

Temocillin dosing in haemodialysis patients based on population pharmacokinetics of total and unbound concentrations and Monte Carlo simulations

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Objectives: To develop a population model describing temocillin pharmacokinetics (PK) in patients undergoing haemodialysis and investigate how pharmacokinetic/pharmacodynamic (PD) targets can be met with different dosage regimens.

Patients and methods: Sixteen patients received the currently licenced dosing of 1, 2 or 3 g of temocillin (total of 61 doses) corresponding to an inter-dialytic period of 20, 44 or 68 h, respectively, and a dialysis period of 4 h. A non-linear mixed-effects model was developed jointly for total and unbound temocillin serum concentrations. The performance of clinically feasible dosing regimens was evaluated using a 5000-subject Monte Carlo (MC) simulation for determining the highest MIC for which the PK/PD target of $40\%fT_{>MIC}$ would be reached in 90% of patients [probability of target attainment (PTA)]. This PK study was registered at ClinicalTrials.gov (NCT02285075).

Results: Temocillin unbound and total serum concentrations (429 samples) were used to fit an open two-compartment model with non-linear albumin binding and first-order elimination. In addition to total body clearance, dialysis clearance was modelled using the Michaels function. The currently licenced dosing achieved a 90% PTA for an MIC up to 8 mg/L. A new temocillin dosage regimen was designed that would achieve a 90% PTA for an MIC of 16 mg/L (MIC₉₀ of target organisms) adjusted to patient weight and inter-dialytic period.

Conclusions: Currently licensed dosage regimen is suboptimal for MICs >8 mg/L (frequently found in clinical isolates). Model-based simulations allowed suggestion of a new dosage regimen with improved probability of microbiological success, applicability in routine clinical practice and more appropriate for empirical therapy.

Introduction

Patients with end-stage renal disease (ESRD) suffer a very high morbidity and mortality, with infection being the second leading cause of mortality.¹ Haemodialysis patients in particular have huge rates of bacteraemia.^{1,2} Although Gram-positive organism infections are predominant in haemodialysis populations, recent studies have highlighted an alarming increase in Gram-negative bacteraemia.^{3–5} In addition, multi-resistant organisms are on the rise in this setting, imposing a target-oriented use of antimicrobial drugs.^{3,5} Temocillin, a Gram-negative spectrum β -lactam antibiotic with a remarkable stability against most β -lactamases, including AmpC β -lactamases, ESBLs and most carbapenemases,⁶ could therefore fill a unmet medical need. Its renaissance in haemodialysis units was, however, challenged as most of its

pharmacokinetic (PK) data dates back to the 1980s.^{7,8} This data no longer reflects the marked advances in dialysis equipment and changes in dosing schemes.

We have conducted and have reported a PK study of temocillin in haemodialysis patients receiving this drug on dialysis days only using non-compartmental analysis.⁹ This study was initiated because dialysis can alter drug PK, influenced by several specific factors such as drug protein binding, dialysis system characteristics and geometry, and dialysis conditions.¹⁰ Based on this study, concerns about temocillin underdosing, if following the originally approved drug dosage recommendations, have been raised⁹ and acted upon by updating the Summary of Product Characteristics (effective in Belgium and France since June 2017).¹¹ An additional difficulty, however, stems from the fact that the PK of temocillin

are non-linear, due to saturable protein binding and extra-renal elimination.^{12,13} Hypoalbuminemia is frequent in ESRD patients¹⁰ and further adds to this complexity, as temocillin is highly protein bound (70%–85% in healthy subjects).⁶ As other β -lactams, temocillin exhibits time-dependent killing.⁶ Therefore, the most important PK/pharmacodynamic (PD) index predicting antimicrobial efficacy is the percentage of the dosing interval during which its unbound concentration is maintained above the MIC for the offending organism ($fT_{>MIC}$).¹⁴ As treatment with temocillin is often empirical, the actual MIC of temocillin for the offending organism(s) is unknown. However, the temocillin MIC₉₀ is 16 mg/L for Enterobacteriaceae.^{15,16} Monte Carlo (MC) simulations are a tool for estimating the probability of attaining a specific PK/PD target, accounting for PK data.¹⁷ They enable the optimization of dosage regimens and maximizing probability of target attainment (PTA), used as a surrogate for successful microbiological outcome.¹⁷

The purpose of the present study was to develop a mechanism-based population PK model of the concentration–time profile of temocillin unbound and total serum concentrations in haemodialysis patients, starting from the raw data of our previous study (see Vandecasteele *et al.*⁹). The present study also investigates the relationship between dosage regimens and achievement of PK/PD targets.

Methods

Study design and population

This PK study was conducted and obtained ethics approval (unique Belgian no. B049201215528) at the AZ Sint-Jan Brugge Hospital in Belgium and was registered at ClinicalTrials.gov (NCT02285075). The study design as well as a non-compartmental analysis of temocillin serum concentration–time data has previously been published⁹ (see Figure S1, available as Supplementary data at JAC Online). This non-randomized, open-label, multiple-dose study reflects the current clinical practice at the study site with 4 h standard haemodialysis sessions. Patients were included if undergoing intermittent haemodialysis for ESRD and prescribed temocillin for documented or suspected infection caused by an organism susceptible to temocillin. Temocillin was administered in 1, 2 or 3 g doses on dialysis days only, for 24, 48 or 72 h inter-dialytic intervals, respectively. Treatment regimen and duration were determined by the attending physician. Exclusion criteria were age (<18 years), limited (<24 h) estimated life expectancy due to major comorbidity, pregnancy, IgE-mediated allergy to penicillins or withholding written informed consent. FX8 and FX10 dialysers (Fresenius Medical Care AG & Co., Bad Homburg, Germany) were used.

Blood was sampled from an arterial or venous catheter as follows: pre-dose sample followed by samples at 0.5, 3, 6, 12, 24, 36, 48 and 68 h, truncated by the next dialysis session. During the 4 h dialysis session three additional hourly samples were collected (see Figure S2). Serum samples were obtained by centrifugation after blood clotting and frozen at -80°C until analysis. Validated HPLC methods, described in detail elsewhere^{18,19}, with a lower limit of quantification of 5 and 0.5 mg/L for total and unbound concentrations (determined in ultrafiltrates), respectively, were used; the non-compartmental analysis of the data was previously reported.⁹

PK analysis

PK data were analysed using non-linear mixed-effects models with NONMEM version 7.3 (ICON Development Solutions, Ellicott, MD, USA). The first-order conditional estimation method with interaction and subroutine ADVAN13 TRANS1 was used during model development.²⁰ Automation and post-processing of results was with Perl-speaks-NONMEM

(version 4.4.8; <https://uopharmacometrics.github.io/PsN/>) and RStudio 0.99.467 with R 3.1.1 (<http://www.r-project.org/>). Pirana 2.9.2 (<http://www.pirana-software.com/>) organized the model development.

The PK model was built to fit two types of data simultaneously: temocillin unbound and total serum concentrations. This required two principal model components: (i) a disposition model for unbound temocillin; and (ii) a model for the relationship between unbound drug and drug bound to serum proteins.

A non-linear binding model^{21,22} was used to relate total serum concentrations (C_{tot}) and unbound concentrations (C_{u}):

$$C_{\text{tot}} = C_{\text{u}} + [(C_{\text{u}} \times B_{\text{max}})/(C_{\text{u}} + K_{\text{d}})] \quad (\text{Eqn 1})$$

where B_{max} is the maximal binding capacity and K_{d} is the equilibrium dissociation constant.

In addition to the intrinsic total body clearance (CL), temocillin dialysis clearance (CL_{dial}) was implemented and set to zero only during inter-dialytic periods. Temocillin CL_{dial} was estimated using Michaels equation (Eqn 2):²³

$$CL_{\text{dial}} = \frac{\text{BFR} \left(\exp^{\frac{\text{KoA}}{\text{BFR}} \left(1 - \frac{\text{BFR}}{\text{DFR}} \right)} - 1 \right)}{\exp^{\frac{\text{KoA}}{\text{DFR}} \left(1 - \frac{\text{BFR}}{\text{DFR}} \right)} - \frac{\text{BFR}}{\text{DFR}}} \quad (\text{Eqn 2})$$

where KoA is the mass transfer area coefficient of the dialysis filter for temocillin (L/h), BFR is the blood flow rate (specific to each session, with typical values of 300–400 mL/min) and DFR is the dialysate flow rate (specific to each session, with constant value in our study of 500 mL/min). It allows description of the haemodialysis operating conditions, by relating dialysis parameters (BFR, DFR and KoA) to the clearance of a solute. After evaluating several statistical models for variability, residual variability was best described by a proportional model and inter-individual variability and inter-occasion variability by a log-normal distribution. An ‘occasion’ was defined as a set of concentration–time data corresponding to a dosing interval. The covariates considered were age, dry body weight, serum albumin, urea concentration pre-dialysis, urea reduction rate, creatinine concentration pre-dialysis and creatinine reduction rate.

Body weight, standardized to 70 kg, was included as an allometric function on all clearance (power coefficients = 3/4) and volume (power coefficient = 1) parameters for their strong theoretical and empirical evidence.^{24,25}

The best-performing base model was used for covariate model building and empirical Bayes estimates plotted against covariate values to explore potential relationships. An observable trend between covariates and PK parameters led to consideration for inclusion in the population model. The influence of subject-specific covariates was assessed by the forward-inclusion and backward-deletion method, using significant levels of $P < 0.01$ and $P < 0.005$, respectively.²⁶ Improvements in the fit obtained with each model were assessed in several ways. The NONMEM-generated objective function value (OFV) was used to perform the likelihood ratio test. When comparing nested models, a decrease in OFV of ≥ 3.84 was required to reach statistical significance ($P < 0.05$, 1 degree of freedom) and choosing the more complex model. Additional considerations were reductions in the inter-individual variability, inter-occasion variability, residual variability and precision of the parameter estimates as well as diagnostic plots and shrinkage.

The final population model was evaluated using the sampling importance resampling (SIR) method²⁷ and prediction-corrected visual predictive checks based on 1000 simulations.²⁸ The SIR was deemed more appropriate than the bootstrap in this case because it is less sensitive to sample size. In addition, it allows fast run times as it does not require estimation steps. The model was also assessed by normalized prediction distribution errors

(NPDE) metrics.²⁹ For a model with good predictability, the NPDE should follow an $N(0,1)$ distribution.³⁰

PD simulations

With model parameters determined, MC simulations were used to explore the probability of achieving a PD target for various MICs. Simulations generated unbound concentration–time profiles for 5000 subjects, with uniform weight distribution from 50 to 100 kg. From this, the $fT_{>MIC}$ was calculated for each subject over the treatment period.³¹ The PTA was defined as the probability of achieving the target of $40\%fT_{>MIC}$, which is a commonly used target for bacteriological cure with β -lactams,³² over a plausible range of potential MICs of temocillin for Gram-negative organisms (1–128 mg/L). The main target organisms for temocillin are ESBL-producing Enterobacteriaceae, presenting an MIC_{90} of 16 mg/L.³³ The PK/PD susceptibility breakpoint was defined as the highest MIC for which the PK/PD target of $40\%fT_{>MIC}$ is achieved in at least 90% of patients, which is the most commonly used acceptable level of PTA.¹⁷

Initially, the dosage regimens used in this study (1 g q24h, 2 g q48h and 3 g q72h), which correspond to the recently updated licensed dosage regimens,¹¹ were evaluated against the above criteria. As these regimens fell short of achieving the treatment target for an MIC and PTA cut-off of 16 mg/L and 90%, a new dosage regimen was developed for 24, 48 and 72 h inter-dialytic periods. Simplicity and ease of use were key criteria for the proposed regimen, while not exceeding single dose administrations of 3 g. In the absence of maximum tolerated doses, current clinical practice has shown that single doses of 3 g lead to well tolerated drug concentrations in the studied population.⁹ Restricting maximum doses to this value further ensures drug concentrations remain in the range observed during model development, hence maintaining the model's validity. The new regimen was obtained by iterative dose optimization for all weights from 50 to 100 kg, evaluated in steps of 2.5 kg.

The cumulative fraction of response (CFR) was calculated according to Mouton *et al.*³¹ to estimate the expected overall response of Enterobacteriaceae to temocillin for different dosage regimens. MIC distributions reported for clinical specimens, including strains with unusual resistance as reported by Woodford *et al.*,³⁴ were used (Table S1). MIC distributions of isolates producing OXA, VIM, IMP or NDM carbapenemases were, however, excluded from the dataset for their known high-level resistance to temocillin, leading to a total of 1920 strains of *Escherichia coli*, *Enterobacter* spp. and *Enterobacter* spp. considered.

Results

Study population

The study included 16 patients of which 14 were male (88%), the median age was 68.5 years (range 24–91 years) and the median dry body weight was 73.1 kg (range 41.5–104 kg). All patients required intermittent haemodialysis and received temocillin as part of regular therapy for suspected or documented Gram-negative infection. Their key characteristics have been published elsewhere.⁷ Median albumin, pre-dialysis creatinine and blood urea nitrogen concentrations were 3.3 g/dL (range 2.1–4.4 g/dL), 6.5 mg/dL (1.26–10.29 mg/dL) and 107 mg/dL (10–169 mg/dL), respectively. Seven patients (44%) were diagnosed with sepsis. Gram-negative bacteria from the Enterobacteriaceae family were identified as the causative organism in 11 (69%) patients: *E. coli* (36.6%; $n = 4$), *Klebsiella oxytoca* (27.3%; $n = 3$), *Enterobacter cloacae* (27.3%; $n = 3$) and *Klebsiella pneumoniae* (9.1%; $n = 1$).

Serum concentration–time profiles

Four hundred and twenty-nine serum temocillin concentration measurements were available, from 48 dosing cycles, one cycle starting with the administration of temocillin and ending after dialysis. They include 4 cycles for 1 g q24h, 31 for 2 g q48h and 13 for 3 g q72h, with a median of 3 (range 1–6) dosing cycles per patient. Haemodialysis duration was constant (4 h), while the inter-dialytic interval was 24, 48 or 72 h depending on the patient's clinical condition. Follow-up was for a median of 5.5 days (range 2–9 days). Non-compartmental analysis of serum concentration–time data for temocillin was published previously.⁹

PK analysis

Serum unbound concentration–time profiles were best described by a two-compartment model with zero-order input and linear distribution from the central and peripheral compartment, after intravenous administration. The final model also included a first-order total body clearance that was estimated at 1.43 L/h. Assuming a typical DFR of 500 mL/min and a BFR of 300 mL/min, the CL_{dial} calculated from the parameter KoA (estimated at 7.83 L/h) was 7.67 L/h. The total temocillin clearance is the sum of CL and CL_{dial} . The OFV did not decrease significantly ($\Delta OFV = -2.6$) compared with the model with constant dialysis clearance, but the Michaelis equation was selected due to its mechanistic and physiological rationale.²³ The final base structural model describing unbound drug and bindings in serum is shown in Figure 1. The addition of inter-occasion variability between dose administrations produced a further improvement in the fit ($\Delta OFV = -38$). Dry body weight, allometrically scaled on clearance and volume parameters, resulted in an improved model ($\Delta OFV = -9.2$). The addition of any other covariates in the model could not be statistically supported. The median elimination $t_{1/2}$ of temocillin for all subjects during the inter-dialytic period, estimated using empirical Bayes estimates of the final model parameters, was 22.8 h (range 11–48.7 h). The final population model parameters are presented in Table 1. The values of B_{max} and K_d describing the protein binding are within the non-linear range of Eqn 1 and as a consequence the median bound fraction experienced across the population is between 32% and 67%. This is expectedly lower than for healthy subjects. Goodness-of-fit plots and correlation of random effects for the final model were evaluated and did not show any model misspecification (see Figures S3 and S4). The prediction-corrected visual predictive check plot (Figure 2) showed a good predictive power until ~ 130 h, as few patients were followed up for longer than that amount of time. The estimated NPDE values followed an $N(0,1)$ distribution (Figure S5).

PD analysis

Figure 3 shows the PTA for $40\%fT_{>MIC}$ versus MIC, for various simulated temocillin dosage regimens as well as their proposed PK/PD-based temocillin breakpoints. The recently updated dosage regimens (1 g q24h, 2 g q48h and 3 g q72h),¹¹ which also correspond to the dosage regimens currently used in the clinical centre treating the patients included in this study, reveal a probability of successful treatment ($PTA \geq 90\%$) for MICs ≤ 8 mg/L. Of note, the doses used to calculate this PTA were already twice the original licensed doses (0.5 g q24h and 1 g q48h), but led to an increase of

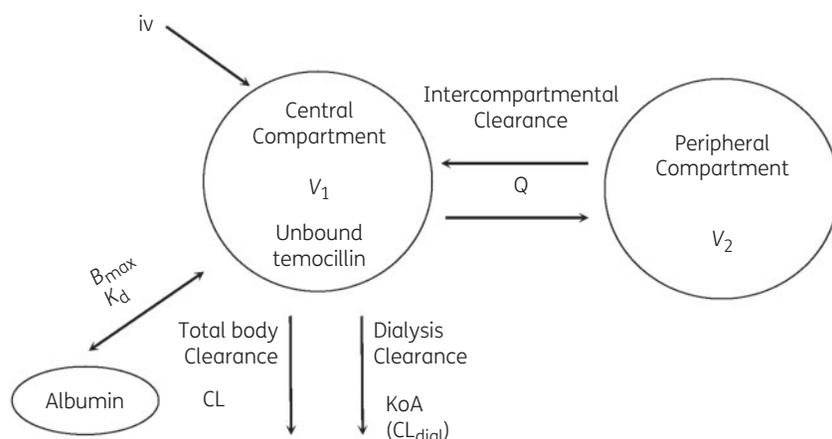


Figure 1. Schematic diagram of the final PK model for temocillin after intravenous (iv) administration. The model parameters are defined in Table 1.

Table 1. Parameter estimates of the final population PK model for unbound temocillin in patients undergoing haemodialysis

Parameter	Population estimate (%RSE)	SIR 95% CI
Structural model parameters		
V_1 (L/70 kg) ^a	22.7 (9.6)	19.3–26.4
V_2 (L/70 kg) ^a	18.6 (9.7)	15.8–21.2
Q (L/h/70 kg) ^a	3.99 (8.0)	3.4–4.7
KoA (L/h) ^b	7.83 (17.1)	6.7–9.1
CL (L/h/70 kg) ^a	1.43 (12.5)	1.2–1.7
K_d (mg/L)	34.3 (21.7)	24.1–46.4
B_{max} (mg/L)	117 (12.7)	96.3–142.3
Inter-individual variability^c (CV%)		
V_1	38.2 (16.6)	31.7–49.3
V_2	32.6 (25.3)	21.2–49.4
CL	50.2 (18.2)	39.0–66.5
K_d	82.1 (23.5)	60.8–106.7
B_{max}	42.2 (25.8)	32.2–58.4
Inter-occasion variability (CV%)		
CL	16.8 (25.7)	12.5–22.6
Proportional residual variability^c (CV%)		
unbound	23.0 (18.9)	21.7–24.6
total	18.0 (18.7)	16.6–19.3

RSE, relative standard error (standard error of the estimate/estimate \times 100); CV, coefficient of variation; Q, inter-compartmental clearance; CL, total body clearance.

^aAllometric model with a standard body weight of 70 kg and an exponent of 1 (to scale the volume of both central and peripheral compartments) or 0.75 (to scale Q and CL).

^b $CL_{Dial} = BFR \times \{EXP[KoA/BFR \times (1 - BFR/DFR)] - 1\} / \{EXP[KoA/BFR \times (1 - BFR/DFR)] - BFR/DFR\}$.²³

^cThe η -shrinkage for inter-individual variability was <19%; ϵ -shrinkage was 4.8%.

only one log₂ (one dilution) in the attainable MIC. For bacteria with an MIC of 16 mg/L, the administered doses of 1 g q24h, 2 g q48h and 3 g q72h would achieve a PTA of only 60%, 72% and 71%, respectively. Because of the poor performance of these modalities of

treatment, a new regimen is proposed based on the model built and using MC simulations. Table 2 shows the dose needed to achieve a PK/PD target of 40% $fT_{>MIC}$ for an MIC of 16 mg/L in at least 90% of patients for 24, 48 and 72 h inter-dialytic periods. Simulations suggest that for the two extremes of patient weight (50 and 100 kg), this new proposed dosage regimen, when used in an intermittent haemodialysis schedule (Figure 4), should be safe for most patients, as they do not exceed the maximal unbound concentrations simulated for currently used doses. During the haemodialysis session, concentrations can drop to \sim 7 mg/L, calling for the need of a replacement dose after each dialysis session.

The CFRs against *E. coli*, *Klebsiella* spp. and *Enterobacter* spp. are summarized in Table 3. They were all <46% at the original licensed dosing, increased to \sim 60% with the updated licensed dosing and were >80% with the new proposed dosing.

Discussion

This article distinguishes itself for being the first known study to use a model-based approach to determine the optimal dosing of temocillin in patients undergoing intermittent haemodialysis with contemporary haemodialysers. In this work, the PK of temocillin were characterized using non-linear mixed-effects modelling to estimate population PK parameters, to evaluate the performance of different dosage regimens and to propose new dosage guidelines.

The best-performing disposition model consisted of two compartments and was in line with other studies.^{12,35–37} A number of covariates were available in the dataset; however, only dry body weight was found valid for inclusion in the final model. The relatively small patient cohort and large heterogeneity within this population probably explains that many of the covariates did not produce statistically significant improvements in the model objective function. Without this, empirical evidence was considered insufficient to include the respective covariate. Interestingly enough, there was no significant correlation between B_{max} and albumin concentrations, implying that there may be other molecules involved in the binding process.^{9,38}

It has been suggested for temocillin and other β -lactams (e.g. piperacillin)³⁹ that an extra-renal elimination pathway (like

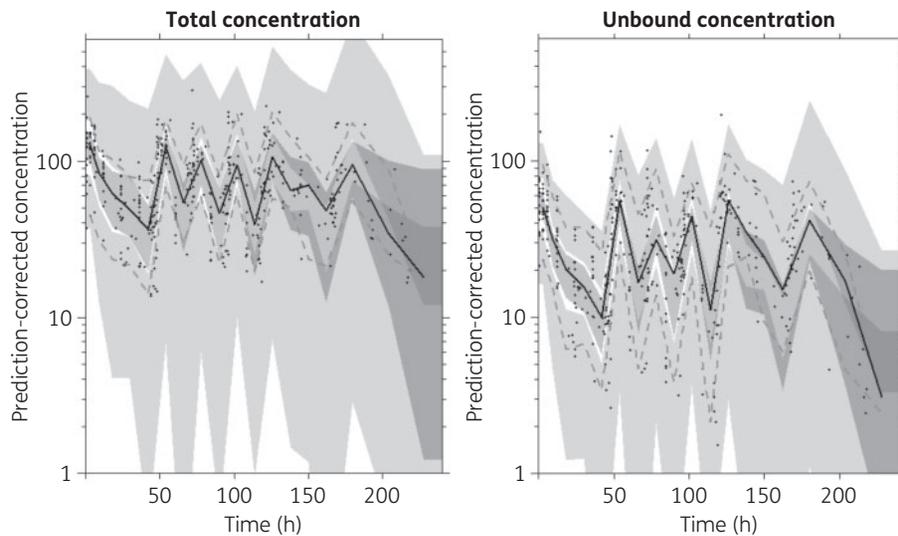


Figure 2. Prediction-corrected visual predictive check of the final model describing the PK of total and unbound temocillin concentrations, in patients undergoing intermittent haemodialysis. The continuous line represents the median observed serum concentrations. The observed 5th and 95th percentiles are represented by broken lines. The area shaded dark grey represents the 95% CI for the simulated-based median and the areas shaded light grey represent the 95% CIs for the simulated-based 5th and 95th percentiles. The prediction-corrected concentrations are plotted as dots.

biliary secretion) assumes a more important role on drug clearance in case of renal dysfunction.^{9,12,13} Thus, during model development, a mixed-order (capacity-limited) elimination process was also evaluated. Although leading to a decrease in the OFV, it was insufficient to reach statistical significance, probably due to the limited sample size. It was, therefore, not included in the final model.

The data in the present study was previously used in a non-compartmental analysis.⁹ Other than this, previous research on temocillin in a haemodialysis setting is limited to two small studies conducted in the 1980s, using haemodialysers which no longer reflect the performance of the contemporary dialysers.^{7,8} Therefore, comparison with this data is of limited value.

Temocillin population PKs have only been reported twice and both times in intensive care patients.^{36,40} De Jongh *et al.*⁴⁰ assumed a constant unbound to total ratio of 25% and modelled only total concentration. This linear relationship was not confirmed by the data in the present study, where the non-linear relationship proposed finds its biological explanation in saturable protein binding. Laterre *et al.*³⁶ modelled the unbound concentration on a cohort of non-regularly impaired intensive care patients. Thus, only some parameters can be compared with this study.³⁶ The volume of distribution of the central compartment found in the present study is nevertheless in line with the one estimated in that study.

The strength of the present study is the joint model of both unbound and total concentrations collected in a routine clinical setting. Such an integrated model has not been reported previously, to the best of our knowledge. The unbound and total samples are processed differently and hence have different assay error distributions. By integrating both into the same model, one can reduce the variability in the estimated model parameters.

This model also offers improved flexibility for inferring and deriving data useful for clinical application. By working with both

unbound and total concentrations, the model can be provided with only the readily obtainable total concentration data and provide estimates of the more clinically relevant (pharmacologically active) unbound concentration expected in patients. Moreover, this model can be used to tailor dosage regimens for a specific target $fT_{>MIC}$, given a bacterium with a known MIC.

Based on the developed model, the MC simulations determined the PK/PD breakpoints for different temocillin regimens. Temocillin is likely to be used against bacteria with MICs up to 16 mg/L, which implies that the updated licensed regimens of 1 g q24h, 2 g q48h and 3 g q72h are insufficient. This updated regimen is an improvement on the former one, which was only effective, on a PK/PD standpoint, against highly susceptible bacteria (MIC < 4 mg/L). However, the updated licensed regimen still delivers an unacceptably low overall CFR (~60%). Furthermore, while it improves the PTA, it is still insufficient to meet the more clinically effective criteria of attaining a PTA for 40% $fT_{>MIC = 16 \text{ mg/L}}$ in 90% of the patient population. The currently licensed dosage regimens produced a PK/PD breakpoint of 8 mg/L, which corresponds to the temocillin clinical breakpoint for systemic infections from BSAC.⁴¹ The corresponding CFRs were < 70% and therefore also unacceptably low. In contrast, the regimen proposed in the present study produced better results, offering the possibility to cover organisms with reported MICs ≤ 16 mg/L (calculated value < 18 mg/L) and reliably produce a CFR of ~80%.

This study has limitations that deserve mentioning. First, the relatively small sample size, due to practical considerations, and the performance of the study in a single clinical centre, may limit the applicability of the conclusions. This is, however, mitigated by the wealth of available data (in terms of assays collected) used to describe the temocillin concentration–time profiles. Second, we did not evaluate the performance of the dosage regimens for more aggressive PK/PD targets (e.g. 80%–100% $fT_{>MIC}$ or even

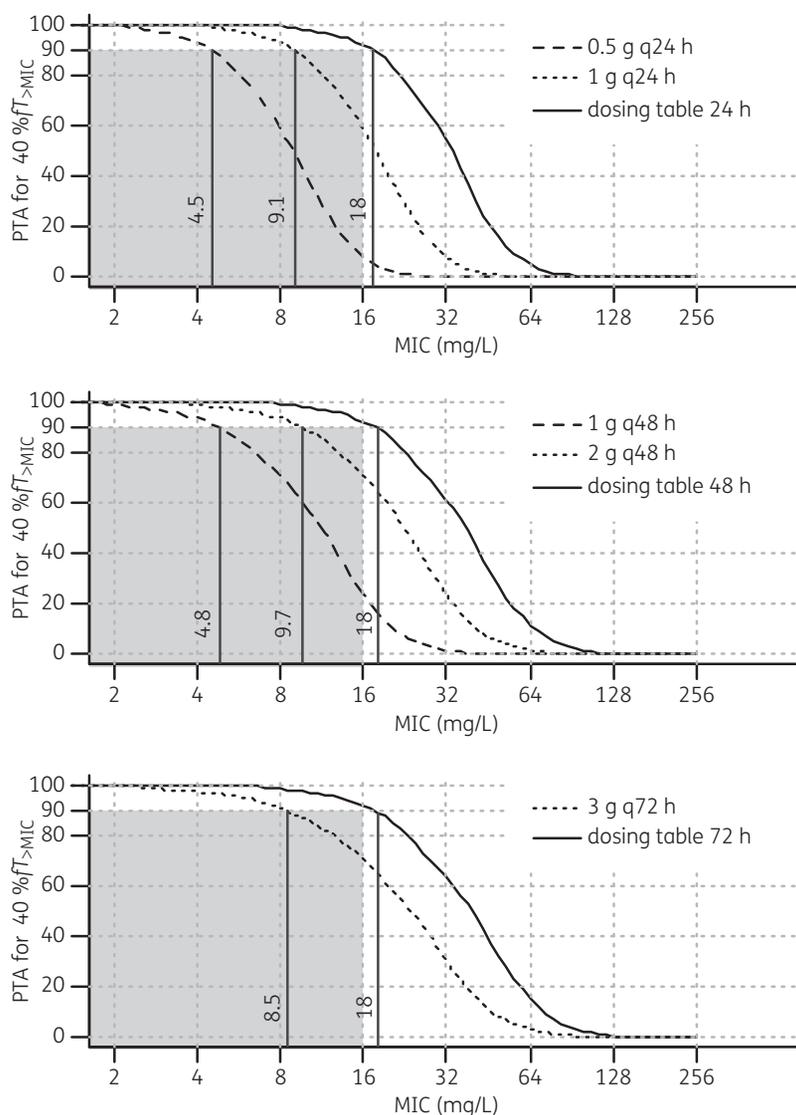


Figure 3. PTA of $40\%fT_{>MIC}$ versus MIC, for simulated temocillin dosage regimens (0.5 g q24h, 1 g q24h, dosing table 24 h; 1 g q48h, 2 g q48h, dosing table 48 h; 3 g q72h, dosing table 72 h) in four consecutive dosing cycles. All regimens assume a uniform weight distribution. Displayed values are the 95% CI lower bound on the binomial estimate of the PTA derived from 5000 simulated patients per regimen. Grey shading corresponds to the area in which treatment target succeeded, assuming an MIC and PTA cut-off of 16 mg/L and 90%, respectively. The solid vertical lines indicate the PK/PD breakpoint for each dosage regimen, i.e. the highest MIC for which the PK/PD target of $40\%fT_{>MIC}$ is achieved in at least 90% of patients.

4–5 \times MIC for $100\%fT_{>MIC}$). For the target of this study ($40\%fT_{>MIC}$), which is also that considered by EUCAST to establish susceptibility breakpoints for penicillins,⁴² some doses were spread across two administrations to avoid potential safety issues. More aggressive targets would probably imply using frequent administration regimens that are impractical in a clinical setting. Furthermore, differences in MIC distributions in various locations were not taken into account, which are needed to accurately assess the probability of treatment success. Also, the study used serum concentrations as a proxy for blood concentrations in the

estimation of dialysis clearance for practical reasons and due to lack of information on temocillin blood cell partitioning. Prospective evaluation of the proposed dosage regimen is therefore necessary. Modelling, which is a cost-effective and quantified precursor step in the development of improved dosing recommendations, informs the design of appropriate future clinical studies.⁴³

In conclusion, a detailed population PK model of temocillin with saturable protein binding is reported. Dry body weight was found to influence temocillin clearance and volume of distribution. Although recently updated, the current licensed dosage regimen

Table 2. Dosing table: proposed temocillin dosage regimen for haemodialysis patients, according to their weight and the inter-dialytic period

Dry body weight (kg)	Inter-dialytic period (h)		
	24	48	72
50–54	1.5 g	3 g	1st dose: 2 g 2nd dose (24 h later): 2 g
55–59			
60–64			
65–69			
70–74	2 g	1st dose: 2 g 2nd dose (24 h later): 2 g	1st dose: 2.5 g
75–79			2nd dose (24 h later): 2.5 g
80–84			1st dose: 3 g
85–89			2nd dose (24 h later): 3 g
90–94			
95–100			

Single or first doses should be administered immediately after dialysis. Inter-dialytic periods can be considered independent from each other. Dosage regimens were rounded up to the closest 0.5 g.

Table 3. Cumulative fraction of response (%) to achieve the target of $>40\%fT_{>MIC}$ for *E. coli*, *Klebsiella* spp. and *Enterobacter* spp., with different temocillin dosage regimens, based on published temocillin MIC distributions³⁴

Temocillin dosage regimen	Major β -lactamase isolates		
	KPC (MIC _{50/90} : 8/32 mg/L), n = 669	other (MIC _{50/90} : 16/32 mg/L), n = 1251	all (MIC _{50/90} : 16/32 mg/L), n = 1920
Former licensed: 0.5 g q24h	38.7	37.5	37.9
Current licensed: 1 g q24h	67.6	59.7	62.4
Proposed: dosing table 24 h	85.9	78.0	80.7
Former licensed: 1 g q48h	47.6	44.1	45.3
Current licensed: 2 g q48h	73.3	65.5	68.2
Proposed: dosing table 48 h	87.0	79.5	82.1
Current licensed: 3 g q72h	73.1	66.0	68.5
Proposed: dosing table 72 h	87.2	80.0	82.5

KPC, organisms expressing KPC-type carbapenemases. Proposed dosage regimens are described in Table 2.

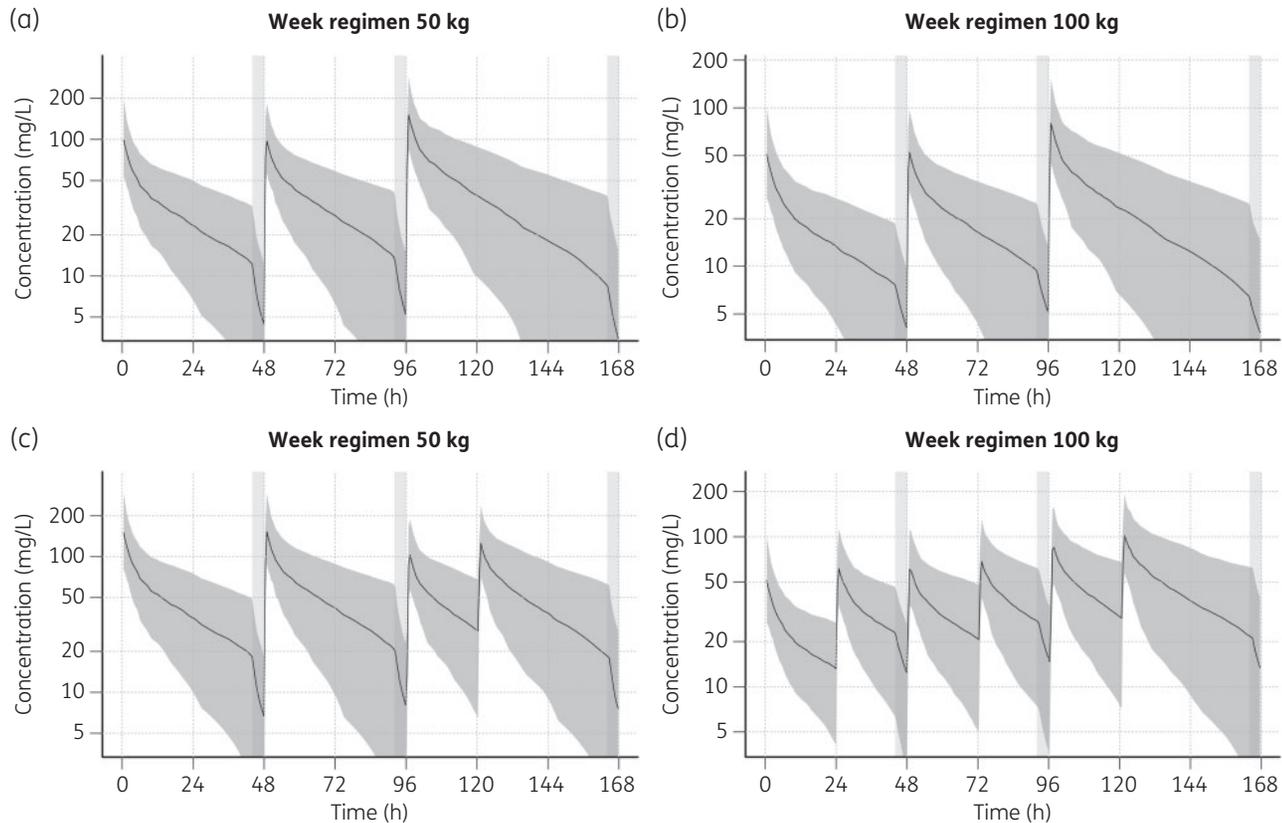


Figure 4. Concentration–time profiles based on 5000 MC simulations of unbound temocillin serum concentrations in haemodialysis patients. A typical thrice-weekly haemodialysis schedule was simulated for two patient weights (50 and 100 kg) when administered at the dosage regimens used in this study (2 g q48h and 3 g q72h) (a and b) and with the new proposed regimen, as per Table 2 (c and d). Dark grey shading corresponds to the 95% CI and the continuous black line corresponds to the median. The times for the haemodialysis session were 44–48 h, 92–96 h and 164–168 h (indicated by light grey shading).

was found to be adequate only for MICs ≤ 8 mg/L and, therefore, suboptimal for higher MICs that are reported in around half of the clinical isolates. Model-based simulations suggest a new dosage regimen with improved probability of treatment success, applicability in routine clinical practice and improved suitability for empirical therapy.

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Transparency declarations

A. C. M. B. and A. S. are employees of the *Université catholique de Louvain*. S. J. V. works at the *AZ Sint-Jan Brugge-Oostende*. P. M. T. was unpaid. P. M. T. is an unpaid advisor to Eumedica, the registration holder of temocillin. F. V. B. is Research Director of the *Fonds de la Recherche Scientifique* (F.R.S.-FNRS).

Supplementary data

Figures S1 to S5 and Table S1 are available as [Supplementary data](#) at JAC Online.

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Temocillin dosing in haemodialysis patients based on population pharmacokinetics of total and unbound concentrations and Monte Carlo simulations

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Supplementary data

Table S1. MIC distributions for *E. coli*, *Klebsiella* spp and *Enterobacter* spp. for temocillin³²

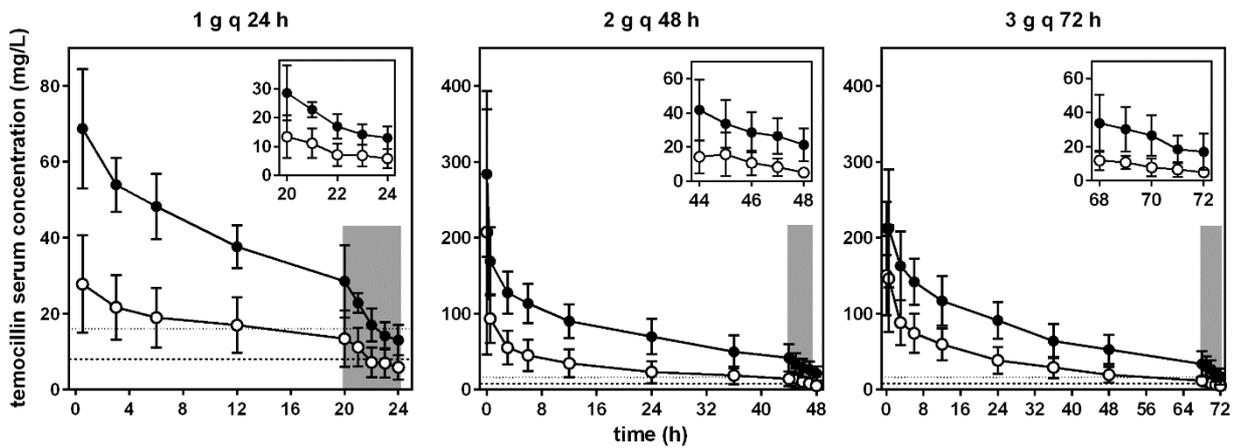
Major β -lactamase	Number (%) of isolates with MIC (mg/L)							
	≤ 1	2	4	8	16	32	64	≥ 128
All isolates								
KPC (<i>n</i> =669)	6 (1)	14 (2)	91 (14)	229 (34)	200 (30)	88 (13)	32 (5)	9 (1)
other (<i>n</i> =1251)	33 (3)	60 (5)	184 (15)	303 (24)	279 (22)	239 (19)	90 (7)	63 (5)
total (<i>n</i> =1920)	39 (2)	74 (4)	275 (14)	532 (28)	479 (25)	327 (17)	122(6)	72 (4)

KPC: *Klebsiella pneumoniae* carbapenemase,

MIC distributions of the OXA-, VIM-, IMP- and NDM-carbapenemase producers were not considered from the original dataset, as these beta-lactamases confer temocillin resistance.

Figure S1. Actual serum concentration-time profiles

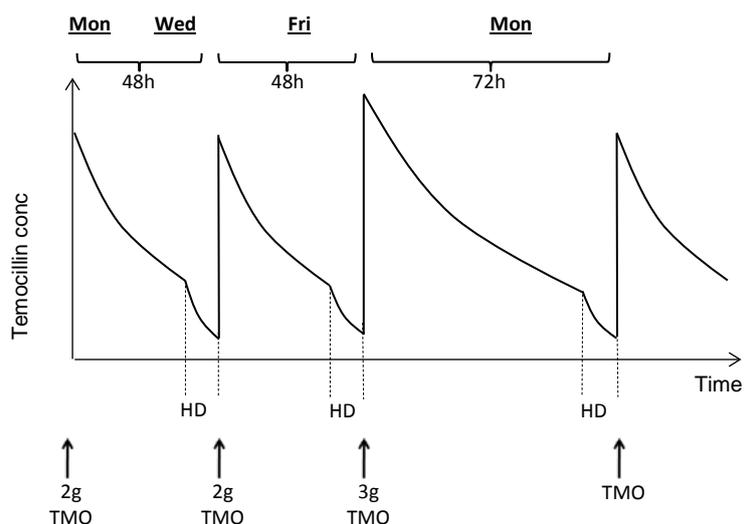
Mean \pm standard deviation of total (closed symbols) and free (open symbols) temocillin concentrations for the 1 g (left panel), 2 g (middle panel) and 3 g (right panel) dosing regimens. Greyed areas correspond to the haemodialysis period (4 h), with values shown in a magnified fashion in the inset. Data from Vandecasteele *et al.** (reproduced with permission)



* Vandecasteele SJ, Miranda Bastos AC, Capron A *et al.* Thrice-weekly temocillin administered after each dialysis session is appropriate for the treatment of serious Gram-negative infections in haemodialysis patients. *Int J Antimicrob Agents* 2015; 46: 660-5.

Figure S2. Temocillin administration and sampling scheme

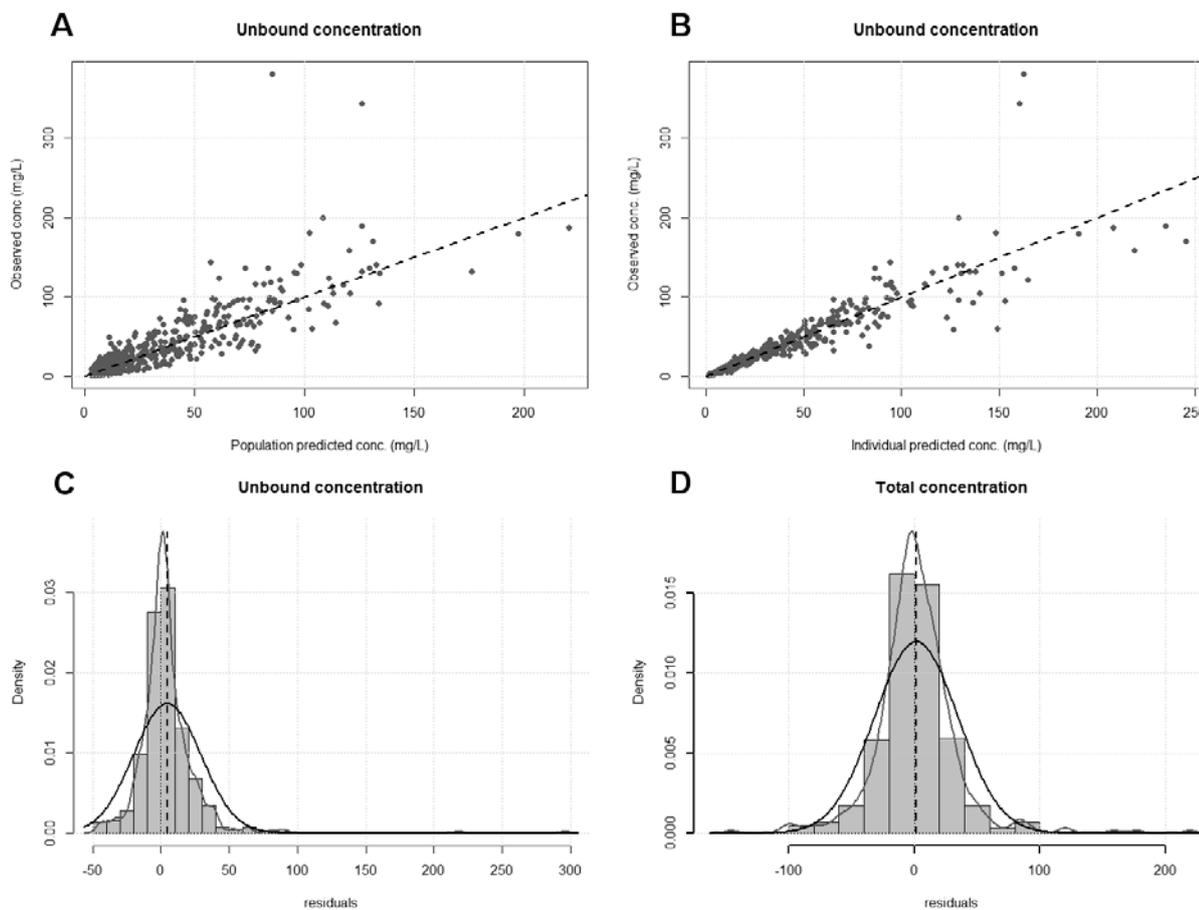
Temocillin (TMO) was administered by IV bolus immediately after the intermittent haemodialysis (HD) session. This figure represents a typical ESRD patient who undergoes haemodialysis thrice weekly, on Mondays (Mon), Wednesdays (Wed) and Fridays (Fri). The study protocol foresaw the administration of 1g, 2g or 3g for an inter-dialytic period of 24h, 48h or 72h, respectively. The 24h inter-dialytic period is not represented in this figure.



Temocillin serum concentrations were measured at the following planned time points in relation to the first dose in all patients: 0 (pre-dose sample), 0.5, 3, 6, 12, 20 (before dialysis) and 24h (at the end of dialysis), when patients were dialysed with a 1 day interval; 0, 0.5, 3, 6, 12, 24, 36, 44 (before dialysis) and 48h (at the end of dialysis), when patients were dialysed with a 2 day interval; 0, 0.5, 3, 6, 12, 24, 36, 48, 68 (before dialysis) and 72h (at the end of dialysis) when patients were dialysed with a 3 day interval). Additional blood samples were taken 1, 2, 3h after the start of dialysis.

Figure S3. Temocillin goodness of fit plots

A: observed versus population-predicted concentrations; **B:** observed versus individual predicted concentrations; **C, D:** histogram of population residuals; **E, F:** Q-Q plot of population residuals; **G, H:** weighted residuals versus time.



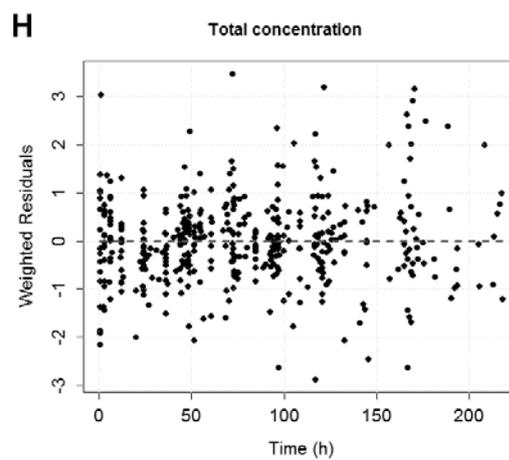
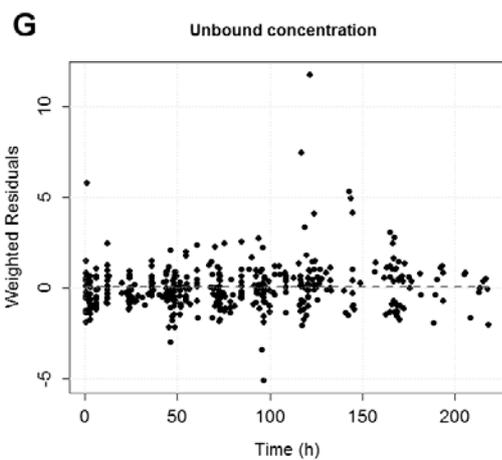
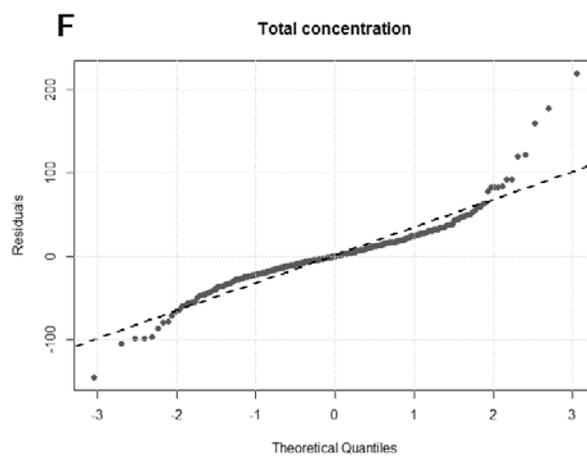
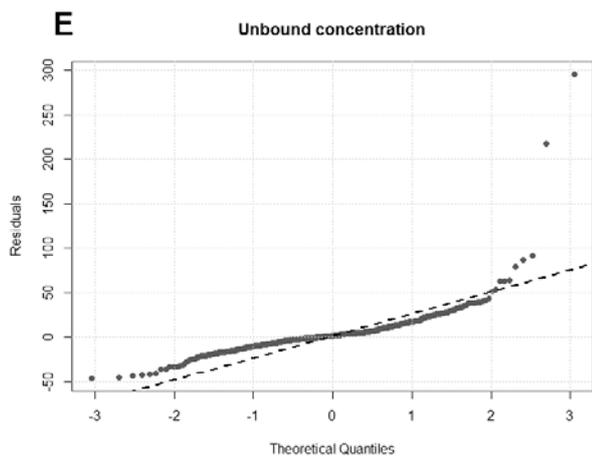


Figure S4. Correlation of ETAs

ETA1: between subject variability V_1 ; ETA2: between subject variability V_2 ; ETA3: between subject variability K_d ; ETA4: between subject variability B_{max} ; ETA5: between subject variability clearance; ETA6: between occasion variability, clearance

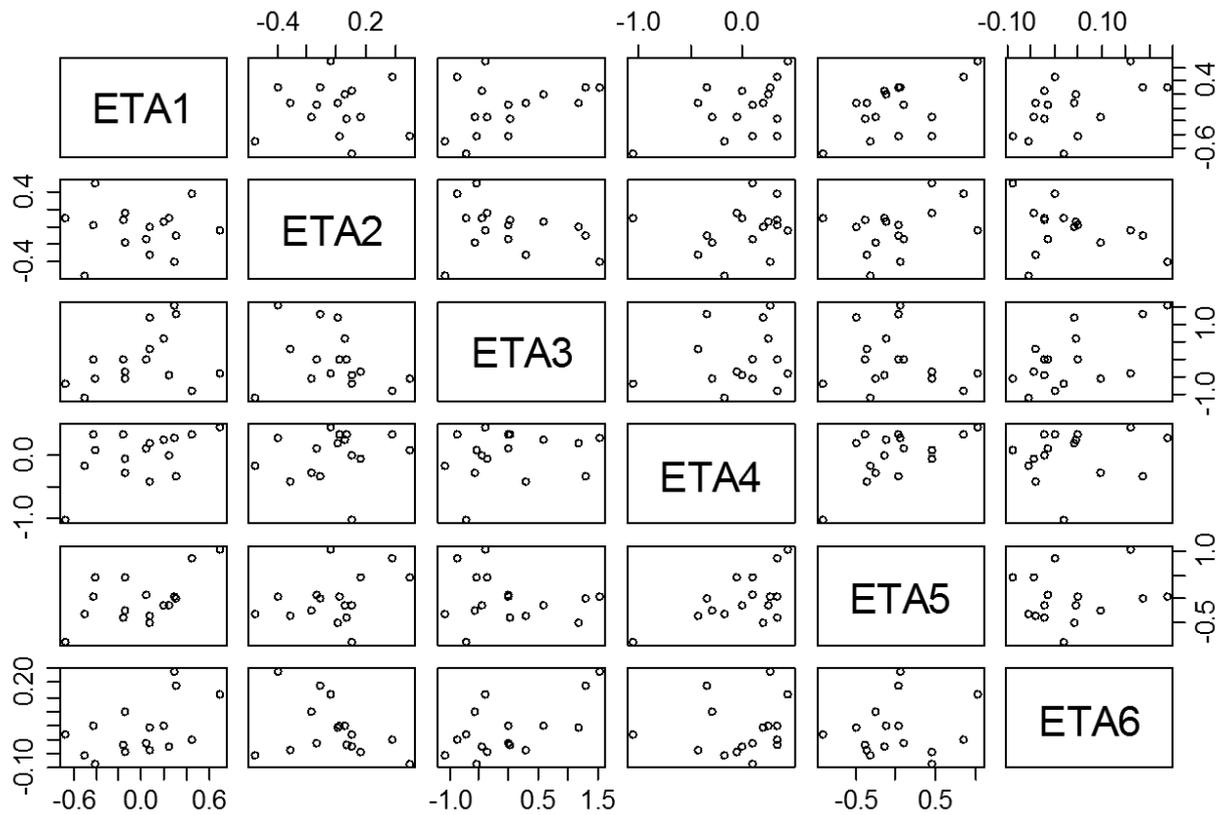


Figure S5. Normalised prediction errors

A, B: histograms plot of normalized prediction errors estimates (NPDE); **C, D:** QQ plot of NPDE; **E, F:** NPDE versus time plots

