Pharmacokinetics

Michael F. Flessner
University of Rochester

GLOSSARY

Active transport Typically drug transport via a specific transporter, requiring energy, and moving solute against its electrochemical gradient.
Bioavailability Fraction of drug absorbed unchanged into the target compartment.
Drug clearance Volume of distribution cleared of drug per unit time.
Half-life Time required for the concentration of a drug to decrease by one half ($t_{1/2}$).
Passive transport mechanisms Mechanisms that use the forces of concentration differences (diffusion) or pressure differences (convection) to move substances from one site to another.
Pharmacodynamics The study of the specific cellular and molecular action of a drug on a biological organism.
Pharmacokinetics The science of quantitation of drug absorption, distribution, and elimination within biological organisms. It is a subset of pharmacology.
Pharmacology The study of drugs, their sources, different preparations, and therapeutic uses.
Volume of distribution Apparent volume to which a dose of drug distributes at the time of injection or administration.

PHARMACOKINETICS is the science of quantitation of drug absorption, distribution, and elimination within biological organisms. It is a subset of *pharmacology*, which is the study of drugs, their sources, different preparations, and therapeutic uses. On the other hand, *pharmacodynamics* is the study of the specific cellular and molecular actions of a drug on a biological organism. Figure 1 illustrates these definitions for the general case. Together, pharmacokinetics and pharmacodynamics encompass the entire process of drug entry into the body of the organism to the ultimate biological effect. This article will focus on pharmacokinetics, which applies mathematics to the following questions:

1. How quickly and how much of a drug enters the organism?
2. To where does the drug distribute?
3. How rapidly is the drug removed from the body?

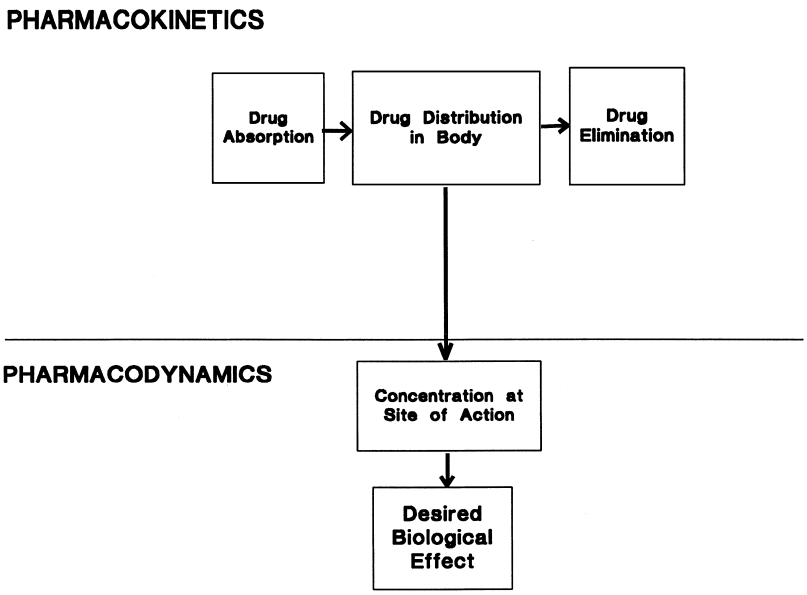

FIGURE 1 Pharmacokinetics versus pharmacodynamics. Pharmacokinetics deals with the phases of drug absorption, drug distribution, and drug elimination. Pharmacodynamics defines the biological effect of a drug at a site of action.

The practical use of the mathematical approaches of pharmacokinetics requires data consisting of measurements of the rate of drug entry into the organism, time-dependent drug concentration in specific compartments within the organism, and the rate of drug removal from the organism. Since the largest amount of data is available for mammals—in particular, humans—mammalian systems will be emphasized in this article. Figure 2 illustrates a more detailed conceptual model of pharmacokinetic processes in humans. Each of these processes will be discussed in turn and specific mathematical approaches will be given. For more detailed approaches, the reader is referred to the Bibliography at the end of the chapter.

I. BASIC PHARMACOKINETIC CONCEPTS

The following basic terminology is used in pharmacokinetics: half-life, volume of distribution, bioavailability, and mechanisms of transport.

A. Half-Life

The *half-life* ($t_{1/2}$) of a drug is equal to the time required for its concentration to decrease by one half. Many drugs follow "first-order" kinetics and, as illustrated in Fig. 3, give a straight line on a semilog plot. This can be mathematically described by the following equation:

$$C = C_0 \exp(-k_{\text{elim}} t), \qquad \text{where} \quad k_{\text{elim}} = \frac{0.693}{t_{1/2}}. \quad (1)$$

Here C_0 is the concentration in the body compartment (typically equal to plasma concentration in a human or animal subject) at time zero, t is the time, and the drug elimination rate constant k_{elim} can be found from the half-life or from the negative slope of the terminal phase of the semilog curve, as illustrated in Fig. 3. The definition

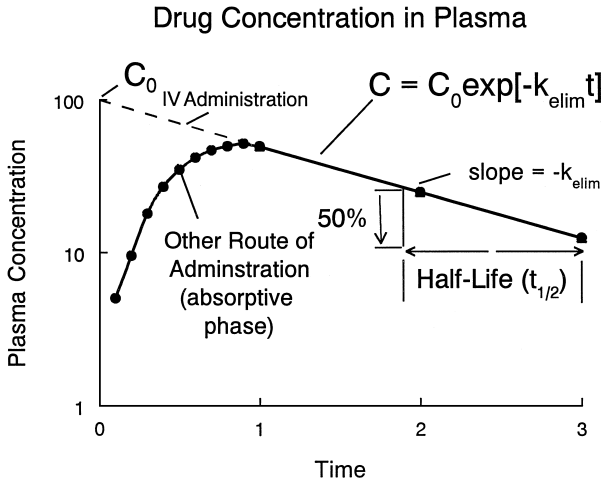

FIGURE 3 Semilogarithmic plot of plasma concentration of a drug versus time in a one-compartment system. The initial part of the curve depends on the route of administration. The half-life of a drug equals the time required for the plasma concentration to decrease by 50%. The drug elimination rate k_{elim} can be found from the terminal slope of the curve. The concentration in the plasma at time zero C_0 is found by extrapolating the plasma concentration curve back to $x = 0$.