Modeling and simulation of temocillin in patients with end stage renal disease undergoing haemodialysis

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Background and Objectives

- Temocillin (TMO) is a narrow-spectrum anti-Gram-negative β-lactam marketed since the '80s. It witnesses renewed interest as a carbapenem-sparing drug, because it resists to degradation by most β-lactamases.[1]
- TMO pharmacokinetics in haemodialysis patients has not been investigated yet.
- The purpose of this study was to develop a population pharmacokinetic model of TMO in patients with end stage renal disease (ESRD) undergoing haemodialysis, and to evaluate by simulation, the clinical performance of current dosing regimens.

Methods

Study Design and subjects

- Open, non-randomized, single-center study
- 12 patients (Table 1) were administered a single dose of 1, 2, or 3g of TMO followed by a inter-dialytic period (off-dialysis) of 20, 44, or 68h, respectively, and a dialysis period of 4h (total of 39 doses) (Figure 1).
- 351 serum samples were collected according to the sampling scheme in Figure 2 and analysed for unbound concentrations using a HPLC-MS/MS assay.

Figure 1. Dosing scheme

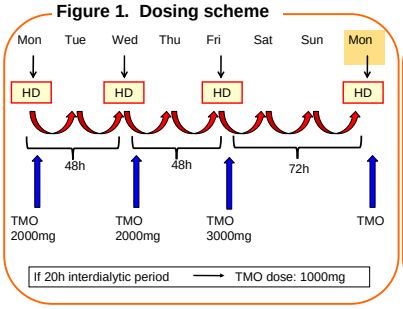
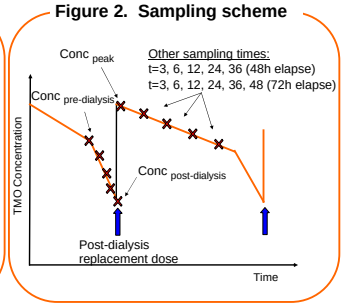


Figure 2. Sampling scheme



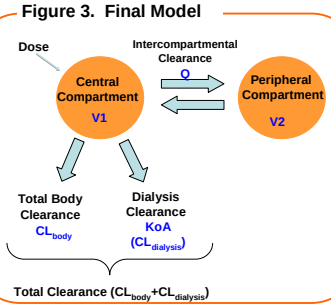
Population PK Modeling

- A population PK model was developed using a non-linear mixed effect model (Figure 3). An apparent dialysis clearance was implemented in parallel to body clearance to describe the accelerated drug clearance by haemodialysis (> 0 during haemodialysis; 0 otherwise). The relationship between blood flow rate and apparent TMO dialysis clearance was described using the Michaels equation. [2]
- Covariates weight and serum albumin were investigated on key model parameters. Proportional error models were used for inter-individual variability and residual error.
- Models were selected based upon decrease in objective function value, improvement in goodness-of-fit, and diagnostic plots (Figure 4 & 5).
- The final PK model was evaluated by a bootstrap analysis (internal evaluation, 1000 runs) and by comparison to an external dataset.

Table 1. Patient Characteristics

	Median	Min-Max
Age (years)	73	24-91
Dry Body Weight (kg)	70	47.6-85.4
Male/female (n)	11/1	-
No. of dose-cycles 1g-24h / 2g-48h / 3g-72h	5/18/11	-
Cycles per subject	3.5	2 - 8
Dialysis Vintage (days)	514	9-2475
Total Protein (g/dL)	6.25	4.9-7.3
AST (U/L)	20	12-40
ALT (U/L)	17	5-74
Serum albumin (g/dl)	3.45	1.9-4.4
Gamma-GT (IU/L)	33	12-155

Figure 3. Final Model



- A 1000-subject Monte Carlo simulation was conducted to determine 95% probability of target attainment (PTA95) versus MIC (based on 40% time above MIC ($fT > MIC$) for measured unbound drug).[3]
- Data analyses and simulations were performed using NONMEM® 7.3, PsN 4.2.0 and RStudio 0.98.501 with R 3.0.2. First order conditional (FOCE) estimation method with INTERACTION was used. Pirana 2.9.0 was used to organise all the population model development process.

Results

- TMO serum unbound concentrations were best described by a two-compartment model.
- The final model estimated all parameters with good precision (relative standard errors) between 11.4% and 25.7% (Table 2)

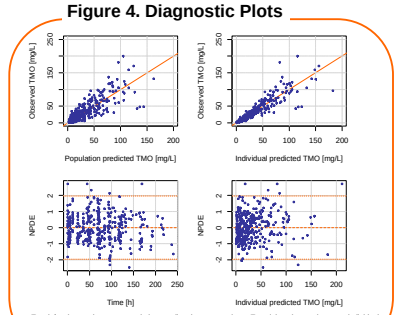
Table 2. Final PK Parameter Estimates

Parameter	Estimate (RSE %)	Bootstrap median (95% CI)[1]
Structural model		
TVV1 = θ_{V1} * (WT/70)^1		
V1 (L)	24.2 (12.1)	24.22 (19.77 - 29.32)
V2 (L)	21.2 (15.5)	21.25 (15.35 - 26.77)
CL_{body}[a] (L/h)	1.35 (15.3)	1.35 (1.05 - 1.76)
KoA[b] (mL/min)	207 (11.4)	205.81 (167.28 - 256.05)
Q (L/h)	3.23 (12.9)	3.25 (2.58 - 4.14)
Inter-individual variability (IIV)		
IIV_{CL1} (CV%)	56.5 (21)	52.91 (31.62 – 72.80)
IIV_{V1} (CV%)	44 (21)	41.23 (26.46 – 57.44)
Residual variability		
Proportional Error (CV%)	29.1 (25.7)	28.98 (22.36 – 34.64)

[1]estimated by applying the final PopPK model to 1000 re-sampled dataset

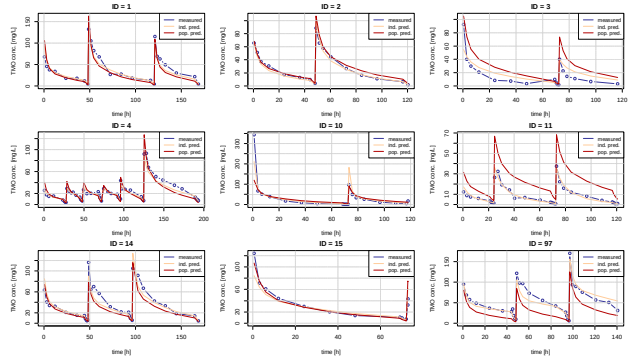
[a] $CL_{total} = CL_{body} + CL_{dialysis}$ RSE, relative standard error; WT, patient's weight;
[b] $CL_{dialysis} = BFR*(EXP(KoA/BFR*(1-BFR/DFR))-1)/(EXP(KoA/BFR*(1-BFR/DFR))-BFR/DFR)$
BFR: blood flow rate (mL/min); DFR: dialysis flow rate (mL/min); KoA: mass transfer area coefficient (mL/min); θ_{V1}, fixed effect estimate for central compartment volume

Figure 4. Diagnostic Plots



Top left: observed versus population predicted concentrations; Top right: observed versus individual predicted concentrations; Bottom left: scatter plot of normalised prediction errors (NPDE) versus independent variable; Bottom right: scatter plot of NPDE versus individual predictions.

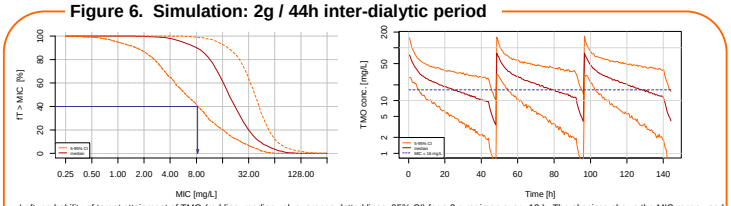
Figure 5. Concentration – time profiles (9 representative patients)



Measured = observed concentrations (DV); ind. pred. = individual predicted concentrations (IPRED); pop. pred.= population predicted concentrations (PRED)

- TMO clearance during dialysis was 8 fold higher than off-dialysis, resulting in significant reduction of TMO serum concentration.
- PTA95 was obtained for a MIC ≤ 8mg/L, for a 2g dose (44h inter-dialytic period, Figure 6).

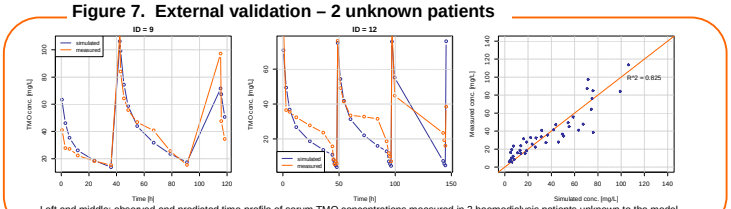
Figure 6. Simulation: 2g / 44h inter-dialytic period



Left: probability of target attainment of TMO (red line: median value; orange dotted lines: 95% CI) for a 2 g regimen every 12 h. The abscissa shows the MIC range used for the simulations and the ordinate the fraction of time (as a %) during which unbound serum levels remain above the corresponding MIC. The horizontal line indicates the 40% $fT > MIC$ 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).
Right: median concentration-time profile and 5% and 95% prediction interval after administration of 2g of TMO every 48h to a patient weighing 70kg.

- The final model successfully predicted the serum TMO concentrations described in two haemodialysis patients unknown to the model (Figure 7).

Figure 7. External validation – 2 unknown patients



Left and middle: observed and predicted time-profile of serum TMO concentrations measured in 2 haemodialysis patients unknown to the model.
Right: correlation between observed and predicted concentrations for the combination of both patients, based on the final model.

Conclusions

A two-compartment PK model for TMO in ESRD patients undergoing haemodialysis was developed and demonstrated to be predictive, including during the dialysis period. This model might serve as a useful tool to provide guidance in the optimization of TMO dosing regimens in haemodialysis patients.

References

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Acknowledgments

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