Novel Skin PBPK model in Action: Clindamycin and Tazarotene Modeling

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INTRODUCTION

- Absence of the immune system in the human body with a complex barrier function as protection from the external environment
- Producing dermal and systemic exposures of drug following topical application is especially challenging when considering the impact of formulation
- Scientists from GlaxoSmithKline, NDA 20
- Its applications span from candidate compound and formulation decisions to maximizing the potential for the right amount of drug to be delivered

METHODS

- TCAT model was used to predict systemic exposures upon topical administration of different Clindamycin formulations after single administration of several topical formulations
- Transdermal Compartmental Absorption & Transit (TCAT™) that allows better understanding of drug penetration through the skin while accounting for the formulation characteristics, exogenous and endogenous factors that influence drug delivery

RESULTS

Clindamycin Modeling
- Pharmacokinetic model based on characteristic dynamic drug disposition and presented in Fig.1. In these studies Clindamycin phosphate was closed but in the phosphate is quickly converted to Clindamycin in the body + Clindamycin is modeled

- A compartmental PK model was used to match observed plasma concentration vs. time profile after 20 mg/m² application of Tazorac to healthy subjects
- Model was able to appropriately characterize exposure differences with different formulations including a Dalacin T solution, Dua Gel, Clindagel and Evoclin Foam
- Simulations for various Clindamycin formulation details were carried out using TCAT model setup as described in the methods and as shown in example screenshots below

Tazarotene Modeling
- Pharmacokinetic model based on characteristic dynamic drug disposition is presented in Fig.6
- Model was verified by simulating the IV studies (600 mg and 1200 mg repeat IV infusions) from Plaisance et al.

CONCLUSIONS

- The TCAT model within GastroPlus is a model that will enable scientists to understand the exposures from different topical formulations
- Its application spans from candidate compound and formulation decisions to maximizing the potential for the right amount of drug to be delivered, all being well understood according to Gattis et al.

REFERENCES