Colistin Use in Critically Ill Patients: In Search of the Optimal Dosing

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To the Editor:

We read with interest the recent article in CHEST (December 2010) by Imberti et al., which described steady-state serum pharmacokinetics and BAL concentration of colistin after IV administration of colistin methanesulfonate (CMS) in adult patients with ventilator-associated pneumonia caused by gram-negative bacteria. After having administered the recommended daily CMS dose of 6 million International Units, divided into three doses, colistin levels in BAL were unetectable, whereas the ratio of the area under the plasma concentration-time curve to the minimum inhibitory concentration (AUC\(_{0-24}\)/MIC) (MIC = 2 mcg/mL) was suboptimal (17.3 ± 9.3 without considering unbounding colistin fraction). As a comparison, as a recent in vitro model showed that optimal bactericidal effects of colistin against Pseudomonas aeruginosa were observed when the ratio of the area under the unbound concentration-time curve to MIC was around 30.

The results of Imberti et al.1 are consistent with those of Markou et al.3 and Plachouras et al., who showed that even administering 9 million units per day of CMS—a dose 50% higher than that recommended by the manufacturer—the average maximum colistin concentration in plasma at the steady state was 2.93 and 2.3 mg/L, respectively, a level that is slightly above the Clinical and Laboratory Standards Institute MIC breakpoint (2 mg/L) for Acinetobacter baumannii and P. aeruginosa, and that most probably result in suboptimal maximal concentration/MIC ratios for many strains in the upper range of the MIC values.

All these papers raise questions about whether the currently used dosages of colistin methanesulfonate are appropriate in the critically ill patients, in whom a larger distribution volume and increased plasma concentrations of α1-acid glycoprotein, an acute-phase protein with polymixin-binding capabilities, may result in free colistin concentrations that are lower than those expected. Unfortunately, suboptimal antibiotic concentrations favor the development of drug-resistant bacterial strains. Because bacterial species against which colistin is used are already multidrug resistant and since no new antibiotics against gram-negative bacteria are expected to be available in the next few years, we think that further studies aimed to define the optimal CMS/colistin dosing regimen are urgently needed.

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