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Can Polymyxins Be Used for Multidrug-Resistant Organisms?

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Question:

Can polymyxins be used for MDRO? Are these antibiotics time-dependent or concentration-dependent?

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The continued spread of multidrug-resistant gram-negative bacteria has been recognized as one of the most significant public health issues of the current decade. In the United States, geographic distribution of extreme drug-resistant *Klebsiella* species has grown from just a few states on the East Coast to essentially all but a few of the least-populated states. Because the pipeline for new antimicrobials to treat serious gram-negative infections is essentially dry, use of older agents such as the polymyxins has seen a resurgence. This article will briefly describe the available published pharmacokinetic (PK)/pharmacodynamic (PD) data for this class and attempt to apply these data, where possible, in guiding appropriate dosing regimens.

Commercially available members of the polymyxin family include colistin (polymyxin E) and polymyxin B. Both agents share a similar spectrum of activity against gram-negative bacteria, including serious multidrug-resistant organisms (MDRO) such as *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and some strains of extreme drug-resistant *Klebsiella* species. Both exhibit concentration-dependent killing, but they have little of the postantibiotic effect seen with aminoglycosides.

Injectable colistin is available only as the inactive prodrug, colistin methanesulfonate (CMS), which is hydrolyzed in vivo to active colistin. The time to conversion can vary, which can potentially compromise early achievement of therapeutic concentrations of active drug. Colistin dosing may be reported in international units (IU) where 12,500 IU are equivalent to 1 mg of CMS, or in milligrams as "colistin base activity" where 1 mg contains about 2.7 mg of CMS. Colistin products are labeled by "colistin base activity" in the United States.

Polymyxin B is not a prodrug like CMS but is available as the active sulfate salt. Each 10,000 IU is equivalent to 1 mg of polymyxin base. Polymyxin B is dosed in international units per kilogram in the United States but in milligrams per kilogram elsewhere.

Much of the clinical and research interest in the treatment of gram-negative MDRO has centered on colistin. This has generated at least 3 reports examining the PK/PD properties of colistin in both in vitro and animal models.[1-3] The best correlated PK/PD relationship for bacterial killing that has been found for colistin is free area under the concentration curve (AUC)/minimum inhibitory concentration (MIC). In vitro models suggest a greater emergence of resistance when colistin is administered once daily vs multiple times daily. Moreover, in animal models, the likelihood of kidney injury is greater with once-daily vs multiple-daily dosing.[1-3]

The data for polymyxin B is much more limited, with only 1 published report currently available using an in vitro model. Based on this report, the same PK/PD relationship (AUC/MIC) appears to hold for polymyxin B. Modifications of simulated dosing schedules had no effect on the development of resistance.[4]

Both agents are renally eliminated and have been associated with nephrotoxicity, which is one of the initial

reasons for their limited use. More recent data have suggested that the toxicity risk, although present and significant, may have been somewhat overstated.[5,6] The product labeling does provide rudimentary guidance regarding dose adjustment for renal insufficiency. However, because these drugs were marketed prior to current regulatory requirements, these recommendations were not based on PK/PD principles. Well-supported guidance for patients with renal dysfunction and patients on renal replacement therapy are sorely lacking.

The colistin product labeling dose of 5 mg/kg/day of colistin base activity given in divided doses[7] is reasonably acceptable for patients with normal renal function. In the absence of guidance, we tend to use loading doses (5 mg/kg) of colistin in our practice to compensate for potentially delayed conversion of the prodrug to the active agent. We administer the total daily dose divided over multiple administrations (eg, 2-3 doses daily) even in patients with substantial renal insufficiency who require a reduced total dosage. This is done in an attempt to minimize toxicity and the potential development of resistance. For patients on continuous renal replacement therapy at flow rates of 3-4 L/hr, we dose colistin as if the patient had normal renal function.

Our experience with polymyxin B is much more limited. When it is used clinically, we generally follow product labeling recommendations.

Given the lack of well-supported recommendations for patients with renal dysfunction and patients on renal replacement therapy, the variability of dose quantification reporting for colistin, the relative paucity of PK/PD data, and the very minimal correlation of these data to patient outcomes, deciding on the correct dose of polymyxin in critically ill patients with MDRO infections is quite challenging. More research is urgently needed to assist clinicians in finding the optimal dose for this class of antibiotics, which is rapidly becoming one of our last lines of defense against multidrug-resistant gram-negative pathogens.

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