Chapter 20

INTEGRAL PROCEDURES IN PHARMACOKINETICS AND THEIR APPLICATION TO THE PARAMETER DETERMINATION OF APPEARING METABOLITES

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The pharmacokinetics of a substance are studied best by the simultaneous measurement of the drug and all of its possible metabolites, especially if they possess similar pharmacological activities, in all monitorable tissues of the animal (1,2). The mathematical delineation of the plasma concentration-time course of the administered drug yields only an equation. Thus, it is difficult to predict the time course of drug and metabolites in plasma and urine under selected conditions of dose and administration. An integrated model, that quantitatively describes the tissue concentrations, interconversions, transformations, and excretory patterns of the drug and its metabolites as functions of the dose, may permit correlations with pharmacodynamic activities and give insight into the mechanisms of action.

These approaches demand novel methods of data manipulation to determine the pharmacokinetic parameters, and levels of abstraction above the mere statement or plotting of the numbers obtained from tissues monitored as a function of time. Such methods may permit the deduction of pharmacokinetic parameters for metabolites after administration of the precursor drug, without performing specific studies involving direct metabolite administration.

With the advent of elegant analytical methodology, such as HPLC, and the ability to simultaneously monitor a drug and its manifold metabolites in body fluids and excreta, there is no reason to conduct future pharmacokinetic studies without such simultaneous monitoring. Thus all modern pharmacokinetic studies
of drugs should be expected to provide pharmacokinetic parameters for all metabolites and all *in vivo* transformations.

The concepts of clearance have been revitalized (3-5). These concepts can be utilized further to describe the integral pharmacokinetics of a drug and its metabolites. In this chapter, the utility and power of such integral methods for characterization and prediction will be stressed and examples given.

**CLEARANCE CONCEPTS**

If the rate of total transformation and elimination, \( \frac{dA_{el}}{dt} \) of a drug to amounts of metabolites \( M \) and amounts in urine \( U \) can be formulated as proportional to the amount of drug \( P \) in the body, where \( A_{el} = M + U \), then:

\[
\frac{dA_{el}}{dt} = kP = kV \frac{C}{p} = CL \cdot C_p
\]

where \( k \) is the first-order rate constant for the elimination, \( V_p \) is the apparent overall volume of distribution of the drug referenced to the plasma concentration and the product \( kV_p \), which is the proportionality constant between the rate of elimination of amounts and the plasma concentration \( (C_p) \), is termed the total (body) clearance of the drug \( (CL) \). The integral expression which implicitly defines clearance can be obtained by integrating Equation (1) with respect to time:

\[
A_{el,t} = CL \cdot AUC_t
\]

where the cumulative amount of drug eliminated at any time \( (t) \) is the constant clearance \( (CL) \) multiplied by the area under the plasma concentration-time curve to that time. The cumulative amount of drug excreted at infinite time \( (A_{el,\infty}) \) is equal to the systemically available dose \( (FD) \) and is related by the total clearance to the total or infinite area under the plasma concentration-time curve \( (AUC_\infty) \):

\[
FD = A_{el,\infty} = CL \cdot AUC_\infty
\]

If the rate of formation of an amount of a metabolite \( M \) or the rate of elimination of an amount of unchanged drug into the urine \( U \) can be formulated similarly as proportional to the amount of drug \( P \) in the body, then the metabolic and renal clearances can be implicitly defined in an analogous manner. That is:

\[
\frac{dU}{dt} = CL_R C_p; U_t = CL_R AUC_t
\]

\[
\frac{dM}{dt} = CL_{met} C_p; M_t = CL_{met} AUC_t
\]