Estimation of the area under concentration-time curve of polymyxin B based on limited sampling concentrations in Chinese patients with severe pneumonia

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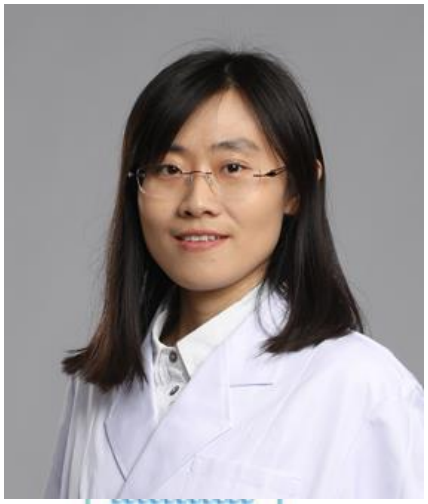


Background and aims

- PK/PD index of polymyxin B (PB) : AUC/ MIC
- appropriate blood sampling time points for the PB therapeutic drug monitoring (TDM).

Subject

- After treatment with at least four doses of PB (50 IU, q12h), the blood samples were collected at different time intervals.
- PB plasma concentrations were determined by UPLC-MS/MS.
- 42 patients were involved and randomly divided into modeling (n = 24) and validation (n = 18) groups.

Methods and results

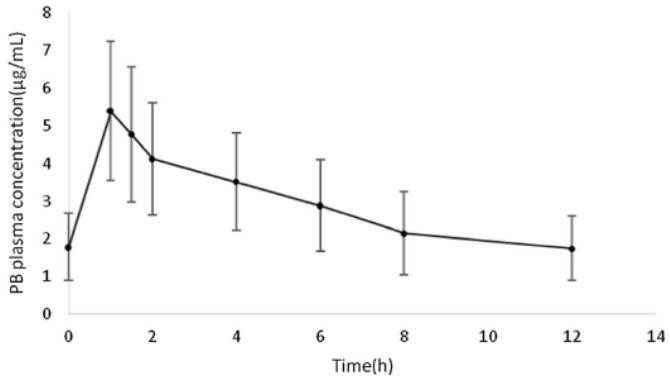


Fig. 1 PB plasma concentration versus time profiles ($n = 42$)

Data analysis

- Limited sampling strategy (LSS)

$$AUC_{ss,24h} = \text{intercept} + \beta_1 \times C_{t1} + \beta_2 \times C_{t2} + \ldots + \beta_i \times C_{ti} \quad (1)$$

where β_i is the partial correlation coefficient and C_{ti} is the PB concentration at sampling time t_i.

Single sampling points C6 shows good correlation with AUC, with the r2 values of 0.984.

Table 3 Comparison of parameters between the C_6 model and bootstrap results

Model	Parameter	Estimate	SE	95% CI	Bootstrap ($n = 1000$)		
					Estimate	SE	95% CI
C_6	Intercept	8.147	1.953	4.096–12.198	8.147	2.215	3.908–12.493
	$\beta_1(C_6)$	21.961	0.599	20.718–23.204	21.961	0.766	20.498–23.597

Methods and results

- one-compartment PK with correction model (1-COM)

$$C = \frac{Dose}{kVT_{in}} \cdot (1-e^{-k \cdot t}) + \frac{Dose}{kVT_{in}} \cdot (e^{k \cdot Tin}-1) \cdot e^{-kt} \cdot \frac{e^{-k \cdot \tau}}{1-e^{-k \cdot \tau}} \qquad 0 \le t \le T_{in}$$

$$C = \frac{Dose}{kVT_{in}} \cdot \frac{1-e^{-k \cdot Tin}}{1-e^{-k \cdot \tau}} \cdot e^{-k(t-Tin)} \qquad Tin < T \le \tau$$

where C is defined as drug concentration, C_{max} is peak concentration, and τ is dose interval.

$$AUC_i = \frac{(C_i + C_{i+1}) \times (t_{i+1}-t_i)}{2}$$

$$AUC_{ss,24h} = \frac{24}{\tau} \cdot E \cdot \sum_{i=0}^{N} AUC_i$$

E was the correction coefficient and evaluated as 0.876 based on data in the modeling group. The observed Cmax and C_0 values were used to fit the concentration-time curve via least-square method and the value of AUCss,24h was calculated. Modeling group's data were used to determine the E value as 0.876,while validation group's data to evaluate the accuracy and precision of the calculation model.

Table 2 Predictive ability of AUC models based on LSS method and one-compartment model (1-COM[a]) in validation group ($n = 18$)

Model No.	Sampling time (h)	PE% (mean ± SD)	AE% (mean ± SD)	Deviation of AUC		
				> 20%	− 20% to 20%	< − 20%
1	0	4.35 ± 22.10	16.87 ± 12.99	4	11	3
2	4	− 6.14 ± 5.74	7.61 ± 4.01	0	18	0
3	6 (one missing data)[b]	− 3.21 ± 7.55	7.04 ± 4.07	0	17	0
4	8	− 0.15 ± 14.78	5.64 ± 8.76	3	14	1
5	0, 1	− 0.69 ± 12.94	9.24 ± 7.18	1	16	1
6	0, 1.5	0.53 ± 13.25	8.20 ± 7.30	2	15	1
7	4, 6	− 4.29 ± 5.35	6.23 ± 3.00	0	17	0
8	4, 8	− 3.46 ± 4.82	4.49 ± 3.13	0	18	0
9	0, 4, 6	− 2.98 ± 4.74	4.85 ± 2.89	0	17	0
10	0, 6, 8	0.79 ± 7.07	6.03 ± 3.78	0	17	0
11	1-COM	− 3.24 ± 9.94	8.40 ± 6.55	0	18	0

[a] One-compartment model used for prediction of AUC was described in "Data analysis" section

[b] One concentration at 6 h after administration was missing during sampling procedure

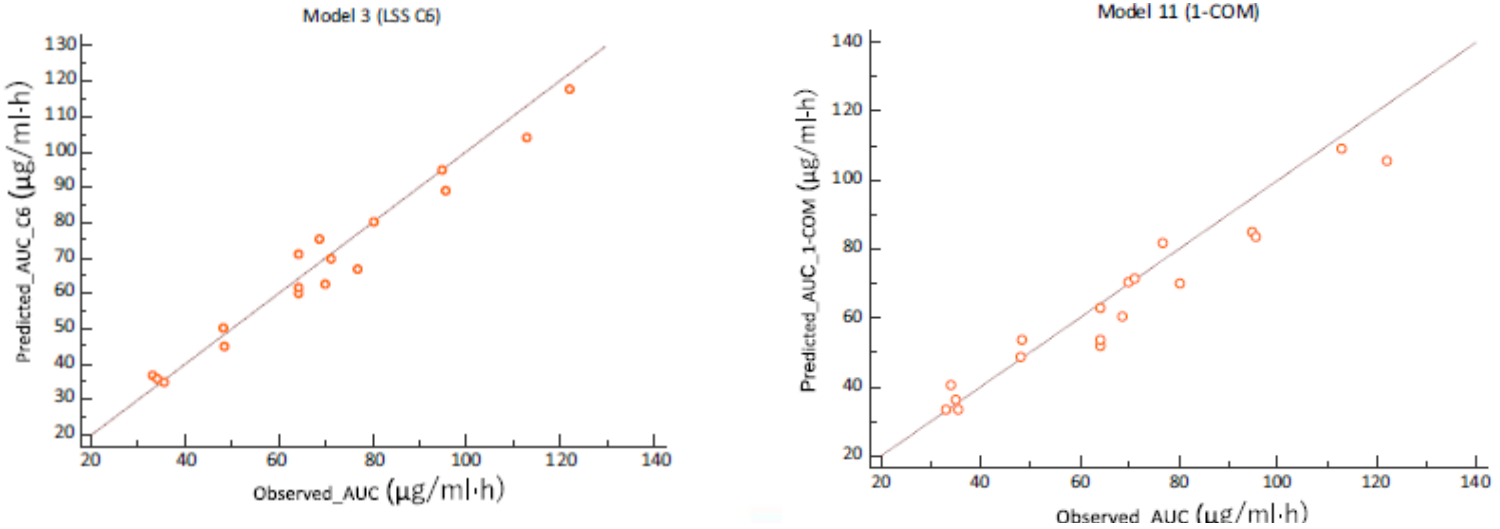
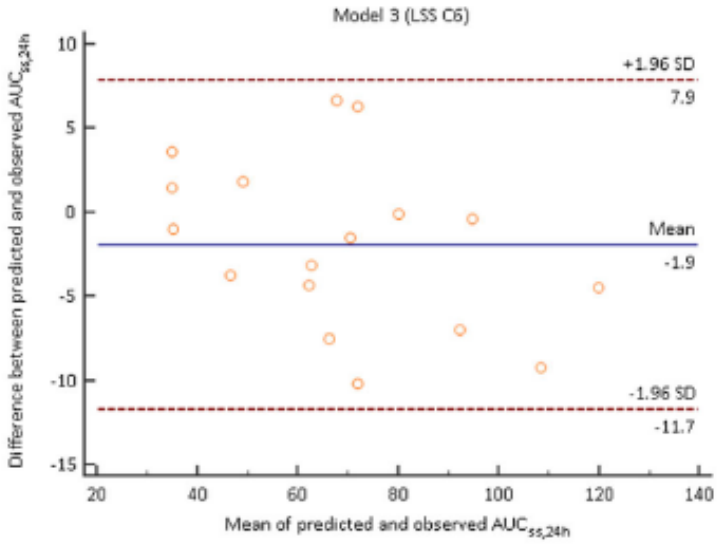


Fig. 2 Correlation between the observed and predicted $AUC_{ss,24h}$ values (μg/ml h)



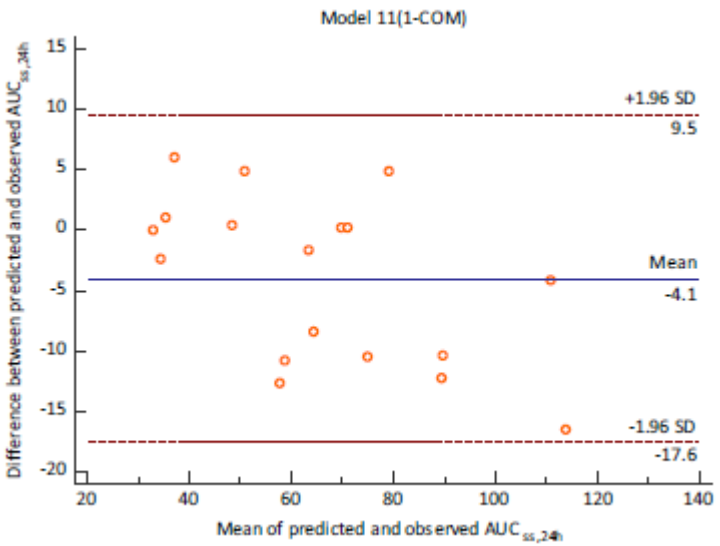


Fig. 3 Bland-Altman analysis of the agreement between the predicted and observed $AUC_{ss,24h}$

Conclusion

C6 scheme was suitable for the TDM of PB, which could provide accura te prediction of AUCss,24h values.

The target value of C6 can be set to 1.9–4.2 μg/ml at steady state to re ach the 50–100 μg h/ml criteria of AUCss,24h.

C0 and Cmax sampling scheme also performed good predicting ability of AUC values based on one-compartment with correction model.

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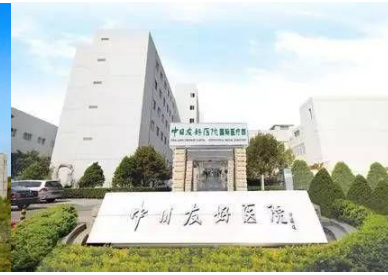

Thank you!