



Population pharmacokinetic analysis of colistin after administration of inhaled colistin methanesulfonate.

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Objectives

Colistin is an antimicrobial agent administered for the treatment of multidrug resistant gram-negative bacterial infections. The aim of the present study was to develop a population PK model of colistin after inhalation of colistin methanesulfonate (CMS), an inactive prodrug of colistin.

Methods

Pharmacokinetic data were obtained from a published study¹, in which 80 mg of CMS were administered to 20 patients via a vibrating-mesh nebulizer and concentrations of colistin in serum were measured before and at 0.16, 0.5, 1, 2, 4 and 8 hours and in lung epithelial lining fluid at 1, 4 and 8 hours after the end of inhalation.

Population Pharmacokinetic analysis was performed using the FOCE method with interaction in NONMEM (version 7.2). Weight, age, creatinine clearance and APACHE II and SOFA scores were tested as potential covariates affecting the pharmacokinetic parameters. Concentrations in ELF were modeled with a monoexponential model in order to estimate the elimination rate constant of colistin from ELF ($k_{e,ELF}$) and test it as a covariate on absorption. A reduction in the objective function value (OFV) of at least 3.84 units for 0.05 level significance and in the inter-individual variability (IIV) were required in order to include a covariate in the model. Model evaluation was performed using goodness of fit plots, generated by Xpose4, bootstrap analysis and visual predictive check (VPC).

Results

A linear one compartment model with absorption being modeled by the Weibull distribution best described the data.

The parameters of the structural model were the apparent clearance (CL/F), the apparent volume of distribution (V/F), the Weibull scale (a) and shape parameters (b). Inter-individual variability was assigned to CL/F and V/F by the exponential model.

Residual variability was modeled by a time dependent error model² to account for higher residual error during the absorption phase. A time breakpoint (bp) was used in order to allow for different magnitude of the error. Furthermore, high Cmax values were observed which do not agree with a monoexponential model and a biexponential model has not been reported in literature for the pk of colistin. Thus, due to the unusually high Cmax values attributed to suspected hydrolysis of CMS to colistin during sample handling, a systematic bias (sb) was introduced to the residual error.

$$\text{Error Model: } Y_{ij} = F_{ij} + F_{ij} \cdot EPS(1) \cdot bp + F_{ij} \cdot EPS(2) \cdot (1 - bp) + F_{ij} \cdot sb$$

$$\text{where } bp = \begin{cases} 0 & \text{if time} \geq 4 \text{ hours} \\ 1 & \text{if time} < 4 \text{ hours} \end{cases} \text{ and } sb = \begin{cases} 0 & \text{if time} \geq 4 \text{ hours} \\ \theta_{sb} & \text{if time} < 4 \text{ hours} \end{cases}$$

CL/F was related to creatinine clearance ($CrCl$) by the power model:

$$T_{v_{CL/F}} = \theta_{CL} \cdot \left(\frac{CrCl}{\text{geomean } CrCl} \right)^{\theta_{CL, CrCl}}$$

An attempt was made to assign inter-individual variability to the absorption parameters, a and b , as well, and use the estimated $k_{e,ELF}$ for each patient as covariate. However, inter-individual variability could not be estimated with the anticipated precision (relative standard error more than 100%) for either of the parameters and the η -shrinkage was higher than 30%.

The parameters of the final pk model (Table 1) were estimated with satisfactory precision. Goodness of fit plots (Figure 1) and the VPC (Figure 2) indicate the adequacy of the model to describe the data.

Taking into account the systematic bias of the residual error and subtracting it from the individual predictions of the model, the “true” Cmax values were predicted (Figure 3). It should be noted that the suspected hydrolysis is a modelling hypothesis and has not been validated for real.

Tables and Figures

Table 1. Summary of estimates and bootstrap results for final PK model

Parameter (units)	Parameter estimate (RSE%)	Bootstrap median (95% CI)
Base model parameters		
θ_{CL} (l/h)	6.79 (6.4)	6.85 (6.02-7.77)
$\theta_{CL, CrCl}$	0.323 (31.3)	0.332 (0.076-0.565)
θ_V (l)	37.2 (5)	37.2 (33.9-41.1)
θ_b	2.08 (2.9)	2.08 (1.96-2.20)
θ_a (h)	1.44 (1.5)	1.44 (1.41-1.49)
θ_{sb}	0.495 (6.1)	0.496 (0.440-0.553)
Inter-individual variability		
ω_{CL} (%CV)	27.8 (13.5)	26.1 (0.179-0.344)
ω_V (%CV)	19 (13.1)	18 (0.13-0.23)
Correlation $CL - V$	0.711 (19)	0.728 (0.310-0.944)
Residual variability		
σ_1 (CV)	0.137 (6.3)	0.134 (0.117-0.153)
σ_2 (CV)	0.0442 (19.4)	0.0424 (0.0234-0.0588)

Figure 1. Goodness of fit plots for final PK model

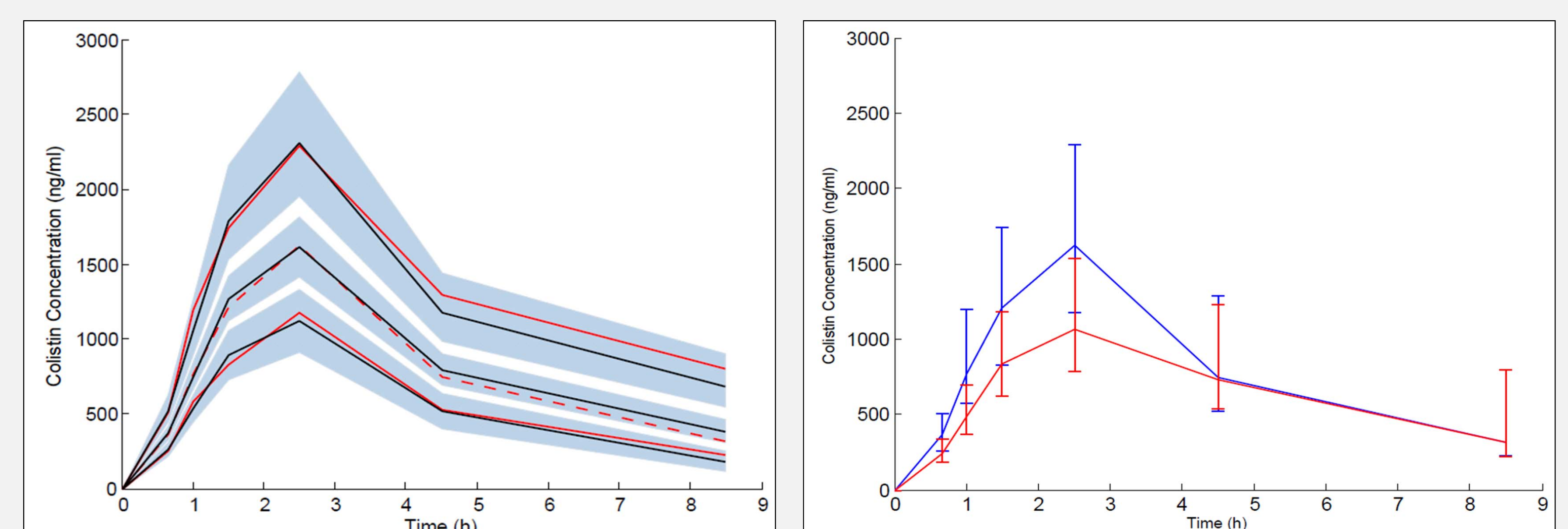
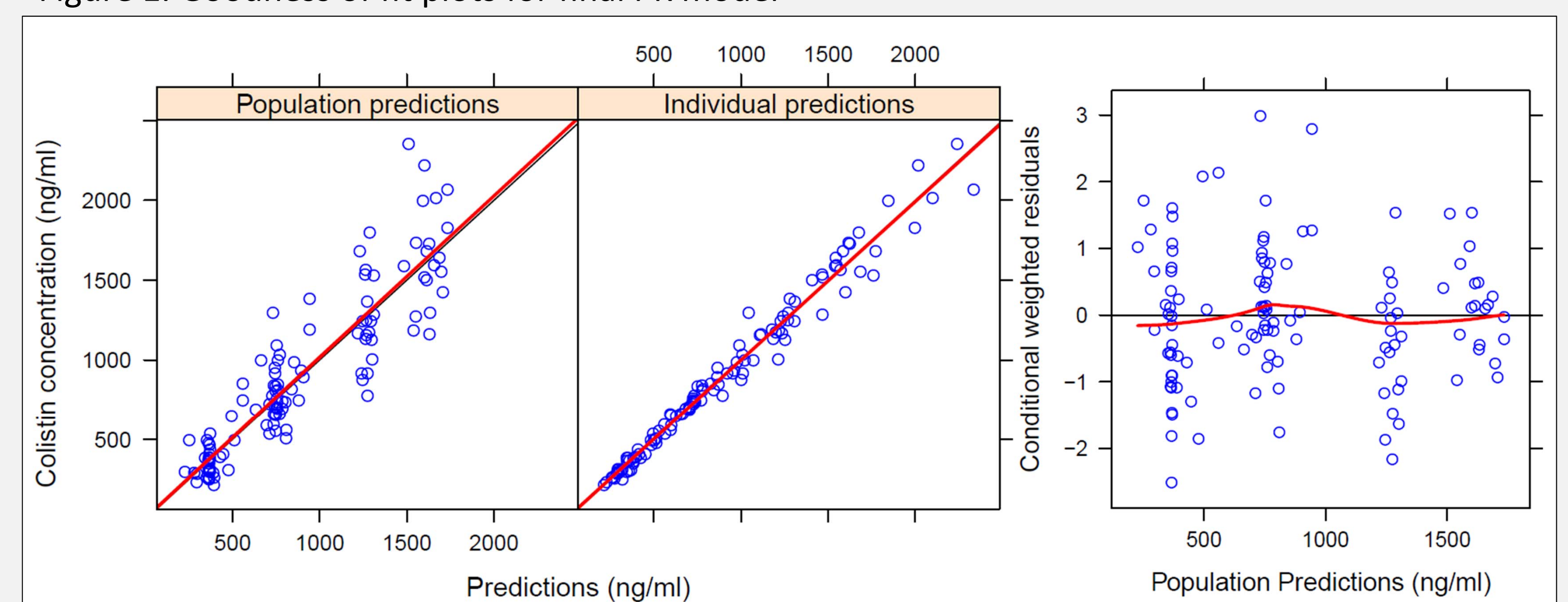


Figure 2. Visual Predictive check. The shaded areas are the 95% confidence intervals of the prediction intervals (black lines) for the 5, 50 and 95 percentiles from the simulations. The red lines are the observation intervals.

Figure 3. The blue line is the median and the error bars are the 90% intervals of the observations. The red line is the median of the IPREDS minus the systematic bias and the error bars are the respective 90% internals.

Conclusions

A population pk model for colistin after administration of inhaled CMS has been developed.

The introduction of a systematic bias in the residual error allows the interpretation of unusually high Cmax values which are suspected to be erroneous, as well as the prediction of the values which are thought to be more consistent with the expected ones.

References

- [1] Athanassa ZE, Markantonis SL, Foustier MZ, Myrianthefs PM, Boutzouka EG, Tsakris A, Baltopoulos GJ. Pharmacokinetics of inhaled colistimethate sodium (CMS) in mechanically ventilated critically ill patients. Intensive Care Med. 2012 Nov;38(11):1779-86.
- [2] Karlsson MO, Beal SL, Sheiner LB. Three new residual error models for population PK/PD analyses. J Pharmacokinet Biopharm. 1995 Dec;23(6):651-72. PubMed PMID: 8733951.