Physiologically-based pharmacokinetic simulations of ciprofloxacin in obese and renally impaired individuals

Stefan Willmann [1)], Walter Schmitt [1)], Heino Stass [2)], Gertrud Ahr [2)], Andrea N. Edginton [1)]

1) Systems Biology, Bayer Technology Services GmbH, Leverkusen, Germany
2) Clinical Pharmacokinetics, Bayer HealthCare AG, Wuppertal, Germany

Bayer Technology Services

Bayer HealthCare

INTRODUCTION

- Physiology-based pharmacokinetic (PBPK) modeling is used to describe ciprofloxacin (CIP) concentration-time profiles using known physiological parameters (body and organ weights, blood flows, tissue composition etc.).
- The PK-Pop module of PK-Sim® (Bayer Technology Services GmbH) contains a population algorithm to extrapolate to a virtual population of individuals with varying anthropomorphic/physiological parameters.
- **Objective:** Evaluate the feasibility of using a PBPK-Pop model to predict the influence of two clinically relevant patho-physiological conditions (obesity & renal impairment) on the PK behaviour of the anti-infective CIP.
- Based on a mechanistic understanding of the patho-physiological changes associated with disease PBPK predicts behaviour in compromised patients.

METHODS

CIP PBPK Basis Model

- A CIP PBPK model was built for healthy subjects based on physico-chemical properties of CIP and Phase I study results.

Obesity

- 2 virtual populations were generated (n = 50) each matching the age, weight and height range of a moderately obese (BW = 110.7 ± 20.2 kg) and normal-weighted (BW = 71.8 ± 9.9 kg) population investigated in an experimental study [1].

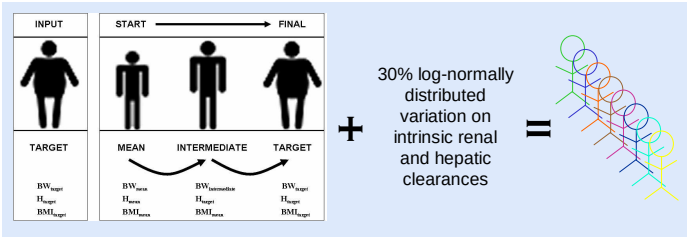

Figure 1. Generation of a virtual population begins with the creation of a single virtual individual whose organ weights and blood flows are stochastically varied according to pre-defined physiological distributions as well as a stochastic variation of clearances.

Renal Impairment

- A virtual population was generated (n = 5,000) matching the age, weight and height range of each experimental group of renally impaired [2,3,4] patients.
- Renal and hepatic clearances as well as the unbound fraction (f_u) were correlated with creatinine clearance (**Fig. 2**), in-line with reported literature.
- Based on stochastic variation of creatinine clearance in the population, each individual was assigned a renal, hepatic clearance as well as an f_u.
- An additional inter-individual variability was added for the intrinsic clearances (30%) and f_u (2%).

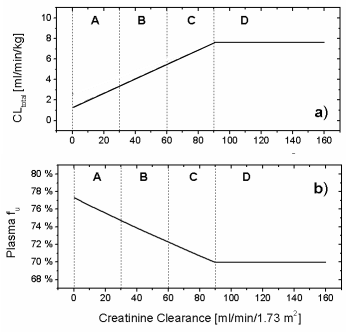

Figure 2. Estimated dependence of the mean total plasma clearance (a) and unbound fraction in plasma (b) of ciprofloxacin as a function of the creatinine clearance used in the simulations.

Comparison to Experimental Data

- Simulated pharmacokinetic parameters of C_{max}, V_{ss} and AUC were compared to those from obese and renally-impaired experimental populations.
- Predicted inter-individual variability for C_{max}, V_{ss} and AUC were also compared between groups

RESULTS

Obesity

- C_{max} and AUC: Mean and relative decrease between the normal and obese population was well described by the model whereas variability of C_{max} was underestimated (**Fig. 3**)
- V_{ss}: The mean value was significantly lower than the observed for the normal population although the observed value was outside of the range for normals [2.2 – 2.7 L/kg (2,3,4)]. Variability and the trend towards decreased V_{ss} with obesity was well described.

Renal Impairment

- The model well described the trends associated with increasing renal impairment (**Fig. 3: left**):
  - ↑ AUC (primarily due to decreased clearance)
  - ↓ V_{ss} (primarily due to a higher unbound fraction in plasma)
  - ↑ C_{max}

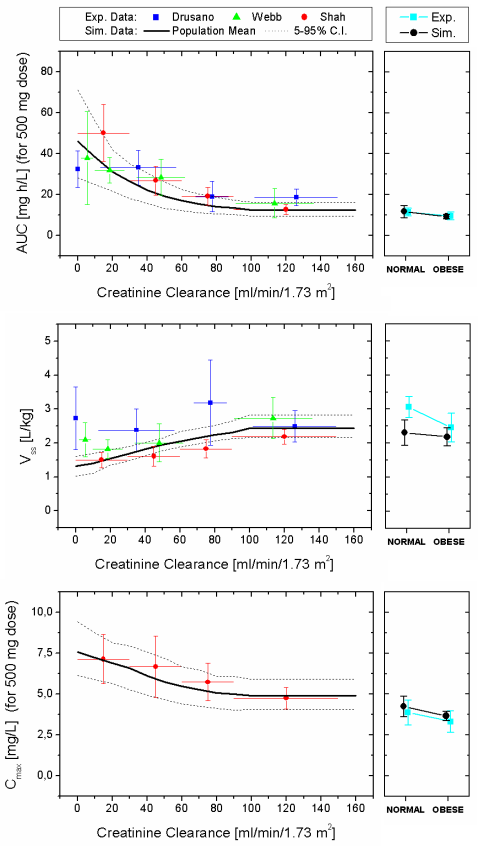

Figure 3. Comparison of the simulation results for the renally impaired virtual population (solid line: mean, dotted lines: 5% and 95% percentiles) with the experimental study data (symbols: mean, bars: standard deviation, line: ranges) (left side graphs). The right side graphs present a comparison of observed and simulated pharmacokinetic parameters of ciprofloxacin in normal and obese individuals..

- While variability was described and observed to be smaller in healthy individuals, it was under-estimated in sick patients. One possible reason is:
  - *Excluded physiological variation*
    Renal impairment is often related to a decrease in intracellular water (muscle atrophy) and increase or maintenance of extracellular water (increase or decrease in adipose mass). The use and duration of dialysis is also important.
- Lack of information on these correlations did not allow for these factors to be included in the model.

CONCLUSIONS

- **The PBPK model accurately described the mean values and trends in ciprofloxacin PK parameters associated with obesity and renal impairment**
- **The PBPK-Pop model allowed for physiological, clearance and f_u variation that was an important predictor of PK variability in obese populations. The complexity of physiology in renally impaired populations requires additional factors to be accounted to accurately describe inter-individual variability**

References: [1] Allard et al. *Clin. Pharmacol. Ther.* 54:368 - 73 (1993). [2] Drusano et al. *Antimicrob. Agents Chemother.* 31:860 - 4. (1987). [3] Shah et al. *J. Antimicrob. Chemother.* 38:103 - 16 (1996). [4] Webb et al. *J. Antimicrob. Chemother.* 18:83 - 7 (1986).