Biopharmaceutics & Pharmacokinetics

fourth edition

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(The contents of this book reflect the personal views of the authors and not that of the FDA.)

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INTRODUCTION TO BIOPHARMACEUTICS AND PHARMACOKINETICS

BIOPHARMACEUTICS

Biopharmaceutics considers the interrelationship of the physicochemical properties of the drug, the dosage form in which the drug is given, and the route of administration on the rate and extent of systemic drug absorption. Thus, biopharmaceutics involves factors that influence the (1) protection of the activity of the drug within the drug product, (2) the release of the drug from a drug product, (3) the rate of dissolution of the drug at the absorption site, and (4) the systemic absorption of the drug. Figure 2-1 is a general scheme describing this dynamic relationship.

The study of biopharmaceutics is based on fundamental scientific principles and experimental methodology. These methods must be able to assess the impact of the physical and chemical properties of the drug, drug stability and large scale production of the drug and drug product on the biological performance of the drug. Moreover, biopharmaceutics considers the requirements of the drug and dosage form in a physiological environment and the drug's intended therapeutic use and route of administration.

Studies in biopharmaceutics use both *in-vitro* and *in-vivo* methods. *In-vitro* methods are procedures employing test apparatus and equipment without involving laboratory animals or humans. *In-vivo* methods are more complex studies involving human subjects or laboratory animals. Some of these methods will be discussed in Chapter 5. Historically, pharmacologists evaluated the relative systemic drug availability *in vivo* after giving a drug product to an animal or human and then comparing specific pharmacologic, clinical, or possible toxic responses. For example, a drug such as isoproterenol causes an increase in heart rate when given intravenously but has no observable effect on the heart when given orally at the same dose level. Therefore, systemic drug availability may differ according to the route

Figure 2-1. Scheme demonstrating the dynamic relationship between the drug, the drug product, and the pharmacologic effect.

of administration. In addition, the bioavailability (a measure of systemic availability of a drug) may differ from one drug product to another containing the same drug. This difference in drug bioavailability may be manifested by observing the difference in the therapeutic effectiveness of the drug products.

PHARMACOKINETICS

Pharmacokinetics involves the kinetics of drug absorption, distribution, and elimination (ie, excretion and metabolism). The description of drug distribution and elimination is often termed *drug disposition*. The study of pharmacokinetics involves both experimental and theoretical approaches. The experimental aspect of pharmacokinetics involves the development of biological sampling techniques, analytical methods for the measurement of drugs and metabolites, and procedures that facilitate data collection and manipulation. The theoretical aspect of pharmacokinetics involves the development of pharmacokinetic models that predict drug disposition after drug administration. The application of statistics is an integral part of pharmacokinetic studies. Statistical methods are used for pharmacokinetic parameter estimation and data interpretation. Statistical methods are applied to pharmacokinetic models to determine data error and structural model deviations. Mathematics and computer techniques form the theoretical basis of many pharmacokinetic methods. Classical pharmacokinetics is a study of theoretical models focusing mostly on model development and parameterization.

CLINICAL PHARMACOKINETICS

Clinical pharmacokinetics is the application of pharmacokinetic methods in drug therapy. Clinical pharmacokinetics involves a multidisciplinary approach to individually optimized dosing strategies based on the patient's disease state and patient-specific considerations. The study of clinical pharmacokinetics of drugs in disease states requires input from medical and pharmaceutical research. Table 2.1 is a list of 10 age-adjusted rates of death from 10 leading causes of death in the USA, 1993. The influence of many diseases on drug disposition is not adequately studied. Age, gender, genetic, and ethnic differences can also result in pharmacokinetic differences that may affect the outcome of drug therapy. The study of pharmacokinetic differences of drugs in various population groups is termed *population*

Accidents and others*	5	2.8
Pneumonia and influenza	6	1.6
Diabetes mellitus	7	1.2
HIV infections	8	6.3
Suicide	9	4.4
Homicide and legal intervention	10	3.8

*Death due to adverse effects suffered as defined by CDC.

Source: CDC-MMWR (Morbidity and Mortality Weekly Report), March 1, 45:8, 1996.

pharmacokinetics (Sheiner and Ludden, 1992). Another important aspect of pharmacokinetics is *therapeutic drug monitoring* (TDM). When drugs with narrow therapeutic indices are used in patients, it is necessary to monitor plasma drug concentrations closely by taking periodic blood samples. The pharmacokinetic and drug analysis services necessary for safe drug monitoring are generally provided by the *clinical pharmacokinetic service* (CPKS). Some drugs frequently monitored are the aminoglycosides and anticonvulsants. Other drugs closely monitored are those used in cancer chemotherapy in order to minimize adverse side effects (Rodman and Evans, 1991).

PHARMACODYNAMICS

Pharmacodynamics refers to the relationship between the drug concentration at the site of action (receptor) and pharmacologic response, including biochemical and physiologic effects that influence the interaction of drug with the receptor. The interaction of a drug molecule with a receptor causes the initiation of a sequence of molecular events resulting in a pharmacologic or toxic response. Pharmacokinetic-pharmacodynamic models are constructed to relate plasma drug level to drug concentration in the site of action and establish the intensity and time course of the drug. Pharmacodynamics and pharmacokinetic-pharmacodynamic models are discussed more fully in Chapter 19.

TOXICOKINETICS AND CLINICAL TOXICOLOGY

Toxicokinetics is the application of pharmacokinetic principles to the design, conduct and interpretation of drug safety evaluation studies (Leal et al, 1993) and used in validating dose related exposure in animals. Toxicokinetic data aids in the interpretation of toxicologic findings in animals and extrapolation of the resulting data to humans. Toxicokinetic studies are performed in animals during preclinical drug development and may continue after the drug has been tested in clinical trials.

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