

Population pharmacokinetics of cefepime in critically ill patients with and without impaired renal function

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Background

Pathophysiological changes in ICU patients with severe infections lead to a high pharmacokinetic variability (1) and risk of inappropriate exposure to antibiotics. Jonckheere et al. (2) concluded that Cockcroft-Gault creatinine clearance (eCRCL) might be a better predictor of cefepime clearance than measured creatinine clearance (mCRCL). This finding is challenged by the invalidity of eCRCL in presence of unstable creatinine kinetics (3) and potential confounding by components of the equation. Therefore it is unclear whether eCRCL should be employed to predict time dependent changes in cefepime clearance and whether intra-individual variability poses a clinically relevant risk to cefepime efficacy. The objective of this study was to evaluate inter and intra-individual variability of cefepime pharmacokinetics and to evaluate eCRCL as a predictor of intra-individual changes in cefepime clearance during cefepime treatment.

Materials and Methods

- Fifteen critically ill patients (median [range] age 62 [22-94] years and body weight 71 [45-120] kg) were included in the study. Five patients received IV hemodialysis (Table 1).
- Median doses of 2 g cefepime were administered twice daily (30-min infusions).
- Plasma samples were obtained on four consecutive days (median daily sample numbers 12, 6, 7, and 6 per subject) and quantified via validated HPLC.
- A compartmental model was developed using NONMEM 7.4.3 and influence of covariates (age, weight, sex, BMI, urea, serum creatinine, 24 h urine creatinine and corresponding mCRCL) was assessed on cefepime clearance and volumes of distribution. Similarly influence of eCRCL calculated on each treatment day was compared to a model comprising solely eCRCL obtained at study start.

Results and Discussion

A two-compartment model with linear elimination (Fig. 1) best described the 406 available cefepime concentrations (median 60 (range 0.6-278) mg/L). Cefepime clearance was linearly related to the renal function of the patients (equation 1). Though eCRCL estimated for each individual day relatively improved the model (dOFV -19, IIV -43%, IOV +2%), no model improvement was observed for mCRCL. The best model was the one based on eCRCL measured on day 1 (dOFV -26, IIV -46%, IOV +0.4%). Goodness-of-fit plots (Fig 2), bootstrap estimates (Table 2) and visual predictive checks (Fig 3) are given below.

$$CL_i = CL_{pop} \times [(1 + \beta) \times (eCRCL - 6)] \tag{1}$$

Where CL_i is the individual clearance, CL_{pop} is the population clearance, β is the covariate effect and $eCRCL$ is the Cockcroft-Gault creatinine clearance standardised to the normal renal function (6L/h).

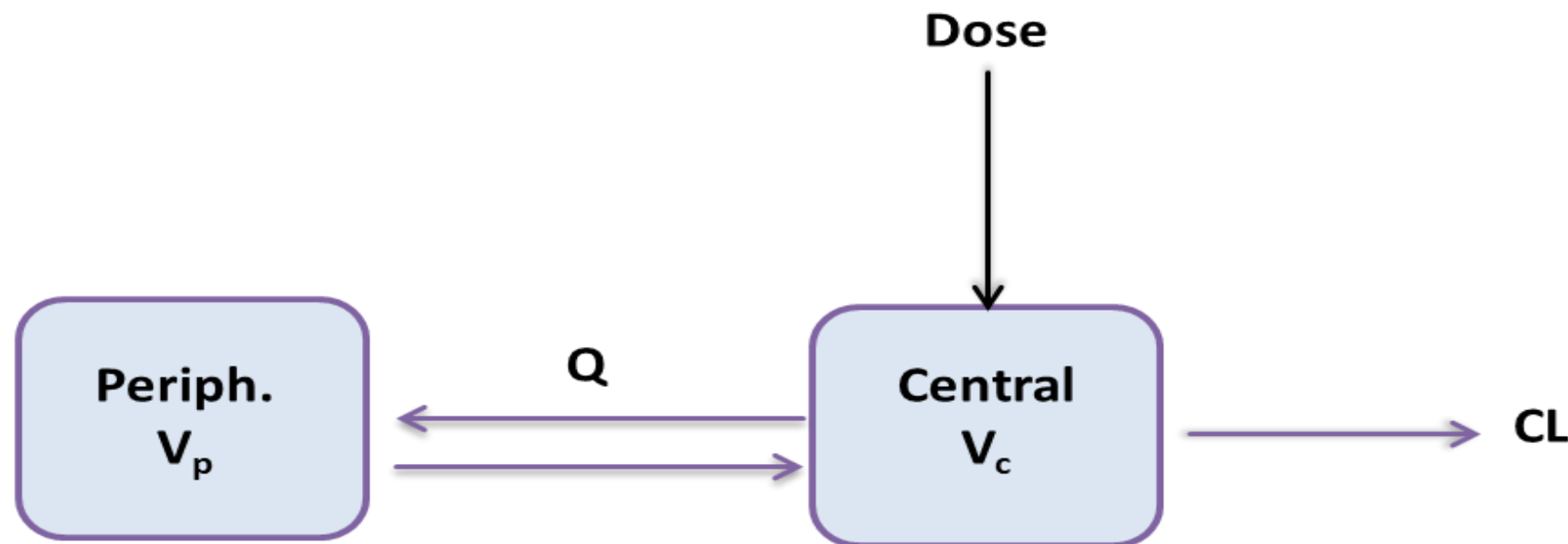


Fig 1. Model structure
Table 1. Patients characteristics

Parameter	Median (range)	Parameter	Median (range)
Sex (Female/Male)	8/7	eCRCL (L/h)	3.5 (0.94-13.03)
Dialysis (Yes/No)	5/10	mCRCL (L/h)*	3.12 (0.06-13.14)
Weight (kg)	71 (45-120)	SOFA score	11 (4-17)
BMI (kg/m²)	25 (20-37)	APACHE score	29 (13-43)
Age (years)	62 (22-94)	Serum creatinine (mg/dL)	1.0 (0.3-4.7)
Height (m)	1.7 (1.5-1.8)	Sepsis (Yes/No)	14/1

*refers only to non-dialysis patients

Conclusion

When accounting for Cockcroft-Gault creatinine clearance, residual inter- and intra-individual variability were of similar magnitude. Adapting the therapy to actual changes in serum creatinine concentrations using the Cockcroft-Gault equation or measured creatinine clearance during therapy seems inappropriate.

References

[1] Blot SI, Pea F, Lipman J. 2014. The effect of pathophysiology on pharmacokinetics in the critically ill patient — Concepts appraised by the example of antimicrobial agents. *Adv Drug Deliv Rev* 77:3–11.
[2] Jonckheere S, De Neve N, De Beenhouwer H, Berth M, Vermeulen A, Van Bocxlaer J, Colin P. 2016. A model-based analysis of the predictive performance of different renal function markers for cefepime clearance in the ICU. *J Antimicrob Chemother* 71:2538–2546.
[3] Chen S, Greene T, Kusek J, Beck G. 2013. Retooling the creatinine clearance equation to estimate kinetic GFR when the plasma creatinine is changing acutely. *J Am Soc Nephrol* 24:877–88.

Results and Discussion

Table 2. Bootstrap estimates of population pharmacokinetic parameters

Parameter	Bootstrap median (90% CI)	IIV CV%[90% CI]	IOV CV%[90% CI]
CL (L/h)	4.26 (3.68-4.80)	22 (10-30)	30 (21-40)
V _c (L)	9.39 (6.22-13.4)	55 (23-85)	45 (30-64)
Q (h)	36.7 (13.7-47.6)	-	-
V _p (L)	18.4 (14.4-21.6)	29 (9.0-45)	-
β (L/h)	0.15 (0.14-17)	-	-
Residual error (CV%)			
Proportional error	50 (44-55)	-	-
Additive error	152 (127-196)	-	-

IIV; Inter-individual variability. IOV; inter-occasion variability, CI; confidence interval, β; covariate effect, CV; coefficient of variation

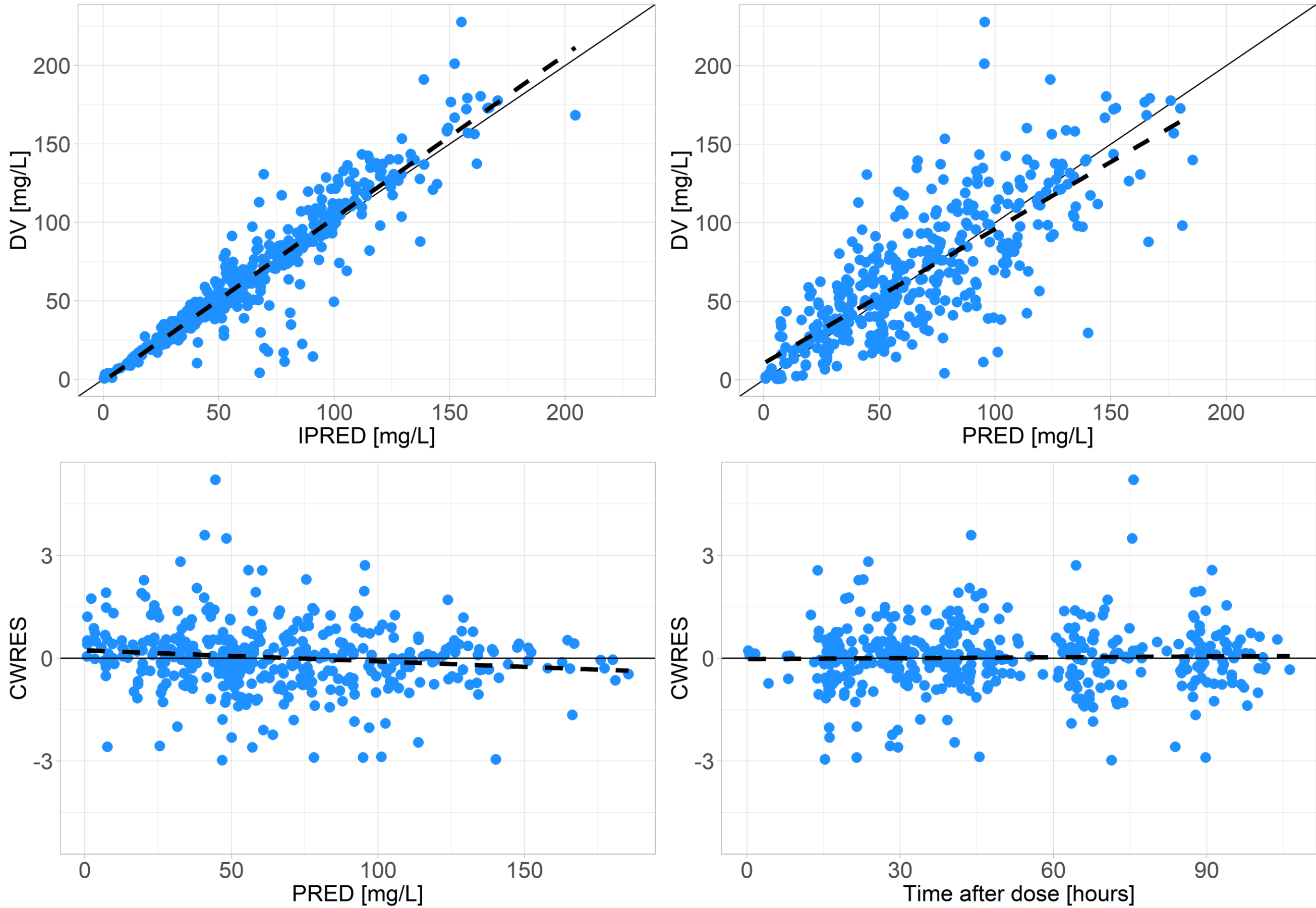


Fig 2. Combined goodness-of-fit plots of cefepime concentrations. DV, observed concentrations; IPRED individual predictions; PRED, population predictions; CWRES conditionally weighted residuals.

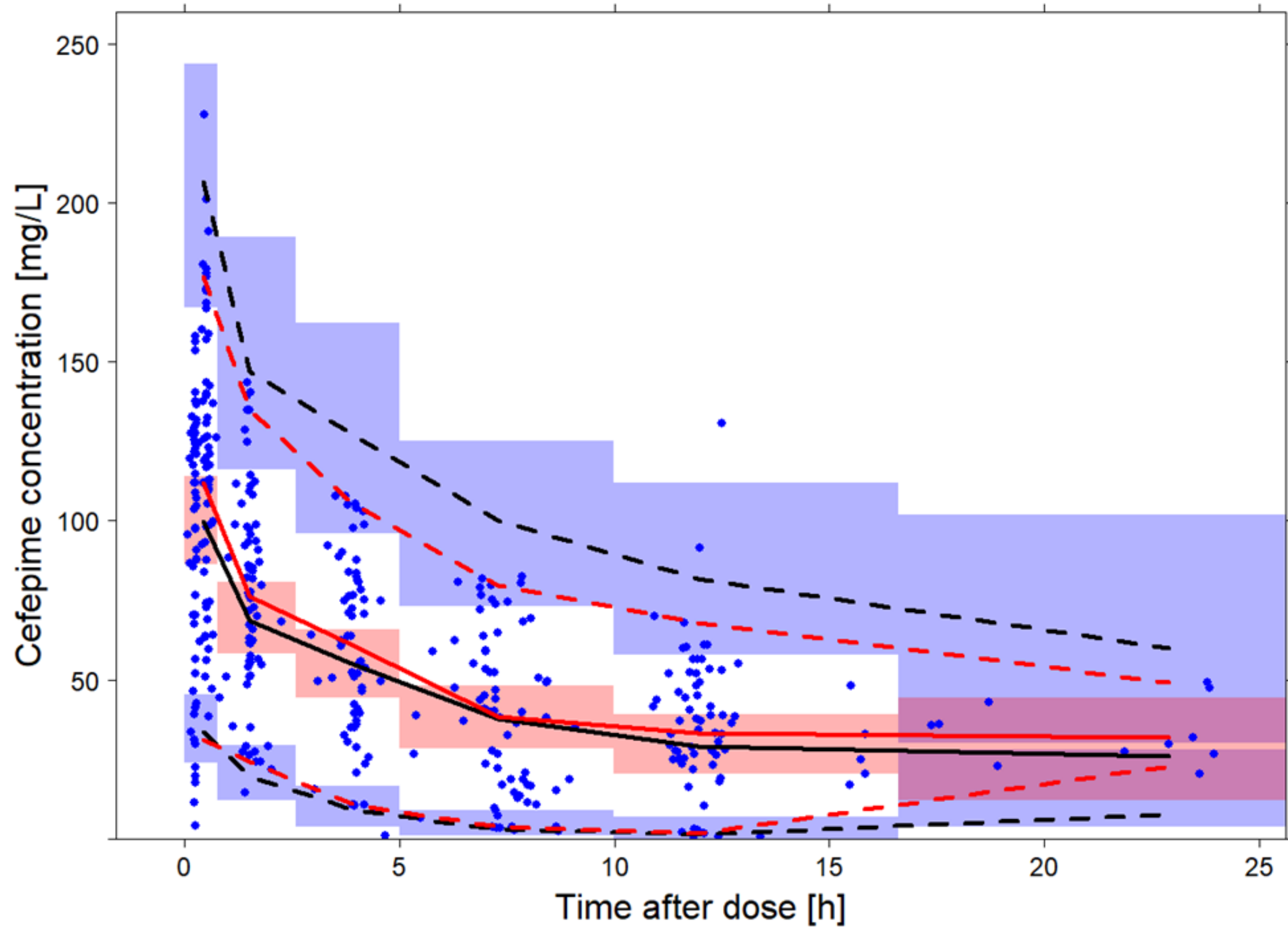


Fig 3. Visual predictive checks (VPC). Red solid and dotted line represent median, 5th and 95th percentiles of the observed data. Confidence intervals of the predicted area is shown as shaded areas. Black solid and dotted lines represent median of the respective prediction intervals.