P0722

Paper Poster Session IV

Update on colistin & polymyxin B

Perspectives for therapeutic drug monitoring of colistin using Bayesian approaches

S. Magréault[1], N. Grégoire[1], S. Marchand[1], P. Gobin[1], F. Roblot[1], O. Mimoz[1], W. Couet[1]

[1]*Inserm U1070 and University of Poitiers, Poitiers, France*

Objective:

Colistin is a re-emerging antibiotic used for the treatment of Gram (-) multidrug-resistant infections in critical care patients, administered as an inactive prodrug, colistin methanesulfonate (CMS). Colistin is relatively toxic and its pharmacokinetics (PK) varies widely between individuals. It is therefore a good candidate for therapeutic drug monitoring (TDM) although it's therapeutic window is difficult to assess. Yet TDM has been conducted in our institution for more than 3 years on approximately 400 occasions. The objective of this study was to use data recently published by our group (1) to assess the feasibility of a Bayesian approach for colistin TDM.

Method:

Based on our background the following general framework is used in our institution. Average colistin concentration at steady-state ( ) between 2-4 µg/mL: within target (green zone), concentrations <1 µg/mL or > 6 µg/mL: require dosing revision (red zone), and values between 1-2 or 4-6 µg/mL: no need for adjustment but more frequent resampling (yellow zone). First Monte-Carlo simulations were performed (n=1000 patients) using previously published PK parameters typical values and variability (1). Since in practice daily doses of CMS are adjusted to creatinine clearance, simulations were conducted for a patient with CL_{CREAT} =40 mL/min receiving 2 MIU of CMS 3 times a day. Number of patients (%) in each zone was estimated after PK parameters were let to vary all at the same time and then one after the other. Second a Bayesian approach was used to predict individual values, using the "measured" residual concentrations after the first dose, obtained by adding a random analytical error to the values predicted by Monte Carlo simulations.

Results:

Monte Carlo simulations showed that only 48% of the patients would have a value within the green zone and 10.5% within a red zone (2.5% < 1µg/mL and 8% > 6µg/mL) when all parameters were let to vary. The unpredictable inter-individual variability of colistin clearance (CL_{COLI}) was the major source of variability with only 61% within 2-4 µg/mL when only CL_{COLI} was let to vary. The uncertainty on CMS renal clearance ($CL_{R,CMS}$) estimate, derived in clinical practice from CL_{CREAT} obtained by the MDRD method, had also a major impact on the . Bayesian estimation of PK parameters was of relatively limited benefit. The average bias on was reduced from 45% to 24% but individuals in the red zones were poorly predicted. Addition of few extra samples after the first dosing had a limited effect.

Conclusion:

Based on presently available information, using a Bayesian approach after determination of the first residual colistin concentration, improves only moderately the prediction of individual colistin PK parameters and in critically ill patients.

1. Grégoire N, et al. AAC. 2014 Sep 29. PubMed PMID: 25267662. Epub 2014/10/01.