Tigecycline population pharmacokinetics in patients with severe sepsis or septic shock resulting from abdominal surgery

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Objectives

Tigecycline is the first glycylcycline antimicrobial drug approved in Europe for the treatment of complicated skin and skin structure infections and complicated intra-abdominal infections at 100 mg initial dose followed by 50 mg every 12 h [1]. However, it has been reported that higher dose regimens of tigecycline may be more effective than recommended dosing [2]. In this study a higher dose of tigecycline was administered to adult patients with severe sepsis or septic shock resulting from abdominal surgery. The objectives of the study were to develop a tigecycline population pharmacokinetic model and assess the relationship between patient covariates and individual PK parameters.

Methods

The analyzed population included 37 patients aged 25-79 years treated in Intensive Care Unit. Each patient received initial dose of 200 mg of tigecycline in a short 30 min infusion, followed by multiple doses of 100 mg in 30 min infusion every 12 h. The covariates recorded for each patient included time-independent covariates: age, weight, height, death, sex, the use of extracorporeal membrane oxygenation, the use of continuous renal replacement therapy and the time-dependent covariates: dialysis volume, ultrafiltration speed, extravascular lung water index, cardiac output, sequential organ failure assessment score and procalcitonin concentration. Population nonlinear mixed effects modeling was conducted using NONMEM software.

Table 1. Patient characteristics of the study population. Values are expressed as median and range for continuous and as count for categorical variables.

Parameter [unit]	**Median [Range] n=37**
Age [years]	61 [25 - 79]
Weight [kg]	80 [50 - 129]
Height [cm]	175 [158 - 190]
Male/Female	26/11
Dead/Survived	23/14
ECMO No/Yes	35/2
CRRT No/Yes/Started during therapy	6/30/1
Dialysis [mL/kg]	23.8 [14.2 - 40.0]
Ultrafiltration [mL/kg/h]	1.54 [0.34 - 6.6]
ELWI [mL/kg]	9 [5 - 41]
Cardiac output [L]	7.49 [2.55 - 15.8]
SOFA score	13 [2.0 - 21]
Procalcitonin concentration [µmol/L]	8.22 [0.16 - 122]

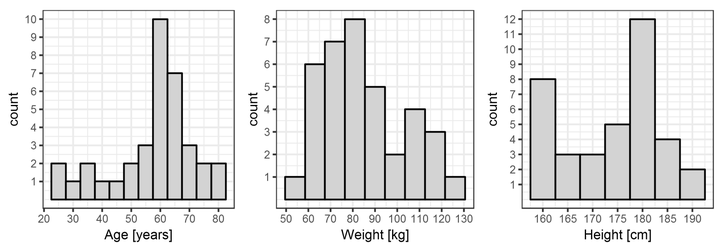

Figure 1. Histograms for age, weight and height of the study population.

Results

Tigecycline pharmacokinetics was described by a two-compartment disposition model. The population model included inter-individual variability in CL, V1 and V terms and inter-occasion variability in individual CL and V2 parameter values. The typical values of elimination and inter-compartmental clearance were 22.1 L/h and 69.4 L/h; the typical values of volume of central and peripheral compartment were 162 L and 87.9 L. The inter-individual variability was intermediate for CL (17.3%) and V1 (19.2%) and higher for V2 (38.7%). The inter-occasion variability for CL and VT was 14.4% and 20.8%, respectively.

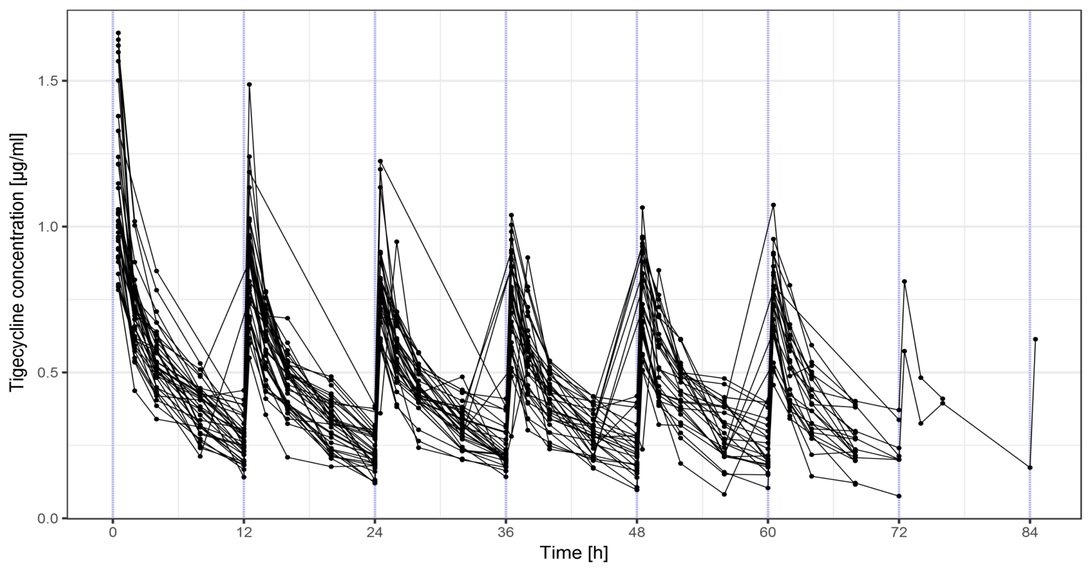

Figure 2. Individual tigecycline concentration-time profiles. Blue vertical lines indicate dosing times.

Table 2. Final model parameter estimates. 90% confidence interval (CI) of the parameter estimate derived from a nonparametric bootstrap analysis (n=1000, unsuccessful=1)

Parameter	**Estimate**	RSE (%)	shrinkage (%)	Bootstrap median	Boostrap 90% CI
θ_{CL} [L/h]	**22.1**	3.16		22.1	20.9 - 23.2
θ_{V1} [L]	**162**	5.3		163	150 - 176
θ_{Q} [L/h]	**69.4**	32.6		67.3	41.9 - 98.4
θ_{V2} [L]	**87.9**	8.67		87.6	76.1 - 101
Inter-individual variability					
ω^2_{CL} (%CV)	**17.3**	19	7.3	17.1	14.2 - 19.7
ω^2_{V1} (%CV)	**19.2**	29.2	6.7	19.1	14.3 - 23.7
ω^2_{Q} (%CV)	**0 FIX**	–	–	–	–
ω^2_{V2} (%CV)	**38.7**	40.8	22.4	37.4	20.4 - 48.5
Inter-occasion variability					
π^2_{CL} (%CV)	**14.4**	35		14.2	9.4 - 18.1
Occasion 1			27.4		
Occasion 2			38.5		
Occasion 3			52.4		
Occasion 4			42.6		
Occasion 5			35.4		
Occasion 6			48.4		
Occasion 7			94.9		
Occasion 8			99.8		
π^2_{V2} (%CV)	**20.8**	66.4		21.7	0.200 - 30.9
Occasion 1			40.2		
Occasion 2			50.2		
Occasion 3			58.5		
Occasion 4			56.4		
Occasion 5			52.9		
Occasion 6			57.2		
Occasion 7			90.6		
Occasion 8			99.6		
Residual error model					
σ_{add} (µg/ml)	**0.0210**	0.41		0.0224	0.000209 - 0.0357
σ^2_{prop} (%CV)	**13.0**	17.7		12.7	8.89 - 16.1

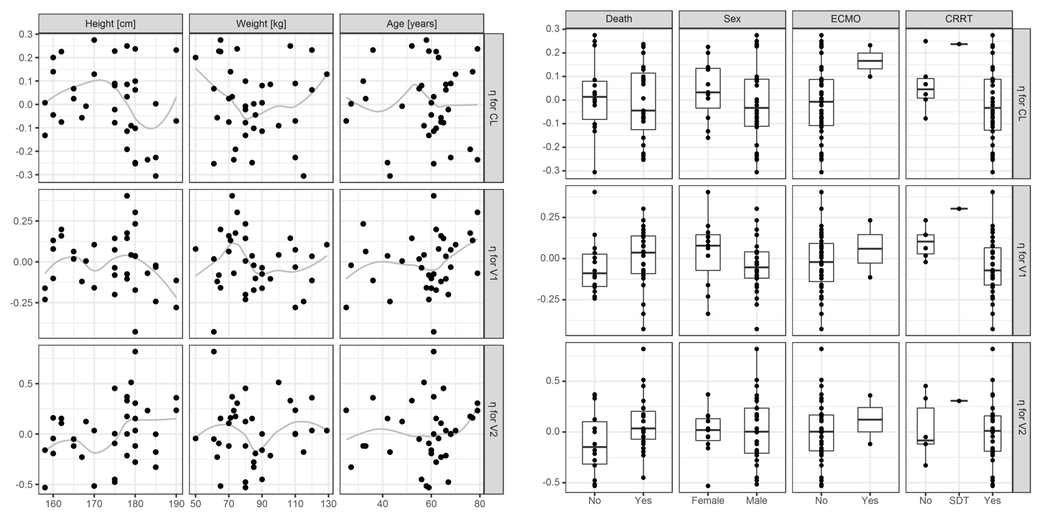

Figure 3. The individual estimates for eta (deviation of the individual estimate from the population mean) of the final PK parameters in relation to continuous and categorical covariates.The grey line indicates the trend in the data (loess smooth).

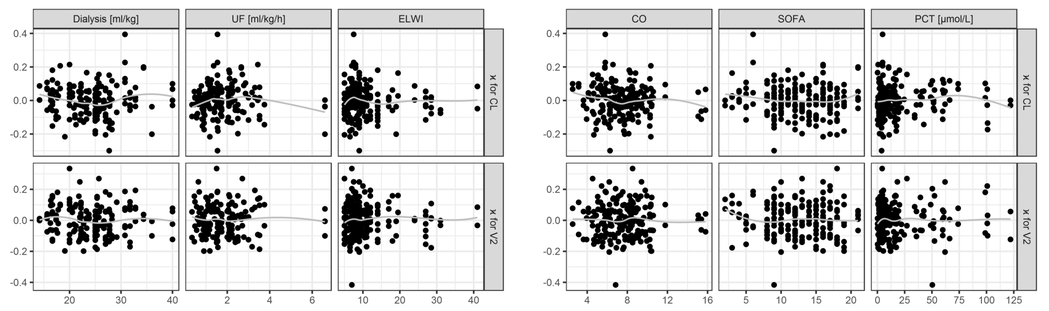

Figure 4. The individual estimates for kappa (deviation of individual parameters between occasions) of the final PK parameters in relation to time-dependent covariates. The grey lines indicate the trend in the data (loess smooth).

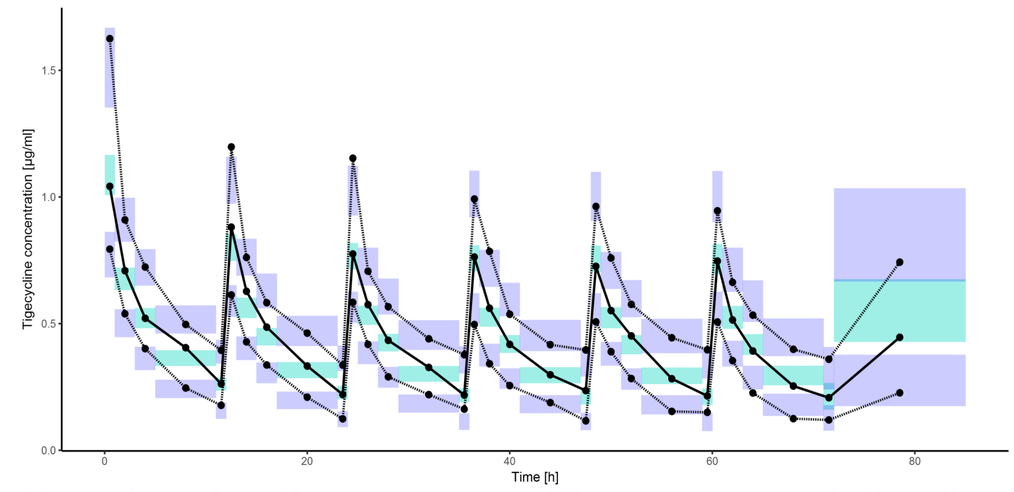

Figure 5. The Visual Predictive Check (VPC) showing the simulation-based 90% confidence intervals around the 5th, 50th, and 95th percentiles of the data in the form of turquoise (50th) and violet (5th and 95th) areas. The percentiles from the observed data are plotted in black color.

Conclusions

The population PK model was successfully developed to describe the time course of tigecycline concentrations in the analyzed population. None of the available covariates was found to explain part of the inter-individual or inter-occasion variability in the pharmacokinetic parameters. The model can be useful for further analysis of tigecycline exposure-response relationships.

References

[1] Pfizer Limited (2006) Tygacil (tigecycline): EPAR - Product Information, Annex I - Summary of product characteristics. http://www.ema.europa.eu: EMEA/H/C/000644-IA/0100

[2] Falagas, M. E., Vardakas, K. Z., Tsiveriotis, K. P., Triarides, N. A. & Tansarli, G. S. Effectiveness and safety of high-dose tigecycline-containing regimens for the treatment of severe bacterial infections. Int. J. Antimicrob. Agents 44, 1–7 (2014).