



Whole Body Physiologically-Based Pharmacokinetic Model for Colistin and Colistimethate sodium in Critically Ill Patients

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Background

- Colistin is used as a salvage therapy for multiresistant gram-negative bacteria (MDR-GNB) infections and is administered as a prodrug, colistimethate sodium (CMS).
- Characterizing tissue distribution of colistin is of importance to optimize bacteria kill and avoid toxicity.
- Whole Body Physiologically Based Pharmacokinetic (WBPBPK) models are increasingly utilized to predict pharmacokinetic behavior of drugs.

Objective

- To develop a WBPBPK model to describe pharmacokinetics of CMS and colistin in critically ill patients in order to predict bacteria kill in tissues.

Methods

Study design

- 31 patients [1,2] with MDR-GNB infections treated with colistin were included in the analysis (10 females; mean age: 62 years; mean CRCL: 80 ml/min).
- CMS was administered at doses of 80, 160, 240 or 480 mg every 8h through a 15-min infusion.
- Venous blood was collected at 2 occasions, typically the 1st and then 4th, 6th, 7th, 8th or 42nd.

WBPBPK Model

- 11 tissue compartments were connected via blood flow to arterial and venous plasma pools in a closed-loop format for both CMS and colistin. Each tissue was considered as a single, perfusion limited and well-stirred compartment (Figure 2).
- CMS is cleared renally (CL_{r1}) and via hydrolysis to colistin (K_{hyd}) assumed to take place in all tissues.
- Colistin elimination is mainly non-renal (K_{nr}) and is assumed to occur in all tissues. Renal clearance (CL_{r2}) of colistin was also included [1,2].
- Total CMS hydrolysis clearance (CL_{hyd}) and total colistin non-renal clearance (CL_{nr}) are calculated as:

$$CL_{hyd} = \sum(K_{hyd} \cdot V_{tissue}) \text{ and } CL_{nr} = \sum(K_{nr} \cdot V_{tissue})$$

- All clearance and K_p values of CMS and colistin were estimated simultaneously using the prior functionality in NONMEM 7.2 and the first order conditional estimation method with interaction (FOCE-I).
- Prior information was collected from literature [3], *in silico* prediction equations [4] and *in vitro* experiments.
- Inter-individual variability (IIV) estimates were used for each clearance term and all K_p factors.
- Combined residual errors were implemented for both CMS and colistin.

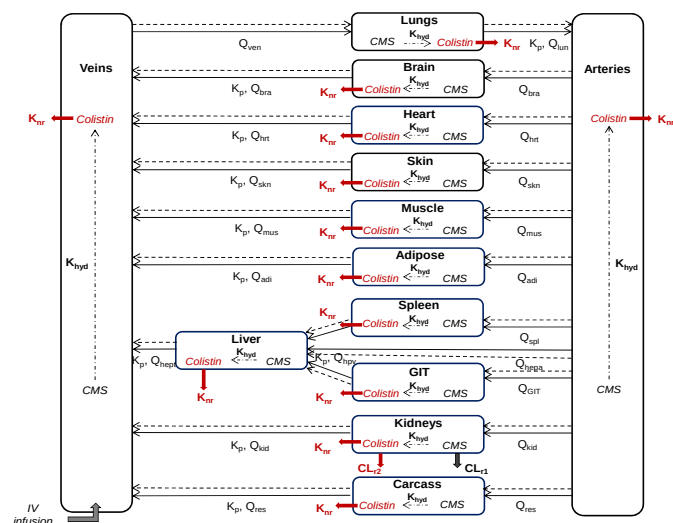


Figure 1. Schematic representation of CMS and colistin WBPBPK model, (dashed line and solid line arrows represent colistin and CMS flows between tissues, respectively)

Conclusions

- The WBPBPK model was used to describe plasma concentration-time profiles for both CMS and colistin.
- The relatively high K_p values, in comparison to those expected for distribution only to interstitial space [5] suggest that colistin enters into cells or binds to cell membranes or interstitial macromolecules.

Results

- Predicted K_p factors were lower for CMS and higher for colistin than the calculated priors (Table 1). Estimated renal clearance of CMS was higher than the prior literature value [3].

Table 1. Prior and posterior mean estimates for K_p factors and clearances for CMS and colistin.

	CMS		Colistin	
	Prior mean (θ)	Parameter estimates (IIV, CV%)	Prior mean (θ)	Parameter estimates (IIV, CV%)
K_p Lung	0.734	0.580 (39)	0.367	0.412 (39)
K_p Brain	0.730	0.576 (39)	0.364	0.414 (39)
K_p Heart	0.692	0.506 (39)	0.346	0.353 (39)
K_p Skin	0.653	0.653 (39)	0.326	0.739 (39)
K_p Muscle	0.688	0.417 (39)	0.344	0.292 (39)
K_p Adipose	0.135	0.159 (39)	0.067	0.097 (39)
K_p Spleen	0.721	0.523 (39)	0.360	0.364 (39)
K_p GIT	0.657	0.516 (39)	0.520	0.608 (39)
K_p Liver	0.692	0.547 (39)	0.345	0.395 (39)
K_p Kidney	0.714	0.549 (39)	0.357	0.368 (39)
K_p Carcass	0.570	0.477 (39)	0.198	0.301 (39)
CL_{r1} (L/h)	4.95	11.9 (56)	-	-
CL_{hyd} (L/h)	1.46	1.76 (43)	-	-
CL_{r2} (L/h)	-	-	0.13	0.11 (70)
V_{ss} (L)	-	-	1.32	1.99 (87)
$T_{1/2}$ (h)	-	4.33	-	10.0

- The model described CMS and colistin observed plasma concentrations (Figure 2).

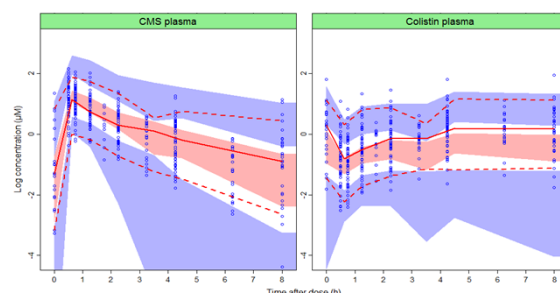


Figure 2. Prediction Corrected Visual Predictive Checks (pcVPCs) of plasma concentration-time after dose profiles for CMS (left) and colistin (right) in critically ill patients (dashed and solid lines: 5th, 50th and 95th percentiles of the observed concentrations; blue and red areas: 95% confidence intervals of the 5th, 50th and 95th percentiles of the predicted concentrations).

- Predicted tissue distributions of CMS seemed to follow the concentration-time profiles in plasma.
- Low tissue distribution of colistin was predicted in the large tissues: adipose, muscle and carcass (Figure 3).

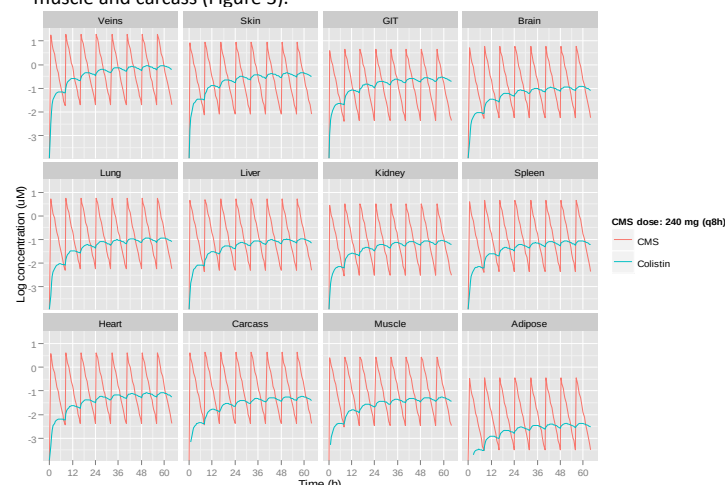


Figure 3. Predicted concentration-time profiles for CMS and colistin in tissues of a typical critically ill patient

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