Are Blood Concentrations Enough for Establishing Pharmacokinetic/Pharmacodynamic Relationships?

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Since the early days of penicillin, the efficacy of β-lactam antibiotics in animal models has been more dependent on the duration of exposure than the magnitude of the concentration [1]. Subsequent studies using dose fractionation techniques in mice with thigh and lung infections for various penicillins, cephalosporins, and carbapenems have shown a high correlation of efficacy with time above the minimum inhibitory concentration (MIC) and very poor correlations with peak/MIC and 24-hour area under the curve/MIC values [2]. The article by Roberts et al in this issue of Clinical Infectious Diseases [3] has defined antibiotic levels in intensive care unit patients (the DALI study) by measuring plasma or serum levels at 50% and 100% of the dosing interval for 8 different β-lactam antibiotics. This was an international study involving 68 hospitals with a total of 361 patients, of whom 248 had infection. Fifty-five percent of the patients received penicillins, 38% received carbapenems, and 17% received cephalosporins. These authors looked at a variety of different pharmacokinetic/pharmacodynamic (PK/PD) magnitudes: free drug $T_{\geq \text{MIC}}$ for 50% and 100% of the dosing interval and >4 times the MIC for 50% and 100% of the dosing interval. These are reasonable parameters as maximum killing by β-lactams occurs at concentrations approximately 4–5 times the MIC, and maintaining maximum killing for the entire dosing interval could possibly shorten the duration of the infection.

The authors limited most of their evaluation to the infected patients. Unfortunately, only 73% of the patients had an organism recovered and only 34% of those had a MIC determined. This was appropriately listed as a limitation of the study. For those without a MIC, they used the susceptible breakpoint for that organism and β-lactam antibiotic combination recorded by the European Committee on Antimicrobial Susceptibility Testing (EUCAST). For those patients without an organism, they used the highest EUCAST breakpoint for the administered drug among all potential pathogens. Their argument for this maneuver was that empiric dose selection is usually based on a worst-case scenario. Another mentioned limitation of the study by the authors was that they did not assess the PK/PD of concomitant antibiotics that were used in 62% of infected patients receiving combination therapy. Nevertheless, they did observe that 16% of infected patients did not achieve 50% free drug $T_{\geq \text{MIC}}$, which was associated with a significant reduction in clinical outcome.

Roberts and colleague also used logistic regression to examine the relationship of the probability of a positive clinical outcome with the magnitude of the drug concentration to MIC ratio at both higher and lower sickness levels. Although a significant relationship was observed using both the 50% and 100% dosing interval concentrations, only the results with the 50% values are shown in graphic form (Figure 3A and 3B) [3]. In the patients with a lower severity of illness, the magnitude of the concentration to MIC ratio rose from about 0 to 32–40 and the probability of cure increased from 60% to 90%. As stated earlier, 55% of the patients received penicillins, but these drugs accounted for about 85% of the failures to reach 50% free drug $T_{\geq \text{MIC}}$. As Escherichia coli and Pseudomonas aeruginosa were the most common organisms recovered, these organisms have EUCAST susceptibility breakpoints of 8 mg/L for amoxicillin-clavulanate and ampicillin (E. coli only) and 16 mg/L for piperacillin-tazobactam (E. coli and P. aeruginosa). If you multiply these MIC values by 32–40, you end up with drug concentrations (256–640 mg/L) that were very rarely achieved in this study (see Figure 1A) [3]. Because only 25% of the patients had determined MICs, the use of these
high values for estimating the MIC puts almost all of the penicillin data on the left side of the graph with lower concentration to MIC ratios and lower outcomes. If we had actual MICs on most of the organisms, some of the data with lower MICs would have higher concentration to MIC ratios and move some of the data to the right side of the graph, which could eliminate the significant correlation the authors observed.

Although I am concerned that the relationship shown in Figure 3 could be due to a lack of actual MIC data, other possibilities need to be considered. A concentration to MIC ratio of 32–40 at 50% of the dosing interval would imply that concentrations would still be above the MIC at 100% of the dosing interval. This goal was actually obtained in only 60% of their patients. Because pneumonia was the major site of infection in these studies, there is increasing data for β-lactams that the ratio of epithelial lining fluid concentration to plasma is <1 [4]. Higher serum or plasma concentrations may be required for adequate drug penetration of β-lactams into epithelial lining fluid. Last, high concentrations may be required for tissue penetration in patients with shock or hypotension [5].

This study is not alone in failing to identify the actual MIC of pathogens in clinical studies. This was a problem in 2 of the major studies showing a clinical benefit of extended infusions of piperacillin/tazobactam and cefepime in patients with P. aeruginosa bacteremia and pneumonia [6, 7]. All the investigators knew was that the MIC was ≤16 mg/L for piperacillin-tazobactam and ≤ 8 mg/L for cefepime. Proper evaluation of the importance of the magnitude of the concentration to MIC ratio at 50% and 100% of the dosing interval not only needs drug concentration measurements but also more precise MICs. It would greatly help all clinical studies on the magnitude of PK/PD indices required for efficacy if commercial antibiotic susceptibility companies would add several different concentrations of major drugs to their panels for drugs used to treat severe infections. For β-lactams, the availability of commercial or locally validated assay results within 24 hours would also enhance timely therapeutic drug monitoring to determine whether doses are too high or not high enough [8]. This would all allow for more personalized antibiotic dosing as recommended by Roberts and his DALI coauthors [3].

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**References**