A joint population pharmacokinetic model of total and unbound temocillin serum concentrations in haemodialysis patients

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Background and Objectives

- Temocillin is a narrow-spectrum anti-Gram-negative beta-lactam marketed since the 80s witnessing renewed interest as a carbapenem-sparing drug, due to resistance to degradation by most beta-lactamases.
- Temocillin PK in haemodialysis patients has not been investigated yet.
- The purpose of this study was to develop a model describing the PK of total and unbound temocillin serum concentrations in end stage renal disease (ESRD) patients undergoing haemodialysis.
- In addition, this study aims to evaluate by simulation, the clinical performance of the model, considering that beta-lactam efficacy is best predicted by the proportion of the dosing interval during which unbound concentrations remain above the MIC (minimal inhibitory concentration) of the offending organism.
- Single-center, open-label, non-randomized study
- 16 patients were administered a dose of 1.2, or 3g of temocillin (total of 61 doses) followed by an interdialytic period (off-dialysis) of 20, 44, or 68h, respectively, and dialysis period of 4h.
- 429 serum samples were collected to measure total and unbound concentrations.
- A population PK model was constructed and evaluated by a bootstrap analysis (internal evaluation, 1000 runs) and visual predictive check. A 100-subject Monte Carlo simulation was conducted to determine 95% probability of target attainment (PTA)56 whether based on 40% time above MIC (FT > MIC) for measured unbound drug.
- Data analyses were performed using NONMEM 7.3, Pirana, PsN and R.

Methods

- Diagnostic plots
- Simulations and probability of target attainment
- VPCs: maximal binding; Unbound conc. (mg/L) Proportional Error
- Sampling scheme
- Goodness of fit evaluation for total and unbound concentrations
- Final PK Parameter Estimates
- Residual variability
- Proportional Error CV% and intercept

Results

- Schematic overview of the mechanism-based final PK model for temocillin in ESRD patients undergoing haemodialysis
- Final PK Parameter Estimates
- Residual variability
- Proportional Error CV% and intercept

Conclusions

- Temocillin PK off-dialysis was best described by a two-compartment model, non-linear binding to albumin (Lamgaut model) and mixed order elimination. Dialysis clearance was best described by Michaelis equation. [2]
- The visual predictive checks indicated acceptable performance for simulation purposes to support future studies.
- Simulations of a typical thrice weekly haemodialysis regimen, with temocillin administered immediately after dialysis, show that patients would be adequately treated (40% FT > MIC ) for a MIC ≤ 8mg/L. However, for higher MICs like 16mg/L, patients might run the risk of sub-therapeutic drug exposure.
- Once the total temocillin serum concentrations are known, the unbound concentrations, which are pharmacologically active, can be predicted.
- This model might serve as a useful tool to provide guidance in the optimization of temocillin dosing regimes in haemodialysis patients.