Use of a Physiology-based Whole-body Population Model to Simulate the Influence of Anthropometric-, Clearance-, and Physiological-variance on the Pharmacokinetics of Drugs

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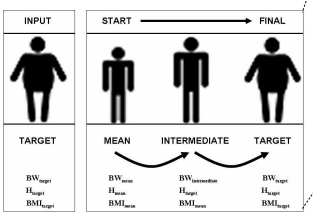
INTRODUCTION

- Physiology-based pharmacokinetic (PBPK) modeling is a tool for the simulation of concentration-time profiles based on physiology (body and organ weights, blood flows, partition coefficients etc.).
- The PK-Pop module of PK-Sim® (Bayer Technology Services GmbH) contains a population algorithm to create a virtual population of individuals with varying anthropomorphic/physiological parameters. An additional stochastic variation of any parameter included in the model may also be generated.
- **Objective:** Assess the accuracy of an inter-individual PK variability prediction based on a physiology-based population pharmacokinetic model and determine the parameters within the model that contribute substantially to the inter-individual PK variability.

METHODS

Creation of a Single Individual and a Virtual Population

- Populations were generated (**Fig. 1**) in PK-Pop based on the age, weight and height range of each experimental group for ciprofloxacin, paclitaxel and cimetidine.



- Additional variability in clearance, gastro-intestinal parameters (cimetidine) and fraction unbound (f_u) (paclitaxel) were stochastically assigned to each virtual individual.
  - Clearance variability based on either the in vitro enzymatic Vmax variability (ciprofloxacin & paclitaxel) or the observed in vivo clearance variability (cimetidine).
  - Gastric emptying time, intestinal transit time and effective surface area varied based on literature.
  - For paclitaxel, its formulation affects the f_u thus a uniform distribution of f_u was used (0.04 to 0.08).

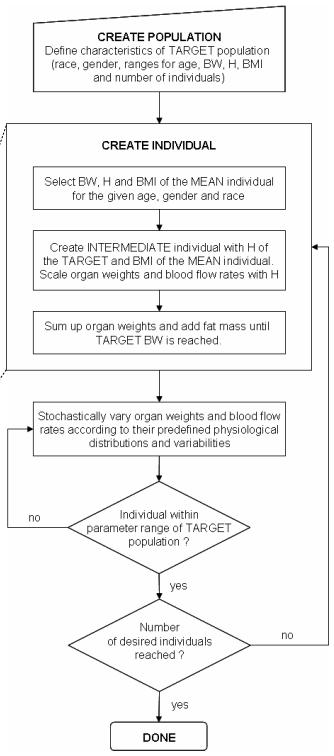


Figure 1. Flow-chart for the creation of a single virtual individual and a virtual population.

Sensitivity Analysis of Varied Parameters

- To assess the influence of inter-individual variability in clearance, GI parameters and f_u separately from the influence of anthropometric and physiological variability, separate populations were simulated where only "Physiology", "Clearance", "f_u" and "GI parameters" were varied.
- PK parameter CVs (%) for each simulation were compared to the CVs of the full model, where all variations were made, and to the experimental CV.

Comparison to Experimental Data

- PK profiles and parameters compared to experimental data for ciprofloxacin [1], paclitaxel [2,3] and cimetidine [4] as an immediate (IR), slow (SR; FaSSIF 70% in 1 h) and extended release (ER; FaSSIF 15% in 1 h) formulation.

RESULTS

- Variability surrounding the pharmacokinetic profile of ciprofloxacin (**Fig. 2A**), paclitaxel (**Fig. 2B**) and cimetidine as an IR (**Fig. 2C**) and SR formulation (**Fig. 2D**) is well represented.

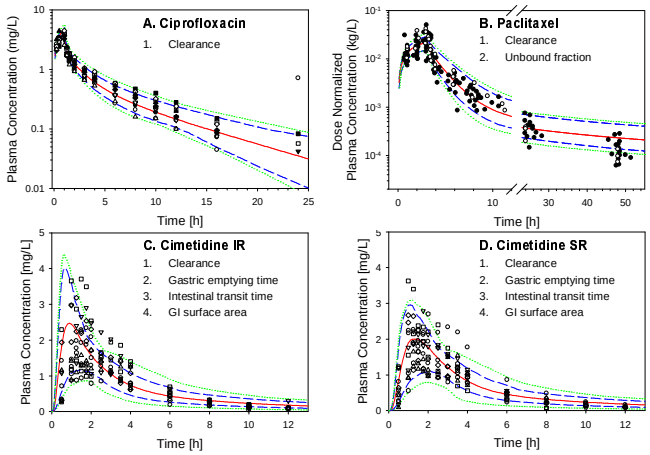


Figure 2. Population simulations for ciprofloxacin (**A**), paclitaxel (**B**) and cimetidine as an immediate release (**C**) and slow release (**D**) formulation. Symbols represent individual plasma concentration time data. The mean, 5% and 95%, and minimum and maximum predicted plasma concentrations are represented as lines. Numbered lists represent the parameters, apart from anthropometric parameters, that were stochastically varied in the simulations.

- Variability in CL (**Fig. 3**) was well predicted from pathway specific in vitro measures of clearance for ciprofloxacin and paclitaxel
- Vss and AUC CVs from the full model (red bars; **Fig. 3**) well represented the observed CVs (green bars; **Fig. 3**)
- The factor contributing the greatest variability was physiology for ciprofloxacin and cimetidine (IR & SR), f_u for paclitaxel and GI parameters for cimetidine (ER).
- The contribution of all parameter variabilities were not additive in the full model for any case.
- The importance of gastric emptying time, intestinal transit time and GI surface area variability to overall cimetidine PK variability increased with slower dissolution time.

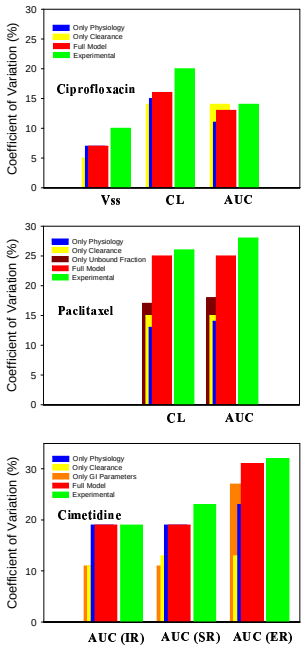


Figure 3. Simulated and experimental coefficients of variation for ciprofloxacin [1], paclitaxel [3], and cimetidine [4] pharmacokinetic parameters. Multiple bars represent the inter-individual CVs for simulations where individuals were varied in body weight, height, gender and age "Only Physiology", and where individuals had the same body weight, height, gender and age with only clearance "Only Clearance", f_u "Only Unbound Fraction" or GI parameters "Only GI Parameters" varied.

CONCLUSIONS

- **The PK-Pop algorithm allowed for physiological variation that was an important predictor of PK variability. The inclusion of additional variation (clearance, unbound fraction, etc.) led to the accurate prediction of inter-individual PK variability for ciprofloxacin, paclitaxel and cimetidine.**
- **Using this module, the contribution of each varied parameter to overall PK variability could be estimated.**

References: [1] Shah et al. *J. Antimicrob. Chemother.* 38(1):103 - 116 (1996). [2] Callies et al. *Br. J Clin. Pharmacol.* 56(1):46 - 56 (2003). [3] Panday et al. *Pharmacol. Res.* 40(1):67 - 74 (1999). [4] Jantratid et al. *Clin. Pharmacokinet.* 45(4):385-99 (2006).

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