Handbook of

Pharmacokinetic/ Pharmacodynamic Correlation

Edited by

Harmut Derendorf, Ph. D.
Günter Hochhaus, Ph.D.

University of Florida
Gainesville, Florida

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Chapter 2

PHARMACOKINETIC-PHARMACODYNAMIC MODELING OF IRREVERSIBLE DRUG EFFECTS

Steven C. Ebert

INTRODUCTION

The mathematical relationship between drug concentration and response generally assumes drug binding to a given population of receptors. Greater occupation of these receptors will result in a greater effect, and vice versa. The variability in receptor affinity accounts for the nonlinear relationship between concentration and effect.

Most research involved in the characterization of pharmacodynamic variables has been done with drugs exhibiting reversible effects. With reversible drug effects, the number and drug affinity of receptors remain relatively constant, allowing reproducible effects with repeated drug exposures. In certain instances, sensitization or tolerance to the drug effect may occur.

In contrast, the goal of antimicrobial therapy is to eliminate the very target at which the drug is directed, i.e., the "receptors" are actually the pathogenic organisms. The desired effect of drug therapy, the death of pathogens, is therefore irreversible. The replication of organisms, with subsequent replenishment of the "receptor" number may occur, however, and result in an apparently reversible effect as measured by the total number of organisms. In this system, the development of tolerance or frank resistance of the remaining "receptors" is more likely to occur, since the most susceptible organisms are killed. Therefore, it would be expected that sustained exposure to an antimicrobial would result in a gradually diminishing effect over time, unless a sufficient drug-free period exists to enable the organism population to fully recover its susceptibility.

Figure 1 shows the relationship between pharmacokinetic variables, pharmacodynamic measures of antimicrobial activity, and drug effect. Intuitively, increasing the dose of an antimicrobial should increase its effect. By understanding the pharmacodynamic features of a given class of antimicrobials, one may, however, be able to further enhance outcome by modifying dosing parameters other than dose size, e.g., dosing frequency. The pharmacodynamic properties of antimicrobials may be estimated *ex vivo*, whereas for other drug classes, response must be estimated *in vivo*. This chapter will address the pharmacokinetic and pharmacodynamic properties of antimicrobials which influence drug response, will characterize drug effects, and will then examine techniques that have been used to link these phenomena.

PHARMACOKINETIC VARIABLES

The pharmacokinetic variables of a drug determine the time course of drug concentration in serum and, ultimately, at the site of infection. Two different categories of pharmacokinetic variables exist. Some pharmacokinetic variables may be altered by adjusting the dosing regimen, whereas others result from the chemical properties of a particular drug, and are minimally influenced by dosing regimen. In the clinical setting, modification of regimen-dependent variables is the goal of pharmacokinetic therapeutic drug monitoring, in order to achieve the desired concentration profile.[2-4]

REGIMEN-DEPENDENT VARIABLES

Most antimicrobials are administered intermittently, i.e., a given total daily dose is divided and the fractions given at fixed intervals. The three pharmacokinetic variables that may be used to

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