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Clinical Pharmacokinetics of Temocillin in Patients With End Stage Renal Disease Undergoing Haemodialysis

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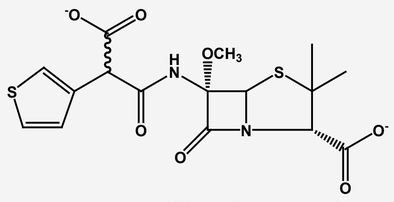
Background and Objective

- ✓ Temocillin is a β-lactam active against most ESBL-producing Enterobacteriaceae, which makes it a useful alternative to carbapenems if *Pseudomonas aeruginosa* can be excluded.[1]



- ✓ Unlike most other β-lactams, temocillin shows a large protein binding in patients. Neither unbound nor total temocillin pharmacokinetics have been investigated yet in hemodialysis patients.
- ✓ The purpose of this study was to characterize the pharmacokinetics of temocillin in serum, before and during haemodialysis, in patients with end stage renal disease (ESRD).

Methods

- ✓ Single-center, open-label, non-randomized study
- ✓ 16 patients were administered a single dose of 1, 2, or 3g of temocillin followed by a inter-dialytic period (off-dialysis) of 20, 44, or 68h, respectively, and a dialysis period of 4h (total of 49 doses) (Figure 1). A total of 467 samples were analysed by HPLC.
- ✓ Data were pooled by dose, and analysed independently, irrespective of sequence of doses.
- ✓ Target attainment rate was calculated considering time above an unbound concentration of 16 mg/L (a presumed MIC for more than 90% Enterobacteriaceae) as a pharmacodynamic endpoint.[1]
- ✓ Data analysis was performed by the non-compartmental method, using RStudio 0.98.501 with R 3.0.2.

Figure 1. Dosing scheme

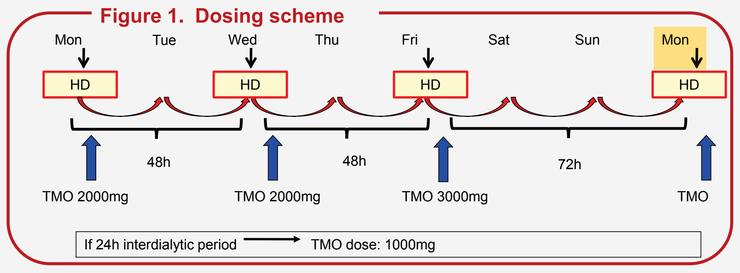
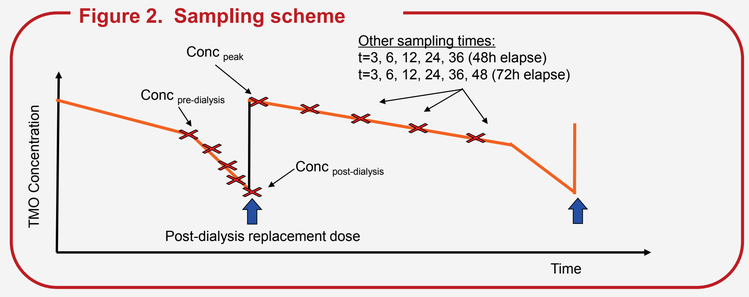
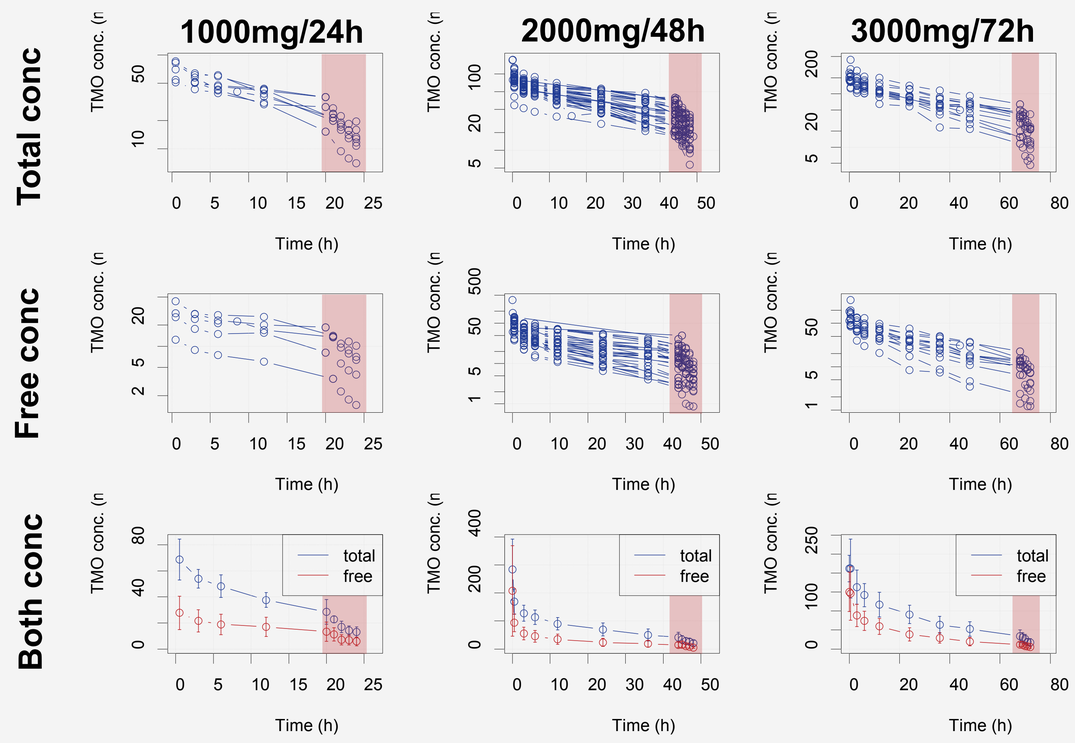


Figure 2. Sampling scheme



Results

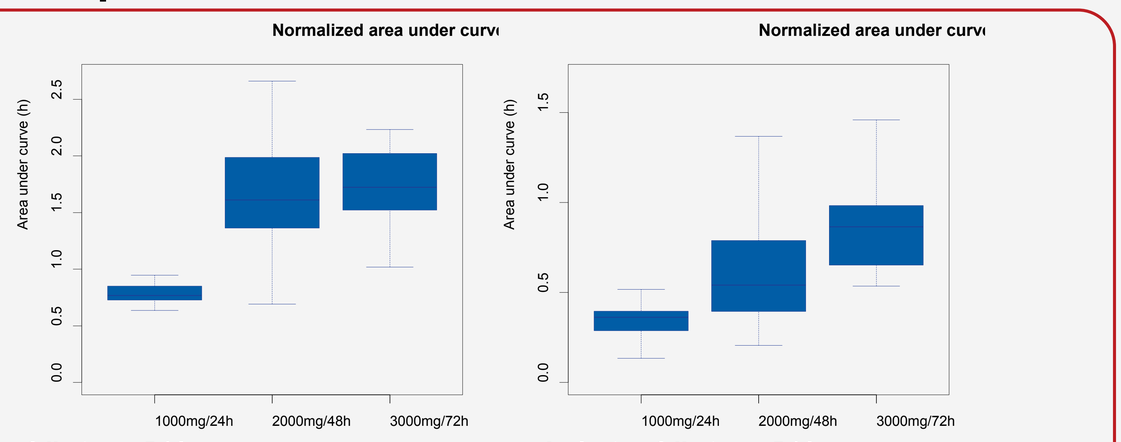
Concentration-Time profile



Rose shaded area corresponds to the haemodialysis period (4h); top and middle rows: concentrations profiles of total and free concentrations for individual administrations; bottom row: mean and standard deviation for total and free temocillin concentration.

- ✓ The number of curves for the three dosing regimens differ as prescribed dosing regimens were driven by patients' clinical condition.
- ✓ The 1000mg/24h regimen was only prescribed in very few critical cases, thus leading to low power estimates derived from this sub-dataset. The 2000mg/48h regimen was the most commonly prescribed dosing regimen.
- ✓ There is a marked reduction in temocillin concentrations during haemodialysis.

Non-linear pharmacokinetics

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Analysis of Variance Table

Response: conc
          Df    Sum Sq  Mean Sq F value     Pr(>F)
dose       1 68703385 68703385  59.068 1.806e-09 ***
Residuals 41 47687829  1163118
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Analysis of Variance Table

Response: conc
          Df    Sum Sq  Mean Sq F value     Pr(>F)
dose       1 19625925 19625925   41.56 1.243e-07 ***
Residuals 39 18417072   472233
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- ✓ The area under the curve was likely not proportional to the dose (visual comparison of normalised doses, and ANOVA analysis), suggesting non-linear pharmacokinetics.

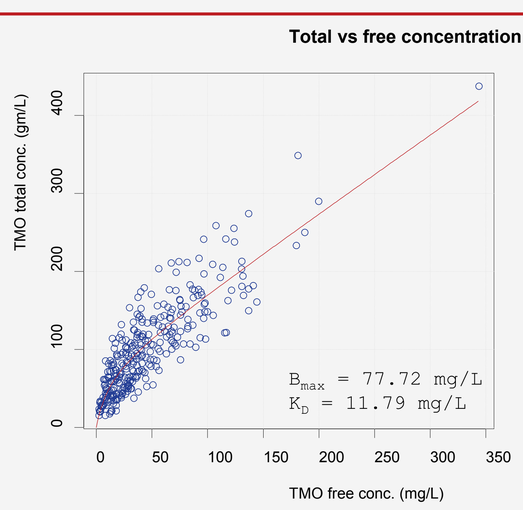
Non-linear protein-binding

$$C_{tot} = C_{free} + C_{bound}$$

$$C_{tot} = C_{free} + \frac{B_{max} \cdot C_{free}}{K_D + C_{free}}$$

Langmuir equation - 1 binding site
(model for saturable binding equilibriums)

B_{max} : maximal binding capacity
K_D : free drug concentration corresponding to half maximal binding (inversely proportional to drug affinity for the protein)



- ✓ Temocillin total concentration varied non-linearly with free concentrations, as explained by the Langmuir model for one class of saturable binding site.
- ✓ A two site binding model was investigated but did not yield a good match. This indicates that there is one binding site for temocillin on albumin.
- ✓ B_{max} and K_D were lower than in healthy patients (B_{max}: 239.37 vs 77.72mg/L; K_D: 28.36 vs 11.79 mg/L). [2] This is consistent with the hypoalbuminemia characteristic of this patient population.

Pharmacokinetic parameters

	1000mg/24h		2000mg/48h		3000mg/72h	
	off dialysis	*on dialysis*	*off dialysis*	*on dialysis*	*off dialysis*	*on dialysis*
Total conc						
AUClast (mg.h/L)	*786 (113)*	*76 (24)*	*3369 (928)*	*123 (53)*	*5452 (1612)*	*88 (44)*
AUC inf (mg.h/L)	*1604 (671)*	*-*	*5121 (2011)*	*-*	*7617 (2878)*	*-*
Vd (L)	*17 (3.9)*	*-*	*15 (5.5)*	*-*	*21 (5.3)*	*-*
CL ($ml.min^{-1}$)	*12 (4.6)*	*155 (50)*	*7.6 (3.0)*	*164 (45)*	*7.5 (3.1)*	*173 (53)*
$T_{1/2}$ (h)	*20 (12)*	*4.3 (2.3)*	*26 (9)*	*4.3 (1.6)*	*36 (17)*	*4.1 (2.6)*
ER	*-*	*0.52 (0.16)*	*-*	*0.50 (0.11)*	*-*	*0.55 (0.16)*
C_{HD} start (mg/L)	*-*	*29 (9.5)*	*-*	*43 (20)*	*-*	*34 (17)*
C_{HD} end (mg/L)	*-*	*14 (5.4)*	*-*	*21 (10)*	*-*	*15 (7.7)*
Free conc						
AUClast (mg.h/L)	*340 (141)*	*38 (21)*	*1262 (653)*	*36 (27)*	*2661 (866)*	*40 (21)*
AUC inf (mg.h/L)	*753 (502)*	*-*	*1809 (991)*	*-*	*3113 (1032)*	*-*
Vd (L)	*49 (26)*	*-*	*44 (20)*	*-*	*34 (10)*	*-*
CL ($ml.min^{-1}$)	*34 (29)*	*135 (5)*	*26 (17)*	*192 (64)*	*18 (6)*	*197 (75)*
$T_{1/2}$ (h)	*21 (14)*	*4.2 (0.5)*	*24 (13)*	*3.6 (2.4)*	*23 (6)*	*3.3 (1.7)*
ER	*-*	*0.48 (0.04)*	*-*	*0.60 (0.17)*	*-*	*0.60 (0.15)*
C_{HD} start (mg/L)	*-*	*13.4 (7.4)*	*-*	*14.5 (10.8)*	*-*	*12.9 (5.0)*
C_{HD} end (mg/L)	*-*	*7.1 (4.4)*	*-*	*4.9 (3.0)*	*-*	*5.3 (3.0)*
%T>16mg/L	*49 (38)*		*67 (30)*		*71 (24)*	

Cell contents: average (stand. dev.)

AUClast: area under the curve up to the last measurable concentration (excluding dialysis); **AUCinf**: area under the curve from zero to infinity (excluding dialysis); **Vd**: volume of distribution; **CL**: clearance; **$T_{1/2}$**: half-life of elimination; **ER**: hemodialysis extraction ratio; **C_{HD} start** and **C_{HD} end**: serum concentrations of temocillin at the beginning and at the end of haemodialysis, respectively; **%T>16mg/L** : percentage of the dosing time that temocillin concentrations are above 16mg/L.

- ✓ Volume of distribution was similar across different dosing regimens and not significantly different from published values. [3]
- ✓ Temocillin concentrations were significantly reduced by hemodialysis.
- ✓ Temocillin serum concentrations at the beginning of hemodialysis appeared independent of the dosing regimen. This points to the possibility of exploring the administration of a higher dose (ex: 3000mg) in a shorter interdialytic period (ex: 44h), to achieve a higher %T>16mg/L.

Conclusions

- ✓ Temocillin appears to exhibit non-linear pharmacokinetics, probably due to saturable protein binding.
- ✓ ESRD patients have high systemic exposure to temocillin, and haemodialysis efficiently eliminates it from the patients' body, making post-dialysis replacement dose required to maintain therapeutic levels.
- ✓ A more detailed analysis using population pharmacokinetic modeling is needed to fully characterize the time course of temocillin concentrations and develop individualized dosage regimens.

References

[1] Livermore DM, Tulkens PM. Temocillin revived. J Antimicrob Chemother (2009); 63: 243-5.
[2] Overbosch D, van Gulpen C, Mattie H. Renal clearance of temocillin in volunteers. Drugs (1985); 29 Suppl 5:128-34.
[3] De Jongh et al. Continuous versus intermittent infusion of temocillin, a directed spectrum penicillin for intensive care patients with nosocomial pneumonia: stability, compatibility, population pharmacokinetic studies and breakpoint selection. J AC 61 (2008) 382-388.

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