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Antibiotics Development and the Emergence of Resistance: Clinical Pharmacology to the Rescue

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Rapidly emerging resistance to currently available antibiotics is a major public health crisis. Increasing morbidity and mortality associated with drug-resistant infections create a major social and economic burden to the United States. Antimicrobial development is not keeping pace with the emergence of resistance, as most of the currently available antibiotics were approved a decade or more ago.[1,2] More worrisome is that the majority of these drugs were approved without establishing appropriate pharmacokinetic/pharmacodynamic (PK/PD) relationships for dynamic antimicrobial effects at the site of action in the relevant patient populations. This includes drugs such as colistin, which is a decades-old drug that fell out of use due to toxicity but is again being considered as a treatment option in desperate clinical situations. Lack of PK/PD-guided dose selection may ultimately result in dosing regimens for many of the approved antimicrobials that are not optimal for the intended populations and types of infections. This lack of PK/PD data for antimicrobials is likely a major contributing factor behind the failure of some current antimicrobial therapies against the so-called "superbugs" and the phenomenon of emerging resistance.

Conventionally, selection of antimicrobials and their dose has been based on a static in vitro parameter, the minimum inhibitory concentration (MIC), possibly combined with PK exposure information using static PK/PD indices. These static indices include the time that concentrations remain above the MIC as a percentage of the dosing interval, the maximal concentration–to-MIC ratio (C_{max}/MIC), or area under the concentration-time curve–to-MIC ratio. Unfortunately, in vivo, the infective bacteria are not exposed to a static antibacterial concentration but rather to constantly changing (dynamic) concentrations with peaks and troughs—a fact not taken into account by the MIC, which is a single static concentration. Additionally, dynamic concentration/effect data are needed to provide information regarding time-dependent aspects of the pharmacology of the drug under study, such as information on the postantibiotic effect or information on the development of resistance through selective pressure. Finally, using static PK/PD indices may be misleading, as selection of the optimal PK/PD index for a given compound is not always straightforward. Even once a target is selected, numerous dosing regimens can often achieve the same target, many of which could be suboptimal and could lead to the development of resistance.

The aim of antimicrobial dose regimen selection should not only be to effectively kill the bacteria but also to prevent selection of resistant strains. Only when both aims are met is the optimal therapeutic benefit of the compound likely to be realized. Certainly, 1 cautionary tale may be derived from the quinolones, as 99% killing can be obtained by quinolones such as ciprofloxacin at a low C_{max}/MIC ratio of 3. However, rapid bacterial regrowth and development of bacterial resistance may also develop at a C_{max}/MIC ratio of

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3. This development of resistance is not seen at a C_{max}/MIC ratio >8.[3]

In addition to dynamic PK/PD characterization, free concentrations at the site of infection, which are ultimately responsible for the desired clinical effect, are often not considered during dose optimization. For ciprofloxacin, C_{max}/MIC ratios of 20 in peripheral blood (serum) translate to a C_{max}/MIC ratio of only 6 at the site of action (the interstitial space fluid), which actually falls within the mutant selection window. Prediction of bacterial eradication and antibiotic dosing regimen based solely on serum concentrations may thus be misleading, as C_{max}/MIC ratios may differ significantly between the serum and tissue compartments. Finally, more recent research has demonstrated the need to study the PK of the antimicrobial agent in the relevant patient population. As an example, suboptimal efficacy may be observed in critically ill patients due to augmented renal clearance.[4] The key to the optimization of the dosing regimen for a given antibiotic is integration of the antimicrobial PK in the relevant patient populations (considering factors such as protein binding and tissue distribution) and the PD (both in vitro and in vivo). However, for most of the current antimicrobials, this PK/PD knowledge integration is missing or incomplete.

The risks and consequences of incomplete characterization of PK/PD relationships may be illustrated by considering 2 examples, daptomycin and GSK1322322. For daptomycin, initial clinical development was suspended after observation of adverse events in the musculoskeletal system in a phase 2 study.[5] However, these observations were made following twice-a-day dosing. A different company continued development of the compound with once-daily dosing after a nonclinical toxicity study in dogs demonstrated that once-daily dosing decreased musculoskeletal findings compared to 3 times a day dosing. One could argue that the original developer might have continued the development of daptomycin with a better understanding of the relationship between the PK/PD of the compound and the dosing interval as it relates to both safety and efficacy.

The second example is GSK1322322. This compound had lower clinical success rates than linezolid (standard of care) in a phase 2 trial in skin and skin structure infections, with response rates of 67% and 89%, respectively.[6] After this clinical trial, in vitro work was performed focusing on resistance. A high frequency of resistance was observed in *S aureus*.[7] In the clinical study, of the patients who had the infecting pathogens identified, nearly half had resistance develop to GSK1322322. One might speculate that if the in vitro resistance work had been done first, further clinical development work might have been halted, thus saving the company the cost of a failed clinical trial. At the very least, the clinical study might have been designed differently.

What Needs to Be Done and by Whom

First and foremost, action is needed from regulators. Understanding the PK/PD of new antibiotics at the site of action in the relevant patient populations is essential to determine the optimal dosing regimen and to avoid resistance development. Drug regulators must embrace these techniques and require that the pharmaceutical industry provide these data for all new antimicrobial submissions. For the pharmaceutical industry, these techniques may actually decrease the cost of antimicrobial drug development programs because they may greatly reduce the risk of failed phase 3 trials. During the initial phase of development, the determination of free/active drug at the target site (using techniques such as microdialysis) in the relevant patient populations will help with dose optimization for antimicrobial drug development. In addition, instead of focusing on MIC-based measures, integration of in vitro and in vivo data should be done utilizing time-kill curves. Although time-kill curves initially appear more labor-intensive, characterization of dynamic pharmacological processes and the ability to simulate virtually any dosing regimen clearly justify the extra burden. Any additional costs associated with using these techniques will be dwarfed by the costs of a failed phase 3 program, especially given the current dire situation of resistance development and increased risk of antimicrobial failures. Finally, it should be noted that although the focus of this article is on antimicrobials, these techniques may also be used in antiviral and antifungal development.

Secondly, national clinical societies such as the Infectious Diseases Society of America and the Society of Infectious Disease Pharmacists as well as clinical pharmacology societies worldwide, such as the American College of Clinical Pharmacology, should take charge of educating drug developers, regulators, and prescribers about the advantages of embracing these techniques through their educational programs, annual meetings, and scientific publications. In turn, regulators need to provide a development framework for antimicrobials that makes the use of these techniques worth the time and effort. The challenge with antimicrobial development is that the costs associated with their development are the same as for many other therapeutic areas; however, antimicrobials are only taken short-term as acute therapy. Changes must be made in the development paradigm for antimicrobials in order to make these drugs profitable to develop. It is the opinion of the American College of Clinical Pharmacology that PK/PD-guided dose selection as well as modeling

and simulation techniques will be a big part of those changes.

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