



Pharmacodynamics of New Antimicrobials

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Pharmacokinetic/pharmacodynamic (PK/PD) relationships of antimicrobials have been established for most classes of drugs. The two major indices describing these relationships are the time the concentration of the antimicrobial remains above the MIC ($T_{>MIC}$) as a fraction of the dosing interval and the area under the time concentration curve over 24 hours divided by the MIC (AUC/MIC ratio). The Peak/MIC ratio correlates with effect for a number of drugs, but in many, if not all, cases the effect can not be clearly distinguished from the AUC/MIC effect. Importantly, for virtually all antimicrobials, it is the free non-protein bound fraction of the drug that best correlates with efficacy, and is of particular significance when drugs are compared with each other within a class and/or across species, including men.

For new drugs, two situations can be distinguished : either the drug is of a known, established class of drugs (e.g. cephalosporins or fluoroquinolones) or the drug belongs to a new class of drugs. In the first case, the PK/PD relationships for the class are generally identified, both with respect to the index itself as well as to the magnitude needed for a static effect or other effect parameters. Studies *in vitro* and in animals will confirm these relationships, and taking into account the degree of protein binding in animals and men, the efficacy of the antimicrobial can be reasonably well predicted. An example is BAL9141, a cephalosporin active against MRSA, currently in development. $T_{>MIC}$ appears to be the PK/PD index correlating best with efficacy, and using these relationships as well as Monte Carlo Simulations, dosing regimens were suggested to use in 2nd and 3rd phase trials.

If the drug belongs to a new class, PK/PD relationships are generally less obvious. Translating PK/PD relationships from experimental data to men may prove to be difficult if there is only one drug in the class. Results from experiments in animal models may provide the PK/PD index best correlating with efficacy and the magnitude of the index needed to obtain a static effect or maximum effect. Daptomycin is an example. AUC/MIC appears to be index best correlating with efficacy and the AUC/MIC value (total drug) needed for static effect in various animal studies varies from 180 to over 500 for staphylococci. The dosing regimen of 4 mg/kg in men as currently suggested should be aimed at those values. However, in other cases it may be more difficult to evaluate PK/PD relationships. If there is only one drug in the class, the effect of proteinbinding for instance may not be readily determined, and if the volume of distribution is large as well, thorough investigations are needed. Tigecyclin is an example. This drug, from the newly establish class of glycylcyclines has a very high volume of distribution, and only a few studies correlating the PK/PD index with efficacy exist. AUC/MIC seems to correlate best with efficacy for this drug, but further studies are clearly needed.