beyond based on individual responses to obtain the desired therapeutic benefits.[11] In Japan, more gradual titration approach starting from 2.5 cm^2 and followed with 5 cm^2, 7.5 cm^2, and 10 cm^2 is also available.[12] All patch sizes have the same loading dose per area (1.8 mg/cm^2), and the amount of rivastigmine delivered from a patch over a 24-h wearing period is approximately 50% of the total loading dose.

After launch, there were some case reports of patch misuse, which raised questions related to efficacy and safety risks (e.g., longer application than 24 h, multiple patches applied at the same time, and so forth).

Previously, modeling has been performed during the development of rivastigmine to describe PK after applications of rivastigmine patch.[10,13] Such noncompartmental or compartmental models, however, were unable to answer these questions, because

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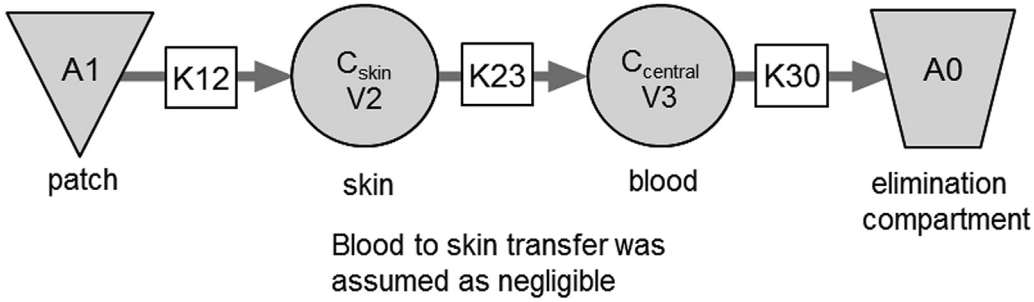

Figure 1. Compartment model to describe the PK profile of rivastigmine after rivastigmine patch application. A1, dose point that represents the applied patch in this model case; C_{skin}, drug concentration in the skin; V2, distribution volume in the skin; $C_{central}$, drug concentration in the central compartment; V3, distribution volume in the central compartment; A0, elimination compartment.

mostly oral administration models were applied, and the models did not quantitatively reflect the amount of drug delivered per the application time, which will be the basis of quantitative simulation of the systemic exposure.

In general terms, pharmacokinetic (PK) models of dermal absorption of chemicals have been created and reported in a series of publications.[14-18] Skin is usually represented either as a single compartment or by 2 compartments separately distinguishing the lipophilic and hydrophilic layers of the skin.[17] Such modeling attempts were generally used in the toxicology rather than clinical pharmacology fields until recently when Polak et al.[18] reported a mechanistic dermal absorption model using Simcyp simulator. Still, there is limited information on dermal absorption models that were put into practical use for simulations of drug concentrations in the clinical setting.

In this study, we report a PK model created by integrating a mechanistic dermal absorption model with a systemic PK model to describe the PK after applications of rivastigmine patch for the purpose of simulating misuse scenarios. The model was created on a Phoenix WinNonlin platform that was selected as an optimal tool to fit the model to clinical data for refinement and verification, after which the model was used for the simulations.

Methods

Compartmental Structure of the Model

A 2-compartment model was developed in WinNonlin, version 5.2, using a user-defined American Standard Code for Information Interchange model to describe the PK profile of rivastigmine after single 24-h dermal application of rivastigmine patch (initial model, Appendix 1). The schematic diagram of the compartmental structure of the model is presented in Figure 1. The model comprised 2 compartments, skin and central compartment, as described by Brown and Hattis[15] in which transfers of rivastigmine between compartments are described by rate constants K12 (for dermal absorption), K23 (skin to blood transfer), and K30 (elimination from systemic compartment; Fig. 1). The parameters for volume of skin and central compartment were defined as V2 and V3, respectively. A PK simulation was conducted to draw a PK profile of rivastigmine after 10-cm^2 patch application using the initial parameters described in the following sections (bottom-up approach).

Initial Values: 1. Dermal Absorption

Initial parameter for the dermal absorption rate constant (K12) was estimated assuming a first-order absorption. First, the initial value was calculated using the data of amount of rivastigmine released from the patch after a 24-h application. An average of 9.4 mg (range, 7.3-11.8 mg) of the total drug content of 18 mg was released from 10-cm^2 patch during 24-h application (n = 19) in a previous clinical study.[19] Calculation using the equation [K12 = ln(released amount/drug content)/24 h] resulted in a mean K12 value of 0.027 h^{-1} (range, 0.018-0.037 h^{-1}). The initial value was also calculated from the time course of *in vitro* human skin permeation data (0.026 h^{-1}; data on file). Because both methods gave similar values, 0.026 h^{-1} was used as the initial value for K12.

Initial Values: 2. Skin-to-Blood Transfer

The rate constant for transfer of the drug from skin to blood (K23) was estimated as follows. The skin and blood are in

Table 1
Initial and Final Parameters Used in the Model

Parameters (Unit)	Initial Values	Mean Values of the Estimated Individual Parameters[a]	Parameters Used in the Final Model
K12 (h^{-1})	0.026[b]	0.027	0.027
K23 (h^{-1})	0.3[c]	0.473	0.473
K30 (h^{-1})	0.693[d]	0.521	K30 = [1/V3] × [$Vmax$/(Km + $C_{central}$)], where V3 = 141,634, K_m = 24, $Vmax$ = 1,760,000 Note: K30 = 0.497 when $C_{central}$ << K_m
V2 (mL)	4[e]	4	4[f]
V3 (mL)	94,800[g]	141,634	141,634

[a] Individual parameters are presented in Table 2.
[b] Initial value estimated assuming first-order absorption based on (1) released rivastigmine from patch after 24-h application and (2) human skin permeation test data.
[c] Parameter for transfer from skin to blood estimated for rivastigmine.
[d] Elimination constant determined from T1/2 following intravenous administration of rivastigmine.
[e] Volume of skin compartment ≈ patch area (10 cm^2) × skin thickness (0.4 cm) = 4 mL.
[f] V2 was changed corresponding to the size of the patch; 2, 4, 6, and 8 mL for patches 5, 10, 15, and 20 cm^2, respectively. See details in Methods section Initial Values.
[g] Volume of central compartment (distribution volume) determined from volume of distribution following intravenous administration of rivastigmine.