Pharmacodynamic Approaches to Optimizing Beta-Lactam Therapy

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- Beta-lactam • Pharmacodynamics • Prolonged infusion
- Continuous infusion

As a class, beta-lactam antibiotics have been a mainstay of therapy since the inception of penicillin approximately 60 years ago. Today, clinical practice guidelines for nearly all infection sites recommend the use of beta lactams, often as first-line therapy.[1–3] Given their popularity and favorable safety profile, it is no wonder that there has been considerable interest in developing strategies to most effectively use beta-lactam therapy. Dating back to those first days of penicillin, it was noted that there was an observed benefit to prolonging the infusion time or dosing more frequently.[4,5] Since that time, considerable research has been performed to help understand and justify these dosing strategies. This article discusses the pharmacology behind these dosing strategies and presents some of the contemporary literature describing the perceived and observed clinical benefits.

BETA-LACTAM PHARMACODYNAMICS

The potency of antimicrobials is determined in vitro by the lowest antibiotic concentration required to inhibit visual growth of the test organism (minimum inhibitory concentration [MIC]) and the interpretation of these values is straight forward; the lower the MIC the more potent the compound. How this in vitro potency translates to in vivo efficacy is exceedingly more complex and is described using pharmacodynamics. Simply put, the pharmacodynamics of antimicrobials describes the relationship between the shape of the concentration-time curve and the efficacy of the compound as a function of the MIC. The 3 recognized pharmacodynamic parameters are the ratio of the area under the free drug concentration-time profile and the MIC (*f*AUC/MIC), the ratio of the

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maximal free drug concentration and the MIC (fC_{max}/MIC), and the percentage of the dosing interval that free drug concentrations remain above the MIC (*f*T>MIC).[6] For each class of antimicrobials, one or more of these pharmacodynamic relationships are indefinable as predictive of in vivo efficacy. For the beta lactams, a clear relationship has been noted between *f*T>MIC and antimicrobial activity using in vitro and in vivo models of infection, as well as clinical data. As such, optimization of beta-lactam therapy rests solely on the ability to maximize the *f*T>MIC.

In designing dosing regimens aimed at optimizing beta-lactam therapy, it is important to understand what targets (*f*T>MIC) are required to maximize antibacterial activity. Generally speaking, these data are derived from animal models of infection and differ slightly between classes of beta lactams. From these animal-based studies, it is recognized that the *f*T>MIC required for stasis (ie, no bacterial growth or killing) is 20% for carbapenems, 30% for penicillins, and 40% for cephalosporins against gram-negative organisms. Similarly, maximal efficacy, often denoted as an approximate 2-log decrease in colony forming units, requires a *f*T>MIC of 40% for carbapenems, 50% for penicillins, and 50% to 70% for cephalosporins.[7,8]

In clinical practice, the efficacy of a given compound is dependent on several variables often not well represented or inherently controlled for within animal models or in vitro studies. Examples of these variables include patient comorbid conditions (ie, peripheral vascular disease, renal function, obesity, and so forth), severity of illness, site of infection, host immune status, and nondrug interventions (ie, surgical intervention, intravenous line removal, and so forth). Despite these potential confounders, clinical studies evaluating *f*T>MIC targets for beta lactams have found values remarkably similar to animal models. Two studies recently conducted by the authors' group evaluating microbiological response to meropenem[9] and cefepime[10] in hospitalized subjects, the authors noted that *f*T>MIC of 54% and 66% were required for predictable response, respectively. Similarly, a study evaluating several antibiotics for the treatment of otitis media in children found a *f*T>MIC of 40% to 50% was required to achieve cure rates of 80% to 85% for penicillins[11] and another study evaluating middle ear fluid concentrations of cefprozil found that the poor clinical outcomes associated with MICs greater than 1 μg/mL coincided with a lack of pharmacodynamic target attainment in the middle ear fluid.[12] Given the deficiency of clinical pharmacodynamic studies and the known correlation between clinical and animal-derived data, most investigators and clinicians rely on animal-derived targets to guide therapeutic decisions.

OPTIMAL DOSING STRATEGIES

When considering the outcome of treating patients for infection there are 3 factors involved: the patient, the pathogen, and the drug.[13] Within this triad, the only modifiable factor is the drug itself, allowing manipulation of both antibiotic selection and dosing regimen. With respect to the dosing regimen, there are 3 ways to alter the shape of the concentration time profile: changes to dose, dosing interval, and infusion time (**Fig. 1**). Of these methods, alterations to dose offer the least benefit in changing *f*T>MIC, the parameter of interest for beta lactams. For example, at an MIC of 32 μg/mL, increasing the dose of piperacillin-tazobactam from 3.375 g (30-minute infusion) to 4.5 g (30-minute infusion) in the median patient as derived from a recent population kinetic model[14] results in a minimal increase in *f*T>MIC (see **Fig. 1**A, B). However, decreasing the dosing interval (see **Fig. 1**C) or increasing the length of infusion (see **Fig. 1**D) can have considerable impacts on *f*T>MIC, thereby optimizing therapy. These differences are even more profound when one considers the variability around these pharmacokinetic parameters through mathematics.[14,15] It should be noted that