Prediction of Human Pharmacokinetics Following Dermal Administration: Integration of a Skin Absorption Module to the Simcyp® Population-Based ADME Simulator with the Aim of Avoiding Animal Studies

S. Polak[1], M. Ahamadi [1], C. Ghobadi [1], H. Mishra [1], M. Jamei[1] and A. Rostami-Hodjegan[1,2]

S.Polak@simcyp.com

1- Simcyp Ltd, Blades Enterprise Centre, John St, Sheffield, S2 4SU, UK ; 2- Academic Unit of Clinical Pharmacology, University of Sheffield, Sheffield, UK

Objective

To predict human pharmacokinetics following dermal administration using an in-silico model integrated in Simcyp ® Population-Based ADME Simulator

Introduction

Animal models to assess dermal absorption are common, however the physico-chemically based methods are now available to predict the fraction and the rate of drug absorption via skin. Simcyp® Population-Based ADME Simulator has been developed to investigate and extrapolate the preclinical data using combined knowledge of genetic, physiological and demographic variability in the population to *in-vivo* pharmacokinetics (PK) of the drugs [1]. Simulation of PK clinical trials, by incorporating inter-individual variability, allows users to identify the individuals at risk from a drug, an attribute which cannot be associated with any animal model.

We describe here a dermal absorption module, recently implemented in version 9 of the platform, and demonstrate its functionality in predicting the drug kinetics and examining the inter-individual variability.

Model

Simcyp® V9 now includes skin as a route of drug administration. The model is an adaptation of the Shatkin & Brown model [2] that incorporates stratum corneum and viable epidermis layers as shown in Figure 1. It also accounts for inter-individual variability in composition and thickness of skin layers. This is available as default values for: north European Caucasians and five different application sites; forearm, upper arm, lower leg, thigh & face. Although users can enter the physiological values for other sites. The input parameters for the skin module (such as the partition and permeability constants) are calculated based on the simple molecular descriptors LogP, hydrogen-bond donors (HBD) and molecular weight of the drug. The model assumptions are:

1) The drug formulation is a water solution.
2) Absorption from skin appendages is negligible.
3) Absorption of drug occurs unidirectionally (perpendicular to the skin surface).
4) Metabolism in the skin is negligible.

Simulations

The predicted kinetics of diclofenac, a commonly used topical drug, were compared with the outcome of human *in-vivo* studies, based on the similar trial designs [2,3,4,5]. The selected trials represent different drug formulations (spray, patch and gel), dosing schemes (single and multiple doses), and application sites (forearm, back and knee). In the simulations instead of back and knee (not default sites), data for upper arm and thigh were used respectively, considering their proximity and also the formulation was assumed to be a water solution (default). The model can also be used to mimic different trial designs by providing the values for different governing coefficients, for various formulations, as shown in Figure 1. The *in-vivo* data and the simulation results were compared in their 5% and the 95% CI ranges.

Results

The simulated plasma concentration-time profiles and the *in-vivo* data were found to be within the 5% and the 95% CI range and comparable on visual inspection (Figure 2), i.e. the predicted the kinetic curve from the simulations traced the *in-vivo* data in three of the four studies.

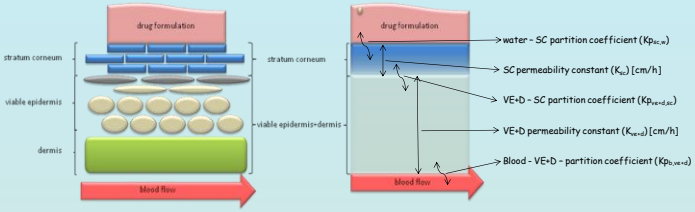

Figure 1: Skin model and the calculated coefficients. SC-Stratum corneum; VE-Viable Epidermis; D-Dermis

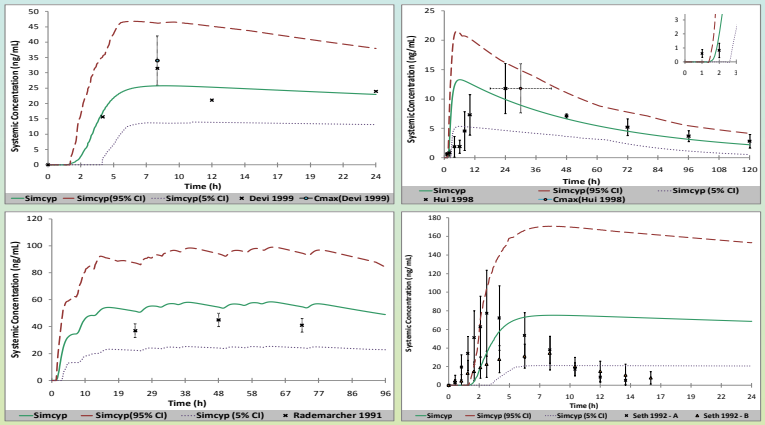

Figure 2: Mean Systemic concentration in Plasma of Diclofenac over time simulated in Simcyp and clinical data

Discussion & Conclusion

The outcome of this comparative study demonstrates that the skin absorption model conforms well with the clinical data in majority (~70%) of the simulated trials, despite its limits as discussed in Simulations section. The model has also been designed to account for the lag time in drug absorption and the predictions are comparable with the clinical data (enlarged graph from Hui 1998 [4]). The clinical data from Seth 1992 [6] show a very rapid absorption and elimination curve (unlike the elimination data from other studies), this may be due to the fact that the area of application site is very large (~800 cm^2) and skin metabolism has to be accounted for. Hui 1998 [4] reported a t_{max} of 30 +/- 12 hr which is longer than the predicted value of ~8 hrs. This may be due to the fact that the reported site of application in the paper was knee; however because this was not available in the model data for thigh was used instead.

Overall, *in-silico* models such as the current model implemented within the Simcyp ® Population-Based ADME Simulator attest to be promising alternatives to animal models for dermal absorption.

References

1. Jamei M et al. (2009), The Simcyp® Population-based ADME Simulator. Expert Opinion on Drug Metabolism & Toxicology, 5:211-223.
2. Shatkin JA and Brown HS (1991), Pharmacokinetics of the Dermal Route of Exposure to Volatile Organic Chemicals in Water: A Computer Simulation Model, Environmental Research, 5:90-108
3. Devi K and Paranjothy KLK (1999), Pharmacokinetic Profile of a New Matrix-Type Transdermal Delivery System: Diclofenac Diethyl Ammonium Patch, Drug Development and Industrial Pharmacy, 25(5), 695–700
4. Hui et.al. (1998), In vivo Bioavailability and metabolism of topical diclofenac lotion in human volunteers, Pharmaceutical research, 15:1589-1595
5. Rademarcher et.al. (1991), Diclofenac concentrations in synovial fluid and plasma after cutaneous application in inflammatory and degenerative joint disease, British Journal of clinical Pharmacology, 31:537-541
6. Seth BL (1992), Comparative pharmacokinetics and bioavailability study of percutaneous absorption of diclofenac from two topical formulations containing drug as a solution gel or as an emulsion gel. Arzneimittelforschung, 42(2):120-122.