Population pharmacokinetics of unbound temocillin in paediatric patients requiring antibiotic prophylaxis following hepatic transplantation

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Background and Aims

- ✓ Temocillin (6-alpha-methoxy-ticarcillin), is a β-lactam antibiotic active on Gram (-) bacteria (except most isolates of *Pseudomonas aeruginosa* [1]), including strains producing extended-spectrum β-lactamases (ESBL) and some carbapenemases [2-3].
- ✓ Temocillin (TMO) is eliminated unchanged by glomerular filtration. It is highly protein bound (up to 85%) and only the unbound concentration is considered as potentially active. It is indicated for the treatment of complicated urinary tract infections (including pyelonephritis), low respiratory infections, bacteremia, and wound infections [4]. Temocillin is used in our institution in liver transplant children for infection prophylaxis (off-label indication). However, little is known about its pharmacokinetics (PK) and optimal dosing in paediatric patients in general, and in this population in particular.
- ✓ The **objective** of the study was to characterize the PK of unbound temocillin in liver transplant children in order to provide guidance on the antibiotic prophylactic dosing.

References

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This study was approved by the Hospital - Faculty Ethics Committee Saint-Luc - UCL (Eudra CT 2014-004224-22)

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Materials & Methods

Study design and investigational Plan

- ✓ Single-center, open-label, non-randomized study.
- ✓ 14 liver transplant male or female children (12-36 months old) who were infused with 25mg/kg temocillin over 30 minutes every 12 hours, one day before (day 1) and five days (day +5) after liver transplantation.
- ✓ First blood samples were drawn on day +1 (dose 1 or 2) and second one among doses 3 to 9; sampling times were 0.5, 2, 4, 8 and 12 hours after dose administration.
- ✓ Plasma unbound concentrations were determined by HPLC-MS/MS (sample preparation including ultrafiltration with Amicon filter Ultra-15 device; NMWL 30K; Merck Millipore Ltd) [5].

Population pharmacokinetic modelling building

- ✓ Population PK modelling was carried out using the nonlinear mixed-effects modelling program NONMEM Version VI (double precision; ICON Development Solutions, LLC, Ellicott City, MD). G77 Fortran was used to compile and execute NONMEM. The program was run with the Perl-speaks-NONMEM (PsN) tool kit and Xpose (Version 4), for statistical and graphic model evaluation [6-7].
- ✓ Both one- and two-compartment models with first-order elimination were tested to describe the concentration-time data of temocillin.

Demographic, biometric & biological characteristics: 14 liver transplant children (6 ♂ and 8 ♀)

Parameters	Ref	Mean (CV%)	Range
Age (months)	NA	19.0 (55.0)	6.0 – 36.0
Weight (kg)	NA	10.0 (30.1)	5.9 – 15.7
Height (cm)	NA	78.0 (14.0)	64.0 – 100.0
Serum creatinine IDMS (mg/dL)	0.6 - 1.3	0.23 (36.0)	0.13 – 0.43
Urea (mg/dL)	15 - 50	17.8 (42.0)	5.0 – 40.5
Albumin (g/L)	38 - 54	36.0 (18.8)	18.0 – 50.0
Total protein (g/L)	56 - 75	50.0 (21.3)	33.5 – 65.0

NA = not applicable

Population parameter estimation

- ➢ Pop PK parameters were assessed using the first-order conditional estimation with interaction method (FOCEI).
- ➢ The model was parameterized in term of volume of distribution and clearance.
- ➢ Interindividual variability (η) was described by an exponential model.
- ➢ The residual variability (ε) was described by an additive, proportional, or a combined proportional and additive error model.
- ➢ Allometric weight model was applied to scale PK parameter values using a standard body weight of 70 kg according to [8 - 9- 10]

Selection of the Model

Model building was guided by the NONMEM objective function value, the precision of estimates, and basic goodness-of-fit plots (i.e. observed versus predicted concentrations, conditional weighted residuals versus predicted concentrations, and conditional weighted residuals versus time after dose) ¨[11].

Validation of the Model

Evaluation of the final model included a nonparametric bootstrap procedure and a visual predictive check (VPC). [12 - 13]

Because of the small sized data sets for TMO (14 patients), empirical selection of covariates on PK parameters was not statistically assessed

Discussion and Conclusions

- ✓ TMO shows bi-compartmental pharmacokinetics.
- ✓ In spite of the large variability among these patients, the data suggest that current licensed dosage regimen is suboptimal for MICs > 4 mg/L or PD targets of 70 or 100% fT≥MIC=4 or 8 mg/L, which may be required in this fragile patient population.

→ **Further analysis are needed**

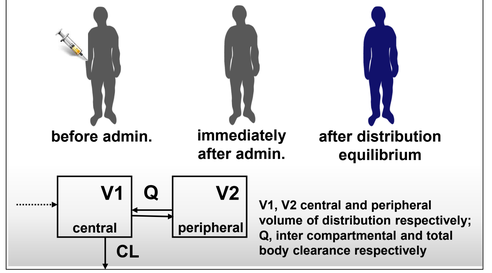
- Search and test relevant confounding factor
- Full validation of the model
- Evaluate the Probability of Target Attainment (PTA)
- Use model to simulate and propose optimized dosing regimen

Acknowledgments

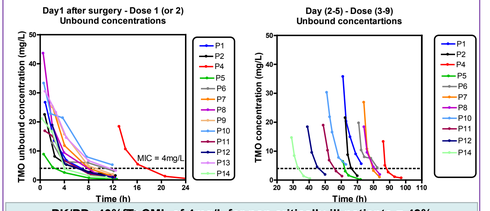
The present work was performed partly with the support of the Region Wallonne. P.N.P., I.K.D., P.W. are employees of the *Université catholique de Louvain*, X.S., D.V.d.L., E.S. are employees of the Cliniques Universitaires St. Luc, A.C. was employed by the Cliniques Universitaires St. Luc and C.M. was postdoctoral fellow on a Region Wallonne program. F.V.B. is Research Director of the Belgian *Fonds de la Recherche Scientifique*, P.M.T. is emeritus professor and unpaid collaborator.

Results

Bi-compartmental model with linear elimination best fitted unbound TMO concentrations



Individual PK profiles of unbound TMO concentrations:



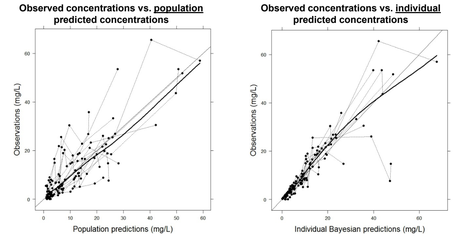
PK/PD: 40%fT>CMI of 4mg/L for non critically-ill patients = 43%
100 % fT>CMI of 4mg/L for critically-ill patients = 0%

Final population pharmacokinetic estimates

Parameter	Estimate (RSE)	Interindividual variability (RSE)
V1	0.82 L/kg (22.7%)	48.0% (60.9%)
V2	0.49 L/kg (12.3%)	
Q	0.10 L/kg (64.5%)	
CL	0.18 mL min^{-1}/kg (14.2%)	48.5% (46.0%)
Cmax	28.9 mg/L	31.0%
Cmin	1.57 mg/L	14.7%
Proportional residual error	60.7% (15.0%)	
Objective function value (OFV)	423	

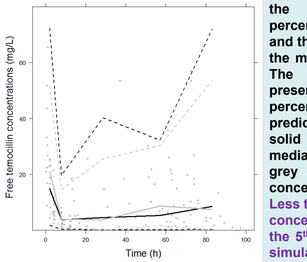
RSE, relative standard error; V1, central volume of distribution; V2, peripheral volume of distribution; Q, intercompartmental clearance; CL, total body clearance; Cmax, maximal concentration; Cmin, minimal concentration

Basic goodness-of-fit plots of the final model of TMO unbound concentrations (n=14)



The line x=y is the identity line. The bold line is the loess smooth. The data points of each individual patient are joined by thin lines.

Visual predictive check of TMO unbound concentrations based on 1000 simulated paediatric patients from the final model



The dashed grey lines present the 2.5th and 97.5th percentiles of observed data, and the solid grey line depicts the median of observed data. The dashed black lines present the 2.5th and 97.5th percentiles (denoting the 95% prediction interval), and the solid black line depicts the median of simulated data. The grey dots are the observed concentrations.
Less than 5 % of observed concentrations are outside the 5th and 95th percentiles of simulated concentrations.