Impact of Loading Doses on the Time to Adequate Predicted Beta-Lactam Concentrations in Prolonged and Continuous Infusion Dosing Schemes

To the Editor—We applaud the work by Roberts et al that was recently published in the Journal [1]. As shown in this work and others, achievement of pharmacokinetic–pharmacodynamic (PK/PD) targets for beta-lactam antibiotics has been correlated with improved mortality among the critically ill [1, 2]. Similarly, hastening time to effective antimicrobial therapy in the setting of septic shock has been shown to improve the probability of survival [3–5]. For beta-lactams, maintenance of free ($f$) drug concentrations above an organism’s minimum inhibitory concentration (MIC) for a given proportion of the dosing interval ($fT > MIC$) has been shown to predict clinical and microbiologic success [1]. To improve the likelihood of achieving PK/PD targets for these agents, beta-lactams are often administered as prolonged (PI) or continuous infusions (CI); though, time to activity has not been well described nor
Figure 1. Probability of and time to first instance of concentrations exceeding the breakpoint minimum inhibitory concentrations (MICs) for piperacillin-tazobactam (TZP; 16 mg/L) and meropenem (MEM; 2 mg/L) for the first 120 minutes of therapy. Probabilities derived from robust simulations of 1000 concentration–time profiles for TZP and MEM exceeding the respective susceptible breakpoint MIC for piperacillin-tazobactam or MEM among 90% of 1000 simulated subjects ($P_{C > MIC}$ on y-axis vs time on x-axis) for the following regimens: A, TZP intermittent infusion, rate of 112.5 mg/min (equivalent to 3.375 g infused over 30 minutes); TZP prolonged infusion, rate of 14.1 mg/min (equivalent to 3.375 g infused over 4 hours); TZP continuous infusion, rate of 7 mg/min (equivalent to 10.125 g infused over 24 hours); TZP continuous infusion after loading dose (LD), rate of 112.5 mg/min for 30 minutes followed by 7 mg/min (equivalent to 3.375 g infused over 30 minutes followed by 10.125 g infused over 24 hours). B, $P_{C > MIC}$ for the following MEM regimens: MEM intermittent infusion, rate of 33.3 mg/min (equivalent to 1 g infused over 30 minutes); MEM prolonged infusion, rate of 5.6 mg/min (equivalent to 1 g infused over 3 hours); MEM continuous infusion, rate of 2.1 mg/min (equivalent to 3 g infused over 24 hours); MEM continuous infusion after LD, LD, Loading dose, rate of 33.3 mg/min for 30 minutes followed by 2.1 mg/min (equivalent to 1 g infused over 30 minutes followed by 3 g infused over 24 hours). Abbreviations: LD, loading dose; MEM, meropenem; MIC, minimum inhibitory concentration; TZP, piperacillin-tazobactam; 90% $P_{C > MIC}$, probability of concentrations exceeding the susceptible breakpoint MIC for piperacillin-tazobactam or meropenem among for the 90th percentile of 1000 simulated subjects.

was this the focus in the Roberts et al article. We evaluated the time to achievement of target $fT_{MIC}$ for meropenem and piperacillin–tazobactam using simulated first-dose drug exposure to answer the question: is a loading dose necessary for PI or CI?

We used previously published population PK models of meropenem [6] and piperacillin–tazobactam [7] to predict concentrations of both agents over an 8-hour dosing interval. We simulated concentration–time profiles using the mean [6] and median [7] PK parameter values within Pmetrics [8,9]. Variability was modeled using the corresponding diagonal of the covariance matrix. Piperacillin–tazobactam clearance was proportionalized to creatinine clearance, and body weight was fixed at 75 kg and creatinine clearance at 60 mL/min. Free-drug, concentration–time profiles were created from each of the 1000 generated sets of parameters. Predicted concentrations were generated every 6 minutes for the first 8 hours of therapy. We used the susceptible breakpoint MIC for Pseudomonas aeruginosa against piperacillin–tazobactam (16 mg/L) and meropenem (2 mg/L) in our PK/PD analysis to assess time to active therapy (when the concentration exceeds the MIC) [10]. We simulated 4 strategies: meropenem and piperacillin–tazobactam as intermittent infusions over 0.5 hours (II), PIs over 3 or 4 hours (for each drug respectively), and CIs with and without loading doses given over 30 minutes. From the 1000 simulated concentration time profiles, we calculated the time to exceed breakpoint MICs for each patient and classified the time by which 90% of patients were expected to exceed the breakpoint (90% $P_{C > MIC}$). Meropenem and piperacillin–tazobactam achieved 90% $P_{C > MIC}$ within 6 minutes and 6 minutes (II), 12 minutes and 96 minutes (PI), and 36 minutes and failed to exceed the breakpoint within the 8-hour window (CI), respectively (Figure 1). Loading doses for both drugs restored activity to within the first 6 minutes of therapy.

Our models suggest that loading doses (LDs) may be necessary for the modeled piperacillin–tazobactam PI and CI infusion schemes and for elevated MICs. LDs are less likely important for meropenem and for susceptible organisms. Our analysis used the susceptibility breakpoint of P. aeruginosa to assess a “worst-case” scenario. As clinicians begin to implement PI and CI regimens for beta-lactams, we suggest further study.

Note

Potential conflicts of interest. The authors have no reported conflicts of interest related to the content of this article. All authors: No reported conflicts.

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