Prediction of skin disposition after topical application of drugs
Simcyp platform as a tool for capturing system information and safety assessment

S. Polak[1,2] (spolak@simcyp.com), N Patel[1], M. Jamei[1], A. Rostami Hodjegan[1,3]

[1] Simcyp Limited (a Certara company), Blades Enterprise Centre, John Street, Sheffield, S2 4SU, UK, [2] Faculty of Pharmacy, Jagiellonian University Medical College, Krakow, Poland, [3] School of Pharmacy and Pharmaceutical Sciences, University of Manchester, Manchester, UK

INTRODUCTION

The safety and efficacy of the topically administered drugs depend on the cutaneous absorption influencing systemic exposure. The systemic exposure can be either desired if the systemic effect is expected or undesirable if the drug is expected to be active only locally. The drug presence in the general circulation can also lead to the interactions with other, concomitantly taken drugs, regardless of their dosing route. As the topical drug application, apart from the local toxic effects, is generally considered safe, such potential effect is not studied although can be clinically important as suggest the safety drugs alerts reporting serious adverse drug reactions [1-4]. Aim of the work was to assess the usability of the in vitro – in vivo extrapolation approach at the population level for the skin and systemic disposition after topical and oral drugs administration for the safety assessment.

MATERIALS AND METHODS

The simulated studies included combination of the topically and orally administered drugs with metabolic drug-drug interactions. The predicted values were compared against the clinical results when possible. All simulations were run on the Simcyp platform (V12R2) [5,6].

STUDY 1 – topical erythromycin {+ oral simvastatin}

A. Administration of a single 0.4 mg of erythromycin (topical - 2cm² area of the forearm) with 40 mg of simvastatin (oral) was used as a model scenario to validate the model and compound. Topical erythromycin anticipated exposure mimicking the corresponding clinical study [7]. Drug related model parameters were predicted with use of the Simcyp built-in QSAR models and lotion formulation was simulated by modification of the permeability constants (x50 for the stratum corneum (SC) and viable epidermis (VE)). Fraction unbound in SC was 0.31 and fraction non-ionised on the skin surface was assumed to be 1. Amount of erythromycin collected from the skin surface and fraction of the dose recovered from the SC were compared against the clinical observations (6 healthy volunteers).

B. Second leg of the study included simulation of the theoretical clinical situation where realistic doses of oral simvastatin (40mg QD, 7 days) and topical erythromycin (40cm² area of the forearm, 40mg per dose, BID, 3 days from day 4) were used. Simulation study included 10 groups of 6 individuals.

STUDY 2 – topical ketoconazole {+ oral simvastatin}

Administration of a single dose with 0.4 mg of ketoconazole (topical – forearm, various areas) with 40 mg of simvastatin (oral) were used as the model scenarios. Drug related model parameters were predicted with use of the Simcyp built-in QSAR models and various formulations/occlusion were simulated by modification of the permeability constants (x2 and x5 for the stratum corneum (SC) and viable epidermis (VE)). As the adverse drug reaction report did not contain type of application details, average (100cm²) and large (400cm²) application areas were tested separately to apply for various possible scenarios. Fraction unbound in SC and fraction non-ionised on the skin surface was assumed to be 1. All simulations were run in 10 replicates (10 trials) for 10 healthy individuals in each trial (proportion of females – 0.5).

REFERENCES

1. Devaraj A, et al. Interaction between warfarin and topical miconazole cream. BMJ 2002;325(7355):77. 2. Lang PG, Jr., LeClercq AH. Increase in anticoagulant effect of warfarin in a patient using econazole cream. J Am Acad Dermatol 2006;55(5 Suppl):S117-S119. 3. Wey PF, et al. Laryngeal dyspnea in relation to an interaction between acenocoumarol and topical econazole lotion. Am J Geriatr Pharmacother 2008;6(3):173-7. 4. Alexandra JF, et al. Overanticoagulation with coumarin and cutaneous azole therapy. Ann Intern Med 2008;148(8):633-5. 5. www.simcyp.com 6. Polak S, et al. Prediction of concentration-time profile and its inter-individual variability following the dermal drug absorption. J Pharm Sci. 2012 Jul;101(7):2584-95.7. van Hoogdalem EJ, et al. Evaluation of the effect of zinc acetate on the stratum corneum penetration kinetics of erythromycin in healthy male volunteers. Skin Pharmacol. 1996;9(2):104-10. 7. Netherlands Pharmacovigilance Centre Lareb, Kwartaalbericht 3e kwartaal 2009 (www.lareb.nl).

RESULTS

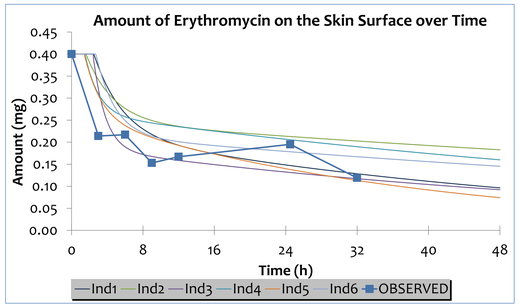
The simulated output were compared against the endpoints measured in the clinical study.

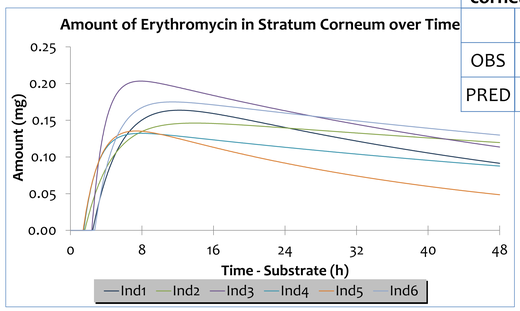
STUDY 1 – topical erythromycin {+ oral simvastatin}

A. *0.4 mg of erythromycin (topical - 2cm² area of the forearm)*

clinical trials data reported as the amount of drug collected from the skin surface and fraction recovered from the stratum corneum

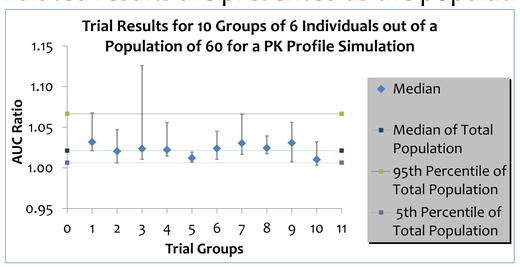
Fraction of the dose recovered from stratum corneum after 6 hours		
	AVERAGE	SD
OBS	23%	10%
PRED	35%	8%

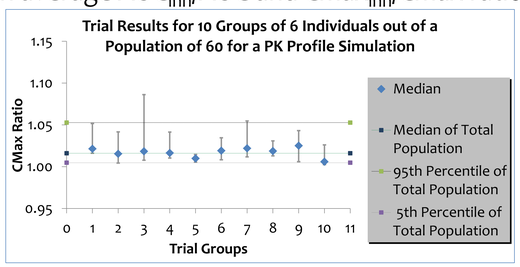




B. *oral simvastatin (40mg QD, 7 days) and topical erythromycin (40cm² area of the forearm, 40mg per dose, BID, 3 days from day 4)*

simulated results are presented as the population average AUC_{inh}/AUC and $Cmax_{inh}/Cmax$ ratios





STUDY 2 – topical ketoconazole {+ oral simvastatin}

single dose with 0.4 mg of ketoconazole (topical – forearm, various areas) with 40 mg of simvastatin (oral)

simulated results are presented as the population average AUC_{inh}/AUC and $Cmax_{inh}/Cmax$ ratios, maximal values derived for individuals are reported separately for various scenarios

		Mean	Std Dev	Min Val	Max Val	Fold
DEFAULT (100 cm²; default diffusion parameters)	AUC Ratio	1.03	0.02	1.00	1.09	1.09
	CMax Ratio	1.02	0.01	1.00	1.06	1.06
LARGE AREA (400 cm²; default diffusion parameters)	AUC Ratio	1.10	0.06	1.00	1.29	1.28
	CMax Ratio	1.07	0.04	1.00	1.18	1.18
OCCLUSION x 2 (100 cm²; diffusion parameters x2)	AUC Ratio	1.05	0.03	1.00	1.13	1.12
	CMax Ratio	1.03	0.02	1.00	1.09	1.09
OCCLUSION x 5 (100 cm²; diffusion parameters x5)	AUC Ratio	1.07	0.04	1.00	1.22	1.21
	CMax Ratio	1.05	0.03	1.00	1.14	1.14
LARGE AREA + OCCLUSION x 5 (400 cm²; diffusion parameters x5)	AUC Ratio	1.17	0.10	1.01	1.51	1.50
	CMax Ratio	1.11	0.07	1.01	1.32	1.31

CONCLUSIONS

Topical drugs application is generally considered safe although there are reports of the clinically observed major side effects resulting from the drugs interactions. Netherlands Pharmacovigilance Center reported in 2009 few cases of the topical ketoconazole/oral simvastatin interaction resulted in myalgia [8]. The simulation results stay in agreement with the clinical observations suggesting lack of the clinically important DDIs but pointing for the potentially sensitive individuals ($AUC_{inh}/AUC > 1.5$ and $Cmax_{inh}/Cmax > 1.3$).