Handbook of Basic Pharmacokinetics

. . . including Clinical Applications

FOURTH EDITION

To my wife, Ingrid

Handbook of Basic Pharmacokinetics

. . . including Clinical Applications

by W. A. Ritschel

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NOTICE

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Dose Dumping is a term used to describe the achievement of sustained drug concentration by simply increasing the dose size or by accidental fast release of drug from a sustained release dosage form.

Dose-Response Curve is the graphical presentation of the pharmacological or clinical effectiveness or toxicity (response) versus dose. A log dose-response curve is sigmoid with a straight-line middle section; a log dose-probability curve results in an entirely straight line.

Dose Size is the amount of drug in μg (= mcg), mg, units or other dimensions to be administered.

Dosing Interval is the time period between administration of maintenance doses.

A Drug is a chemical compound of synthetic, semisynthetic, natural or biological origin which interacts with human or animal cells. The interactions may be quantified, whereby these resulting actions are intended to prevent, to cure or to reduce ill effects in the human or animal body, or to detect disease-causing manifestations.

A Drug Specialty or **Brand Product** is a drug product, usually of unvarying composition, labeled with a registered trade mark of a single company.

Drug Release or **Liberation** is the delivery of the active ingredient from a dosage form into solution. The dissolution medium is either a biological fluid or an artificial test fluid (in vitro). Drug release is characterized by the speed. (liberation rate constant) and the amount of drug appearing in solution.

A Drug Product or **Dosage Form** is the gross pharmaceutical form containing the active ingredient(s) [drug(s)] and vehicle substances necessary in formulating a medicament of desired dosage, desired volume and desired application form, ready for administration.

Drug-Receptor Interaction is the combining of a drug molecule with the receptor for which it has affinity, and the initiation of a pharmacologic response by its intrinsic activity.

Elimination Half-Life of a drug is the time in hours necessary to reduce the drug concentration in the blood, plasma or serum to one-half after equilibrium is reached. The elimination half-life may be influenced by: dose size, variation in urinary excretion (*p*H), intersubject variation, age, protein binding, other drugs and diseases (especially renal and liver diseases).

Loss of drug from the body, as described by the elimination half-life, means the elimination of the administered parent drug molecule (not its metabolites) by urinary excretion, metabolism or other pathways of elimination (lung, skin, etc.).

Enterohepatic Recirculation (Biliary Recycling) is the phenomenon in which drugs emptied via bile into the small intestine can be reabsorbed from the intestinal lumen into systemic circulation.

Enzyme Induction is the increase in enzyme content or rate of enzymatic processes resulting in

Equation 17.41 can be rewritten for total drug concentration:

$$C^{ss} = \frac{D/\tau}{f_u \cdot Cl_{intr}} \qquad \text{Eq. 17.49}$$

and, hence, the free drug concentration is:

$$C^{ss} \cdot f_u = \frac{D/\tau}{Cl_{intr}} \qquad \text{Eq. 17.50}$$

The influence of protein binding due to displacement from binding on pharmacokinetic parameters is shown in Table 17-14.

Inspection of Tables 17-3 and 17-4 reveals some important facts which can be summarized as follows:

- Change in liver blood flow will influence the rate of metabolism of drugs with high extraction ratios ($E > 0.7$). Increase in liver blood flow will increase hepatic and total clearance.
- Change in liver blood flow will not influence drugs with low extraction ratios ($E < 0.3$).
- Change in protein binding of drugs with high extraction ratios ($E > 0.7$) will not influence total clearance.
- Decrease in protein binding increases the total clearance of drugs with low extraction ratios ($E < 0.3$).
- Decrease in protein binding does not influence the total clearance of drugs with high extraction ratios ($E > 0.7$). However, because the intrinsic clearance decreases, the free drug concentration increases; hence, pharmacodynamic response may increase.

- In the relationship between Cl_{tot}, V_d and $t_{1/2}$, total clearance and volume of distribution are the independent variables, the elimination half-life is the dependent variable:

$$t_{1/2} = \frac{0.693 \cdot V_d}{Cl_{tot}} \qquad \text{Eq. 17.51}$$

For clinical applications, it is not feasible to collect a sufficient number of blood samples to either perform pharmacokinetic parameter calculations after curve-fitting, or to calculate the AUC. Two methods can be used for estimating the total clearance from a single blood sample. If the bioavailability is not known, the clearance is Cl_{tot}/f:

Method I

Method I is based on a blood sample C(t) taken during the terminal phase, the literature value for V_d, and the body weight, BW:

$$Cl_{tot}/f = \left[\ln\left(\frac{D}{V_d/f}\right) - \ln C(t)\right] \cdot \frac{V_d/f}{t} \cdot BW \qquad \text{Eq. 17.52}$$

Method II

Method II is based on the postulate that in the absence of enzyme induction or enzyme inhibition, the total area under the curve after a single dose, $AUC_{0\rightarrow\infty}$, is equal to the area under the curve during one dosing interval at steady state,

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