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

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ABSTRACT

Polymyxin B (PB) is used as the last line of defense against multidrug-resistant infections.The efficacy and toxicity of PB are closely related to its pharmacokinetic/pharmacodynamic (PK / PD) indices, such as area under the concentration-time curve (AUC) to minimum inhibitory concentration (MIC)ratio. The purpose of this study was to obtain PK data for PB in Chinese severe pneumonia patients and establish appropriate blood sampling time points for the therapeutic drug monitoring (TDM) of PB. A total of 42 patients with severe pneumonia were selected and treated with PB(50IU, q12h).After treatment with four doses of PB, the blood samples were collected at 0(before administration), 1, 1.5, 2, 4, 6, 8 and 12h after administration. The concentrations of PB were determined using an ultra performance liquid chromatography - tandem mass spectrometer (UPLC-MS/MS).The obtained data were analyzed by non-compartment PK method. It was found that the values of C_{max}, $AUC_{ss,24h}$, K_{10} and $T_{1/2,\beta}$ were 5.5 ± 1.9 μg/ml, 72.7 ± 28.9 μg/ml·h 0.080±0.022$h^{-1}$and 8.69± 2.49 h, respectively. All patients were randomly divided into modeling (n=24) and validation (n=18) groups. The relationship between $AUC_{ss,24h}$and plasma concentration at each time point in modeling group was analyzed by a limited sampling strategy. Two timepoint schemes C_4, C_6 and C_4, C_8(R^2 = 0.990) and three timepoint scheme C_0, C_4, C_6(R^2 = 0.994)were found to be suitable for the TDM of PB. Moreover,the accuracy of the models was considered good based on the data obtained in validation group.In addition, the values of AUC were estimated by measuring peak and trough concentrations based on one-compartment model at steady state after multiple infusions. The deviation of the AUC values of 18 patients was within ± 20%, and 15 of them were within ± 15%.

Furthermore, the prediction results of the model were good.In conclusion, this study provides a clear plan for the implementation of TDM of PB, which is useful for optimizing the dosing regimen and individualizing treatment in severe pneumonia patients.

KEYWORDS

Polymyxin B; limited sampling strategy; therapeutic drug monitoring; AUC; pharmacokinetics

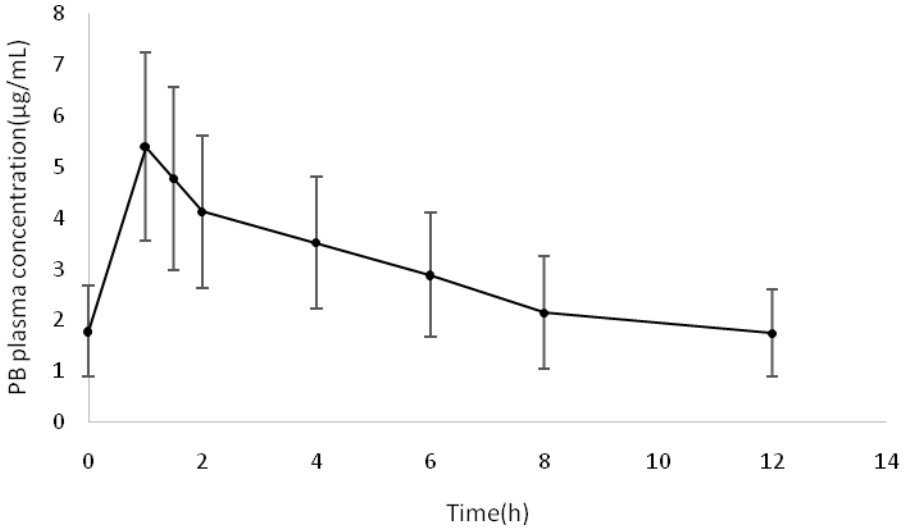

Figure1. PB plasma concentration versus time profiles (n=42).

Table 1.Demographic information and laboratory data of severe pneumoniapatients(n=42).

Category	Mean	SD
AGE（year）	64	16
SEX（Male/Female）	33/9	
HT（cm）	168.4	7.1
WT（kg）	65.3	16.3
BMI（kg/m^2）	22.8	4.8
ALT（IU/L）	34.8	30.4
AST（IU/L）	46.0	41.6
ALB（g/L）	34.2	5.7
TBIL（μmol/L）	24.6	21.9
CR（μmol/L）	143.2	97.7

CRCL（ml/min）	57.7	39.0
SOFAscore	11.1	4.4
CVVH（Y/N）	20/22	

Table2. Multiple linear regression model of the$AUC_{0\text{-}24h}$ of PB(n=24).

Model	Sampling time(h)	Equation	R^2
1	0	$21.323+28.189 \cdot C_0$	0.900
2	1	$0.262+12.902 \cdot C_1$	0.746
3	1.5	$9.408+12.828 \cdot C_{1.5}$	0.752
4	2	$-4.079+18.019 \cdot C_2$	0.662
5	4	$-5.601+21.479 \cdot C_4$	0.975
6	6	$8.147+21.961 \cdot C_6$	0.984
7	8	$16.168+25.222 \cdot C_8$	0.943
8	12	$17.198+30.214 \cdot C_{12}$	0.940
9	0,1	$6.811+20.569 \cdot C_0+2.030 \cdot C_1$	0.948
10	0,1.5	$9.349+20.195 \cdot C_0+5.344 \cdot C_{1.5}$	0.958
11	0,2	$3.119+14.215 \cdot C_0+10.228 \cdot C_2$	0.974
12	0,4	$-0.717+7.805 \cdot C_0+16.225 \cdot C_4$	0.986
13	0,6	$9.303+5.384 \cdot C_0+18.220 \cdot C_6$	0.988
14	4,6	$2.030+8.532 \cdot C_4+13.465 \cdot C_6$	0.990
15	4,8	$0.196+13.903 \cdot C_4+9.725 \cdot C_8$	0.990
16	4,12	$0.546+14.120 \cdot C_4+11.235 \cdot C_{12}$	0.991
17	0,4,6	$3.467+4.853 \cdot C_0+7.980 \cdot C_4+10.635 \cdot C_6$	0.994
18	0,6,8	$7.641+4.158 \cdot C_0+20.045 \cdot C_6-0.526 \cdot C_8$	0.991
19	4,6,12	$2.559+9.518 \cdot C_4+7.739 \cdot C_6+6.894 \cdot C_{12}$	0.993
20	0,4,6,8	$2.879+3.489 \cdot C_0+7.637 \cdot C_4+10.691 \cdot C_6+1.914 \cdot C_8$	0.995
21	0,4,6,12	$3.439+3.541 \cdot C_0+8.801 \cdot C_4+7.503 \cdot C_6+4.696 \cdot C12$	0.995

Table 3.Predictive ability of AUC simplified model formula in validation group(n=18).

Sampling time(h)	PE% （mean±SD）	AE% （mean±SD）	Deviation of AUC		
			>15%	-15%-15%	<-15%
4	-6.14±5.74	7.61±4.01	0	18	0
6	-3.21±7.55	7.04±4.07	0	18	0
8	-0.15±14.78	5.64±8.76	3	15	0
4,6	-4.29±5.35	6.23±3.00	0	18	0
4,8	-3.46±4.82	4.49±3.13	0	18	0
0,4,6	-2.98±4.74	4.85±2.89	0	18	0
0,6,8	0.79±7.07	6.03±3.78	0	18	0
0,4,6,8	-4.24±4.34	4.24±2.68	0	18	0

Table 4. Comparisons between theobserved and predicted AUC values as well as estimated $C_{ss,avg}$and C_0values in patients with severe pneumonia.

ID	AUC_{obv} (μg·mL^{-1}·h)	AUC_{pred} (μg·mL^{-1}·h)	RSD（%）	C_0 (μg·mL^{-1})	$C_{ss\ avg}$ (μg·mL^{-1})	RSD（%）
1	68.8	60.3	-12.4	1.53	2.87	-46.7
2	80.3	69.8	-13.1	1.44	3.34	-56.9
3	95.1	84.6	-11.0	3.05	3.96	-23.0
4	48.3	48.6	0.8	1.08	2.01	-46.3
5	122.2	105.6	-13.6	3.29	5.09	-35.4
6	69.9	70.1	0.3	1.48	2.91	-49.2
7	95.8	83.5	-12.8	2.55	3.99	-36.1
8	64.3	51.6	-19.8	1.12	2.68	-58.2
9	64.3	53.5	-16.8	0.87	2.68	-67.5
10	48.6	53.4	9.8	1.32	2.02	-34.8
11	33.1	33.1	-0.1	0.65	1.38	-52.9
12	71.1	71.3	0.2	2.17	2.96	-26.8
13	35.0	36.1	2.9	1.11	1.46	-24.0

14	113.1	108.9	-3.7	2.45	4.71	-48.0
15	34.1	40.1	17.6	0.94	1.42	-33.9
16	64.4	62.6	-2.7	1.56	2.68	-41.9
17	35.7	33.2	-7.0	0.91	1.49	-38.8
18	76.9	81.8	6.3	2.33	3.21	-27.3

Funding

This study is supported by the Fund of Clinical Pharmacy Research Project of Beijing Pharmaceutical Association (2019); Youth Program of National Natural Science Foundation of China(No. 81302843); National Key Research and Development Program of China(No.2016YFC1304300); and National Natural Science Foundation of China(No.81870072).

Competing interests

There are no competing interests to declare.