

APPENDIX

Pharmacokinetics

Pharmacokinetics is one of the two basic areas of pharmacology, in addition to pharmacodynamics. It deals with the quantitation of the process of drug absorption, distribution, biotransformation, and excretion. These factors, coupled with prescribed drug dose, determine the time course of drug concentrations *in vivo*. Pharmacokinetic studies of drugs are clinically useful to predict the intensity of drug effects if the relationship exists between the drug concentrations and pharmacologic or toxic effects of drugs.

Time to reach the maximal serum concentration (T_{\max})

The T_{\max} corresponds to the time required to reach the maximum serum concentration after drug administration. It is a measure of the rate of drug absorption which exceeds its early disposition. Until a time T_{\max} is reached that the rate of elimination matches the rate of absorption. The unit of T_{\max} is a unit of time e.g., hr or min.

The maximal serum concentration (C_{\max})

The C_{\max} represents the maximal or the peak serum drug concentration after drug administration. The unit for C_{\max} is a concentration unit (e.g., $\mu\text{g/ml}$).

The absorption rate constant (K_a)

Absorption rate constant is a constant value described the rate of absorption of drug from site of administration to systemic circulation. The unit for K_a is hr^{-1} .

The volume of distribution (V_d)

Volume of distribution is one of the two major independent pharmacokinetic parameters in addition to clearance. It is not a real volume, however, is the apparent volume related to the total amount of drug in the body if it were presented throughout the body at the same concentration found in the blood or plasma. The major determinant of V_d is the relative lipid versus water solubility as well as the avidity for the plasma versus tissue protein binding properties of the drug. The unit of V_d is L or L/kg.

The mean residence time (MRT)

The mean residence time (MRT) is the average time the numbers of molecules introduced (N) reside in the body (time between its input and its

elimination from the body). Individual molecules cannot be count, of course, but groups of them can. Extending this concept to account for all molecules administered, the mean residence time becomes

$$\text{MRT} = \sum_{i=1}^m (t_i \times n_i) / N$$

where

i = The i^{th} group.

m = The number of groups.

n_i = The number of molecules in the i^{th} group.

t_i = Their average time in the body.

N = The total number of molecules introduced.

The area under concentration-time curve from administration to the last time point ($\text{AUC}_{0-t \text{ last}}$).

The $\text{AUC}_{0-t \text{ last}}$ is a measure of the total amount of intact drug absorbed that reaches the systemic circulation. It is calculated from the integral of total area under the concentration-time curve, from time zero ($t = 0$) to the last time point. The unit of $\text{AUC}_{0-t \text{ last}}$ is a unit of drug concentrations multiplied by time (e.g. $\mu\text{g}\cdot\text{hr}/\text{ml}$).

The area under concentration-time curve from administration and extrapolated to infinity ($AUC_{0-\infty}$)

The $AUC_{0-\infty}$ is a measure of the total amount of intact drug absorbed that reaches the systemic circulation. It is calculated from the integral of total area under the concentration-time curve, from time zero ($t = 0$) to infinity (∞). The unit of $AUC_{0-\infty}$ is a unit of drug concentrations multiplied by time (e.g. ug.hr/ml).

The clearance (Cl)

Clearance is the term that describes the efficiency of irreversible elimination of a drug from the body. It is defined as the volume of blood cleared of drug per unit of time. The units of Cl are thus volume per time, usually L/hr or ml/min.

The elimination rate constant (K_e)

Elimination rate constant is a constant which describes the rate of removal (elimination) of drug from the body. The unit for K_e is hr^{-1} .

The elimination half-life ($t_{1/2}$)

Elimination half-life is the time taken for the amount of drug in the body (or the plasma concentration) to fall by half. The unit for $t_{1/2}$ is a unit of time (e.g., hr, min).

The relative bioavailability (F_{rel})

Bioavailability (F) refers to the rate and extent of administered dose of drug which reaches the systemic circulation.

F_{rel} is the percentage or fraction of the AUC of a generic drug product as compared to the innovator reference drug. The relative bioavailability of the two drug products given at the same route of administration can be obtained from the following equation.

$$F_{rel} = \frac{AUC_{test} \times D_{ref}}{AUC_{ref} \times D_{test}}$$

where

- AUC_{test} = AUC of the test drug
- AUC_{ref} = AUC of the reference drug
- D_{ref} = Dose of reference drug
- D_{test} = Dose of test drug

When the same dosage are administered, the following equation is used.

$$F_{rel} = \frac{AUC_{test}}{AUC_{ref}}$$

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