Dose Adjustment of Polymyxins for Renal Insufficiency

In a recent article, Garonzik et al. (4) importantly advanced our knowledge of the pharmacokinetics (PK) of colistin methanesulfonate (CMS) and the active drug that it forms, colistin. In their elegant population PK study of critically ill patients, the authors demonstrated that creatinine clearance (CL_{CR}) significantly affects the total body clearance of CMS and colistin (4). It is important to note that, as shown by the authors, the correlation of the active drug, colistin, with CL_{CR} is the result of a complex interplay between the kinetics of CMS and colistin (4).

Following direct administration to animals, colistin was shown to be predominantly cleared by nonrenal mechanisms (6), suggesting that dose adjustment for renal dysfunction would not be necessary. In contrast, Garonzik et al. showed that after administration of CMS, plasma colistin concentrations at a given CMS dose increased as CL_{CR} declined. However, this occurs as a consequence of the presence of a larger fraction of CMS, which is dependent on CL_{CR} and which becomes available to be converted in vivo to colistin (4). In summary, colistin is not directly dependent on CL_{CR}; nonetheless, the concentration of this antibiotic increases as renal function declines because it is administered as the prodrug CMS, which has its total body clearance depending directly on CL_{CR}.

This interplay between CMS and colistin is extremely important, and any data on CMS/colistin PK cannot be directly extrapolated to polymyxin B, the other commercially available polymyxin, since it is administered as its active form, polymyxin B sulfate (1). Polymyxin B has also been increasingly used worldwide, and we have previously found that renal clearance of this drug was very low in critically ill patients (7). A more recent case report also corroborates our finding (5). This preliminary evidence suggests that polymyxin B, unlike CMS, should not be adjusted for any degree of renal dysfunction. Of course, these findings must be confirmed in larger PK studies, especially considering the issue of toxicodynamics.

Clinicians must closely observe such differences between polymyxin B and colistin, since area under the concentration-time curve for the free, unbound fraction of a drug (fAUC)/MIC is the PK/pharmacodynamic index that best correlates with the efficacy of polymyxins (2), and maximal daily doses are usually required to optimize the fAUC (3). Additionally, it was clinically demonstrated that higher daily doses of polymyxin B were independently associated with lower in-hospital mortality in patients treated with this drug (3). Thus, adequate prescription of polymyxin B in renal dysfunction is of paramount importance to avoid underdosage regimens in these patients.

As has occurred with colistin, large studies, which fortunately are taking place, are required to improve our knowledge of the PK of polymyxin B, the other important “salvage” drug.

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BEDFORD LABORATORIES, Bedford, OH.


Alexandre P. Zavascki
Infectious Diseases Service
Hospital de Clínicas de Porto Alegre
2350 Ramiro Barcelos St.
Porto Alegre
Rio Grande do Sul, Brazil 90.035-903

Phone and fax: 55 51 33598152
E-mail: azavascki@hcpa.ufrgs.br

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