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

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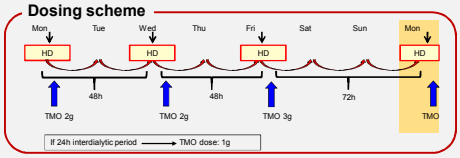
Background and Objectives

- 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 β lactamases[1].
- Temocillin PK in hemodialysis 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 hemodialysis.
- In addition, this study aims to evaluate by simulation, the clinical performance of current dosing regimens, considering that β-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.

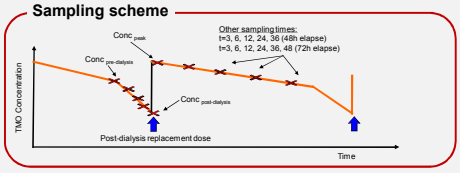
Methods

- 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 1000-subject Monte Carlo simulation was conducted to determine 95% probability of target attainment (PTA95) versus MIC, based on 40% time above MIC ($\int T > MIC$) for measured unbound drug.
- Data analyses were performed using NONMEM 7.3, Pirana, PsN and R.

Dosing scheme

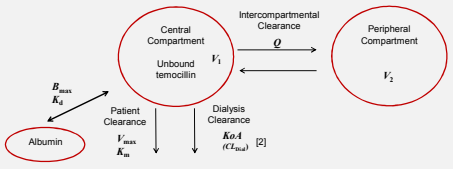


Sampling scheme



Results

Schematic overview of the mechanism-based final PK model for temocillin in ESRD patients undergoing hemodialysis



Compartment 1

Off-dialysis

$$\frac{dA_1}{dt} = -\frac{V_{max} * \frac{A_1}{V_1}}{K_m + \frac{A_1}{V_1}} - Q * \frac{A_1}{V_1} + Q * \frac{A_2}{V_2}$$

On-dialysis

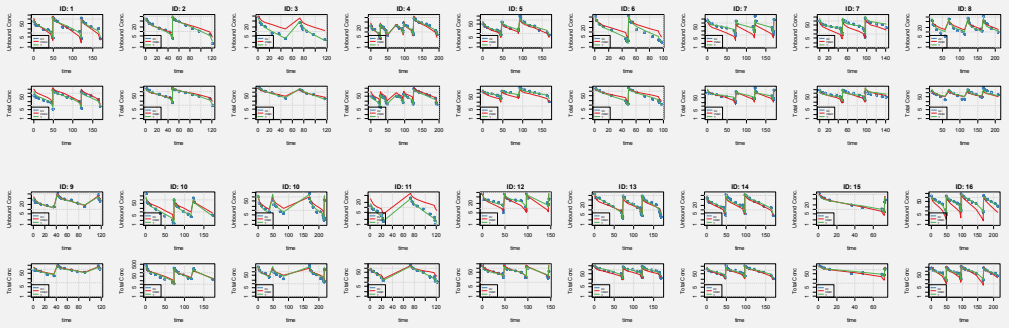
$$\frac{dA_1}{dt} = -\frac{V_{max} * \frac{A_1}{V_1}}{K_m + \frac{A_1}{V_1}} - CL_{Dial} * \frac{A_1}{V_1} - Q * \frac{A_1}{V_1} + Q * \frac{A_2}{V_2}$$

Compartment 2

$$\frac{dA_2}{dt} = Q * \frac{A_1}{V_1} - Q * \frac{A_2}{V_2}$$

CL_{Dial}= BFR*(EXP(KoA/BFR*(1-BFR/DFR))-1)/(EXP(KoA/BFR*(1-BFR/DFR))-BFR/DFR) [2]
BFR: blood flow rate (L/h); DFR: dialysis flow rate (L/h); KoA: mass transfer area coefficient (L/h)

Goodness of fit evaluation for total and unbound concentrations



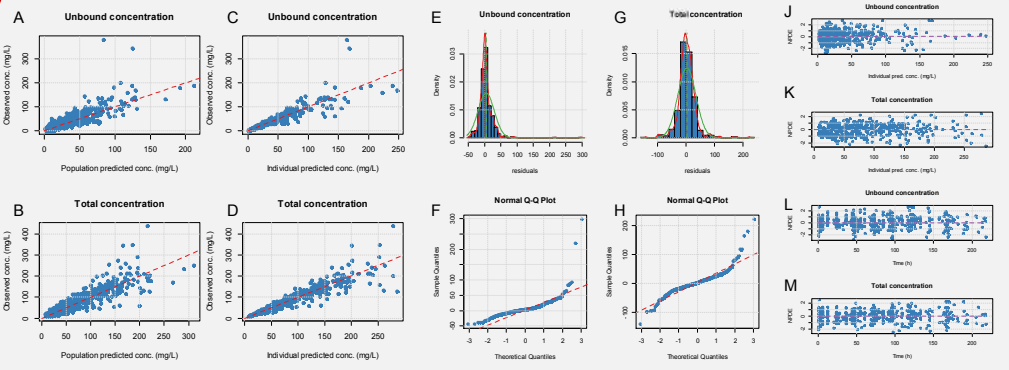
DV = observed concentrations; Y = individual predicted concentrations; PRED = population-predicted concentrations

Final PK Parameter Estimates

Parameter	Estimate (RSE %)	Bootstrap median (95% CI)†	IIV CV% (RSE%)
Structural model			
V_1 (L)[a]	23.5 (10)	24.3 (20.9 - 28.7)	38.2 (19)
V_2 (L)[a]	24.9 (13)	25.7 (21.4 - 31.7)	37.3 (32)
Q(L/h)[a]	4.03 (12)	4.04 (2.8 – 4.5)	-
KoA[b] (mL/min)	7.77 (16)	7.8 (5.9-9-9)	-
V_{max} (mg/h)	161 (37)	142.9 (101.1 -188.1)	34.8 (25)
K_m (mg/h)	81.1 (51%)	68.5 (40.5-94.8)	52.3 (26)
K_d (mg/L)	32.8 (18)	36.3 (25.7 – 54.3)	81.9 (21)
B_{max} (mg/L)	114 (12)	121.0 (100.2 – 146.1)	42.1 (26)
Residual variability			
Proportional Error CV% unbound conc	23.9 (17)	23.7. (20.1 – 26.2)	-
Proportional Error CV% total conc	19.5 (18)	19.1 (16.3 – 21.5)	-

†estimated by applying the final PopPK model to 1000 re-sampled dataset
[a] parameter allometric weight scaled,
[b] CL_{Dial}= BFR*(EXP(KoA/BFR*(1-BFR/DFR))-1)/(EXP(KoA/BFR*(1-BFR/DFR))-BFR/DFR) [2]
RSE, relative standard error; CV, coefficient of variation; IIV, interindividual variability; Q, intercompartmental clearance; KoA: mass transfer area coefficient (L/h); Vmax, maximum elimination rate of the system; Km, drug concentration that produces 50% of the maximal elimination rate of the system; Kd, unbound drug concentration corresponding to half maximal binding; Bmax, maximal binding capacity.

Diagnostic plots

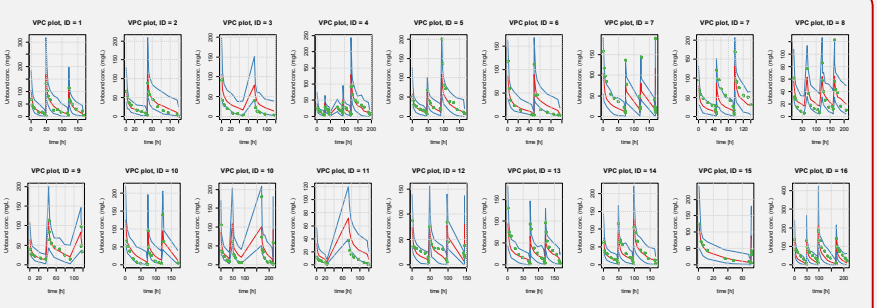


A, B: observed versus population-predicted concentrations; C, D: observed versus individual predicted concentrations.

E, G: Histogram of population residuals for unbound and total concentration
F, H: Q-Q plot of population residuals for unbound and total concentration

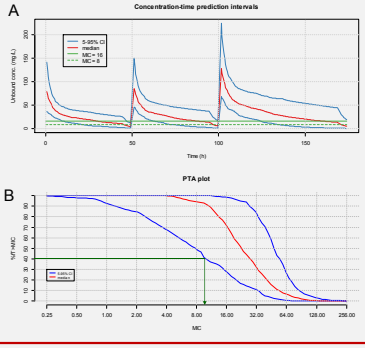
J, K: Scatter plot of normalised prediction errors (NPDE) versus individual predictions;
L, M: Scatter plot of NPDE versus time.

Visual predictive checks



VPCs displaying observed data (green dots) and prediction intervals for simulated data (blue: 5%-95%, red: median).

Simulations and probability of target attainment



A, Monte-Carlo simulations for the concentration-time profile of temocillin when administered thrice weekly (2g q48h, 2g q48h, 3g q72h) immediately after hemodialysis.

B, Probability of target attainment (PTA) plot for a thrice weekly (2g q48h, 2g q48h, 3g q72h) temocillin administration.

The horizontal line indicates the 40% $\int T > MIC$ limit achieving a bacteriostatic effect. The vertical arrow shows the PTA 95, i.e. highest MIC at which this target will be obtained (95% probability).

Conclusions

- Temocillin PK off-dialysis was best described by a two-compartment model, non-linear binding to albumin (Langmuir 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 hemodialysis regimen, with temocillin administered immediately after dialysis, show that patients would be adequately treated (40% $\int T >$ MIC) for a MIC $\leq$ 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 regimens in hemodialysis patients.

[1] Livermore DM, Tulkens PM. Temocillin revived. J Antimicrob Chemother (2009); 63: 243-5.
[2] Michaels AS. Operating parameters and performance criteria for hemodialyzers and other membrane-separation devices. Trans Am Soc Artif Intern Organs (1966) 12:387-92.

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