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Population pharmacokinetics and pharmacodynamics modeling of β-lactams in critically ill patients with severe sepsis: sulbactam study model to optimize dosage regimens

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The emergence of multidrug-resistant (MDR) microorganisms worldwide has become a significant public health threat and remains a cause of increased rates of morbidity and mortality in critically ill patients with severe sepsis. Acinetobacter species, especially *Acinetobacter baumannii*, have been shown to be associated with serious nosocomial infections in critically ill patients in intensive care units for several years. These microorganisms have developed resistance to several classes of antimicrobial agents, resulting in the dangerous situation of physicians having only a few, or even sometimes no, effective antibiotics for the treatment of infections caused by MDR *A. baumannii*. Sulbactam, a β-lactamase inhibitor, is being considered as an alternative concomitant medication with other effective antibiotics for the treatment of MDR *Acinetobacter baumannii* infections. Pathophysiological changes in critically ill patients with severe sepsis, resulting in altered pharmacokinetic (PK) patterns for antibiotics, are important factors in determining therapeutic success. This agent, the same as β-lactams, exhibits primarily time-dependent killing, and the percentage of the exposure time during which the free drug concentration remains above the MIC (% $T_{>MIC}$) is the pharmacokinetic/pharmacodynamic (PK/PD) index that best correlates with efficacy. The aims of this study were (i) to examine the population PK parameters, and (ii) to assess the probability of target attainment (PTA) for sulbactam in patients with severe sepsis caused by *A. baumannii.* PK studies were carried out following administration of 2 g of sulbactam every 12 h on the 4th day of drug administration in twenty-seven patients and a Monte Carlo simulation was performed to determine the PTA of achieving 40% exposure time during which the plasma drug concentration remained above the MIC ($T_{>MIC}$) and 60% $T_{>MIC}$. The central and peripheral volumes of distribution were 14.56 and 9.55 liters, respectively and total clearances of sulbactam were 2.26 liters/h and 7.64 liters/h in patients aged >65 years and ≤65 years, respectively. The high PTAs (≥90%) for targets of 40% $T_{>MIC}$ and 60% $T_{>MIC}$ with a MIC of 4 μg/ml were observed when sulbactam was administered by a 4-h infusion of 1 g every 12 h and 1 g every 8 h, respectively. Sulbactam would be an alternative antibiotic option to coadminister with colistin for the treatment of infections caused by MDR *A. baumannii.* However, for pathogens with MICs of >4 μg/ml, higher dosage regimens of sulbactam are required.

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