Population pharmacokinetic modelling of total and unbound temocillin in the plasma of healthy volunteers after intravenous administration

Perrin Ngougni Pokem[1], Peter Matzneller[2], Beatrix Wulkersdorfer[2], Arnaud Capron[3], Laure Elens[4], Pierre Wallemacq[3], Paul M Tulkens[1], Markus Zeitlinger[2], Françoise Van Bambeke[1]

[1]Pharmacologie cellulaire et moléculaire, Louvain Drug Research Institute, Université catholique de Louvain, Brussels, Belgium; [2]Department of Clinical Pharmacology, Medical University of Vienna, Austria; [3]Clinical Chemistry Department, Cliniques Universitaires St. Luc, Université catholique de Louvain, Brussels, Belgium ; [4]Integrated PharmacoMetrics, PharmacoGenomics and PhamacoKinetics, Université catholique de Louvain, Brussels, Belgium;

Mailing address: Françoise Van Bambeke
av. Mounier 73 B1.73.05; 1200 Brussels - Belgium
francoise.vanbambeke@uclouvain.be

Background and Aims

- ✓ Temocillin (TMO) 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]. It is therefore a useful alternative to carbapenems and is indicated for the treatment of complicated urinary tract infections (including pyelonephritis), low respiratory infections, bacteremia, and wound infections [4].
- ✓ Temocillin is eliminated unchanged by glomerular filtration. It is highly protein bound (up to 85% [4]) and only the unbound concentration is considered as potentially active.
- ✓ The **aim** of this phase I study was to develop a joined Population-based (Pop)PK model of total and unbound TMO plasma concentrations in healthy volunteers.
- ✓ Subsequently, this model was used to test different dosing regimens aiming at a 90% probability of target attainment (PTA), i.e. unbound concentrations at least 40% of the dosing interval above the minimal inhibitory concentration (40%$fT_{>MIC}$) of susceptible organisms [5].

References

1. Chalhoub et al; Sci Rep. 2017;7:40208. PMID: 28091521
2. Livermore. J Antimicrob Chemother. 2006;57:1012-4. PMID: 16531428
3. Livermore, Tulkens. J Antimicrob Chemother. 2009; 63:243-5. PMID: 19095679
4. Belgian SmPC, last revision 05/2017; Eumedica (data on file)
5. Glupczynski et al. Eur J Clin Microbiol Infect Dis. 2007; 26:777-83. PMID: 17668253
6. Ngougni Pokem et al. Clin Biochem. 2015;48:542-5. PMID: 25712752

This study was approved by the ethical committee of the Medizinische Universität Wien (Eudra CT 2015-003457-18)

A copy of this poster will be made available after the meeting at http://www.facm.ucl.ac.be/posters.htm

Materials & Methods

- ✓ Single-center, open-label, non-randomized study.
- ✓ 8 male healthy volunteers received a single dose of 2 g of TMO as IV infusion over 40 minutes. Plasma samples were collected from 40 min to 12h after the end of infusion.
- ✓ Plasma concentrations were determined by HPLC-MS/MS for total (sample preparation including protein precipitation with methanol) and unbound (sample preparation including ultrafiltration with Amicon filter Ultra-15 device; NMWL 30K; Merck Millipore Ltd) TMO [6].
- ✓ The PopPK model of total and unbound plasma concentrations were fitted using a non-parametric approach with Pmetrics software version1.4.1 (LAPKB, Los Angeles, CA, USA.). One- and two-compartmental PK models were tested for total TMO plasma concentrations; the model that best described the data was selected to derive the TMO unbound concentrations. Final model selection was based on the Bayesian information criterion (BIC), goodness-of-fit plots, normalized prediction error (npde) distribution and visual predictive check (VPC).
- ✓ 1000 Monte Carlo simulations per subject receiving TMO 2g q12h[1] and 2g q8h[2] were performed using the final PopPK model. The total and unbound concentrations of TMO were estimated and the 5th, 50th and 95th percentiles compared to the observed concentrations.
- ✓ PTA ($fT_{>MIC}$ of 40%) were then computed with 2 different dosing regimens (2g/12h[1] or 2g/8h[2]) assuming either a mean free fraction of 6.0 ± 1.4% or of 13.0 ± 4.0% being the values observed for total concentrations < 150 mg/L or > 150 mg/L, respectively (see results).

[1] conventional dose, [2] dose registered for severe infections.

Discussion and Conclusions

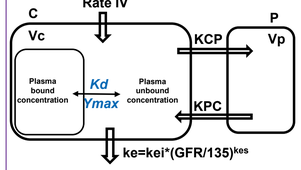
- ✓ TMO shows a bi-compartmental pharmacokinetics.
- ✓ TMO protein binding is high but saturable, with unbound concentrations ranging from 3 to 20% of total concentrations within the limits of the total concentrations observed in volunteers.
- ✓ PTA is low for conventional dosage, arguing for the use of more frequent administrations and/or continuous infusion.

→ Current licensed dosage regimen is suboptimal for MICs > 8 mg/L based on PK in healthy volunteers, due to high protein binding in this population. Further studies are needed to evaluate the PK of unbound TMO in target patients' populations.

Acknowledgments

The present work was performed without specific financial support. P.N.P., L.E., P.W. are employees of the *Université catholique de Louvain*, F.V.B. is Research Director of the Belgian *Fonds de la Recherche Scientifique*, P.M.T. is emeritus professor and unpaid collaborator.

Schematic overview of the mechanism based final PK model for TMO in healthy volunteers



- IV: Intravenous
- C; P: Central; Peripheral compartment
- Vc; Vp: Volume of the compartment
- KCP; KPC : Transfer rate
- *Kd*: unbound TMO concentration corresponding to half of the maximal binding capacity
- *Ymax*: maximal binding capacity
- ke: Elimination constant
- kei: typical value of ke; kes: parameter estimated by the model representing the effect of the GFR on the typical kei value.
- Glomerular filtration rate (GFR)
- 135: mean value of the GFR of study pop.

- ✓ **Bi-compartmental model with linear elimination best fitted total and unbound TMO concentrations.**
- ✓ **Equation output of final model:**
  - **Y(1) = X(1)/V;**
  - **Y(2) = Y(1)*Km/(Ymax-Y(1));**

  Y(1) and Y(2) (total and unbound TMO concentrations respectively), X; TMO dose V (apparent volume of distribution)
- ✓ **Covariate: GFR was retained as covariate in the final model (Δ -2LL = 138).**
- ✓ **Error model: Polynomial error and proportional error (Gamma factor).**

$SD_{total} = 0.19*Y(1) + 1.17*Y(1)^2$

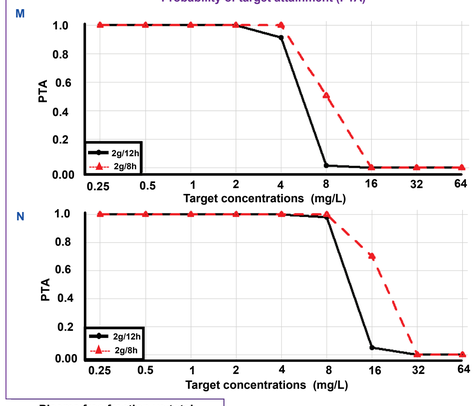
$SD_{unbound} = 0.0018 + 0.24*Y(2) + 0.11*Y(2)^2$

- ✓ **Gamma error factor for the final model was 0.32.**

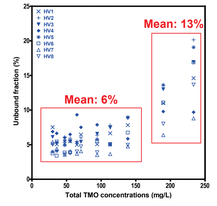
SD (standard deviation).

- ✓ **Final model converged after 1171 cycles**

Probability of target attainment (PTA)



Plasma free fraction vs total TMO concentrations

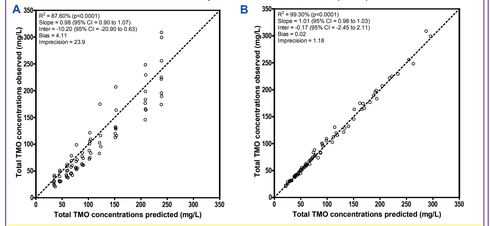


PTA plots for standard dosing (2g/12h) versus higher dosing (2g/8h) considering as target $fT_{>MIC}$ during 40% of the time, based (M) on a mean unbound fraction of 6.0 ± 1.4% (mean of values observed for total concentration < 150mg/L), (N) on a mean unbound fraction of 13.0 ± 4.0% (mean of values observed for total concentration > 150mg/L).

- ✓ **The probability of reaching a target of 8 mg/L depends on TMO protein binding for both dosing options.**

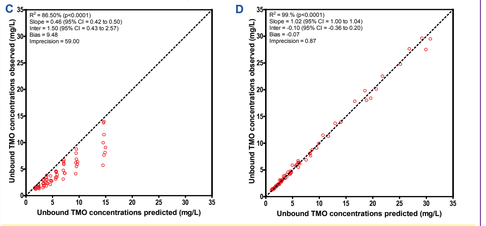
Results

Goodness-of-fit plot for total temocillin (TMO):



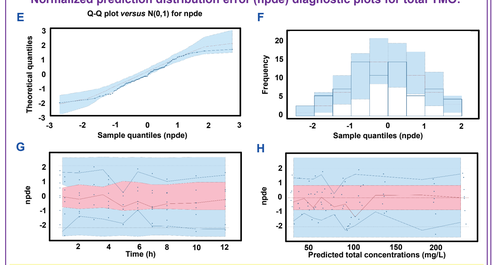
Linear regression of individual observed versus predicted total TMO concentrations using (A) the median model PK parameter values and (B) the median of the individual Bayesian posterior parameter distributions. The black dashed lines and the open black circles represent the unity lines and the individual total concentrations, respectively.

Goodness-of-fit plot for unbound temocillin (TMO):



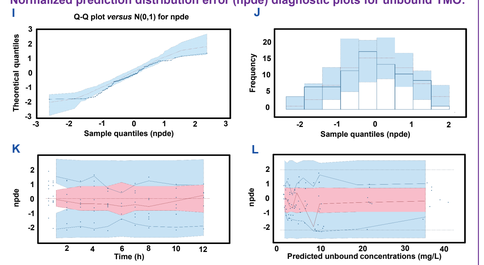
Linear regression of Individual observed versus predicted unbound TMO concentrations using (C) the median model PK parameter values and (D) the median of the individual Bayesian posterior parameter distributions. The black dashed lines and the open red circles represent the unity lines and the individual unbound concentrations, respectively.

Normalized prediction distribution error (npde) diagnostic plots for total TMO:



Q-Q plot (E), Histogram with expected normal distributions indicated by the dashed lines (mean) and light blue boxes ($CI_{95\%}$ ranges) (F), npde with respect to post-intake time (G), and to predicted total TMO concentrations (H) with individual observations (blue dots), observed 5, 50, 95th percentiles (blue and red lines), predicted percentiles (dashed black lines) and CI 95% (blue and red ribbons).

Normalized prediction distribution error (npde) diagnostic plots for unbound TMO:



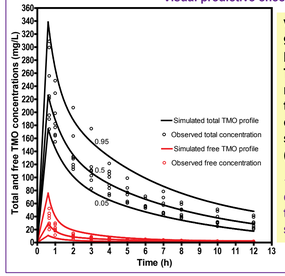
Q-Q plot (I), Histogram with expected normal distributions indicated by the dashed lines (mean) and light blue boxes ($CI_{95\%}$ ranges) (J), npde with respect to post-intake time (K), and predicted unbound TMO concentrations (L) with individual observations (blue dot), observed 5, 50, 95th percentiles (blue and red lines), predicted percentiles (dashed black lines) and CI 95% (blue and red ribbons).

Pharmacokinetic parameters of the final model.

Parameters	Mean	SD	CV%	Median
kei (h^{-1})	0.24	0.06	26.68	0.22
kes	0.18	0.13	76.94	0.14
KCP	0.35	0.21	60.93	0.25
KPC	0.57	0.23	41.20	0.54
V (L)	7.70	1.78	23.21	7.61
Ymax (mg/L)	346.55	132.2	38.14	314.94
Kd (mg/L)	14.63	9.60	65.59	12.11

kei (typical value of ke) and kes (parameter estimated by the model representing the effect of the GFR on the typical kei value), KCP and KPC (transfer rate between the compartments), V (apparent volume of distribution), Ymax (maximal binding capacity), Kd (free TMO concentration corresponding to half maximal binding), SD (standard deviation), CV (coefficient of variation).

Visual predictive check (VPC):



VPC of simulated (5th, 50th and 95th percentiles) of total (solid black lines) and unbound TMO concentrations (solid red lines) represented *vs* time. The individual values of observed concentrations are shown as black (total) or red (unbound) circles.

- ✓ **Less than 5 % of observed concentrations are outside the 5th and 95th percentiles of simulated concentrations.**