Textbook of Therapeutics

Drug and Disease Management

EIGHTH EDITION

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Clinical Pharmacodynamics and Pharmacokinetics

1

Bernd Meibohm and William E. Evans

In applied pharmacotherapy, usage of medications is adjusted to the individual need of the patient to maximize efficacy and safety, i.e., to achieve the maximum therapeutic response with a minimum likelihood of adverse events. The rational use of drugs and the design of effective dosage regimens are facilitated by the appreciation of the relationships among the administered dose of a drug, the resulting drug concentrations in various body fluids and tissues, and the intensity of pharmacologic effects caused by these concentrations. These relationships and thus the dose of a drug required to achieve a certain effect are determined by the drug's pharmacokinetic and pharmacodynamic properties. Thus, pharmacokinetic (PK) and pharmacodynamic (PD) information form the scientific basis of modern pharmacotherapy.[1,2]

Pharmacokinetics describes the time course of the concentration of a drug in a body fluid, preferably plasma or blood that results from the administration of a certain dosage regimen. In simple terms, pharmacokinetics is "*what the body does to the drug.*" Pharmacodynamics describes the intensity of a drug effect in relation to its concentration in a body fluid, usually at the site of drug action. It can be simplified to "*what the drug does to the body.*"[3]

The plasma concentration-time profile resulting from drug administration is determined by pharmacokinetic parameters and the administered dosage regimen. While the pharmacokinetic parameters are characteristic for the disposition or handling of a drug in a specific patient and thus usually cannot be altered during pharmacotherapy, the dosage regimen is the clinician's tool to affect drug concentrations for maximum therapeutic benefit. For most drugs, therapeutic response and/or toxicity are related to free concentration of the drug at the site of action. However, drug often related to the observed effect under the assumption that the drug concentrations in the measured body fluid and at the site of action are in a constant relationship. Even though this assumption frequently is not accurate, it has proven to be a useful simplification that allows most drugs to achieve the desired effect levels via modulation of their plasma concentration, especially during prolonged pharmacotherapy with multiple dose regimens.

THERAPEUTIC RANGE

The relationship between dosage regimen and effects of a drug, also known as the dose–concentration–response relationship, or exposure–response relationship, is not identical for all patients. Biologic variability in pharmacokinetics and pharmacodynamics as well as their modification by physiologic, pathophysiologic, and environmental factors result in different effect intensities when the same dosage regimen of a drug is given to different patients. Thus, different patients may require different dosage regimens to achieve the same effect intensity. Factors that contribute to variability in the relationship between dose and effect intensity include age, weight, ethnicity and genetics, gender, disease type and severity, concomitant drug therapy, and environmental factors.

The variability in the relationship between dosage regimen and effect intensity is caused by pharmacokinetic variability, pharmacodynamic variability, or a combination of both. Knowledge about the variability in the plasma drug-concentration-effect relationship allows establishing a drug-specific *therapeutic range*. A therapeutic range is a range of drug concentrations within which the *probability* of desired clini-

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tween-patient pharmacodynamic variability with the therapeutic as well as toxic effects of a drug. It is important to note that the therapeutic range should not be considered in absolute terms as the limits for this probability range are oftentimes chosen arbitrarily. In addition, the therapeutic range is not well defined for a large fraction of the drugs that are used clinically.

The left panel in Figure 1.1 *(see color insert)* shows a drug concentration-effect relationship. The probability of achieving the desired response is very low when drug concentrations are less than 5 mg per L, as is the chance of observing toxicity. As drug concentrations increase from 5 to 20 mg per L, the probability of desired response increases significantly, while the probability of toxicity increases more slowly. One could select a therapeutic range of 10 to 20 mg per L, where the minimum probability of a therapeutic response is at least 50% and the probability of toxicity is less than 10%. An optimal dosage regimen can be defined as one that maintains the plasma concentration of the drug within the therapeutic range. The right panel in Figure 1.1 demonstrates this concept by comparing two dosage regimens. The dosing interval (time between doses; in this case 8 hours) is the same, but the discrete doses given in regimen B are twice as large as those given in regimen A. As shown, drug accumulates in the body during multiple dosing. Regimen A keeps the concentration-time profile within the therapeutic range, which will result in the majority of patients with adequate therapeutic efficacy with only rare occurrence of undesired toxicity. Regimen B will likely result in most patients with only a marginal increase in efficacy compared to regimen A, but with a much larger likelihood of undesired toxicity. It should, however, be stressed, that despite having plasma concentrations within the therapeutic range at all times, some of the patients treated with regimen A may not experience an adequate drug response or may experience drug-related toxicity.

CLINICAL PHARMACOKINETICS

The utility of pharmacokinetics does not lie in diagnosing the disease or selecting the "drug of choice," but in deciding the best way to administer a given drug to achieve its therapeutic objective. The manner in which a drug is taken is referred to as the *dosage regimen*. The dosage regimen tells us "how much" and "how often" a drug must be taken to achieve the desired result. It is these two questions (how much?, how often?) that form the basis for the discipline of pharmacokinetics.[4,5]

Clinical pharmacokinetics is the application of pharmacokinetic principles in a patient care setting for the design of optimum dosage regimens for the individual patient. Probably the most difficult aspect of clinical pharmacokinetics is understanding the full potential and practical limitations and pitfalls of using specific pharmacokinetic models of drug disposition to attain target concentrations based on only a limited number (usually 1–2) of drug concentration measurements. Although a good understanding of common pharmacokinetic concepts is crucial, the competent clinician will have knowledge of not only the mathematics of these concepts, but also the principles, assumptions, and potential errors underlying their application in a clinical setting. Furthermore, a broad therapeutic knowledge is also necessary because measured drug concentrations must be interpreted with respect to the patient's clinical condition and the pharmacodynamic profile of the therapeutic agent.

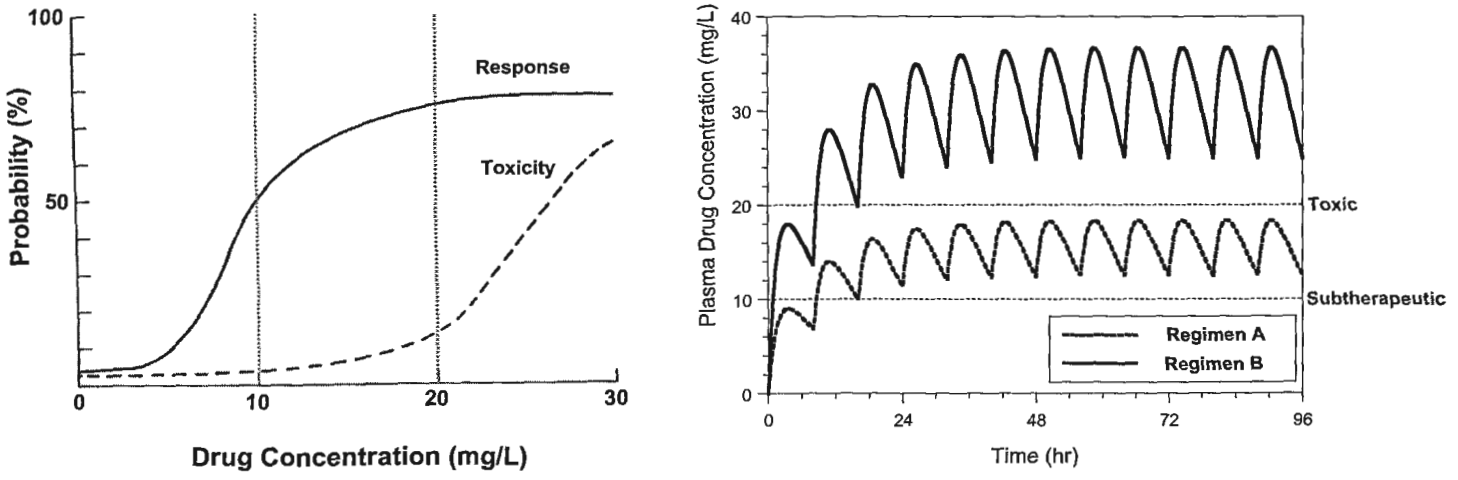

FIGURE 1.1 The concept of a therapeutic range. The **left panel** shows a relationship between the probability of achieving the desired response as well as the chance of observing toxicity in relation to drug concentration in plasma. A therapeutic range of 10 to 20 mg/L could be defined as a range of concentration with relatively high probability of a therapeutic response but low probability of drug-related toxicity. The **right panel** demonstrates the application of the therapeutic range concept in designing multiple dose regimens. In the concentration-time plot, regimen A keeps drug concentrations within the therapeutic range, whereas regimen B

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