Using modeling and simulation to design and evaluate dosing strategies for temocillin in haemodialysis patients

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Background and Objectives

- ✓ Temocillin is an anti-Gram-negative β-lactam active against many ESBL-producing Enterobacteriaceae but with limited population pharmacokinetics data on patients undergoing haemodialysis.
- ✓ Current dosing recommendations:[1]

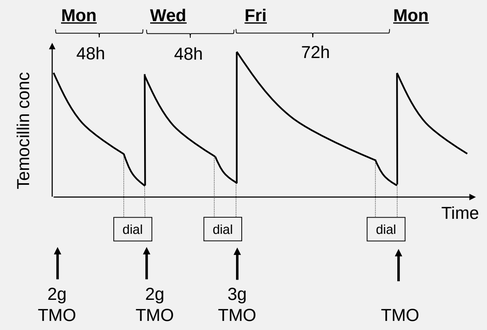
Haemodialysis regimen	Temocillin dose
every 24h	500 mg
every 48h	1000 mg

- ✓ The purpose of this study was to develop a joint PK model of total and unbound temocillin serum concentrations in this patient population.
- ✓ This model was also used to design and evaluate a dosing regimen aiming at a 90% probability of target attainment, i.e. unbound concentrations at least 40% of the dosing interval above the largest minimal inhibitory concentration (40%$fT > MIC$) of the main susceptible organisms (≤ 16mg/L).

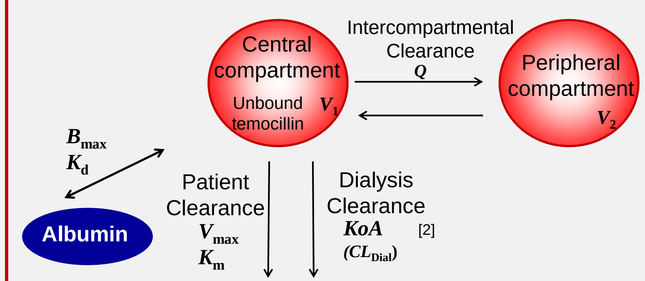
Methods

- ✓ 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.
- ✓ A nonlinear mixed effects model was fitted, taking both total and unbound temocillin concentrations from 429 serum samples into account.
- ✓ A 10,000-subject Monte Carlo simulation was conducted to determine the required dose to achieve 90% probability of target attainment over a wide range of patients' weights (50-100kg). These simulations also investigated the performance of various clinically feasible dosing regimens.
- ✓ Data analyses were performed using NONMEM 7.3, Pirana, PsN and R.

Typical dialysis and dosing regimen



Mechanism-based final PK model



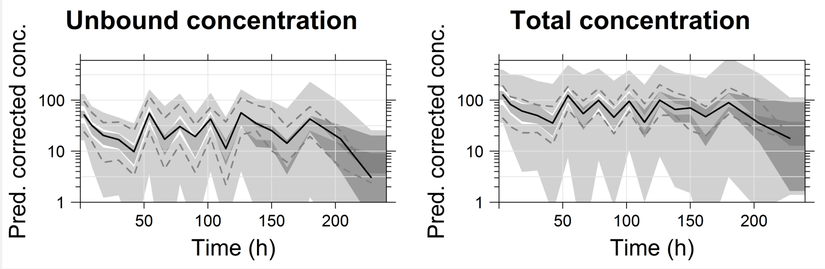
Results

Final PK parameter estimates

Parameter	Estimate (RSE %)	Bootstrap median (95% CI)†	IIV / IOV CV% (RSE%)
Structural model			
V_1 (L/70kg)*	22.7 (10.1)	23.4 (20.0 - 27.9)	38.1 (16.6)
V_2 (L/70kg)*	20.7 (10.5)	22.0 (18.2 – 26.4)	31.0 (22.9)
Q(L/h/70kg)♯	4.16 (5.5)	4.1 (3.4 – 4.8)	-
KoA[a] (L/h)	7.99 (17.4)	8.0 (5.5-10.6)	-
V_{max} (mg/h/70kg)♯	411 (73)	258.4 (117.7 -474.6)	§47.4 (19.1) / 13.9 (30.2)
K_m (mg/L)	253 (87.7)	143.8 (50.8-301.9)	
K_d (mg/L)	34.2 (21.2)	37.2 (24.2 – 58.4)	81.7 (21.4)
B_{max} (mg/L)	117 (12.7)	124.8 (102.6–154.9)	42 (26.2)
Residual variability			
Prop. Error CV% unbound conc	22.9 (18.9)	22.5 (18.4 – 26.1)	-
Prop. Error CV% total conc	18.0 (19.3)	17.4 (13.8 – 19.7)	-

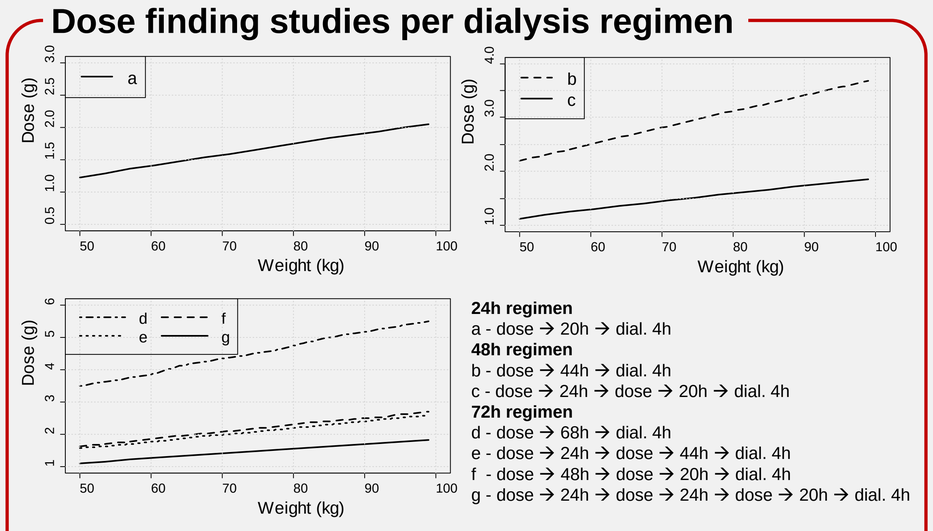
RSE, relative standard error; CV, coefficient of variation; IIV, interindividual variability; IOV, interoccasion variability; Q, intercompartmental clearance; KoA: mass transfer area coefficient; Vmax, maximum elimination rate of the system; Km, drug concentration that produces 50% of the maximal elimination rate of the system; Kd, unbound drug concentration corresponding to half maximal binding; Bmax, maximal binding capacity.
†estimated by applying the final PopPK model to 1000 re-sampled dataset
*,♯ allometric model with a standard body weight of 70kg and an exponent of 1 (to scale the volume of both central and peripheral compartments) or 0.75 (to scale Q and V_{max}).
§ IIV and IOV for clearance (CL). Patient clearance was defined as
$CL = V_{max}/(K_m+C1) * EXP(IIV\_CL + IOV\_CL)$
[a] CL_{Dial}= BFR*(EXP(KoA/BFR*(1-BFR/DFR))-1)/(EXP(KoA/BFR*(1-BFR/DFR))-BFR/DFR) [2]

Prediction-corrected visual predictive checks



pcVPC of the final model describing the PK of temocillin concentrations, in patients undergoing intermittent haemodialysis. The solid line represents the median observed serum concentrations. The observed 5% and 95% percentiles are presented with dashed lines. The shaded dark grey represents a simulated-based 95% confidence intervals for the median, and the shaded light grey corresponds to the model predicted percentiles. Where shaded areas overlap darker shades can appear. The actual concentrations are not plotted in this figure.

Dose finding studies per dosing regimen



24h regimen
a - dose → 20h → dial. 4h
48h regimen
b - dose → 44h → dial. 4h
c - dose → 24h → dose → 20h → dial. 4h
72h regimen
d - dose → 68h → dial. 4h
e - dose → 24h → dose → 44h → dial. 4h
f - dose → 48h → dose → 20h → dial. 4h
g - dose → 24h → dose → 24h → dose → 20h → dial. 4h

Required temocillin dose to achieve a PKPD target of 40%fT>MIC_{16} as a function of body weight with 90% probability for a 24h (a), 48h (b, c) and 72h (d, e, f, g) interdialytic regimen. The simulated dosage schedule indicated in the respective graph was repeated 4 times.

Dosing table

Dry body weight (kg)	Interdialytic period 24h	48h	72h
50 – 55	1.5g	2.5g	
56 – 60		3g	1st dose: 2g
61 – 65			2nd dose (24h later): 2g
66 – 70	2g		
71 – 75			
76 – 80		1st dose: 2g 2nd dose (24h later): 2g	1st dose: 2.5g
81 – 85			2nd dose (24h later): 2.5g
86 – 90			
91 – 95			1st dose: 3g
96 – 100	2.5g		2nd dose (24h later): 3g

Proposed temocillin dosing regimen for haemodialysis patients, according to their weight and the interdialytic period. Single or first doses should be administered immediately after dialysis. Dialytic cycles can be considered independent from each other. Dosage regimen were rounded up to the closest 0.5g.

Simulations, probability of target attainment and PKPD breakpoints

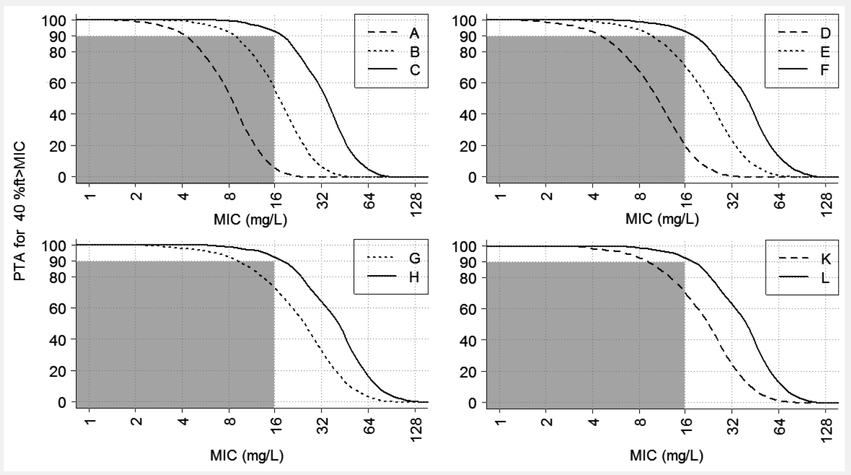
	Day 1	Day 2	Day 3	PKPD breakpoint (mg/L)
A	0.5g	Dial.&↻		4
B	1g	Dial.&↻		9
C	Dosing table 24h			18
D	1g	-	Dial.&↻	4
E	2g	-	Dial.&↻	9
F	Dosing table 48h			18
G	3g	-	- Dial.&↻	9
H	Dosing table 72h			18

Weekly regimens

	Mon	Tue	Wed	Thu	Fri	Sat	Sun	PKPD breakpoint (mg/L)
K	2g	-	Dial.→2g	-	Dial.→3g	-	- Dial.&↻	9
	Regimen E		Regimen E		Regimen G			
L	Dosing table 48h		Dosing table 48h		Dosing table 72h			18
	Regimen F		Regimen F		Regimen H			

Dial.&↻ : dialysis session and immediately repeat temocillin dosage cycle.

Dial.→**X**g : Dialysis session immediately followed by a temocillin dose of **X**g.



Tables: Simulated temocillin dosage regimens (A to L) in 4 consecutive cycles, and corresponding PKPD breakpoint, i.e. highest MIC for which the PKPD target of 40%$fT > MIC_{16}$ is achieved in at least 90% of patients. All regimens assume an uniform weight distribution.

Graphs: Probability of treatment achieved (PTA) of 40%fT>MIC vs. MIC, for the simulated temocillin dosage regimens described in the tables. Displayed values are the 95% confidence lower bound on the binomial estimate of the PTA derived from 10,000 simulated patients per regimen. Greyed field corresponds to the area of treatment target failed, assuming a MIC and PTA cut-off of 16mg/L and 90%, respectively.

Conclusions

- ✓ A joint PK model of total and unbound serum concentrations described the time course of temocillin in patients undergoing haemodialysis. 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 prediction ability of the model decreases after approximately 130h. This likely reflects the fact that there are few patients (less than half) that are followed up for longer that amount of time.
- ✓ Model-based simulations suggested a new temocillin dosing regimen for patients undergoing intermittent haemodialysis, in order to maintain drug concentrations over a MIC ≤ 16 mg/L for at least 40% of the dosing interval. The typical thrice weekly hemodialysis regimen used in this study (regimen K) shows that patients would only be adequately treated (40% $fT > MIC$) for a MIC ≤ 8mg/L.
- ✓ Future clinical trials are warranted to confirm these results.

[1] Temocillin Summary of Product Characteristics 2014. http://www.fagg-afmps.be/fr Last accessed: 04-04-2016
[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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