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Applying PK/PD – will it help against resistance?

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Antimicrobial pharmacokinetics and pharmacodynamics (PK/PD) have proven to be extraordinarily valuable tools in developing our understanding of optimum antimicrobial dosing. We can now recognise three patterns of activity, leading to three different PK/PD parameters that predict efficacy in vivo (Table).

In vitro killing effect	Persistent Effects	PK/PD Parameter Predicting Efficacy	Agents
1. Time-dependent	Minimal or None	Time above MIC	All β -lactams
2. Time-dependent	Moderate to Prolonged	AUC/MIC ratio	Macrolides & Azalides Lincosamides Glycopeptides Tetracyclines Streptogramins Oxazolidinones
3. Concentration-dependent	Moderate to Prolonged	AUC/MIC ratio or Peak/MIC ratio	Aminoglycosides Quinolones Ketolides Daptomycin Nitroimidazoles

Knowledge of the PK/PD parameter that predicts efficacy has led to a range of changes in dosing schedules for older agents. For drugs where the predictive parameter is AUC/MIC the dosing regimen should be designed as "higher doses less frequently". This has been widely applied to the dosing of aminoglycosides, and once-daily dosing using the same total daily doses as were given with intermittent dosing is now standard for most clinical indications. For those agents where Time above MIC is the best predictor of efficacy, the concept of "lower doses more frequently" applies, although there are obviously limitations with intermittent dosing. However, the continuous infusion of β -lactams has found a role in some serious infections and in outpatient intravenous therapy.

It is likely that dosing regimens play a role in how resistance is selected, which in turn leads to the possibility that PK/PD concepts could be extended from predicting efficacy to designing dosing regimens that might reduce or eliminate the risk of resistance selection. PK/PD dose optimisation could do this in a number of ways including:

1. Optimising bacterial eradication rates and permitting shorter courses, thereby reducing drug exposure and the time-dependent risk of becoming colonised with resistant pathogens
2. Preventing the emergence of (mutational) resistance during treatment, where this is known to occur
3. Determining regimens that minimise the risk of transfer of resistance between species
4. Determining regimens that minimise the risk of amplification of important resistant pathogens in normal flora

At present our understanding of the role of PK/PD in preventing resistance comes almost exclusively from studies directed at preventing the emergence of resistance during treatment. The bulk of studies have been directed at *Pseudomonas aeruginosa*, and the drug classes that have been the focus of attention include the aminoglycosides and the fluoroquinolones. The first major step towards understanding resistance selection during treatment came in 1982 from an animal model study of the effects of gentamicin and ticarcillin on *P. aeruginosa*. The researchers found that aminoglycoside resistant variants that could be detected by population analysis profiling could be selected rapidly over 24-48 hours of treatment with gentamicin, and subsequently showed that

this could be prevented with co-administration of ticarcillin. Subsequently other investigators using an in vitro pharmacodynamic model were able to show the same resistance selection potential against *P. aeruginosa* with netilmicin and the quinolone enoxacin. Overall the evidence suggests that the best method of suppressing resistance selection with aminoglycosides when used alone is to ensure high peak concentrations.

While they are not such a large proportion of the base population as aminoglycoside-resistant subpopulations, fluoroquinolone resistant subpopulations are also found in *P. aeruginosa*. Indeed, given a sufficient inoculum, fluoroquinolone-resistant subpopulations can be detected in many pathogens. As a consequence, the concept of the mutant prevention concentration has been developed and popularised into the broader concept of a mutant selection window, a range of concentration where resistance selection is likely, and above and below which resistance selection is unlikely. However, these concepts are based on in vitro static concentrations, and cannot be used directly to predict dosing regimens that will protect against resistance. Recent animal model studies have been focussed on the existence of an equivalent PK/PD window. For instance, it has been shown that lower exposures (AUCs) select for resistance to levofloxacin in *P. aeruginosa* in the mouse thigh than higher exposures where resistance can be totally suppressed. The resistance selected was due to up-regulation of efflux pumps, especially MexCD-OprJ, and not to *gyrA* or *parC* mutants. There are some clinical data from patients with ventilator-associated pneumonia treated with ciprofloxacin that support the need for a minimum exposure (AUC/MIC ratio) to prevent resistance emerging during treatment. The preferred method for preventing resistance emergence to fluoroquinolones in *P. aeruginosa*, however, is to combine with an antibacterial from another class, as has been shown in a retrospective analysis of pneumonia patients.

The presence of an in vivo “mutant selection window” for levofloxacin has also been shown for *Staphylococcus aureus* in an animal model. Further, there has been recent work in an in vitro model to show a possible relationship between low exposures to vancomycin and the emergence of resistance.

Overall, it needs to be remembered that the current evidence for the role of PK/PD in preventing resistance selection is restricted to a narrow range of specific antibacterial classes and bacterial species where resistance selection during treatment is a significant and frequent problem. Nevertheless, it highlights the need for understanding the interaction of antibacterials with organisms beyond the MIC, and in particular examining for the presence of resistant subpopulations in otherwise “susceptible” bacteria.