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 effect of drugs.

The maximum plasma concentration (C_{max})

The C_{max} represents the maximal or the peak plasma drug concentration after administration. The unit of C_{max} is concentration unit (e.g. μg/ml).

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

The T_{max} corresponds to the time required to reach the maximum plasma 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. min or hr).

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

The $AUC_{0\text{-}t\ last}$ 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 plasma concentration-time curve, from time zero (t=0) to the last time point. The unit of the $AUC_{0\text{-}t\ last}$ is a unit of drug concentration multiplied by time (e.g. μg.h/ml).

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

The $AUC_{0\text{-}\infty}$ 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 plasma concentration-time curve, from time zero (t=0) to infinity (∞). The unit of the ($AUC_{0\text{-}\infty}$) is a unit of drug concentration multiplied by time (e.g. μg.h/ml).

The area under the moment curve (AUMC)

The AUMC 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 plasma concentration-time curve, from time zero (t=0) to any time point. The unit of the AUMC is a unit of AUC multiplied by time (e.g. $\mu g.h^2/ml$).

The mean residence time (MRT)

The mean residence time (MRT) is the average time that the numbers of molecule of drug introduced (n) resides in the body (time between its input and its elimination from the body). Individual molecule cannot be counted, however, groups of them can. Extending this concept to account for all molecules of drug administered, the mean residence time becomes.

$$MRT = {}^{m}\sum_{i=1} (Rt_i)/n$$

where

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

t_i = The average time that the molecules of the i^{th} molecule reside in the body.

m = The number of groups.

n = The total number of molecules introduced.

In addition, MRT can be calculated from the following equation.

$$MRT = (CL \times AUMC_{0-\infty}) / (CL \times AUC_{0-\infty})$$
$$= (AUMC_{0-\infty})/ (AUC_{0-\infty})$$

where

CL = Clearance.

AUMC = Area under the moment curve

AUC = Area under the concentration-time curve.

$0-\infty$ = Time from zero to infinity

The unit for MRT is a unit of time (e.g. min or hr).

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

The elimination half-life is the time taken for the amount of drug in the body (or the plasma concentration) to fall by half. It can be calculated from the following equation.

$$T_{1/2} = 0.693/K_e$$

where

K_e = Elimination rate constant.

The unit for $T_{1/2}$ is a unit of time (e.g. min or hr).

The clearance (CL)

Clearance is the term that describes the efficiency of irreversible elimination of drug from the body. It is defined as the volume of blood cleared of the drug per unit time. Total body clearance includes the elimination of drug that occur in the liver and kidney. Clearance can be calculated from the following equation.

$$CL = (Dose \times F) / AUC$$

where

F = Bioavailability of drug.

AUC = Area under the concentration-time curve.

Dose = The given dose of drug.

The unit for CL is a unit of volume per unit time (e.g. l/h or ml/ min)

The volume of distribution (V_d)

The volume of distribution is one of the major independent pharmacokinetic parameters in addition to clearance. It is not a real value, however, it 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. V_d can be calculated from the following equation.

$$V_d = \text{Amount of drug in the body} / \text{Plasma concentration}$$

where

Amount of drug in the body = Amount or dose of given drug.

Plasma concentration = Drug concentration in plasma.

The unit for V_d is unit of volume (e.g. l).

Bioavailability (F)

Bioavailability (F) refers to the fraction of the rate and extent of drug which reachs the systemic circulation.

Bioavailability can be classified into 2 types:

Absolute bioavailability (F): the comparative AUC between extravascular (e.g. oral) and intravascular drug administration. Absolute bioavailability can be calculated from the following equation.

Absolute bioavailability (F) = $[(AUC_{e.v.})\times(Dose_{i.v.})] / [(AUC_{i.v.})\times(Dose_{e.v.})]$

where

$AUC_{e.v.}$ = Area under the concentration-time curve after extravascular administration.

$AUC_{i.v.}$ = Area under the concentration-time curve after intravascular administration.

$Dose_{e.v.}$ = Dose of extravascular administration.

$Dose_{i.v.}$ = Dose of intravascular administration.

Relative bioavailability (F_{rel}): the comparative bioavailability of two different pharmaceutical preparations when given by the same route of administration, that could be calculated from the following equation.

Relative bioavailability (F_{rel}) $= F_1 / F_2$

$= [(AUC_1) \times (Dose_2)] / [(AUC_2)\times(Dose_1)]$

If given in equal dose $= AUC1 / AUC_2$

Where

F_{rel} = Relative bioavailability.

F_1 = Bioavailability of generic drug.

F_2 = Bioavailability of innovative drug.

AUC_1 = Area under the concentration-time curve of generic drug.

AUC_2 = Area under the concentration-time curve of innovative drug.

$Dose_1$ = Dose of generic drug.

$Dose_2$ = Dose of innovative drug.

The unit for F and F_{rel} are the unit of ratio or percent (%)

The Wagner-Nelson absorption method

Wagner-Nelson absorption method is the method that used to calculate absorption kinetics from plasma concentration-time data following an extravascular (e.v.) dose. It relies on mass balance considerations. At any time, the amount absorbed is given by the familiar mass balance equation.

Aab	=	A	+	Ael
Amount absorbed		Amount in body		Amount eliminated

If $A = V \cdot C$ and $Ael = CL \cdot \int_0^t C \cdot dt$, which on substitution into above equation, gives

$$Aab = V \cdot C + CL \cdot \int_0^t C \cdot dt$$

Hence, if CL and V are known from i.v. data, changes in Aab with time can then be calculated. The value rises until absorption stops. Then, Aab = F • dose, allowing bioavailability to be determined. Notice that no assumption is made regarding the nature of absorption process; it could be simple or complex. Indeed, the calculated absorption-time profile can be analyzed further to characterize the absorption process.

Because $CL = k \cdot V$, so that division of equation by V yields

$$Aab/V = C + k \cdot \int_0^t C \cdot dt$$

Thus, knowing the elimination rate constant, k, the ratio Aab/V can be determined from the plasma concentration-time data, with AUC to each time estimated by the appropriate numeric method.

Ultimately, the value calculated using above equation reaches an upper limit, signifying that absorption has stopped. This limiting value is therefore F • Dose/V, which also equals $k \bullet \int_0^{\infty} Cdt$, as $F \bullet Dose = k \bullet V \int_0^{\infty} Cdt$. Accordingly, the fraction of bioavailable dose that is absorbed with time can be estimated; it is given by

$$\text{Fraction of bioavailable drug absorbed} = (C + k \bullet \int_0^t C \bullet dt) / k \bullet \int_0^{\infty} C \bullet dt$$

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