Pharmacokinetic Principles in Pediatric Pharmacology

*William J. Jusko, Ph.D.**

Pharmacokinetics is gaining increasing importance for the practical interpretation and prediction of pharmacologic data in human beings. The cornerstone of pharmacologic principles is the concept of a drug molecule interacting with a receptor to produce a response. Because the drug levels which elicit this response are transient, the effect is likewise transient. Increasing the dose can enhance the intensity and duration of the effect but may produce undesired toxicity, while too low a dose may yield inadequate therapy. Many pharmacologic effects are difficult to measure directly and therapy must await delayed judgment. Thus, dosage and time are the factors which make the pharmacologic use of drugs both useful and hazardous. Because of this, pharmacokinetic techniques have been developed to seek and utilize mathematical methods to relate drug dosage, pharmacologic effects, and time as a means of evaluating and controlling drug therapy.

The primary variables which determine the time course of pharmacologic effects are the absorption, distribution, metabolism, and excretion of the drug and the intrinsic affinity of the drug for the receptor. Therapeutic difficulties can arise when one or more of these factors are complicated by patient variables such as age, pathology, genetics, and environment. The purpose of this report is to consider several aspects of pharmacokinetics which are applicable to pediatric pharmacology.

GENERAL DYNAMIC PROCESSES

The major factors which determine the time-course of pharmacologic effects of a drug are depicted in Figure 1. In general, drug levels and pharmacologic effects are dependent on the physicochemical properties of the particular drug and the physiology of the patient.

During the process of absorption, the rate at which the drug dis-

*Assistant Professor of Pharmacology, Boston University Medical Center, and Section of Clinical Pharmacology, Veterans Administration Hospital, Boston, Massachusetts

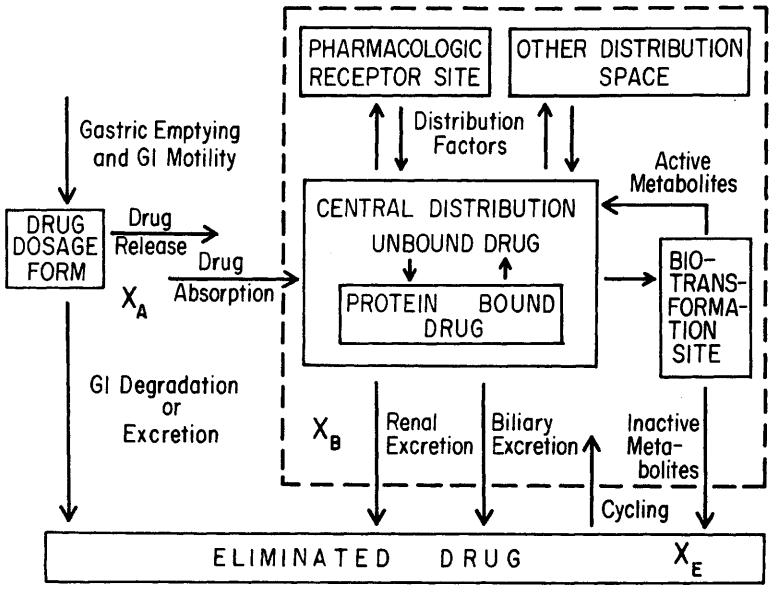


Figure 1. Schematic representation of the major factors which control body levels of drugs and affect the intensity and duration of pharmacologic effects.

solves will often determine the bioavailability of the agent. The release properties of the drug are related to the acid-base-salt form, its water solubility and degree of ionization in gastrointestinal fluids, and the formulation of the dosage form. Since infants and children usually receive drugs in solution, suspension, or chewable form, formulation palatability and drug stability are of additional concern. Physiologic factors such as gastric and intestinal pH, composition of the gastrointestinal contents, gastric emptying, intestinal motility, the integrity of the gastrointestinal membranes, and the mesenteric blood flood affect drug absorption and are subject to variability with age.[3, 4, 25]

The distribution of drugs in the body is partially dependent on the retention of drug in the blood owing to plasma protein-binding. The low concentration of plasma proteins found in the neonate can thus alter drug response. Drug availability to receptor, tissue, and elimination sites is also related to the lipid solubility and degree of ionization of the drug as well as physiologic factors which can vary with age, including local blood flow, the type and integrity of membrane barriers, and the water and protein content of tissues.[3, 4, 22]

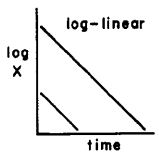
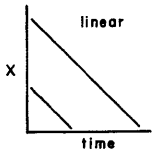
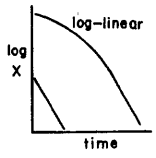
The predominant mechanisms of drug elimination are renal excretion, metabolism, and biliary excretion. The net effect of glomerular filtration, renal tubular secretion, and tubular reabsorption results in renal clearance of both natural and foreign compounds. In addition to the excretory mechanism, the renal clearance of drugs is also dependent on blood flow to the kidneys, plasma protein-binding and the distribution of the drug while factors such as urine pH, urine volume, and glomerular

integrity are sometimes of importance. Developmental changes in renal function are well recognized in pediatrics.[2, 3]

Drug metabolism involves a large number of reaction mechanisms which result in alteration of foreign substrates.[6] Detoxification usually involves drug conjugation with carbohydrates, amino acids, acetate, sulfate, and methyl groups, to form products which are more water soluble than the original drug and are thus more readily excreted in urine and bile. A large number of oxidation processes result in removal from or attachment to drugs of moieties such as hydroxyl, amino, hydrogen, alkyl, or halogen groups. Reduction reactions can produce amino groups from nitro or azo compounds, while hydrolysis involves splitting of ester or amide linkages. All mechanisms except conjugation reactions can produce either an active or an inactive pharmacologic compound. Done[3] has noted that hydrolytic processes are least likely to be affected by immaturity.

Of major importance is the relationship between age and intrinsic sensitivity to drugs. Goldenthal[5] has compiled LD_{50} values for over 200 drugs in newborn and adult animals. Almost every drug listed is more

Table 1. *Characteristics of the Principal Rate Processes Observed in Pharmacokinetics*

	FIRST-ORDER	ZERO-ORDER	CAPACITY-LIMITED
Rate constant	k_1	k_0	V_{max}, K_m
Dimensions	$time^{-1}$	amount/time	dose-dependent
Rate of drug loss	Proportional to the amount present (X)	Constant amount per unit time	Varies with amount: First-order at low levels; O-order at high levels
Differential equation (DE) for drug loss:	$\frac{dX}{dt} = -k_1 \cdot X$	$\frac{dX}{dt} = -k_0$	$\frac{dX}{dt} = \frac{-V_{max} \cdot X}{K_m + X}$
Solution to DE: (D_0 = dose)	$X = D_0 \cdot e^{-k_1 \cdot t}$	$X = D_0 - k_0 \cdot t$	$t \cdot V_{max} = D_0 - X + K_m \cdot \ln \frac{D_0}{X}$
Graphical behavior: (at low and high doses)			
Half-life	Constant	Increases with dose	Generally increases with dose
Common Examples	Renal clearance, Drug diffusion, Blood transport, Drug metabolism	Drug dissolution, Drug infusion, Multiple-dosing	Saturable metabolic, transport, or reaction processes.

toxic in the newborn than in the adult animal. This can be attributed to altered drug distribution and elimination, or to greater reactivity of the newborn to drugs, or to both.

In order to consider the role of pharmacokinetics in pediatrics, it is necessary to understand both mechanisms of drug movement in the body and their expression as mathematical rate processes. The principal types of rate processes encountered in pharmacokinetics are first-order, zero-order, and capacity-limited. The definition and the mathematical and graphical behavior of a single mechanism involving drug removal by each of these rate processes is shown in Table 1. Rate processes which are first-order are easiest to quantitate since they are dose-independent. For example, if drug absorption and elimination are both first-order, then body levels of drug will always be proportional to the dose at a specific time. In contrast, both the amount of drug involved and the duration of the process determine the time course of body levels for zero-order processes. Capacity-limited or Michaelis-Menten type processes exist when an enzyme or transport mechanism has a limited number of receptors available for drug substrate. Because of this, capacity-limited processes behave in a zero-order manner at high drug levels but are first-order at very low drug levels. Fortunately, most of the rate-processes which are represented as arrows in Figure 1 are either first-order or drug dosages are low enough so that Michaelis-Menten processes can be regarded as first-order.

The basic information sought in a pharmacokinetic analysis of pharmacologic data is listed in Table 2. These parameters are available either from direct measurement of drug levels in the body or from the elicited pharmacologic response. Therapeutic control based on the patient response is obviously desirable and feasible for drug effects such as anesthesia, cardiac function, or antipyresis, but it is difficult to control therapy for effects such as analgesia or chemotherapy. In either case, it is useful for the physician to be guided by drug level-effect information gained from previous experience, particularly when age and development are critical factors in choosing a dosage regimen. Thus, the clinical pharmacologic investigation of a drug has come to involve the pharmacokinetic analysis of blood level data (usually plasma or serum concentrations), urinary excretion data, and occasionally feces, cerebrospinal fluid, bile, milk, lymph, and tissue biopsy samples in addition to the type and time-course of pharmacologic and toxicologic effects.

KINETICS OF DRUG DISPOSITION

In many instances, the behavior of the drug is such that the body can be assumed to be a single homogeneous compartment. The dose (D_0) can thus be accounted for as being unabsorbed (X_A), in the body (X_B), or eliminated (X_E) in the manner:

$$X_A \xrightarrow{\text{Absorption}} X_B \xrightarrow[K_E]{\text{Elimination}} X_E \qquad \text{(Scheme I)}$$

Table 2. *General Parameters of Concern in the Elaboration of Pharmacodynamic Data*

Control of body levels of drug
Elimination rate constants and mechanisms
  Rate constant for renal excretion.
  Rate constants for metabolism.
Absorption parameters
  Fraction of dose absorbed by various routes.
  Rate constants for absorption.
Distribution parameters
  Volume(s) of distribution.
  Distribution rate constants.
  Protein-binding constants.
Single and multiple dose-dependence of absorption, distribution, and elimination.

Control of the pharmacologic effect
Relationships between the amount in the body and time and the pharmacologic effect.
Relationship between amount in the body and occurrence of side or toxic effects.

Evaluation of patient variables such as: physiologic, pathologic, genetic, developmental, and environmental factors affecting body levels of drug and pharmacological effects.

where K_E is the first-order rate constant for overall drug elimination. The parameters which are most often associated with the evaluation of data using this model are listed in Table 3. Except for the fraction absorbed (F) and the absorption constant (k_a), these parameters can be obtained by following the time course of blood levels and/or urinary excretion rates of drug following administration by a route involving instantaneous or very rapid absorption. In this case, the amount of drug in the body will be proportional to the dose, according to the exponential (e) relationship:

$$X_B = D_0 \cdot e^{-K_E \cdot t} \qquad \text{(Eq. 1)}$$

Table 3. *Pharmacokinetic Parameters of the One-Compartment Model For Drug Absorption, Distribution, Metabolism, and Excretion*

SYMBOL	DIMENSIONS	PARAMETER*	USUAL SOURCE**	SPECIMENS REQUIRED***
$t_{1/2}$	time	Elimination half-life	D	B or U or O
K_E	$time^{-1}$	Elimination rate constant	C	B or U or O
V_d	volume	Apparent volume of distribution	C	B
F	–	Fraction of dose absorbed	C	B or U
Cl	volume/time	Renal clearance	D	B and U
k_e	$time^{-1}$	Rate constant for renal excretion	C	U
k_m	$time^{-1}$	Rate constant for metabolism	C	U
k_a	$time^{-1}$	Rate constant for absorption	C	B or U
AUC	conc. time	Plasma level area	D	B
Cl_t	volume/time	Body clearance	C	B

*All rate constants are assumed first-order.
**Source: D = Experimental data, C = Calculated from D.
***Specimens: B = Serum or Plasma: U = urine; O = other

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.