P1229

Population Pharmacokinetics of Colistin: Implications for Clinical Use For Gram Negative Pathogens

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Introduction and Purpose

The objective of this study was to characterize the pharmacokinetics of colistin methanesulphonate (CMS) and colistin in critically ill patients following the administration of a 4.5 MU CMS loading dose follow by 3MU CMS Q8. A population PK model and Monte Carlo simulation were used to calculate the probability of target attainment (PTA) against *Acinetobacter baumannii* and *Pseudomonas aeruginosa* by considering a range of MIC values seen in the clinic.

Methods

A clinical trial (MagicBullet) was conducted at the ICU of Virgen del Rocío University Hospital, Spain and Attikon University Hospital, Greece. Critically ill adult patients who met the following inclusion criteria were enrolled: >96h of mechanical ventilation, ventilator-associated pneumonia defined by clinical and radiological criteria, CPIS >4, tracheo-bronchial respiratory culture; pregnancy was an exclusion criterion.

The following information was collected: gender, age, creatinine concentration (Cr) and creatinine clearance (CrCl) on days 1, 3, 7, 14 and 21 (Cockcroft-Gault equation). Serial venous blood collections were taken immediately at 1, 2, 4, 6 and 8 h after the beginning of the CMS infusion on day 1 and at 1, 2, 4, 6 and 8 h, at steady state. Colistin A and B and their prodrugs, CMS A and CMS B were measured using LC-MS/MS. A multi-compartment PK model was fitted to the data using the program Pmetrics. The differential equations driving the distribution of CMS and colistin are shown in equations (1) to (3). R1 represents the infusion rate of CMS, x1 and x2 the mass of CMS in the central and peripheral compartments, respectively, and x3 the mass of colistin in the single compartment for this drug. A graphical description of the model is shown in Figure 1:

CMS	$\frac{dx_1}{dt} = R_1 - K_{12}x_1 - \frac{SCL_1}{V_1}x_1 - K_{13}x_1 + K_{21}x_2$
	$\frac{dx_2}{dt} = K_{12}x_1 - K_{21}x_2$
Colistin	$\frac{dx_3}{dt} = K_{13}x_1 - \frac{SCL_3}{V_3}x_3$

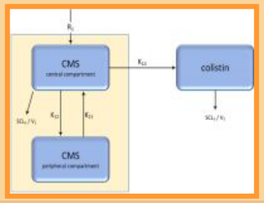


Figure 1. Graphical description of the PK model

For the Monte Carlo simulations, a semiparametric sampling method was used. A colistin free fraction of 34% was used. The probability target attainment (PTA) was assessed for each dosing regimen using a range of *f*AUC$_{0\text{-}24h}$/MIC targets determined from experimental models for both *P. aeruginosa* and *A. baumannii* (JAC, Cheah *et al*. 2015).

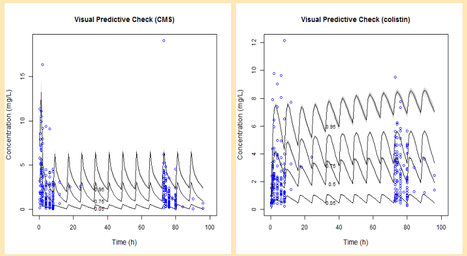
Table 1. Demographic and clinical data

Patient´s no.	Gender	Age (years)	BMI	APACHE II score	Mortality 28 days	Creatinine concentration (mg/dL)					Creatinine Clearance (mL/min)					Isolated microorganisms SV
						Day 1	Day 3	Day 7	Day 14	Day 21	Day 1	Day 3	Day 7	Day 14	Day 21	
01-001	M	68	39,6	29	Alive	0.7	0.5	0.9	0.4	0.5	179.1	222.2	126.3	260.9	260.9	*A. baumannii*
01-002	M	47	25.3	10	Alive	0.8	0.8	1.2	3.5	2.7	137.8	137.8	82.7	29.3	38.7	*A. baumannii*
01-016	F	67	40,0	17	Alive	0.5	0.4	0.3	-	-	152.1	198.9	221.6	-	-	*A. baumannii*
01-026	F	56	20.2	24	Dead	0.9	1.2	-	-	-	62.8	48.7	-	-	-	-
01-035	M	54	29.2	8	Alive	0.8	0.9	1,0	0.4	0.4	151.2	121.9	119.4	265.4	322.8	*Streptococcus spp.*
01-047	M	68	55.7	22	Dead	0.5	0.7	0.5	-	-	319.1	220.6	306.1	-	-	-
21-072	F	86	19.3	18	Dead	0.2	0.3	0.4	0.3	-	194.4	129.6	97.2	129.6	-	*A. baumannii* *P. aeruginosa*
21-079	F	79	34.5	11	Alive	0.5	0.7	0.7	0.7	-	122.4	87.5	87.4	87.4	-	*Klebsiella pneumoniae*
21-087	M	18	23.1	10	Alive	0.6	0.6	0.6	0.7	-	211.8	211.8	211.8	181.5	-	-
01-096	F	79	31.3	11	Alive	0.7	0.6	0.5	0.2	0.3	81.1	91.4	110.8	250.5	169.4	*Burkholderia cepacia*
21-103	M	38	25.1	17	Alive	0.5	0.4	0.7	0.6	-	212.5	265.6	151.8	177.1	-	-
01-112	M	65	30.1	17	Alive	1.1	0.9	0.8	0.6	-	83.0	104.2	110.3	135.8	-	-
21-140	F	28	38.8	11	Alive	0.3	0.3	0.3	0.2	-	493.6	493.6	493.6	740.4	-	-
01-149	F	71	32,0	17	Alive	0.8	0.7	0.5	-	-	80.4	89.3	120.7	-	-	*Staphylococcus aureus*
01-172	M	69	21.9	18	Alive	0.3	0.6	0.5	-	-	170.0	79.5	93.0	-	-	*Enterobacter aerogenes*
01-175	F	58	33.3	16	Alive	0.3	0.3	0.4	0.2	-	256.2	300.4	212.5	414.9	-	-
21-176	M	55	32.2	14	Alive	0.6	0.5	0.9	-	-	200.7	240.8	133.8	-	-	-
01-197	M	42	26.1	11	Alive	1.3	-	-	-	-	54.7	-	-	-	-	-
01-213	M	79	29.4	14	Alive	0.4	0.4	0.4	-	-	247.5	277.2	253.2	-	-	*E. coli*

Table 2. Population pharmacokinetic parameters

Parameter	Mean	SD	%CV	Median
V_1	33.034	25.862	78.287	21.547
V_3	48.717	33.085	67.912	45.658
K_{12}	4.952	3.207	64.760	4.991
K_{21}	1.214	1.144	94.224	1.190
K_{13}	0.390	0.178	45.729	0.310
SCL_1	11.986	6.764	56.434	11.895
SCL_3	13.965	4.379	31.359	15.333

Figure 2. Visual predictive check for plasma concentrations of CMS and colistin. Blue dots show the observed data, lines show percentiles (5th, 75th and 95th).



Results

Demographic and clinical data are shown in Table 1. Nineteen patients were enrolled in the study. None of the patients required renal replacement therapy during the treatments.

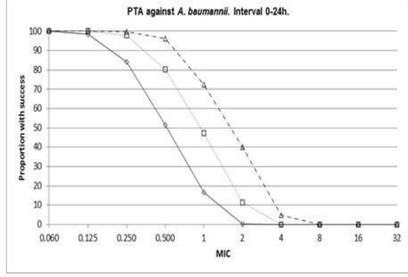
The coefficients of determination (r2) for observed versus individual fitted CMS and colistin plasma concentrations were 0.528 and 0.812, respectively. The mean and standard deviation of the parameters generated in the simulation were 31.52 (26.15) for V1, 31.31 (28.69) for V3, 6.99 (2.45) for K12, 2.00 (1.55) for K21, 1.11 (1.10) for K13, 6.13 (5.26) for SCL1 and 8.95 (4.47) for SCL3.

PTA against *A. baumannii* and *P. aeruginosa* for the treatment of pneumonia are shown in figure 2.

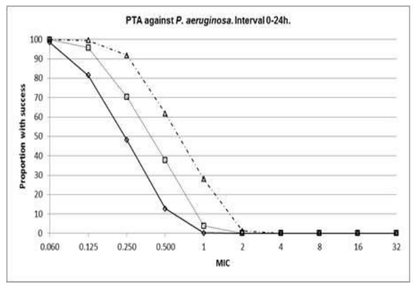
Figure 2. PTA against *A. baumannii* and *P. aeruginosa* for the treatment of pneumonia. Loading dose 4.5 MU CMS (360 mg) and 3 MU CMS (240 mg) Q8h. Static effect (triangle), 1-log (square) and 2-log (diamond) CFU/ml of bacterial reduction.

A. baumannii | ***P. aeruginosa***

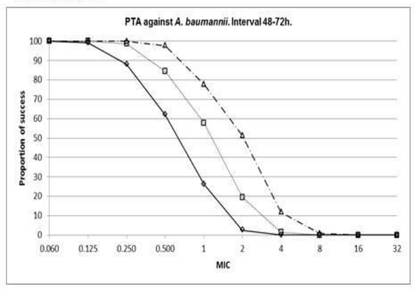
A. baumannii PTA for pneumonia 2, 1 –log reduction and stasis. $AUC_{0\text{-}24h}$/MIC. Colistin simulated data. Loading dose 4.5 MU and 3 MU/Q8h of CMS.



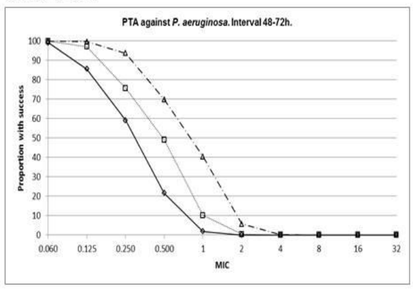
P. aeruginosa PTA for pneumonia 2, 1 –log reduction and stasis. $AUC_{0\text{-}24h}$/MIC. Colistin simulated data. Loading dose 4.5 MU and 3 MU/Q8h of CMS.



A. baumannii PTA for pneumonia 2, 1 –log reduction and stasis. $AUC_{48\text{-}72h}$/MIC. Colistin simulated data. Loading dose 4.5 MU and 3 MU/Q8h of CMS.



P. aeruginosa PTA for pneumonia 2, 1 –log reduction and stasis. $AUC_{48\text{-}72h}$/MIC. Colistin simulated data. Loading dose 4.5 MU and 3 MU/Q8h of CMS.



Conclusion

Our model suggests that a 4.5 MU (360 mg) loading dose, followed by 3 MU (240 mg)/Q8h, produced have a low PTA against *A. baumannii* and *P. aeruginosa* when the MIC are higher than 0.125 mg/L. These results can be used to provide decision support for establishing breakpoints for colistin against these nosocomial pathogens.

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