# Concepts in Clinical Pharmacokinetics

## Fifth Edition


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LESSON

# 1

# Introduction to Pharmacokinetics and Pharmacodynamics

## OBJECTIVES

After completing Lesson 1, you should be able to:

1. Define and differentiate between *pharmacokinetics* and *clinical pharmacokinetics*.
2. Define *pharmacodynamics* and relate it to pharmacokinetics.
3. Describe the concept of the therapeutic concentration range.
4. Identify factors that cause interpatient variability in drug disposition and drug response.
5. Describe situations in which routine clinical pharmacokinetic monitoring would be advantageous.
6. List the assumptions made about drug distribution patterns in both one- and two-compartment models.
7. Represent graphically the typical natural log of plasma drug concentration versus time curve for a one-compartment model after an intravenous dose.

*Pharmacokinetics* is currently defined as the study of the time course of drug absorption, distribution, metabolism, and excretion. *Clinical pharmacokinetics* is the application of pharmacokinetic principles to the safe and effective therapeutic management of drugs in an individual patient.

Primary goals of clinical pharmacokinetics include enhancing efficacy and decreasing toxicity of a patient's drug therapy. The development of strong correlations between drug concentrations and their pharmacologic responses has enabled clinicians to apply pharmacokinetic principles to actual patient situations.

A drug's effect is often related to its concentration at the site of action, so it would be useful to monitor this concentration. Receptor sites of drugs are generally inaccessible to our observations or are widely distributed in the body, and therefore direct measurement of drug concentrations at these sites is not practical. For example, the receptor sites for digoxin are thought to be within the myocardium. Obviously we cannot directly sample drug concentration in this tissue. However, we can measure drug concentration in the blood or plasma, urine, saliva, and other easily sampled fluids (Figure 1-1). *Kinetic homogeneity* describes the predictable relationship between plasma drug concentration and concentration at the receptor site where a given drug produces its therapeutic effect (Figure 1-2). Changes in the plasma drug concentration reflect changes in drug concentrations at the receptor site, as well as in other tissues. As the concentration of drug in plasma increases, the concentration of drug in most tissues will increase proportionally.

Similarly, if the plasma concentration of a drug is decreasing, the concentration in tissues will also decrease. Figure 1-3 is a simplified plot of the drug concentration versus time profile after an intravenous drug dose and illustrates this concept.

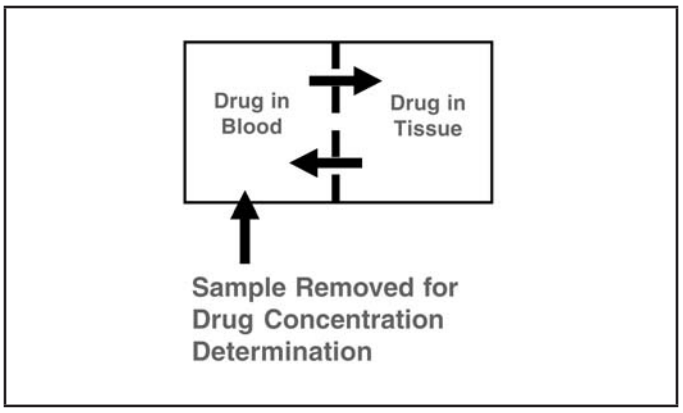


**FIGURE 1-1.**
Blood is the fluid most often sampled for drug concentration determination.

The property of kinetic homogeneity is important for the assumptions made in clinical pharmacokinetics. It is the foundation on which all therapeutic and toxic plasma drug concentrations are established. That is, when studying concentrations of a drug in plasma, we assume that these plasma concentrations directly relate to concentrations in tissues where the disease process is to be modified by the drug (e.g., the central nervous system in Parkinson's disease or bone in osteomyelitis). This assumption, however, may not be true for all drugs.

### CLINICAL CORRELATE

Drugs concentrate in some tissues because of physical or chemical properties. Examples include digoxin, which concentrates in the myocardium, and lipid-soluble drugs, such as benzodiazepines, which concentrate in fat.

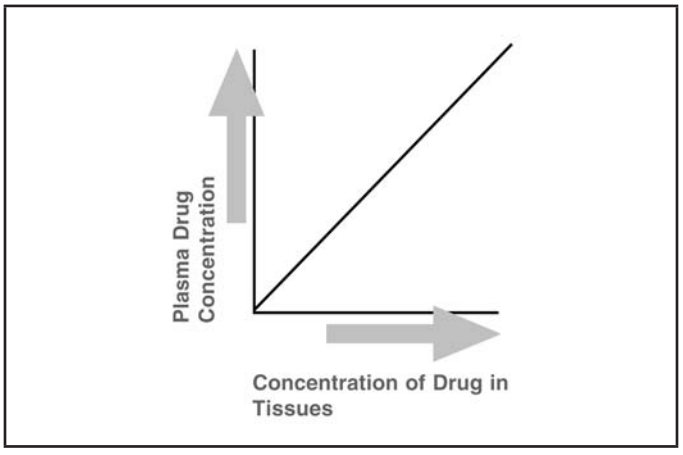


**FIGURE 1-2.**

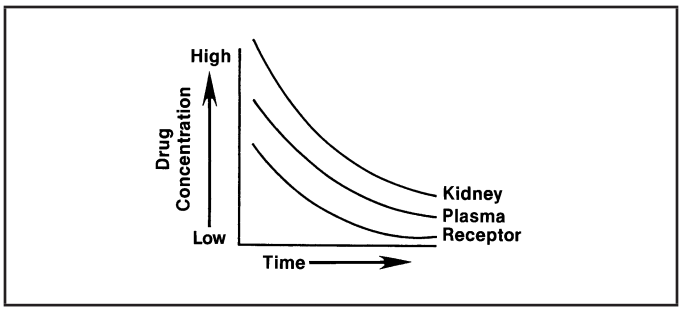


**FIGURE 1-3.**
Drug concentration versus time.

## BASIC PHARMACODYNAMIC CONCEPTS

*Pharmacodynamics* refers to the relationship between drug concentration at the site of action and the resulting effect, including the time course and intensity of therapeutic and adverse effects. The effect of a drug present at the site of action is determined by that drug's binding with a receptor. Receptors may be present on neurons in the central nervous system (i.e., opiate receptors) to depress pain sensation, on cardiac muscle to affect the intensity of contraction, or even within bacteria to disrupt maintenance of the bacterial cell wall.

For most drugs, the concentration at the site of the receptor determines the intensity of a drug's effect (Figure 1-4). However, other factors affect drug response as well. Density of receptors on the cell surface, the mechanism by which a signal is transmitted into the cell by second messengers (substances within the cell), or regulatory factors that control gene translation and protein production may influence drug effect. This multilevel

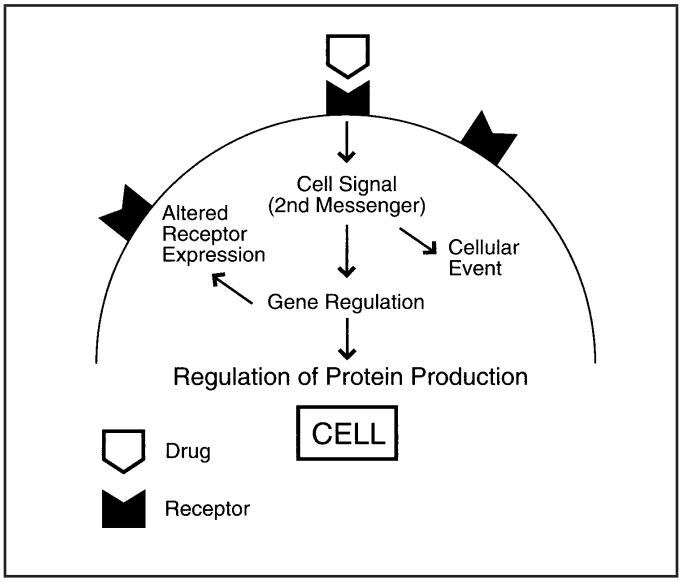


**FIGURE 1-4.**
Relationship of drug concentration to drug effect at the recep-

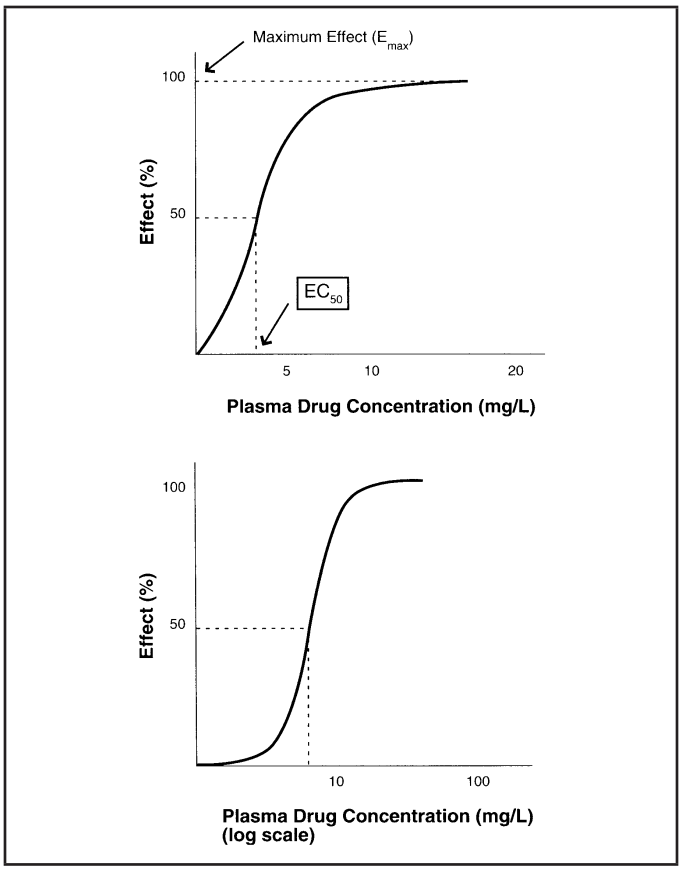


**FIGURE 1-5.**
Relationship of drug concentration at the receptor site to effect (as a percentage of maximal effect).

regulation results in variation of sensitivity to drug effect from one individual to another and also determines enhancement of or tolerance to drug effects.

In the simplest examples of drug effect, there is a relationship between the concentration of drug at the receptor site and the pharmacologic effect. If enough concentrations are tested, a maximum effect ($E_{max}$) can be determined (Figure 1-5). When the logarithm of concentration is plotted versus effect (Figure 1-5), one can see that there is a concentration below which no effect is observed and a concentration above which no greater effect is achieved.

One way of comparing **drug potency** is by the concentration at which 50% of the maximum effect is achieved. This is referred to as the *50% effective concentration* or $EC_{50}$. When two drugs are tested in the same individual, the drug with a lower $EC_{50}$ would be considered more potent. This means that a lesser amount of a more potent drug is needed to achieve the same effect as a less potent drug.

The $EC_{50}$ does not, however, indicate other important determinants of drug response, such as the duration of effect. Duration of effect is determined by a complex set of factors, including the time that a drug is engaged on the receptor as well as intracellular signaling and gene

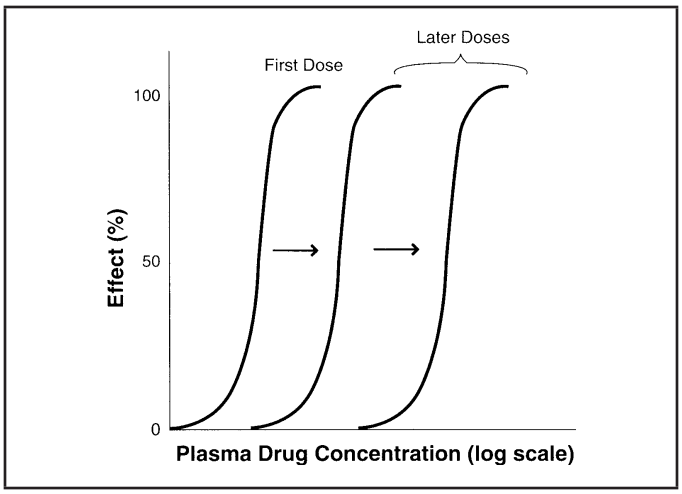


**FIGURE 1-6.**
Demonstration of tolerance to drug effect with repeated dosing.

For some drugs, the effectiveness can decrease with continued use. This is referred to as *tolerance*. Tolerance may be caused by pharmacokinetic factors, such as increased drug metabolism, that decrease the concentrations achieved with a given dose. There can also be pharmacodynamic tolerance, which occurs when the same concentration at the receptor site results in a reduced effect with repeated exposure. An example of drug tolerance is the use of opiates in the management of chronic pain. It is not uncommon to find these patients requiring increased doses of the opiate over time. Tolerance can be described in terms of the dose–response curve, as shown in Figure 1-6.

To assess the effect that a drug regimen is likely to have, the clinician should consider pharmacokinetic and pharmacodynamic factors. Both are important in determining a drug's effect.

### CLINICAL CORRELATE

Tolerance can occur with many commonly used drugs. One example is the hemodynamic tolerance that occurs with continued use of organic nitrates, such as nitroglycerin. For this drug, tolerance can be reversed by interspersing drug-free intervals with chronic drug use.

### CLINICAL CORRELATE

One way to compare potency of two drugs that are in the same pharmacologic class is to compare $EC_{50}$. The drug with a lower $EC_{50}$ is considered more potent.

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