Alexander A. Vinks · Hartmut Derendorf
Johan W. Mouton *Editors*

Fundamentals of Antimicrobial Pharmacokinetics and Pharmacodynamics

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Part I
Basic Concepts and Principles

Chapter 1
Introduction to Pharmacodynamics

William A. Craig

Abstract Since the early appreciation of differences in the time course of antimicrobial activity, much has been learned about the pharmacodynamics of antimicrobials. Specific PK/PD indices have been identified which are of major importance for efficacy and for the prevention of the emergence of resistance. Of major importance, the magnitudes of these PK/PD indices for efficacy have been shown to be very similar in animal infection models and human infections. Modeling has also identified that there are few differences in the index magnitude with different dosing intervals, among drugs within the same antimicrobial class (providing free drug concentrations are used), with different infection sites (except occasionally for pneumonia), and among susceptible and resistant strains of the same type of bacteria. Addition studies have shown that the magnitude of indices can increase significantly with a higher inoculum for *S. aureus* and that neutrophils have a minor enhancing effect on antimicrobial activity against Enterobacteriaceae but a more variable enhancing effect on activity against *S. pneumonia* for different antimicrobials. Pharmacodynamic modeling has many applications including establishing new optimal dosing regimens, developing new antimicrobials and formulations, determining susceptibility breakpoints, providing guidelines for empiric therapy, and formulary development.

Keywords Pharmacodynamics • Modeling • PK/PD indices • Protein binding • Animal models • Neutrophil activity • Inoculum size • Susceptibility testing

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Introduction

Antimicrobial pharmacodynamics deals with the relationship between measures of drug exposure and the efficacy and toxicity of antimicrobial agents. Since the early days of penicillin, researchers have been interested in determining which pharmacokinetic parameter is most important in determining microbiologic and clinical efficacy. For example, bacterial killing of staphylococci by penicillin was much different than by streptomycin (Garrod 1948). The rate of killing by penicillin was not dependent on the height of the drug concentration, while streptomycin demonstrated enhanced killing at higher concentrations. Studies in mice-infection models suggested that the duration of drug exposure was the most important parameter determining in vivo therapeutic efficacy of penicillin (Eagle et al. 1950). Interest in antimicrobial pharmacodynamics increased in the 1960s and 1970s when infections due to *Pseudomonas aeruginosa* with high MICs to multiple drugs appeared with increasing frequency (Rolinson 1973). This interest in antimicrobial pharmacodynamics has been further enhanced by the emergence of antimicrobial resistance to many drugs during the last 15–20 years.

Time Course of Antimicrobial Activity

A major determinant of the time course of antimicrobial activity is whether the drug exhibits bactericidal activity and whether the killing is enhanced by increasing concentrations or by longer exposure times. The second major determinant is whether the drug exhibits persistent inhibition of growth that lasts after the drug exposure. There are numerous in vitro persistent effects described in the literature that usually act together in the in vivo situation. The in vitro postantibiotic effect (PAE) describes the extent of continuing retardation in organism growth when the drug is suddenly removed by repeated washing, dilution, filtration, or inactivation (McDonald et al. 1977; Bundtzen et al. 1981). The postantibiotic sub-MIC effect (PA-SME) identifies additional prolongation in regrowth that results from sub-MIC drug concentrations (Cars and Odenholt-Tornqvist 1993). The postantibiotic leukocyte enhancement (PALE) identifies growth retardation that occurs when organisms in the postantibiotic state of growth are exposed to leukocytes (McDonald et al. 1981).

As stated above, these various in vitro persistent effects act together in describing the in vivo activity of antimicrobials. By injecting penicillinase intravenously in neutropenic mice when drug levels of piperacillin or aspoxicillin were expected to drop below the MIC, Oshida et al. (1990) were able to show that sub-MIC concentrations accounted for a little less than half of the 3.3 and 5.2 h in vivo postantibiotic effect observed with both drugs, respectively, against *Staphylococcus aureus*. Increasing the dose (and AUC) of amikacin sixfold increased the duration of the in vivo postantibiotic effect with *Klebsiella pneumoniae* in neutropenic mice from 3.4 to 7.4 h, while the duration of sub-MIC values was less than an hour and virtually the same for both doses (Craig et al. 1991). However, prolonging the half-life of

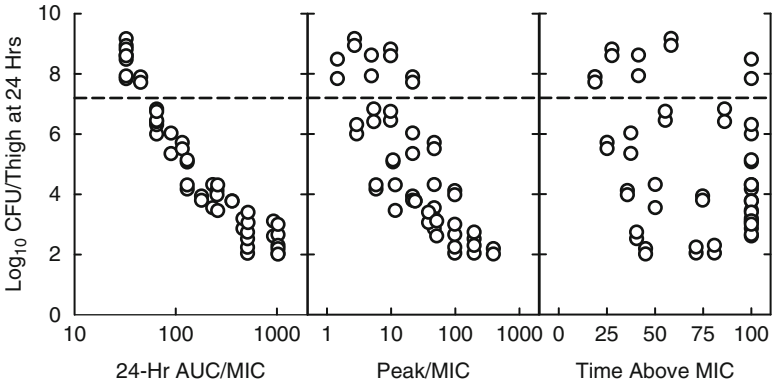

Fig. 1.1 Relationship between three PK/PD indices for total drug of levofloxacin and the $\log_{10}$ CFU/thigh at 24 h for *Streptococcus pneumoniae* ATCC 10813 in the thighs of neutropenic mice. Reproduced with permission from Andes and Craig (2002)

amikacin from 18 to 110 min by inducing renal impairment also enhanced the AUC about sixfold, but the longer duration of sub-MIC concentrations increased the in vivo postantibiotic effect from 7.4 to 12.2 h. The role of leukocytes on the in vivo PAE has also been assessed. Studies with similar doses of gentamicin against the same strain of *K. pneumoniae* have reported in vivo PAEs of 7.8, 12.0, and 16.5 h in neutropenic, normal, and granulocytic mice, respectively (Shimizu et al. 1989).

Patterns of Antimicrobial Activity

Three major patterns of antimicrobial activity have been observed. The first applies to antimicrobials with concentration-dependent killing along with prolonged persistent effects. This pattern is observed with aminoglycosides, fluoroquinolones, polymyxins, daptomycin, and some of the new glycopeptides, such as telavancin and oritavancin, which also exhibit an additional membrane effect mechanism of action. One would predict that the ratio of the AUC and peak concentration to the MIC would be the primary PK/PD indices correlating with antimicrobial efficacy. Done-fractionation studies in animal models of infection in which five or six total doses are divided into many smaller doses given at different dosing frequencies have been useful in reducing the interdependence among the PK/PD indices and confirming which PK/PD index is most important for efficacy. The relationship of all the PK/PD indices based on total drug concentrations (protein binding in mice 15 %) to efficacy of levofloxacin against *Streptococcus pneumoniae* in the thighs of neutropenic mice are shown in Fig. 1.1 (Andes and Craig 2002). The 24-h AUC/MIC showed the best correlation for efficacy followed by the peak/MIC ratio. The time above MIC looked more like a scattergram.

The second pattern of antimicrobial activity is the exact opposite of the first pattern with concentration-independent killing and no or very short persistent effects. This pattern is characteristic of all of the ß-lactam antibiotics, such as penicillins,

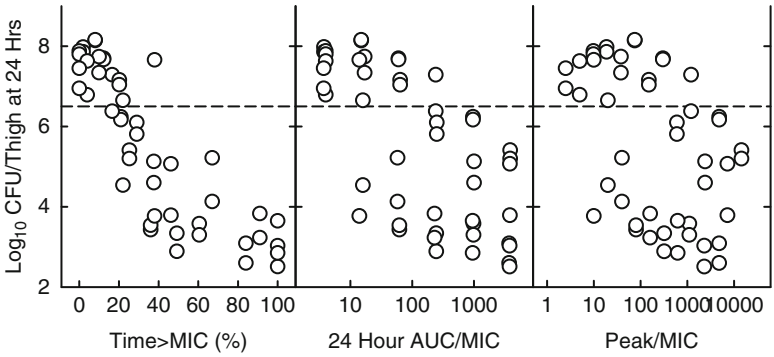

Fig. 1.2 Relationship between three PK/PD indices for total drug of imipenem and the $\log_{10}$ CFU/thigh over 24 h for *Pseudomonas aeruginosa* ATCC 27853 in the thighs of neutropenic mice

cephalosporins, carbapenems, and monobactams. With this pattern, one would predict that the duration of time that active antibiotic concentrations exceeded the MIC would be the important PK/PD index for efficacy. Figure 1.2 demonstrates the relationships among the various PK/PD indices for total drug concentration of imipenem, a carbapenem ß-lactam antibiotic with protein binding <5 % in mice, against a standard strain of *Pseudomonas aeruginosa* in the thighs of neutropenic mice. The percentage of the dosing interval that concentrations exceeded the MIC showed the best correlation with organism growth and killing, while the relationships with AUC/MIC and peak/MIC looked more like scattergrams.

The third pattern of antimicrobial activity also exhibits concentration-independent killing but these antimicrobials induce prolonged persistent effects. This pattern is observed with a large number of antimicrobials including the tetracyclines, tigecycline, macrolides, azithromycin, clindamycin, linezolid and other oxazolidinones, chloramphenicol, trimethoprim, sulfonamides, vancomycin, and dalbavancin. Because the prolonged persistent effects will protect against regrowth when active drug concentration fall below the MIC, one would predict that the amount of drug or the AUC/MIC would be the important PK/PD index for these drugs. Figure 1.3 illustrates that relationship between the change in efficacy from the start of therapy and the various PK/PD indices based on total drug concentrations for vancomycin (protein binding 13 % in mice) (Rybak 2006). The best correlation for efficacy was seen with 24-h AUC/MIC index. Peak/MIC and time above MIC showed much more variation in efficacy at different magnitudes of the index.

Magnitude of Index Required for Efficacy

Once the important PK/PD index driving efficacy is identified, the next piece of information needed is what magnitude of the index is required for antimicrobial efficacy. A large number of animal studies on the efficacy of ß-lactams against