TEMPORAL AND PHARMACOKINETIC ASPECTS
IN DELIVERY OF PEPTIDES AND PROTEINS

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The rational administration of any drug to a patient requires some knowledge of the anticipated efficacy and toxicity for a particular dose of that drug. When an understanding of how an individual patient will absorb and eliminate a drug is coupled together with knowledge of the pharmacologic effects of a given amount of the drug, a particular dose can be selected that will result in clinical efficacy and minimal toxicity. Such considerations have been defined adequately for many classical drugs; however, this approach has not been used as yet for the new peptide and protein therapeutic agents. Thus, today we are interested in gaining an understanding of the pharmacokinetics and pharmacodynamics of peptide and protein drugs. Pharmacokinetics may be simply described as the mathematical relationship that exists between the dose of a drug and the measurable concentration in a readily accessible site in the body (e.g., plasma or blood). Pharmacodynamics extends this relationship to a correlation between measured concentrations of drug and the pharmacologic effect. As a simple description, pharmacokinetics describes what the body does to the drug, as opposed to pharmacodynamics which describes what the drug does to the body.

There are two major uses for pharmacokinetics. First, as a tool in therapeutics to help the clinician choose the right dosage regimen for a particular drug in a specific patient. Second, pharmacokinetics may be used as a tool in defining drug disposition. As indicated above, up to the present time the therapeutic use of pharmacokinetics for proteins and peptide drug compounds has not been realized. However, regulatory agencies do require information concerning drug disposition which can be best described using pharmacokinetic principles, i.e., the use of pharmacokinetics as a tool in defining drug disposition.

A large number of pharmacokinetic parameters may be determined in defining a new drug substance. However, certain critical parameters are of primary importance (Benet, 1984). The first of these is clearance, a measure of the body’s ability to eliminate the drug. In therapeutic terms, clearance defines the dosing rate since the product of total body clearance and the desired steady state drug concentration in the body is equal to the appropriate dosing rate. In defining the drug substance, regulatory agencies will also want to know how clearance is divided into its component parts. For example, what fraction of the total body clearance results from metabolic pathways? In addition, for classical drugs, regulatory agencies will want information related to the specific meta-
bolic processes involved and an understanding of the pattern of metabolism. It is generally necessary to define the fraction of the clearance due to renal mechanisms. Since pharmacokinetic parameters are often determined using plasma concentration measurements, knowledge of the blood to plasma ratio is necessary if one wishes to relate clearance as a fraction of the blood flow to any particular eliminating organ.

The second fundamental kinetic parameter useful in discussing drug disposition is volume. The volume of distribution relates the amount of drug in the body to the concentration of drug in the blood or plasma, depending upon the fluid measured. When pharmacokinetics is used as a tool in therapeutics, an understanding of the volume of distribution is of only minor consequence. However when kinetics is used as a tool in defining drug disposition, the volume of distribution describes the space available in the body into which the drug may distribute. Since the clearing organs can only remove drug from the blood flowing through them, a drug that distributes into a large volume of distribution (i.e., out of the plasma) will not be available for rapid elimination. As may be expected the volume of distribution can be strongly influenced by protein binding. A drug which has a high degree of binding to plasma proteins will generally exhibit a small volume of distribution and a change in protein binding may result in an increase in the distribution space.

The third fundamental pharmacokinetic parameter is half-life, an expression of the relationship between volume and clearance. Since the organs of elimination can only clear drug from the blood or plasma in direct contact with the organ, the time course of drug in the body will depend upon both the volume of distribution and the clearance:

$$t_{1/2} = 0.693 \frac{V}{CL}$$

where $V$ is the volume of distribution and $CL$ is total body clearance. Half-life is an extremely useful kinetic parameter in terms of therapeutics, since this parameter defines the dosing interval at which drugs should be administered. Half-life also dictates the time required to attain steady-state or to decay from steady-state conditions after a change in the dosing regimen (i.e., starting or stopping a particular rate of drug administration). However, as an indication of either drug elimination or distribution, half-life has little value. Early studies of drug pharmacokinetics in disease states were compromised by reliance on drug half-life as the sole measure of alterations in drug disposition. Disease states can affect both of the physiologically related parameters, volume of distribution and clearance; thus, the derived parameter, $t_{1/2}$ will not necessarily reflect expected changes in drug elimination.

The fourth major pharmacokinetic parameter of interest, and of particular interest to the topic of this text, is bioavailability. Bioavailability is defined as the fraction of the unchanged drug reaching the site of drug action, or more usually the systemic circulation, following administration by any route. For an intravenous dose of the drug, bioavailability is defined as unity. For a drug administered orally, bioavailability may be less than one due to several causes: the drug may be incompletely absorbed; it may be metabolized in the gut, the gut wall, the portal blood or the liver prior to entry into the systemic circulation; or it may undergo enterohepatic cycling with incomplete absorption following elimination in the bile. Although bioavailability is most often described following oral dosing, the processes related to absorption and first pass metabolism can occur when drugs are administered via other routes of administration. For the therapeutic use of pharmacokinetics, bioavailability defines the adjustment which must be made in the