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.

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. ng/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 h).

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 multipled by time (e.g. ng.h/ml).

The area under the concentration-time curve from administration to the 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 multipled by time (e.g. ng.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 multipled by time (e.g. $ng.h^2/ml$).

The mean residence time (MRT)

The mean residence time (MRT) is the average time that the numbers of molecules of drug introduced (n) reside 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} group 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.

$$MRT = \frac{Cl \times AUMC_{0-\infty}}{Cl \times AUC_{0-\infty}} = \frac{AUMC_{0-\infty}}{AUC_{0-\infty}}$$

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 h).

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.

$$t_{1/2} = \frac{0.693}{K_e}$$

where K_e = Elimination rate constant.

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

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 time. Total body clearance includes the eliminations of drug that occur at liver and kidney. Clearance can be calculated from the following equation.

$$Cl = \frac{Dose}{AUC} \times F$$

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 time (e.g. L/h or ml/min).

The volume of distribution (V_d)

Volume of distribution is one of the major independent pharmacokinetic parameters in addition to clearance. It is not a real value, however, is the apparant 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.

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

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 reaches 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.

$$\text{Absolute bioavailability (F)} = \frac{(AUC_{e.v.}) \times (Dose_{i.v.})}{(AUC_{i.v.}) \times (Dose_{e.v.})}$$

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

$AUC_{i.v.}$ = Area under the concrntration-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.

$$\text{Relative bioavailability } \{F_{(rel)}\} = F_1 / F_2 = \frac{(AUC_1) \times (Dose_2)}{(AUC_2) \times (Dose_1)} = AUC_1 / AUC_2$$

where $F_{(rel)}$ = Relative bioavailability.

F_1 = Bioavailability of generic drug.

F_2 = Bioavailability of innovative drug.

$Dose_1$ = Dose of generic drug.

$Dose_2$ = Dose of innovative drug.

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

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

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

Percent dissolution (%)

Percent dissolution refers to amount of the active ingredient of the preparation dissolved in dissolution medium in the specified

condition. Percent dissolution can be calculated from the following equations.

a)

$$\text{Percent dissolution} = \frac{\text{Dissolved amount of the active ingredient}}{\text{Labeled amount of drug}}$$

where Dissolved amount of the active ingredient = The total amount of the active ingredient of drug issolved in dissolution medium.

Labeled amount of drug = The total amount of the active ingredient contained in the preparation.

b)

$$\text{Percent dissolution} = \frac{\text{Abs-Blank}}{\text{Mean } {}^{1\%}E_{1cm}} \times \frac{1000}{100} \times \frac{\text{V.D.}}{2} \times \frac{100}{\text{L.C.}}$$

where Abs = Absorbance of the test solution.

Blank = Mean ${}^{1\%}E_{1cm}$ of the dissolution medium.

mean ${}^{1\%}E_{1cm}$ = Mean ${}^{1\%}E_{1cm}$ of the standard solution.

V.D. = Volume of the dissolution medium.

L.C. = Labeled content.

$$^{1\%}E_{1cm} = \frac{\text{Absorbance of the standard solution}}{\text{Weight of the reference sample (mg)}} \times \frac{1000}{100} \times \frac{\text{S.V.}}{2}$$

where S.V. = Volume of the standard solution.

The unit for percent dissolution is percent (%).

VITA

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