Topic –
Compartment Model

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Contents

- What is mathematical model?
- What is compartment model?
- Classification of pharmacokinetic models.
- Classification of compartment models.
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MATHEMATICAL MODEL

- A model is a mathematical description of biologic system and used to express quantitative relationships.
- Mathematical models are a collection of mathematical quantities,operations and relations together with their definitions and they must be realistic and practical.
- A model is a hypothesis that employs mathematical terms to concisely describe quantitative relationships.

QUALITIES OF A MATHEMATICAL MODEL

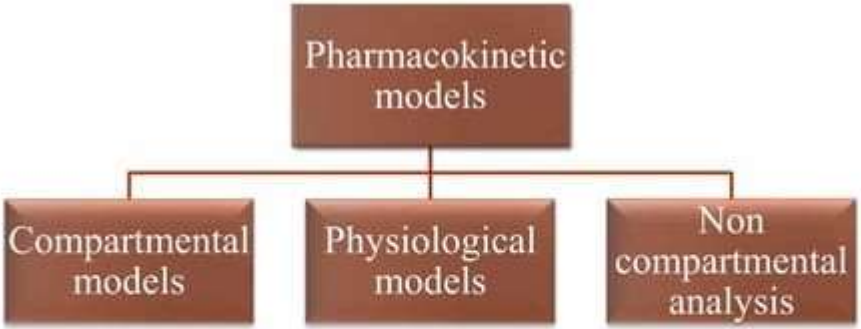
- **Validity:** It should have practical applicability and should be valuable in describing events chosen accurately with high precision.
- **Prediction ability:** These models predict the qualitative and quantitative changes in these parameters that are rate constants and half lives of drugs.
- **Computability:**
- **Consistency of results:** Reproducibility is an important quality of a mathematical model.

APPLICATIONS OF PHARMACOKINETIC MODELS

- Characterizing the behavior of drugs in patients.
- Calculating the optimum dosage regimens for individual patients.
- Evaluating the bioequivalence between different formulations of same drug.
- Determining the influence of altered physiology or disease state on drug ADME.
- Explaining the drug interactions.

TYPES OF PHARMACOKINETIC MODELS

- There are three different types of pharmacokinetic models they are:



COMPARTMENTAL MODELS

- A compartment is a group of tissues with similar blood flow and drug afinity. A compartment is physiologic or anatomic region.
- Compartment is the traditional and most widely used approach to pharmacokinetic characterization of drug. These models simply interpolate the experimental data and allow on emperical formula to estimate drug concentration with time.

ASSUMPTIONS OF COMPARTMENTAL MODELS

- The body is represented as a series of compartment arranged in series or parallel to each other.
- The rate of drug movement between compartment is described by first order kinetics.
- Rate constants are used to represent rate of entry into and exit from compartment.
- A statistical analysis of plasma concentration time data is another method used to find out no.of compartments.

APPLICATIONS OF COMPARTMENT MODELING

- It is a simple and flexible approach and is widely used.
- It gives a visual representation of various rate processes involved in drug disposition.
- It is useful in predicting drug concentration time profile in both normal and pathological conditions.
- It is useful in relating plasma drug levels in therapeutic and toxic effects in body.
- Its simplicity allows for easy tabulation of V_d,$t_{1/2}$ etc.

TYPES OF COMPARTMENT MODELS

Based on whether the compartment is arranged in parallel or series the compartmental models are classified into four types they are:

1. Mammillary model.
2. Catenary model.
3. Open model.
4. Closed model.

MAMMILLARY MODEL

- This is the most common compartment used in pharmacokinetics.
- The model consists of one or more peripheral compartments connected to a central compartment.
- The central compartment consists of plasma and highly perfused tissues in which drug distributes rapidly.
- The no.of rate constants which will appear in a particular compartment model is given by R.

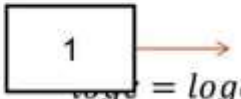
  For intravenous administration R=2n-1.

  For extravascular administration R=2n.

where n=no.of compartments.

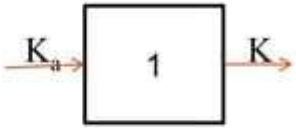
DEPICTION OF VARIOUS MODELS:

- Model 1: one compartment open model i.v injection



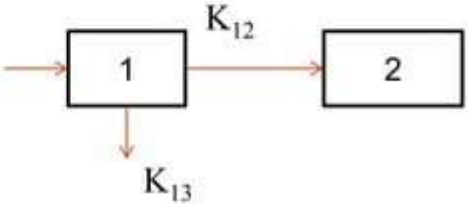
$$\log c = \log c_0 - \frac{k_E t}{2.303}.$$

- Model 2: one compartment open model with first order absorption.



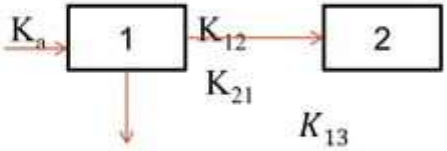
$$C = KaFX_0/Vd(Ka - Ke)[e^{-ket} - e^{-Kat}]$$

- Two compartment open model i.v injection.



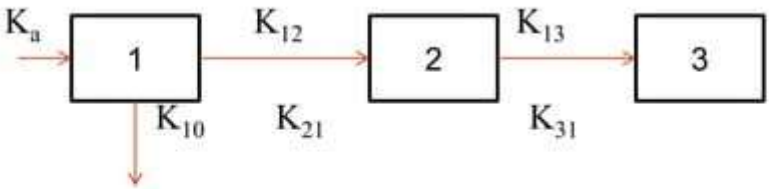
$$c = Ro/VcK_E(1 + (KE - {}^{\beta}/_{\beta-\alpha})e^{-\alpha t} + (K_E\text{-}\alpha/\alpha - \beta)e^{-\beta t}).$$

- Two compartment open model with first order absorption.



CATENARY MODEL

- In this model compartments are joined to one another in a series like compartments.
- This model is directly linked to blood and this model is rarely used.

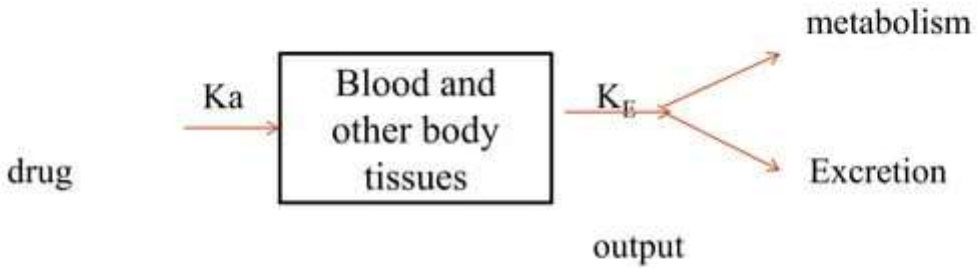


ONE COMPARTMENT OPEN MODEL

ONE COMPARTMENT OPEN MODEL

- The time course of drug concentration determined after the administration can be satisfactorily explained by assuming the body as single well mixed compartment with first order disposition process.
- The body is constituted as a single kinetically homogenous unit that has no barriers to movement of drug.
- Elimination is a first order process with first order rate constant.
- Drugs move dynamically in and out of the compartment then rate of input is greater than rate of output.

- The term OPEN indicates that input and output are unidirectional and that the drug can be eliminated from body.



- One compartment open model is generally used to describe plasma levels following administration of a single dose.

CLASSIFICATION OF ONE COMPARTMENT OPEN MODEL(INSTANTANEOUS DISTRIBUTION DATA)

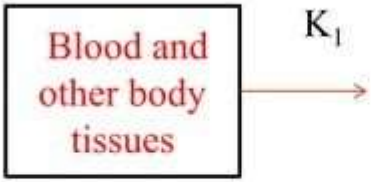
- Depending upon rate of input several one compartment models are defined:

- One compartment open model- intravenous bolus administration.
- One compartment open model- continuous intravenous infusion.
- One compartment open model- extravascular zero order absorption.
- One compartment open model- extravascular first order absorption.

INTRAVENOUS BOLUS ADMINISTRATION

- When a drug that distributes rapidly in the body is given in the form of a rapid intravenous injection, it takes about one or three minutes for complete circulation.

The model can be diagrammatically depicted as



- It can be mathematically represented as

- The rate of drug presentation in body is expressed as

$\frac{dx}{dt}$= availability- Elimination

- In bolus injection absorption of drug is absent so availability is zero then the equation is depicted as

$$\frac{dx}{dt} = -K_E X$$

- After applying integrations to the above it can be written as

$$x = xoe^{-kt}$$

- Transforming the above equation

$$logx = logx_0 - \frac{K_E t}{2.303}$$

ESTIMATION OF PHARMACOKINETIC PARAMETERS BY I.V BOLUS

- From i.v bolus the elimination phase can be characterized by three parameters they are:

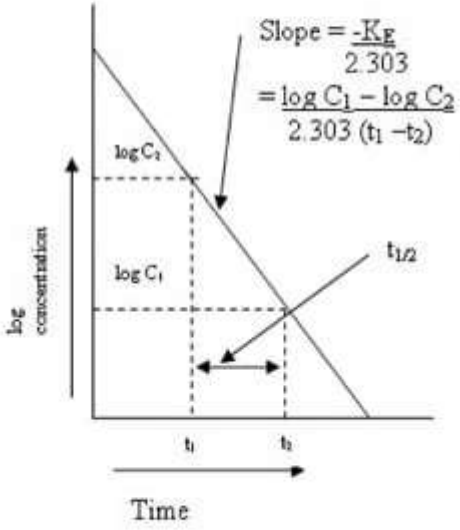
- ✓ Elimination rate constant.
- ✓ Elimination half life.
- ✓ Clearance.

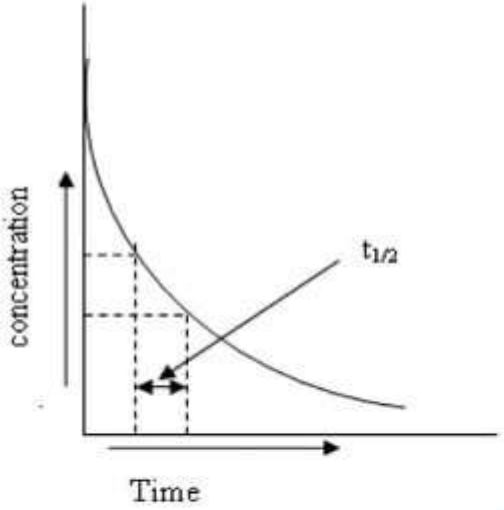
- **Elimination Rate Constant** It can be expressed as

$$logc = logc_0 - \frac{K_E t}{2.303}$$

- A graph is plotted by taking log concentration versus time it gives a straight line and slope gives the elimination rate constant i.e.

$$\frac{-KE}{2.303} = \text{slope}$$





- The elimination rate constant is an additive property and they are said to be overall elimination constants

$K_E = Ke + Km + Kb + K_1$.....

- The units of elimination rate constant are min^{-1}.
- Elimination half life can be also be called as biological half life. It can be defined as the time taken for the amount of drug in body to decline by one half or 50% of its initial volume. It can be depicted as $t_{1/2}$.

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

- **Clearance:**

- It is the most important parameter in drug clinical drug applications and is useful in evaluating the mechanism by which a drug is eliminated.
- Clearance is a parameter that relates plasma drug concentration with rate of drug elimination from below equation

$$clearance = \frac{rate\ of\ elimination}{plasma\ drug\ concentration}$$

$$clearance = \frac{dx/dt}{c}$$

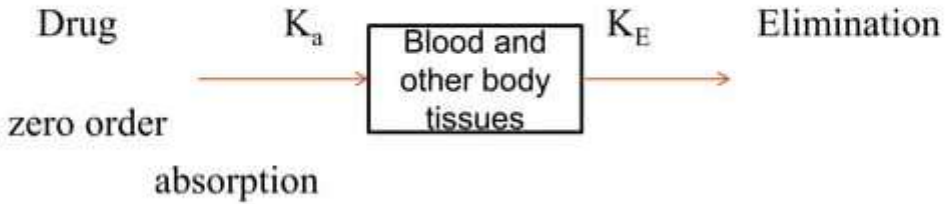
- The clearance is expressed as ml/min or lit/hr.

INTRAVENOUS INFUSION

- Rapid i.v injection is unsuitable when the drug has the potency to precipitate toxicity.
- **Advantages**

- Ease of control of rate of infusion to fit individual patient needs.
- Prevents fluctuating maxima and minima plasma levels. It is especially when a drug has narrow therapeutic index.
- In critically ill patients the drugs that administered by infusions such as electrolytes and nutrients.

- The model can be diagrammatically depicted as



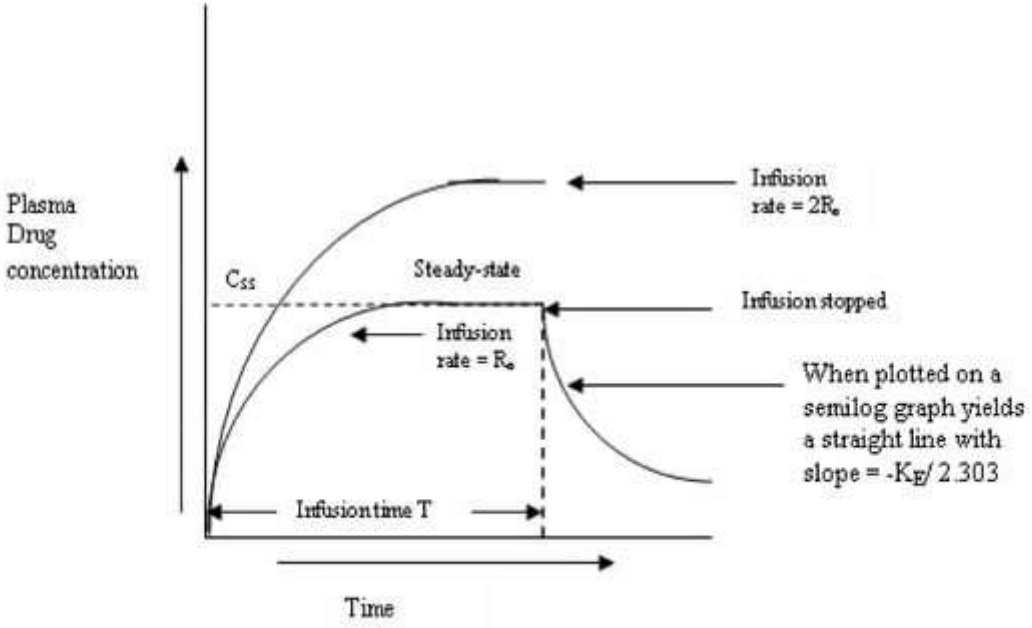
- In an infusion the rate of change in amount of drug in a body is the difference between zero orderrate of infusion R_0 and first order elimination $-K_EX$.

$$\frac{dx}{dt} = R_0 - KEX$$

Applying proper integration the above can be written as

$$c = \frac{R_0}{cl_T}(1\text{-}e^{-KEt})$$

- The concentration of drug in plasma approaches a constant value called as steady state plateau or infusion equilibrium.



- Transforming the above equation in concentration terms

$$C_{ss} = \frac{Ro}{K_E Vd} = \frac{R_o}{Cl_T} \text{ or } \frac{infusion\ rate}{clearance}$$

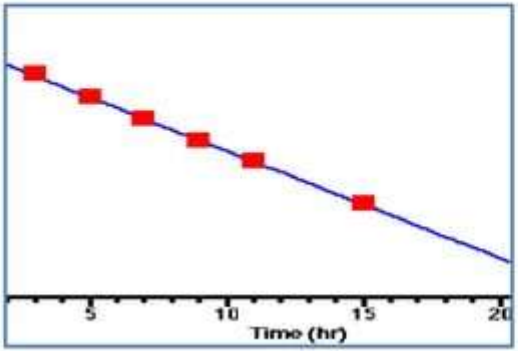
substituting in above equation

$$C = Css(1 - e^{-KEt})$$

- Transforming into log form the equation becomes

$$\log\left(\frac{C_{ss} - C}{C_{ss}}\right) = \frac{-KEt}{2.303}$$

$$\log\left(\frac{C_{ss} - C}{C_{ss}}\right)$$



- The time to reach steady state concentration is dependent upon elimination half life and infusion rate.
- If n is the no.of half lives passed since start of infusion can be written as

$$C = Css(1 - (1/2)^n)$$

- For therapeutic response more than 90% of steady state concentration in blood desired which reached 3.3 half lives.
- It takes 6.6 half lives for concentration to reach 99% of steady state.
- Shorter the half life sooner is the steady state concentration reached.

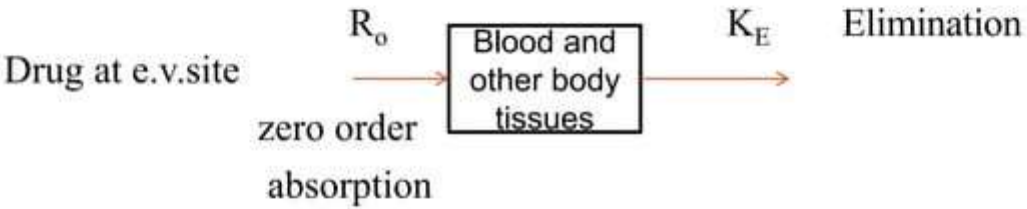
EXTRAVASCULAR ADMINISTATION

- When a drug is administered by extravascular absorption is an essential for its therapeutic activity and efficacy.
- The rate of absorption can be mathematically depicted by two processes they are:

1. Zero order absorption process.
2. First order absorption process.

ZERO ORDER ABSORPTION MODEL

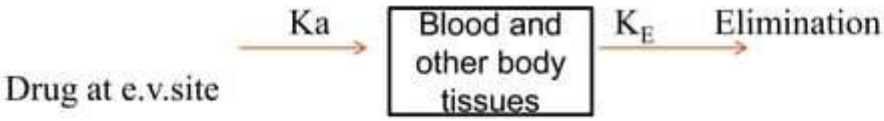
- It is similar to that of constant rate of infusion.



- The rate of drug absorption incase of several controlled drug delivery systems.

FIRST ORDER ABSORPTION MODEL

- When ever the drug enters into body it follows first order absorption process according to one compartment kinetics.
- The model can be represented as



first order absorption

The differential form of above equation can be

$$\frac{dx}{dt} = K_a X_a - KeX$$

- Integrating the above equation

$$X = \frac{KaFX_0}{(K_a - KE)}[e^{-KEt} - e^{-Kat}]$$

Transforming into c terms as $X = V_d C$

$$c = \frac{KaFX_0}{(K_a - KE)V_d}[e^{-KEt} - e^{-Kat}]$$

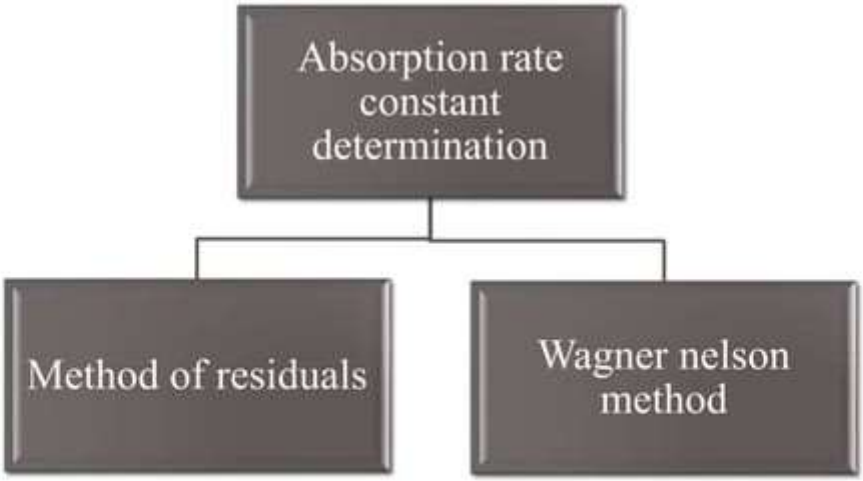
F=Fraction of drug absorbed systematically after e.v.administration

- Here from the EV absorption study the t_{max} and c_{max} can be calculated

$$t_{max} = \frac{2.303\log(\frac{Ka}{Ke})}{Ka - Ke} \quad C_{max} = \frac{FX0}{Vd} e^{-Ketmax}$$

DETERMINATION OF ABSORPTION RATE

- It is the most important pharmacokinetic parameter when a drug follows first order absorption. It can be calculated by two methods in one compartment open model they are:



METHOD OF RESIDUALS

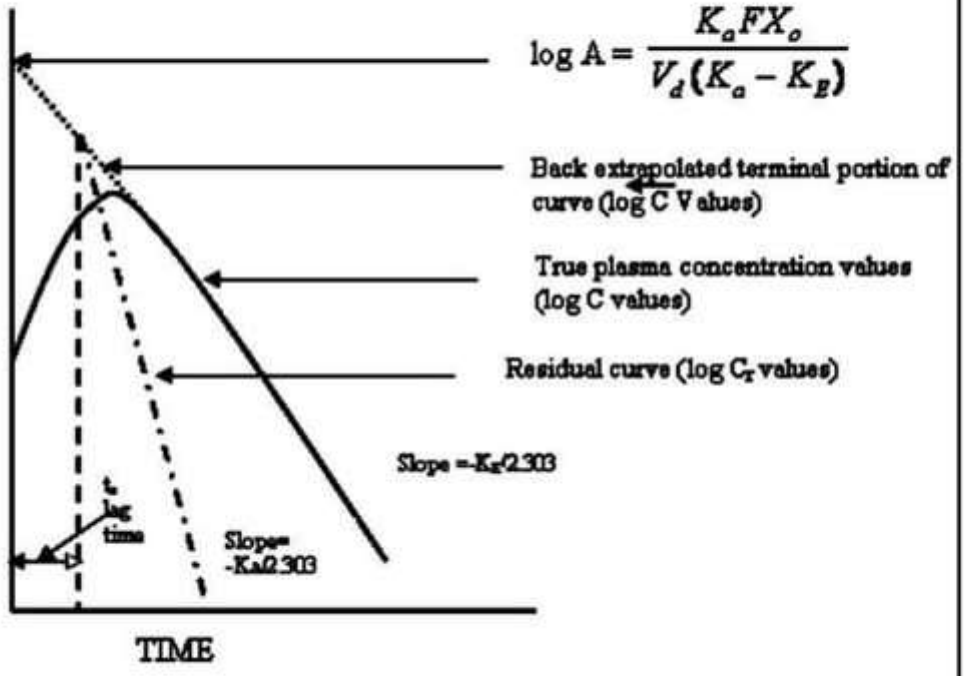
- This method also called as feathering, peeling and stripping.

  For a drug that follows one compartment and it is a biexponential equation.

- $C = \frac{K_a F X_0}{V_d(Ka-KE)} [e^{-KEt} - e^{-Kat}]$
- $C = Ae^{-KEt} - Ae^{-Kat}$
- $\overleftarrow{C} = Ae^{-KEt}$

$$\log \overleftarrow{C} = \log A - \frac{-KEt}{2.303}$$

Graphical representation of method of residuals



- Subtraction of true values to extrapolated concentration that is residual concentration.

$$C_r = Ae^{-Kat}$$

$$logC_r = logA - \frac{-Kat}{2.303}$$

- If $K_E/K_a \geq 3$ the terminal slope eliminates K_a and not K_E. The slope of residual lines gives K_E and not K_a.

- This is also known as flip-flop kineticsas the slopes of two lines exchanged their meanings.

Extrapolated concentration (C_E)	Original concentration (C_0)	Residual concentration (C_E-C_0)
5.8mg/ml	2.5mg/ml	3.3mg/ml

Residual concentration= C_E-C_0

- **Lag time:**

- It is defined as the time difference between drug administration and start of absorption. It is denoted by t_0.
- This method is best suited for drugs which are rapidly and completely absorbed and follow one compartment kinetics even when given i.v.

WAGNER NELSON METHOD

- One of the best alternatives to curve fitting method in the estimation of K_a is Wagner Nelson method.
- This method involves the determination of K_a from percent unabsorbed time plots and does not require the assumptions of zero or first order absorption.
- According to this the amount of drug in body is depicted as

$$X_A = X + XE$$

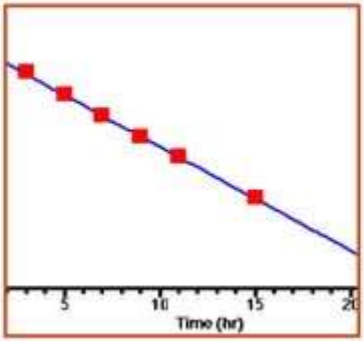
- $X_A^t = V_d C + VdK[AUC]_0^t \longrightarrow (1)$
- $X_A^\infty = V_d C^\infty + V_d K[AUC]_0^\infty \longrightarrow (2)$
- $\frac{(1)}{(2)} = \frac{X_A^t}{X_A^\infty} = \frac{V_d C + VdK[AUC]_0^t}{V_d K[AUC]_0^\infty}$

$$= \frac{X_A^t}{X_A^\infty} = \frac{C + K[AUC]_0^t}{K[AUC]_0^\infty}$$

If the fraction of total amount of drug absorbed = 1

- Amount remaining to be absorbed = $1-\frac{X_A^{\,t}}{X_A^{\,\infty}}$.
- Amount remaining to be absorbed = $1-\frac{C+K[AUC]_0^{\,t}}{K[AUC]_0^{\,\infty}}$
- % amount remaining to be absorbed= $(1-\frac{C+K[AUC]_0^{\,t}}{K[AUC]_0^{\,\infty}})\ 100$
- A graph is plotted by taking log%ARA on Y-axis and time on X-axis a straight line is obtained from that slope K_a is determined.

Log%ARA



URINARY EXCRETION STUDIES

- It is the best method to describe and determine the excretion and elimination rate constants.
- **Advantages**

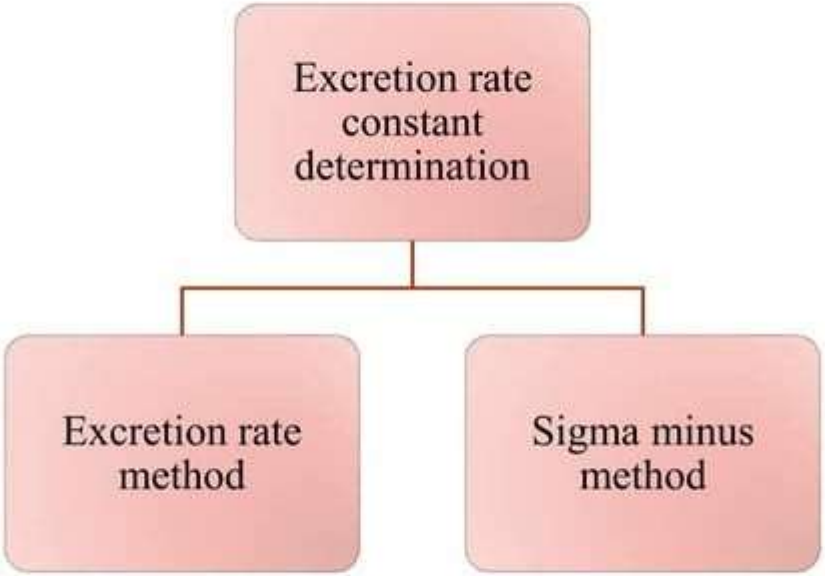
✓ The method is non-invasive and therefore better subject compliance is assured.

✓ This method is more convenient since it involves the collection of urine samples in comparison to drawing of blood periodically.

✓ When coupled with plasma level time data it can also be use to estimate renal clearance of unchanged drug according to the formula

$$cl_R = \frac{total\ amount\ of\ drug\ excreted\ unchanged}{area\ under\ plasma\ level\ time\ curve}$$

Estimation of excretion rate constant:



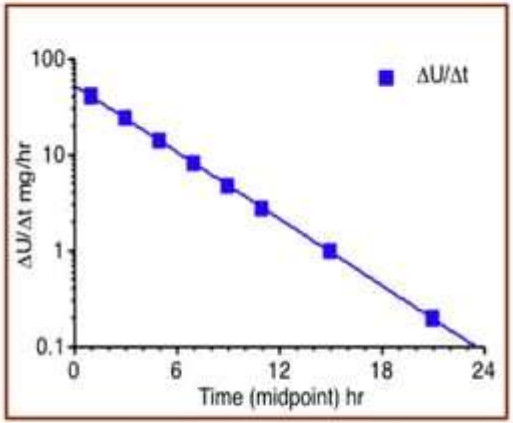
EXCRETION RATE METHOD

- The appearance of drug in urine can be mathematically depicted as

$$\frac{dx_u}{dt} = K_E X$$

$$\frac{dx_u}{dt} = k_E X_0 e^{-kt} \quad (X = X_0 e^{-kt})$$

$$log \frac{dx_u}{dt} = log k_E X_0 - \frac{kt}{2.303}$$



- ✓ In this both the elimination and excretion rates are determined.
- ✓ The main disadvantage is that the rate of excretion is not constant and the values are scattered.

SIGMA MINUS METHOD

- The appearance of drug in body can be represented as

$\frac{dx_u}{dt} = K_E X$

$\frac{dx_u}{dt} = \mathrm{kEX}_0 e^{-kt}$ integrate on both sides

$$x_u = xu^{\infty}\left(1 - e^{-kt}\right)$$

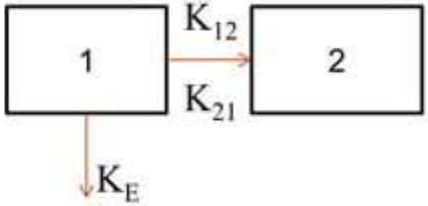
Applying log on both sides

$$log(x_u{}^{\infty} - xu) = logx_u{}^{\infty} - \frac{kt}{2.303}$$

- The main disadvantage is the total urine collected has to be carried out until no unchanged drug can be detected in urine up to 7 half lives which may be tedious for drugs having long $t_{1/2}$.

TWO COMPARTMENT OPEN MODEL

- It is common in all multi compartment models.
- It consists of central compartment i.e., compartment 1 comprising of blood and highly perfused tissues and peripheral compartment i.e., compartment 2 comprising of poorly perfused tissues such as skin and adipose tissues.
- **INTRAVENOUS BOLUS:**



The model can be mathematically represented as

$$\frac{dc_c}{dt} = K_{21}C_p - K_{12}C_c - KEC_c$$

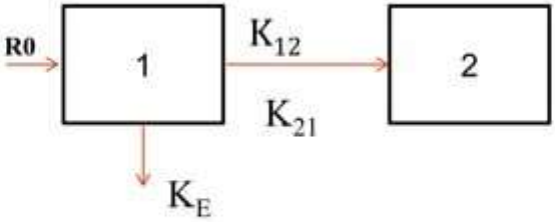
$C_c = Ae^{-\alpha t} - Be^{-\beta t}$

α and β are hybrid constants then

$\alpha + \beta = K_{12} + K_{21} + K_E$

$\alpha \beta = K_{21} K_E$

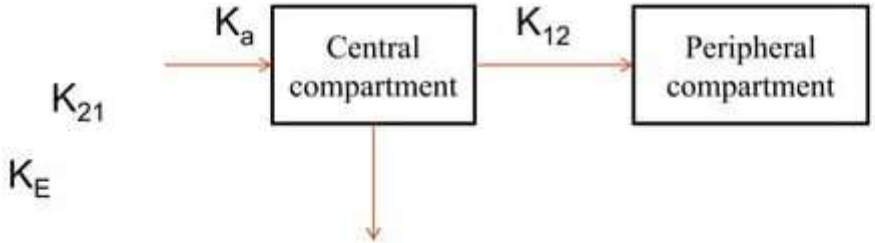
Intravenous infusion



$c = Ro/VcK_E(1 + (KE - {}^{\beta}/_{\beta-\alpha})e^{-\alpha t} + (K_E - \alpha/\alpha - \beta)e^{-\beta t})$.

EXTRAVASCULAR ADMINISTRATION

- In two compartment open model for extravascular administration it can be depicted as



$$C = Ne^{-Kat} + Le^{-\alpha t} + Me^{-\beta t}$$

The absorption rate is calculated by Loo-Regeilmann method.

LOO REGEILMANN METHOD

According to mass balance equation

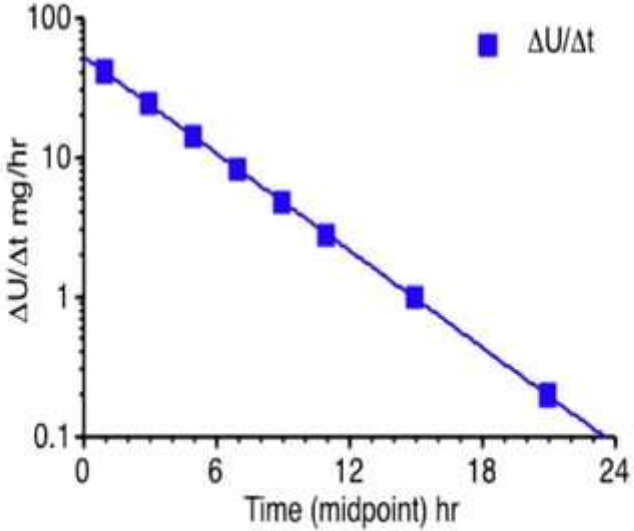
$$X_a = X_c + X_t + X_3$$

from the formula $X=V_dC$

- Fraction remaining to be absorbed= $1-\frac{X_A^t}{X_A^\infty}$.
- ARA $= 1-\frac{C_c+Ct+K[AUC]_0^t}{K[AUC]_0^\infty}$

%ARA $= (1-\frac{C_c+Ct+K[AUC]_0^t}{K[AUC]_0^\infty})100.$

- A graph is plotted by taking log %ARA on y-axis and time on x-axis a straight line is obtained and slope of that gives absorption rate i.e., slope= $\frac{-Ka}{2.303}$.



CONCLUSION

- Compartment model provides a framework for the study of the dynamic flow of chemicals (nutrients, hormones, drugs, radio-isotopes, etc.) between different organs which are assumed as compartments in the human body.

- Multi-compartment models have applications in many fields including pharmacokinetics, epidemiology, biomedicine, systems theory, complexity theory, engineering, physics, information science and social science.

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THANK YOU

Topic –
Pharmacokinetic parameters

Presented By
Mr. Vishal V. Kalal
Ass. Prof.

JES'S College Of Pharmacy Nandurbar.

Scheme of presentation

1. Introduction

- Pharmacokinetics & ADME processes
- Important terminologies

2. Pharmacokinetic parameters that can be estimated

° Absorption4 K, Bioavailability, Salt factor

- Distribution Vp Distribution eqm., Distr. Rate constt.
- Elimination4 $t_1 t_2$ Clearance,0,1st,m. order kinetics, K_{el}

Processes of drug therapy

1. Pharmaceutical process

   "Is the drug getting into the patient ?"

2. Pharmacokinetic process

   "Is the drug getting to its site of action ?"

3. Pharmacodynamic process

   "Is the drug producing the required pharmacol. Effect ?"

4. Therapeutic process

   "Is the pharmacol. Eff. Being translated into a ther. Eff. ?"

Pharmacok. & Clin. Pharmacok.

Pharmacokinetics[1] "The study of kinetics of absorption, distribution, metabolism & excretion (ADME) of drugs & their corresponding pharmacologic, therapeutic, or toxic responses in man and animals"

Clinical pharmacokinetics[2] Application of pharmacokinetic principles to safe & effective therapeutic management of drugs in a patient

1 - American Pharmaceutical Association

ADME processes

1. Absorption -3' Drug proceeds from site of admin. to site of measurement (usu. bl., plasma/serum)
2. DistributionU Reversible transfer of drug to & from the site of measurement (usu. bl. or plasma)
3. Metabolism Conversion of one chemical species to another chemical species
4. Elimination -3' Irreversible loss of drug from site of measurement (blood, serum, plasma)
   - Occurs by either metabolism / excretion, or both

Biopharmaceutics

“The study of factors influencing bioavailability of a drug in man & animals & the use of this information to optimize pharmacological & therapeutic activities"[1]

1 - American Pharmaceutical Association

Pharmaceutical/Chem. equivalence

- 2 / more dosage forms of the same drug contain same labeled quantities of drug as specified in pharmacopoeia
- Dosage forms meet req. estd. By USP / NF such as —

1. Purity
2. Content uniformity
3. Disintegration time

- Eg.U Dilantin & Eptoin may be chem. equiv. if they contain same qty. of Phenytoin on chemical assay

Bioequivalence

- 2 / more chemically / pharmaceutically equivalent products produce comparable bioavailability char. ("big three" parameters) in any individual when administered in equivalent dosage regimen

- Parameters compared are:-

1. AUC
2. Max. plasma conc. (C „)
3. Time of peak plasma conc. (t „)

Eg. -3' Dilantin & Eptoin may be bioequiv. if their plasma level profiles are comparable & super imposable within prescribed limits

Therapeutic equivalence

- 2 / more chemically or pharmaceutically equivalent products produce the same efficacy & / or toxicity in the same individuals when administered in an identical dosage regimen
- Eg. Trifluperazine (Phenothiazine grp.) may be ther. Equiv. to Haloperidol (Butyrophenone grp.) if both provide equiv. ther. Results in the t/t of Schizophrenia

Clinical equivalence

- 2 brand products of the same drug produce "identical in *vivo* pharmacological response" (Control of symptoms / disease)
- Eg. Dilantin & Eptoin may be clinically equiv. if both prOduce same pharmacological response

Parameters that will be estimated

1. Absorption
   - Bioavailability {$C_{m„,}$, $t_{m„,}$, ALIC)
   - Absorption rate constant (K_a)
   - Salt factor
2. Distribution
   - Volume of distribution
   - Distribution equilibrium
   - Distribution rate constant
3. Elimination
   - Clearance
   - Half-life
   - 1st order, 0 order and mixed order kinetics
   - Elimination rate constant (@,), K_u, Kg

Bioavailability

"The relative amount of an administered dose that reaches the general circulation & the rate at which this occurs" [1]

"The rate & extent to which the active ingredient or therapeutic moiety is absorbed from a product & becomes available at the site of drug action" [2]

"Fraction of the dose of drug (F) that is absorbed & escapes any first pass elimination" ^

1 - American Pharmaceutical Association

2 – US FDA

3 – Goodman & Gilman's Pharmac. Basis of therap. 12th Edition

$$Bioavailability = \frac{t \quad of\ drug\ reaching\ sys.\ circ.}{\text{Qty. } of\ drug\ \text{Admin.}}$$

Indicators of rate of absorption4 $C_{ma.,'ma.}$

Indicator of extent of absorption -' AUC (mg-hr/ml)

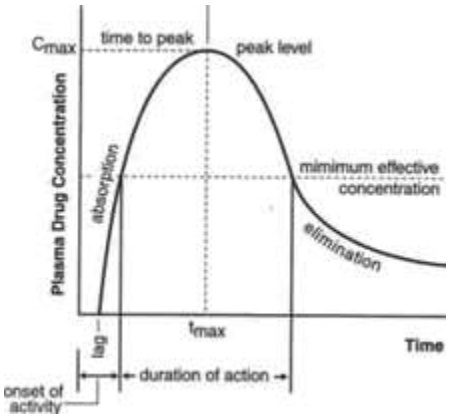
Inc. rate of abs.U Higher peak at a shorter time

C „ Peak plasma conc.

Te_a, Time taken to reach peak plasma conc.

AUC -3 Total systemic exposure of body to the drug

Plot of plasma conc. v/s time



Types of bioavailability

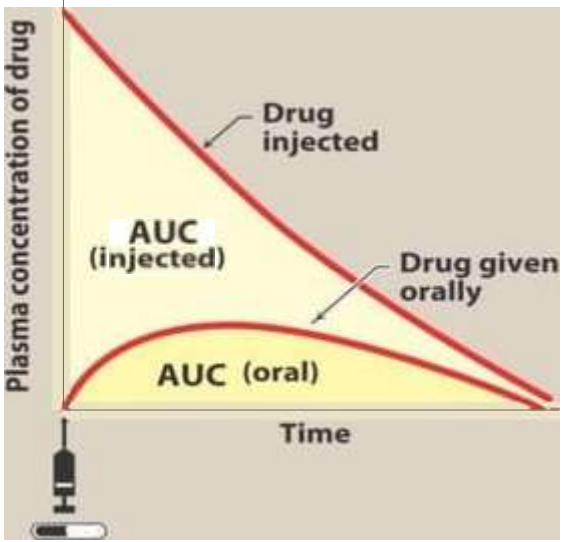
1. Absolute -' Comparing values of AUC &/or X, loll. Admin. of drug in an extravasc. Dosage form & an equal dose of the same drug i.v. (i.v. bolus)
2. Comparative (Relative) -' Comparing bioavail. parameters derived from

    a) PI. drug conc. v/s time plot data &/or

    b) Urinary excretion data foll. Admin. of drug in 2 diff. dosage forms (Tablet & Syrup, Capsule & suspension) &/or

    c) 2 diff. extravasc. routes of adm. (Oral & i.m.)

$$\text{Bioavailability} = \frac{\text{AUC oral}}{\text{AUC injected}} \times 100$$



Drug admintrterod

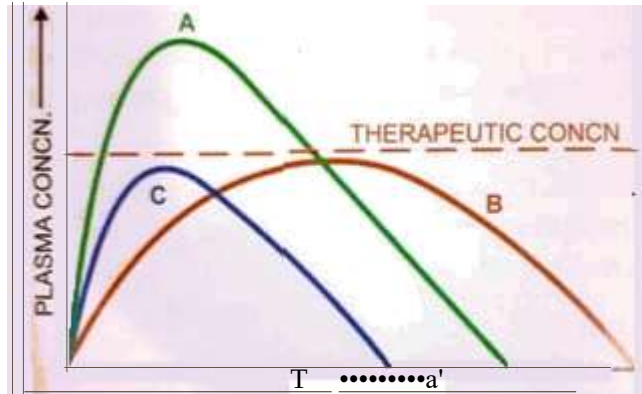


Fig. k6: Plasma roenlratton-I tia ounres depic1i

a drug containing the s¥me amount
NkKe that Iorr¢ulalion 6 is mora sbwly abcorbed thar,
W tlough ullimately t›oth are abaoñ›ed lo the saw
(aha 0Fd8£ N6 MN8 }, g may got produ
Me*®gau!i¢ 8lf8¢t: C is Bbcorbed to a Ie8aer exlent
lower bioavailability

Absolute bioavailability

1. From AUC

- $F = \frac{tAUC\ \ )exti\ avascular}{(AUC_0^{\infty})i.v.} \times \frac{Dose,}{Dose_{extravascular}}$

2. From urinary data

- $F = \frac{(X_u)\ \ ^{extravascuio3}_{t-7t\ \ /p}}{(X_u)\ \ ^{i.v.}_{t=7t_{1/2}}} X \frac{Dose_{i.v.}}{DaS€\ extr\ ovascu\ far}$

NOTE :-

1. F Fraction of drug absorbed
2. F is always fi 1
3. X = * Cumulative mass of drug exc. in urine

Relative bioavailability

1. From AUC

- $F_{rel} = \frac{(AUC_0^{\infty})tablet}{(ACf6\quad)soiution} \quad \frac{Dos\ e_{so}\ Ini\ tort}{Dose\ z\ bI\ \langle}$ OR

$$rel \quad \frac{(AUC_0^{\infty})i.m.}{(AUC_0^{\infty})oral} X \frac{Dose_{oral}}{Dose_{i.m.}}$$

2. From urinary data

$$F_{rel} \quad \frac{(\quad It\ )\quad tablet}{(y\quad)\quad solution} \frac{L-7\ /z}{1/2} \quad \frac{Dos\ l_{soi}union}{Doseqz\ olet}$$ OR

- $F_{rel} = \frac{(X_u)\quad t=7t\ /}{(X_u)\quad oral\ t=7t_{1/2}} X \frac{Dose_{oral}}{Dose,}$

$\Longrightarrow$ F_{rel} 1 1

Examples

1. Valium (Diazepam) Tablet (oral) & injection (i.m.)
2. Tagamet (Cimetidine) -2 Tablet & syrup
3. Cephalexin -3 Capsule (generic product) marketed by 2 diff. manufacturers

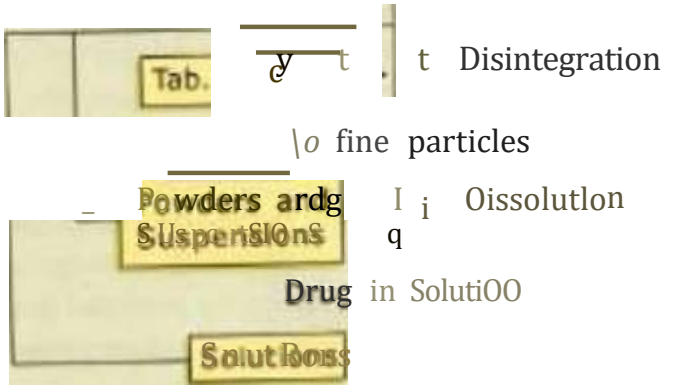
Factors affecting bioavailability

1. Pharmaceutical factors
    - i) Particle size
    - ii) Salt form
    - iii) Crystal form
    - iv) Water of hydration
    - v) Nature of excipients & adjuvants
    - vi) Degree of ionisatiOn

o‹ai adrninlsEraFion of drug

(Dosaqe Form: Tab/Cap/Powdery

Sotgtion/Euspension \



t Disintegration

\o fine particles

I ¡ Oissolutlon

q

Avai Table f•t abSOrgtio• through GIT

Tablet	Capsule	Suspension	Solution

2. Pharmacological factors

i) Gastric emptying & GIT motility

ii) Gastrointestinal disease

iii) Food & other substances

iv) First pass effect

v) Drug-drug interactions

vi) Pharmacogenetic factors

vii) Miscellaneous factors

a) Route of administration

b) Area of absorbing surface

c) State of circulation at abs. site

Bioavailability

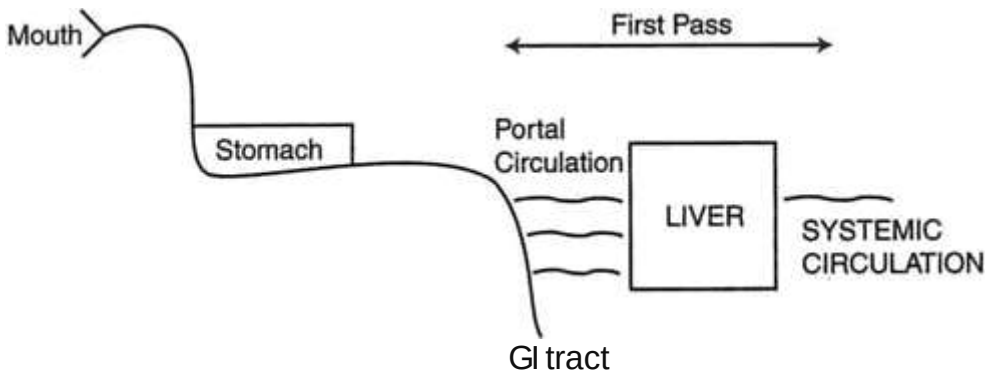
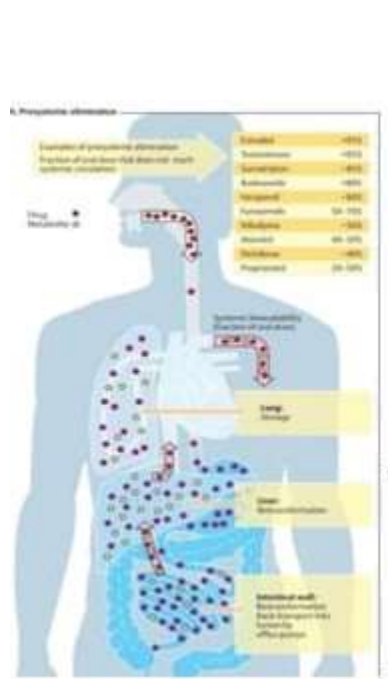
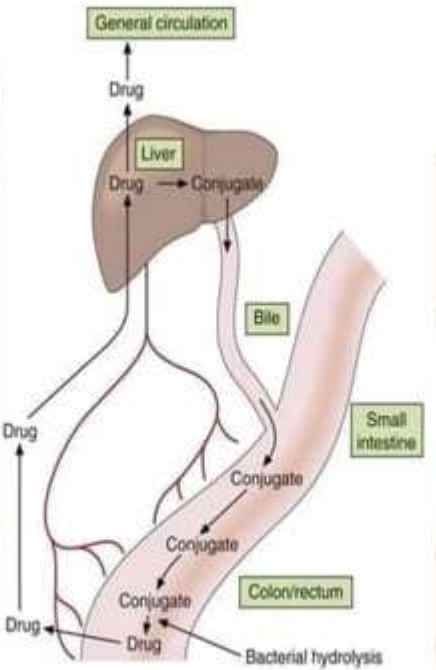
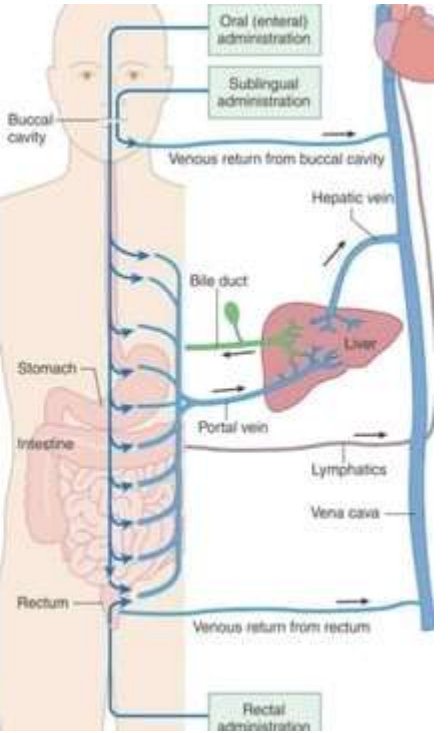


Figure I-IN. Bioavailablìlty and Flret-Paee Metabollsm

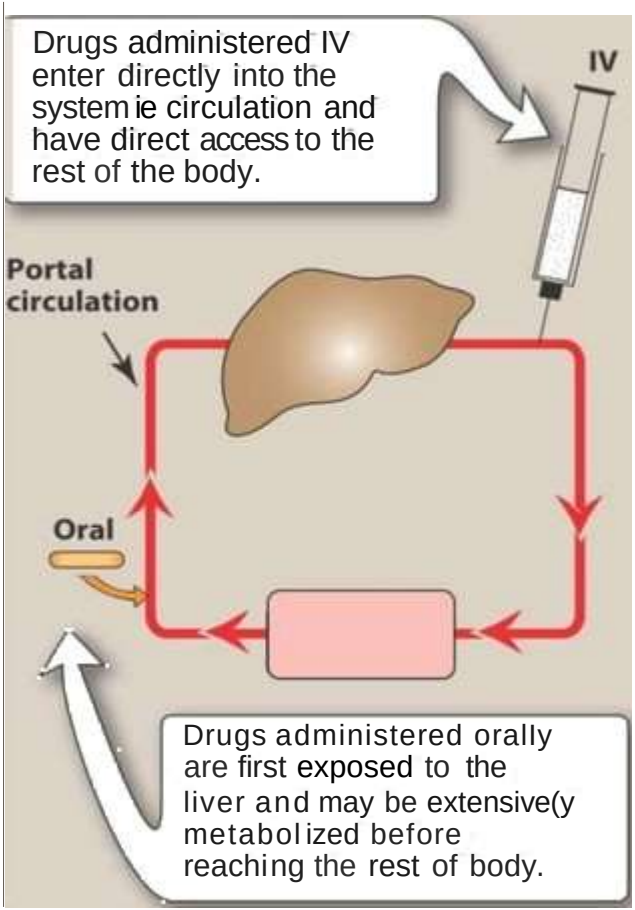
First pass metabolism







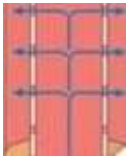
Drugs administered IV enter directly into the systemie circulation and have direct access to the rest of the body.

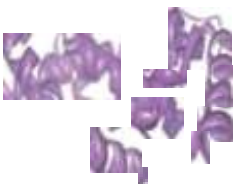


Drugs administered orally are first exposed to the liver and may be extensive(y metabolized before reaching the rest of body.

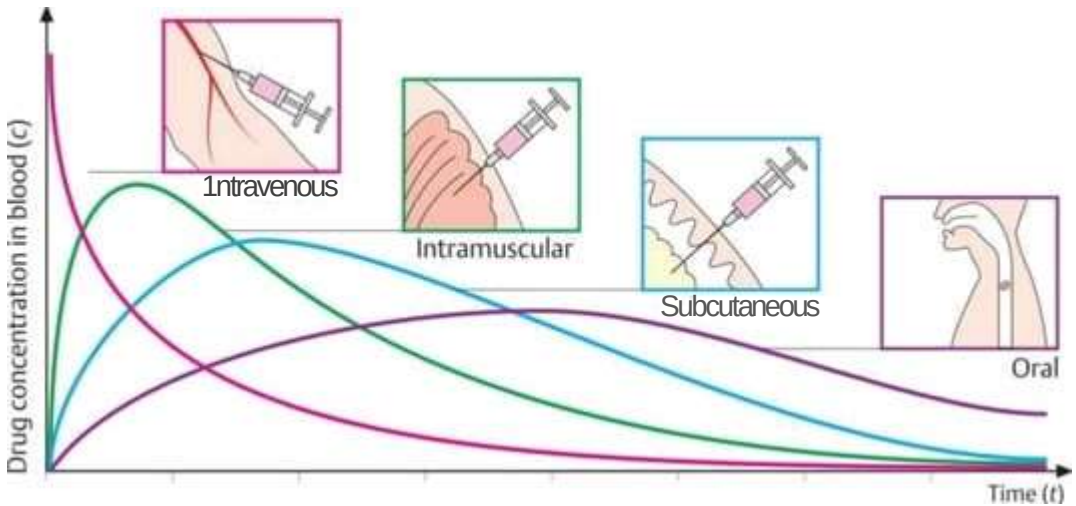
„-„ ‚m.

’ ‘

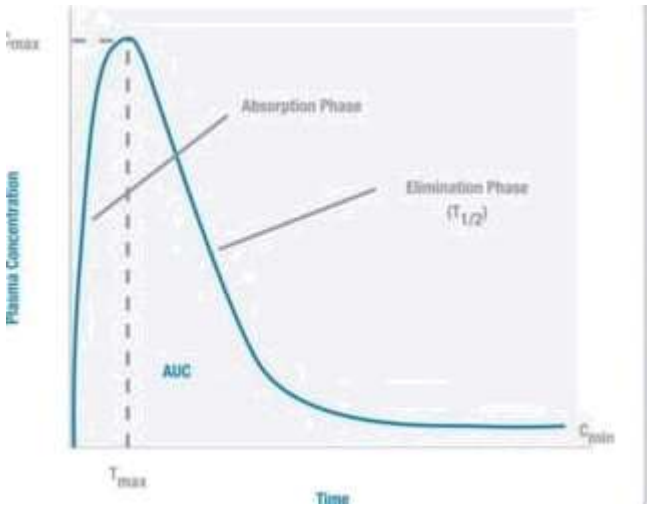


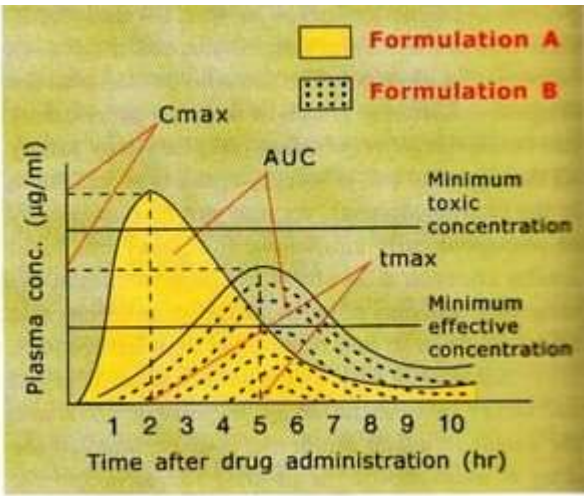


8- ßł•de ef application and Nme concse efdrug concenDation



C de,t ke^ Area under curve (AUC)





Common AUC estimates

1. AUC (exact AUC)
2. AUCp., or AUC „st -3' AUC calc. from time 0 to time of last observed conc.
3. AUC, 4 AUC calc. from time 0 to the last sampling point
4. AUCy „(estimated) -3' $AUC_{0\cdot t}$ + AUC_t.

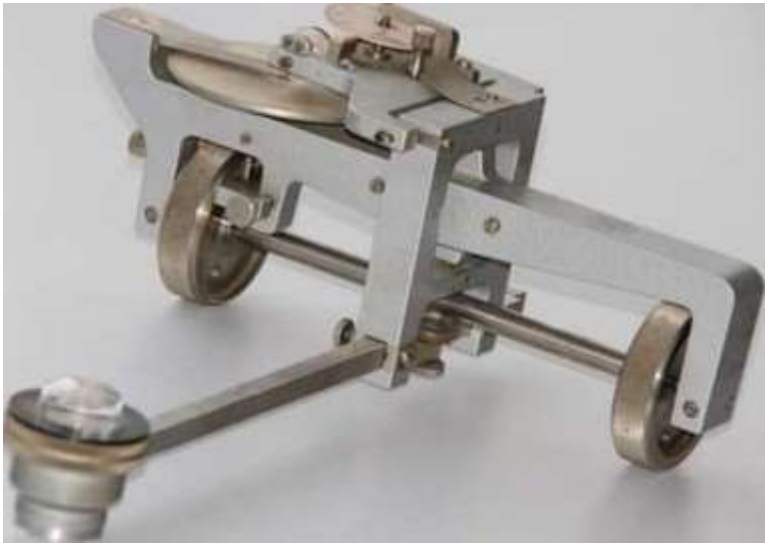
$$AUC_{t-\infty} = \frac{C1nsr}{K_{el}}$$

- Coa4 Last observed conc.
- K_ey-' Elim. rate con

Methods to measure AUC

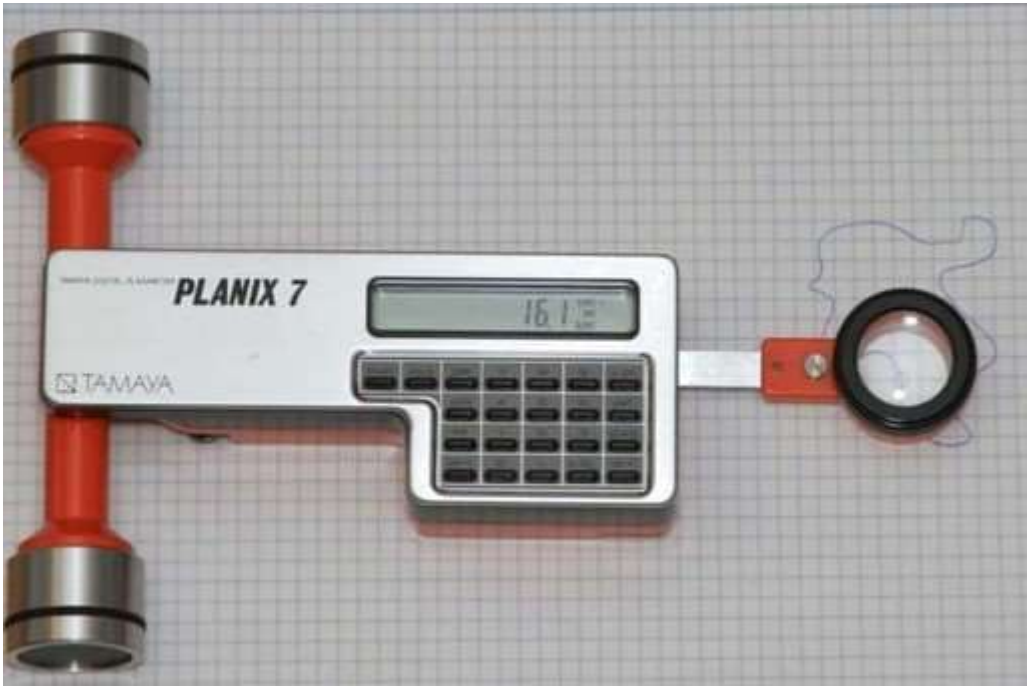
1. Planimeter W An instrument for mechanically measuring the area of plane figures
2. ”Cut and weigh” method
3. Trapezoidal rule
   - Linear method
   - Logarithmic method
4. Integration method
5. Tai's formula

Linear planimeter



Polar planimeter

Digital Planimeter



Linear plani.

Polar plani.

Principle of linear planimeter

Cut & weigh method

Curve is plotted on a rectilinear graph paper

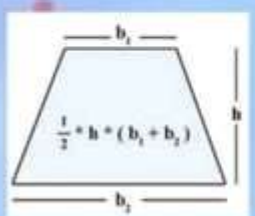
Area is cut out

Weighed on an analytical balance

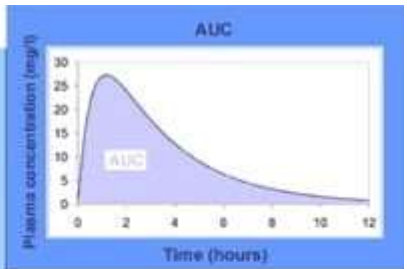
Trapezoidal rule

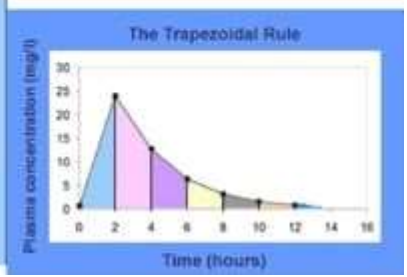
Calculating the area of a trapezoid

- $h = (t_2 - t_1) = \Delta t$
- $b_1 = C_2$
- $b_2 = C_1$



$$AUC_{t_1-t_2} = \frac{1}{2} * \Delta t * (C_1 + C_2)$$





AUC = AUC0-2 + AUC2-4 + AUC4-6 + AUC6-8 + AUC8-10 + AUC10-12 + AUC last-infinity

Linear or Logartihmic ?

Linear method (most common method) used if —

1. Conc. Are increasing over time (abs. phase)
2. Conc. Are decreasing in polyexponential fashion
3. Any generic drug application

Logaritnmic method used if —

1. Conc. Are decreasing in monoexponential fashion
2. At the end of curve when AI is large

Numerical Estimation

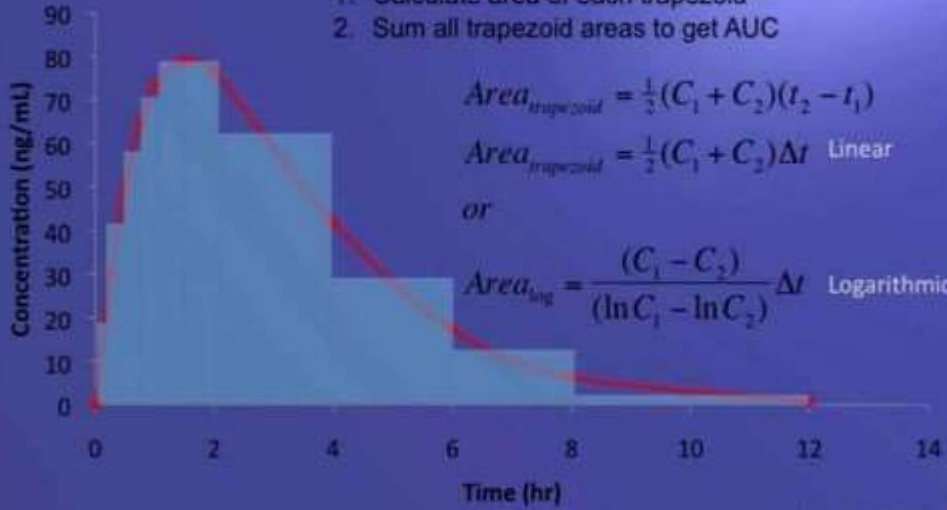
1. Calculate area of each trapezoid
2. Sum all trapezoid areas to get AUC

$$Area_{trapezoid} = \frac{1}{2}(C_1 + C_2)(t_2 - t_1)$$

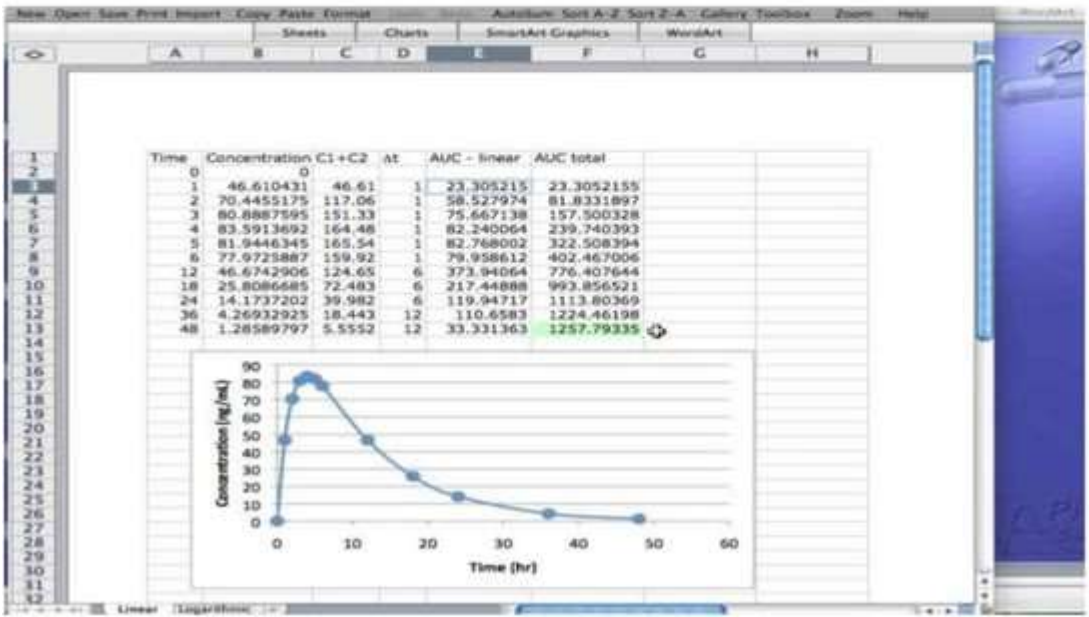
$$Area_{trapezoid} = \frac{1}{2}(C_1 + C_2)\Delta t \quad \text{Linear}$$

or

$$Area_{log} = \frac{(C_1 - C_2)}{(\ln C_1 - \ln C_2)}\Delta t \quad \text{Logarithmic}$$

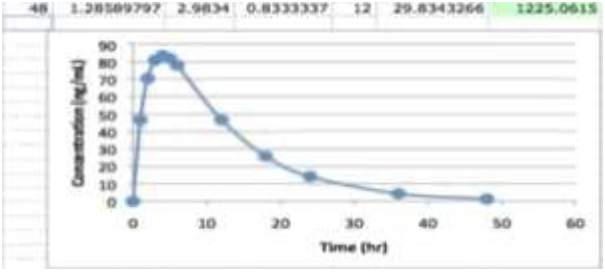


Linear method



Time	Concentration	C1+C2	Δt	AUC - linear	AUC total
0	0				
1	46.610431	46.61	1	23.305215	23.3052155
2	70.4455175	117.06	1	58.527974	81.8331897
3	80.8887595	151.33	1	75.667138	157.500328
4	83.5913692	164.48	1	82.240064	239.740393
5	81.9446345	165.54	1	82.768002	322.508394
6	77.9723887	159.92	1	79.958612	402.467006
12	46.6742906	124.65	6	373.94064	776.407644
18	25.8086685	72.483	6	217.44888	993.856521
24	14.1737202	39.982	6	119.94717	1113.80369
36	4.26932925	18.443	12	110.6583	1224.46198
48	1.28589797	5.5552	12	33.331363	1257.79335

Logarithmic method



Integration method

- / *Cydt —(AUC)0* $\frac{Dose}{CL_S} = \frac{X_0}{VK}$

  Cp -2 Plasma conc. At time t
- X_0 Administered dose
- V Apparent volume of distrib.
- K -2 1^s*order elimination rate constant
- CLV Systemic clearance

Tai's formula

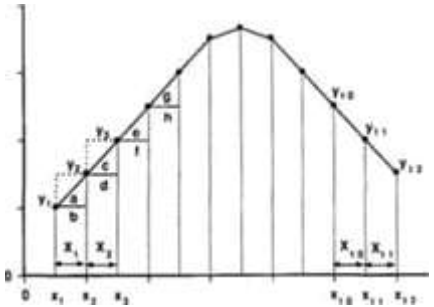


Figure 1—*Total area under the curve is the*

$$\text{Area} = \frac{1}{2}\sum_{i=1}^{n} x_{i-1}\,(y_{i-1} + y_i)$$

Interpolation & Extrapolation

- Interpolation W Estimating values b/w 2 known data points
- Extrapolation -3' Estimating values outside the known data
- 2 methods of interpolation

1. Linear interpolation
2. Log-linear interpolation

Interpolation equations

- Linear

  AfJI ,. t; =‘ (rø ti)(f•i + Cø)

- Log-linear

$$AUC_{t_1-t_2} = (t_2 - t_1)\frac{(C_1 - C_2)}{ln\left(C_1/C_2\right)}$$

Absorption rate constant (a)

- Fractional rate of drug absorption from the site of administration into the systemic circulation
- Rate of abs. Mass of drug avail. For abs. X K_a
- Clinical imp. -' K_a determines time reqd. for admin. drug to reach an effective plasma concentration

U Influences both C, „ & t „

- $t_{max} = \frac{\ln(K_a) - \ln(K_{el})}{K_a - K_{el}}$

Salt factor (S)

- Drug is admin. as a salt
- Proportion of the parent drug contained in the salt (weight/weight basis)
- Dose of salt - Dose of drug reqd. (D) / Salt factor (S)
- AminophyllineU Theophylline + ethylenediamine
- D=400 mg; S=0.8
- Aminophylline reqd.U 500 mg

Apparent volume of distribution (V)

U NOT a physiological volume

-' Gives info. On HOW the drug is distrib. In the body

E A proportionality constant to relate

-3' Plasma conc. (Cl)

4 X (Mass of drug in the body at a time)

E Desc. extent to which drug is distr. in body tissues

U Essential to determine the dose of a drug reqd. to attain the desired initial plasma conc.

- It also reflects
  - If drug is lipophilic / hydrophilic ?
  - Chemical str. Of a drug
- VU Gtr. Is the extent to which drug is distr. In body tissues & lesser the initial plasma conc.
- V is constant for a given drug
- V is independent of
  - Administered dose
  - Ra ute of dru g admi nistratiDn

$$P - \frac{\text{“}}{Conc.of\ \ddot{a}ritg\ \text{in}\ pInsma\quad \text{tu}g/L}\ \text{OR}$$

$$\frac{Dose\ administered\ \text{i. r.}}{Plasma\ conc.}$$

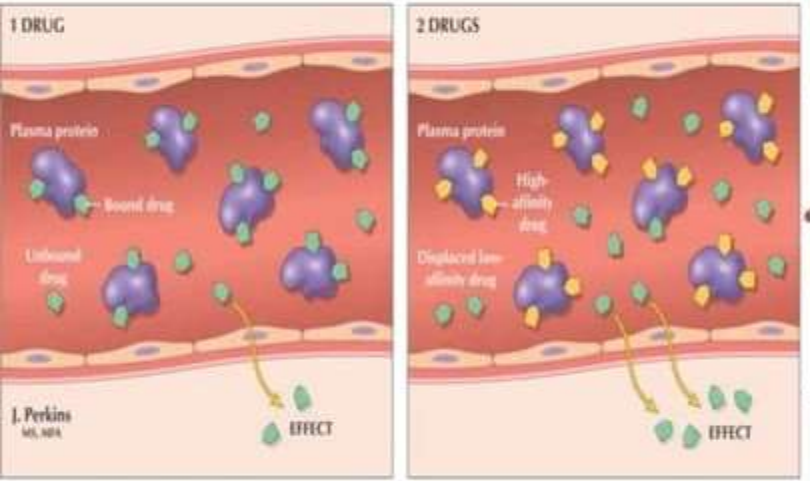
Why “Apparent” V ?

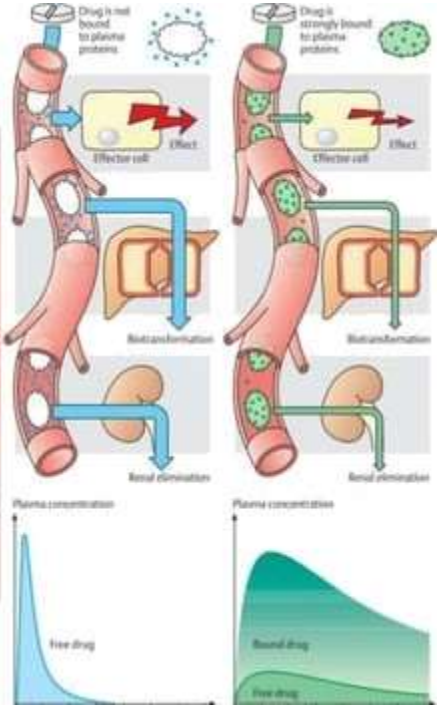
- Signifies that the volume determined has the appearance of being true but is actually not
- It is not a TRUE volume but it does have the appearance of being the actual volume into which a given amt. of drug would be diluted in order to produce the observed conc.

Factors affecting distribution

1. Lipid solubility
2. Ionization at physiological pH
3. Plasma protein binding
4. Presence of tissue specific transporters
5. Differences in regional blood flow

Plasma protein binding





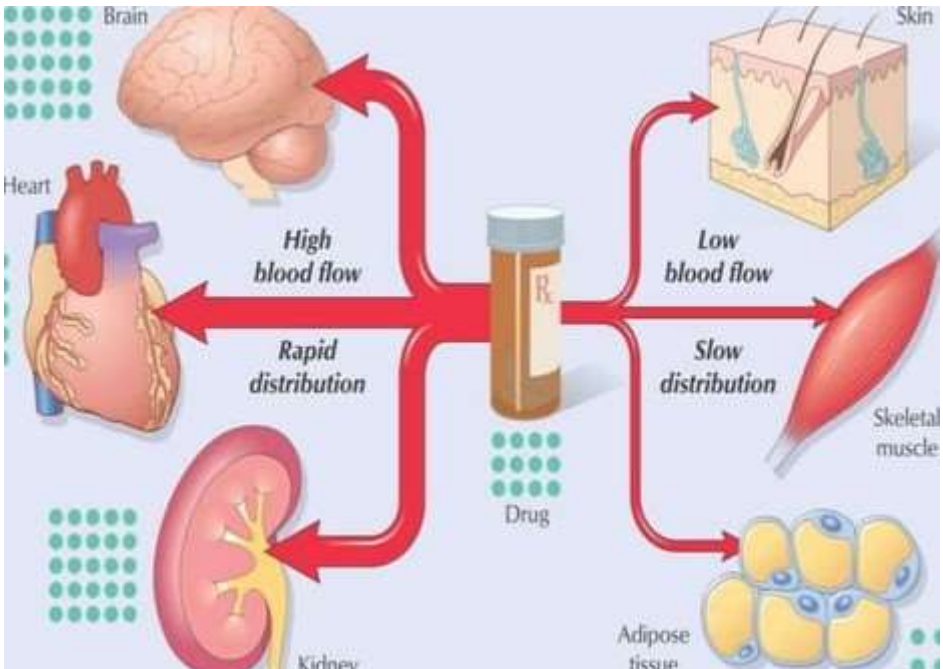
Distribution equilibrium

- Rate of transfer of drug from blood to various organs & tissues = Rate of transfer of drug from various tissues & organs back into the blood
- Rapid distrib. -2 Rate of transfer of drug from blood to all organs & tissues & vice-versa have become equal instantaneously following administration (intra/extra vascular) of the dose of a drug

Distribution rate constant (kT)

- Measure of how rapidly drug would leave tissue if the arterial concentration were to drop to zero
- Fractional rate of drug distribution from an organ to blood

Redistribution



- Seen in highly lipid soluble drugs

Thiopentone given i.v.

Enters brain in 1 circul. time (1 min. after i.v. inj.)

General anaesthesia

Rapidly diffuses out of brain through blood circulation

Redistributed in muscle, lean tissues & fat

Action gets terminated

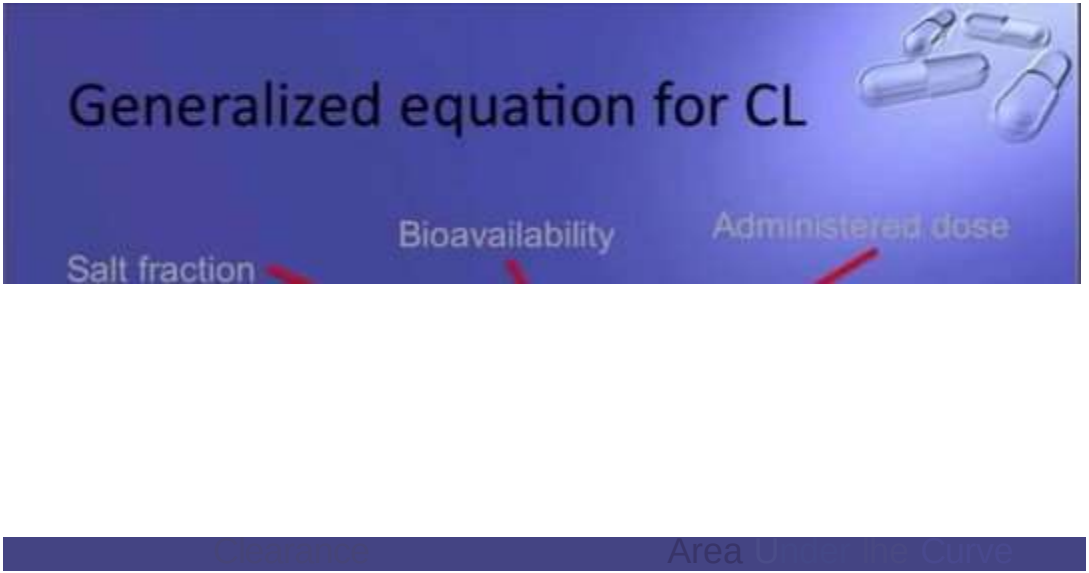
Clearance (CL)

"The hypothetical volume of blood (plasma/serum) OF Other biolog. fluids from which the drug is tOtdIly & irreversibly removed per unit time"

$$L_{S'} \quad L_{n} + CLV$$

$$CL = K \times V$$

- Larger the clearance -3' More efficient Is the eliminating organ (Kidney & liver)
- Limiting factor
    1. Vol. of bl. presented to the E'liminating organ/unit time
    Z. Extraction ratio of the organ
- KidneyU 19 ml/min./kg
- Liver -' 1.5 L/min.
- Rate of elimination = Syst. CI. X Plasma conc.
- ('"——) ** (Cp) t where
- XU Mass of drug in body at time t


Generalized equation for CL
Bioavailability
Administered dose
Salt fraction
Clearance
Area Under the Curve

Types of clearance

1. Systemic (CL,) / TBC4 Sum of all indiv. Organ CL
2. Renal (CL,) -3' Drug removed by renal excretion
3. Metabolic (CLV)4 Drug removed from blood by metabolism, from whatever metabolic organ
4. Hepatic (CLV) -3' Drug removed by hep. Metabol.
5. Intrinsic (CL„,)4 Organ clearance a drug would have if it was not restricted by organ BI. Flow rate
6. Intrinsic free/Unbound (CL'„,)4 Intrinsic cl. A drug would have in the absence of plasma protein binds ng

   CL'„, - (CL„,) / f„

   f_un Fraction of drug unbound in plasma

Organ clearance

Q W Blood flow through an eliminating organ (ml/min)

Cy -3' Drug conc. in venous blood leaving organ (kg/ml)

C_A4 Drug conc. in arterial Blood entering organ (kg/ml)

Rate at which drug enters organ4 C X Q (kg/min)

Rate at which drug leaves organ4 C_V X Q (kg/min)

Rate of elimination = Blood flow rate X conc. Difference

Q (C_A— C)

$$c \qquad \frac{Q'C_A - \mathrm{Cg})}{C_A}$$

Extraction ratio (E)

Dimensionless term

-3'Ratio of rate of elimin. To the rate at which drug enters an organ

U Quantifies efficiency of organ to eliminate the drug

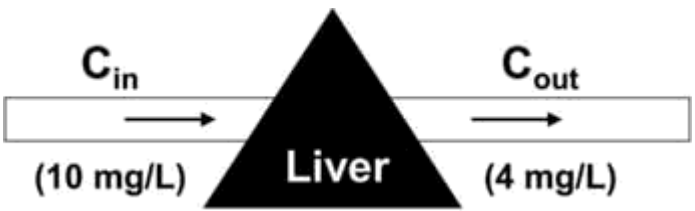
EValue of E is b/w 0 & 1

Elf organ elf. Is minimumU C_A= CyU E = 0

4lf organ elf. Is maximum W C = 0 -' E = 1

$$\rightarrow E = \frac{Rate\ o/\ eiiminntion}{Rate\ in} \qquad \frac{Q\langle C_A - Cy)}{O\ Co)}$$

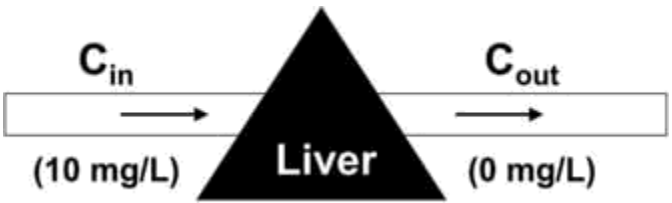
Extraction ratio



$$E = \frac{C_{in} \quad C_{ouî}}{C_{in}}$$

$$E = \frac{10 - 4}{10} = \frac{6}{10} = 0.6 \text{ or } 60\%$$

Complete extraction

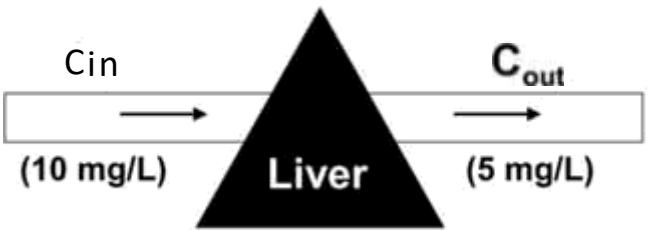


Q = 2 L/min

E = 1.0

Cl = 2 L/min

Partial extraction



- 2 L/min

E —0.5

CI = 2L/min x 0.5 = 1 L/min

Half life (t_1/)

- Elimination / Biological $t_{1\ 2}$ -2 Time duration in which the principal pharmacological eff. Of drug declines by
- Distribution / Plasma t_1t_2U Time duration in which plasma conc. of the drug falls by 50^0/oof the earlier value (Value at equilibrium due to distribution / storage in body's tissue reservoirs)

Determination of elim. $T_1/_2$

Cl $(C)_0 e^{-'t}$; here Cl = 0.5 $(C)_0$, t=t,/y

0.5 = e *'

t ' 04693 K_{el} OR

t} = 0.693 X V_d / CL

NOTE :- $t_1/4$ Constant for a drug

4 Independent of

- Administered dose

Route of drug adm n!stration

Uses of half—life

1. As a guide to the time it takes for a drug to be eliminated from the body
2. As a guide to the rate of accumulation of drug in the body during multiple dosing
3. As a guide to the relationship b/w the loading dose & the maintenance dose

Rate processes

- After drug admin. -3' ADME

° Y -2 Function which changes with time t

It is either :

1. Mass of drug in body (X)
2. Mass of drug in urine (X,), or
3. Conc. Of drug in (Cp) or serum (C,)

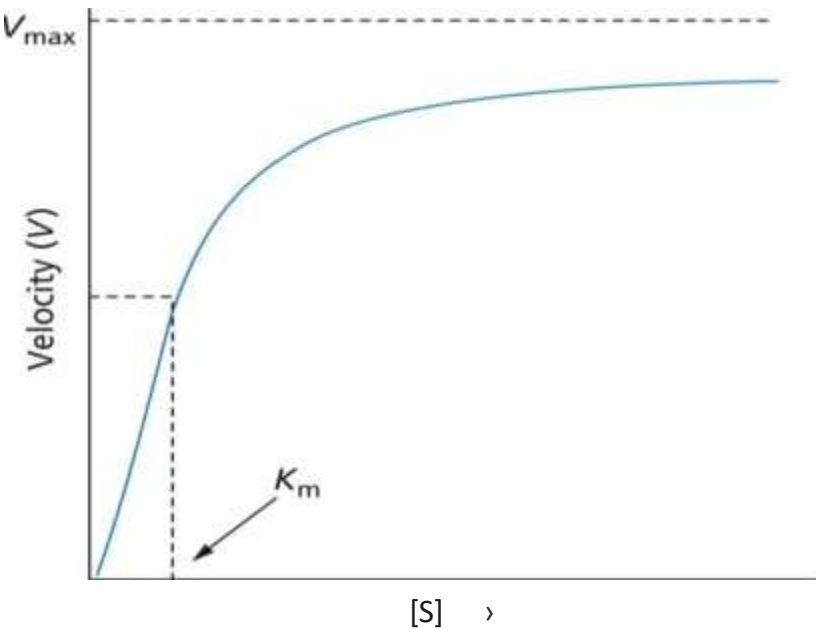
- Y -2 Dependent variable
- T W Independent variable

- For a very small time interval :-
  - $\frac{dY}{dt} \quad \frac{Y2 - Y1}{t2 - t1}$.
- Where
  - dY/dt4 Instantaneous rate of change in function Y with respect to an infinitesimal time interval (dt)

$\frac{dY}{dt}$ —~~K~~ *W* Numerical value (n) of the exponent of the substance (Y) undergoing change is the ORDER of the process

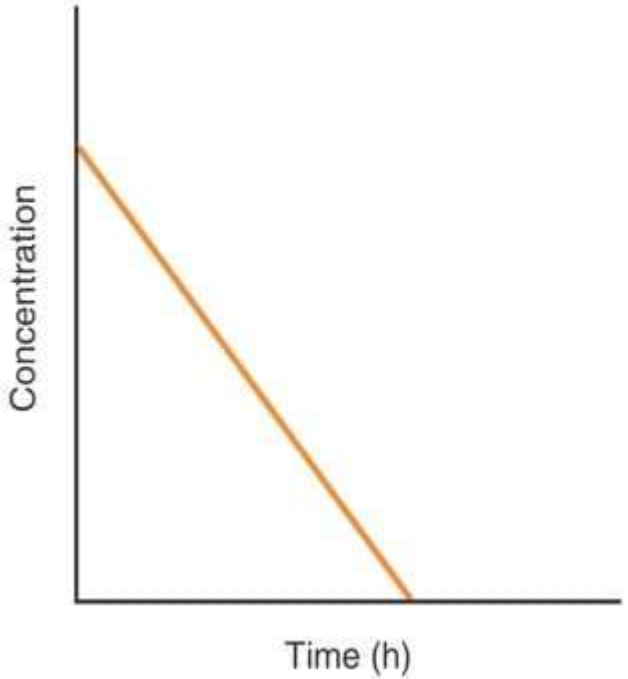
Order of a process

1. Zero order
2. 1st order
3. Mixed order



Zero order kinetics or capacity limited elimination

1. Constant amount of drug is elim. in unit time
2. Rate of elimination remains constant irrespective of drug conc.
3. Clearance dec. with inc. in conc.
4. $T_1/$ is variable
5. Most commonly seen in ethanol
6. If log pl. conc. v/s time4 Curvilinear (Plasma conc. Falls at a constt. Rate unaff. By plasma levels existing in the body)



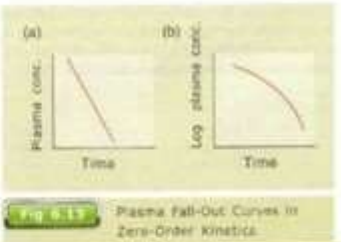


Fig 6.13 Plasma Fall-Out Curves in Zero-Order Kinetics

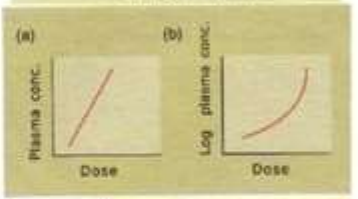


Fig 6.14 Plasma Conc. Curve in Zero-Order Kinetics

Fig 6.15 Variable $t_{1/2}$ in Zero-Order Kinetics

First order kinetics

1. Constant fraction of drug is elim. Per unit time
2. Rate of drug elim. ‹x Plasma conc.
3. Clearance remains constant
4. $T_1/_2U$ Constant irrespective of the dose
5. Single dose ^*i/z —› 97% of drug gets eliminated
6. Fixed dose at every $t_1t_2$4 Conc. T 5 tI/2 —› 979a of steady state level -3• Rate of abs. = Rate of elim.

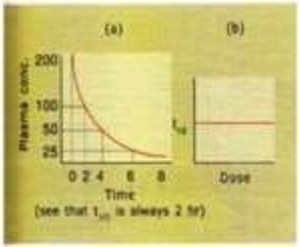


Fig 6.7 Constant $t_{1/2}$ in First-Order Kinetics

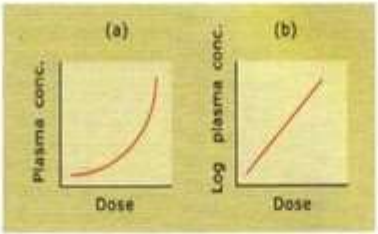


Fig 6.9 Plasma Concentration Curve in First-Order Kinetics

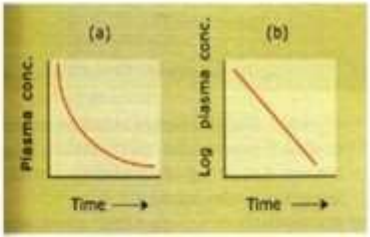
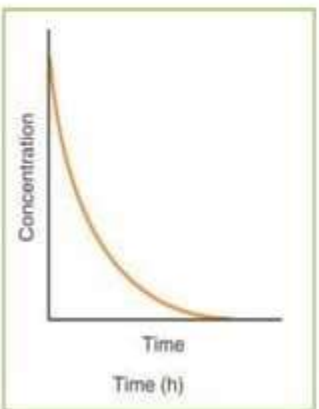
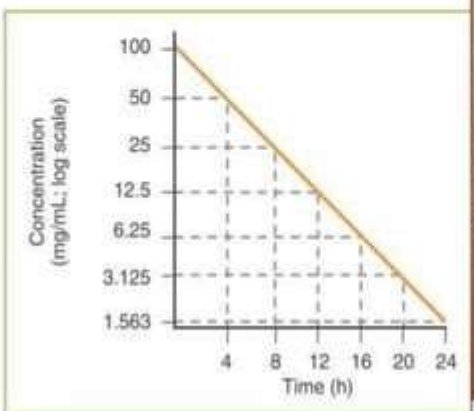


Fig 6.8 Plasma Fall-Out Curve in First-Order Kinetics





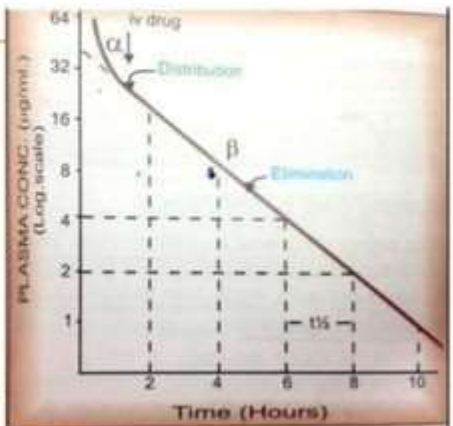


Fig. 3.5: Semilog plasma concentration-time plot of a drug eliminated by first order kinetics after intravenous injection

Michaelis Menten kinetics or Mixed order kinetics or Saturation kinetics

- Dose dependent kinetics

Plasma fall out' curve (Arith. scale)4 Linear (0 order)4 Curvilinear (1" order)

Plasma "fall out" curve (Log scale)4 Curvilinear (0 order)4 Linear (1st order)

Plasma conc. Curve (Arith. scale)4 Curvilinear (1St order)4 Linear (0 order)

Plasma conc. curve (Log scale)4 Linear (1st order)4 Curvilinear (0 order)

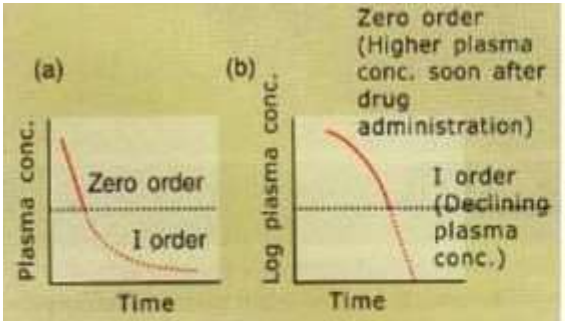


Fig 6.15 Plasma Concentration Fall-Out Curve in Mixed-Order Kinetics

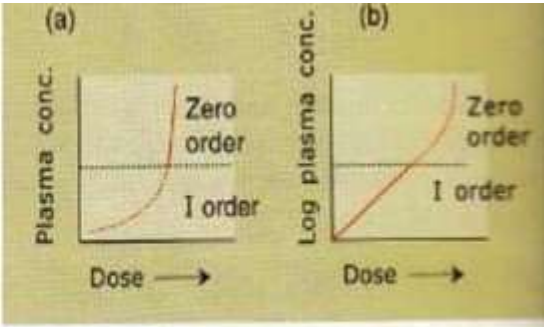


Fig 6.16 Plasma Concentration Curve in Mixed-Order Kinetics

Small dose W 1*t order kineticsE dose W

plasma conc. Metabolizing enz. Sat.

Zero order kinetics

Elimination rate constant ($K/K_e y$)

- Overall drug elimination from the body ($K_u + K_{m}$)
- K_u Excretion rate constant
- $K_{.}$ -* Metabolic rate constant
- ° If drug completely metabolizedU $K_e y$ K_m
- If drug removed in unchanged W $K_e = K_u$
- Calculation of $K/K_e y$by following formula :-

$$K \frac{0.693}{t_{1/2}}$$

Calculation of K_u Kg

- Administered dose of drug X —250 mg
- Amt. of drug X exc. = 125 mg
- Elim. T_1t_2 of drug X = 4 hrs.
- Amt. of drug X removed as metabolite 1 = 75 mg
- Amt. of drug X removed as metabolite 2 = 50 mg
- K = 0.693/4 = 0.173/hr.

- % excreted = 125/250 X 100 = 50%

  °/oremoved as metabolite 1 —75/250 X 100 = 30°/

- % removed as metabolite 2 = 50/250 X 100 = 20%

- K, & $K_.$ are given as % exc./m-bolized X K

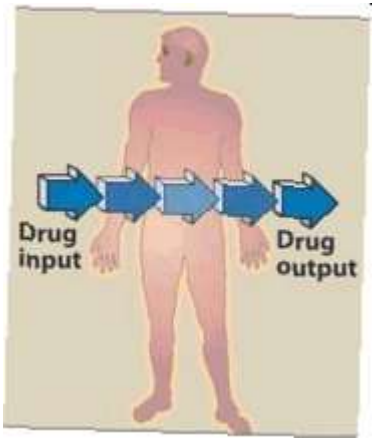
  $\Longrightarrow K_u$ '05X0173=00866/hr

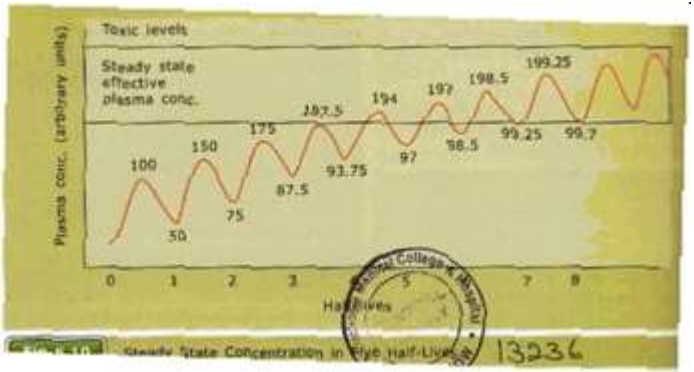
- KU = 0.173 X 0.3 = 0.051 / hr.

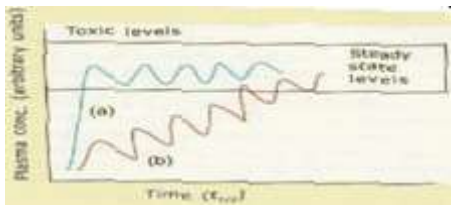
- K_m, = 0.173 X 0.2 = 0.0345 / hr.

  K = K_u K_{m1}" K $_2$

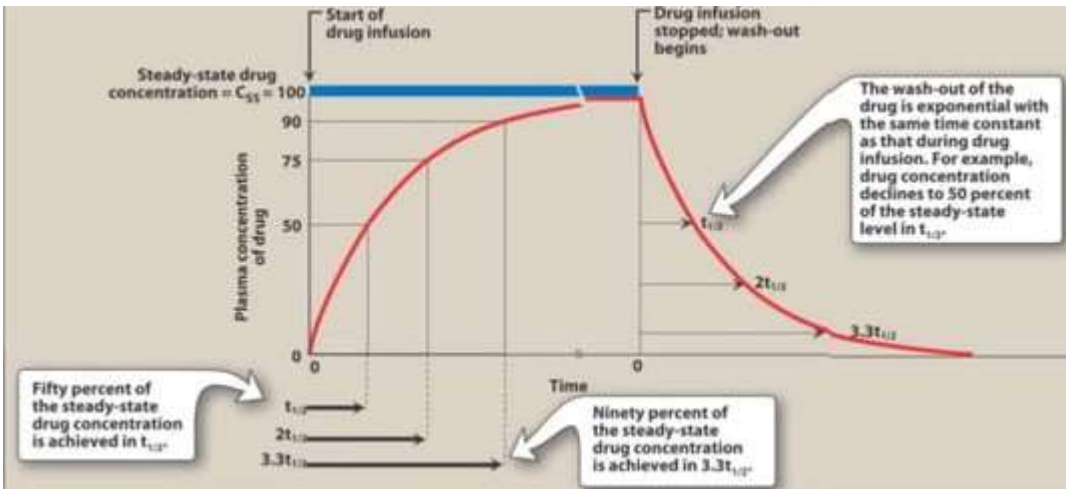
Steady state







Attainment of steady state



Rate of infusion

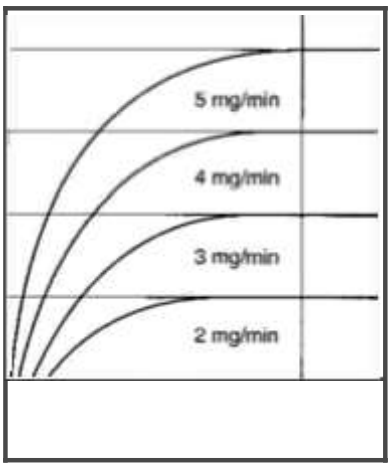


Figure I-1-12. Effect of Rate of Infusion on Plasma Level

Repeated drug administration

- Drug repeated at short intervals4 Accumulates in body4 Rate of elim. = Rate of input4 Steady state plasma conc. (Cpss) is attainRd
- $Cpss = \frac{Dose\ rate}{CL}$ m $Dose\ rate$ —target $Cpss\ X\ CL$
- 1st order kinetics4 $Dose\ rate$ — t e s C
- 0 Drder kinetics4 *Rate of drtz8 elim.* — $\frac{(V_{max})(C)}{K_m+C}$
- C4 Plasma conc. Of drug ; V „4 Max. rate of drug el.
- Kg -3' Plasma conc. At which elimination rate is X max.

2 dose strategy

- Drugs having high Vp are given
- 1ˢ‘ -' Large dose given to attain steady state quickly (Loading dose)
- LaterU To maintain plasma conc., smaller dose is given (Maintenance dose)

$Loading\ dose \xrightarrow{*d} TaY\ get\ plasma\ conc.$

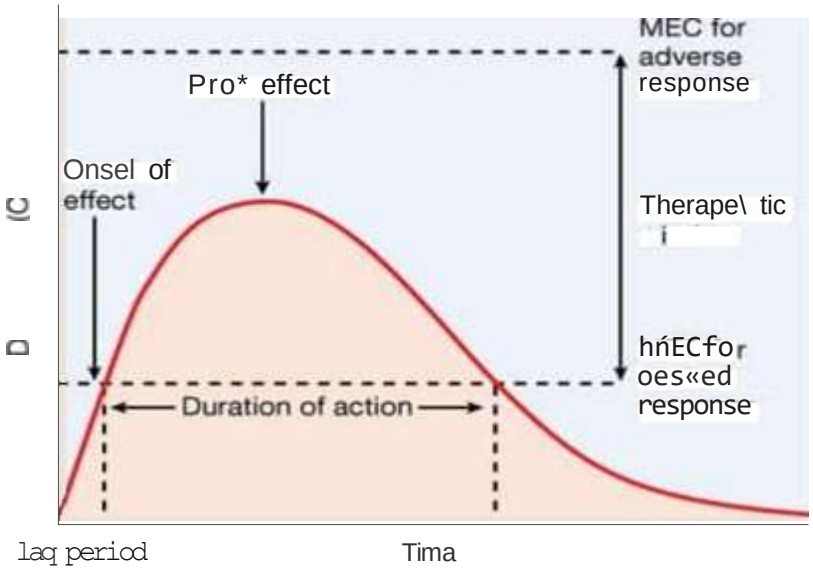
$Maintenance\ dose \xrightarrow{CL\ X} TaY\ get\ plasma\ conc.$

Adv4 Rapid therapeutic effect with long term safety

Maintenance dose

- Drugs administered in a series of repetitive doses or as a continuous infusion -3' Maintain a steady-state concentration of drug associated with the therapeutic window
- Primary goal -3' Calculation of maintenance dosage
- Rate of drug administration is adjusted4 Rate of input = rate of loss

- $Dosing\ Yate\ —target\ Cp\ X\ \frac{CL}{F}$
- If the clinician
  - Chooses the desired concentration of drug in plasma
  - Knows the clearance and bioavailability for that drug in a particular patient
  - Appropriate dose and dosing interval can be calculated


MEC for adverse response
Pro* effect
Onsel of effect
Therape\ tic
hńECfor oes«ed response
Duration of action
laq period
Tima

- Oral digoxin is to be used as a maintenance dose to gradually "digitalize" a 63 year old, 84-kg patient with CHF. A steady-state plasma concentration of 0.7-0.9 ng/mL is selected as an appropriate conservative target based on prior knowledge of the action of the drug in patients with heart failure to maintain levels at or below in the 0.5-1.0 ng/mL range (Bauman et al., 2006).

- Based on the fact that the patient's creatinine clearance (CLCr) is S6 mL/min, digoxin's clearance 4.6 L/hour. Oral bioavailability of digoxin is 70^{0}/o(F = 0.7)

- Dosing rate —Target Cp CL/F = 0.75 ng - mL—1 x (0.92/0.7) mL min—1 kg—1 = 0.99 ng min—1 kg—1 or 83 ng min—1 for an 84-kg patient or 83 ng min—1 x 60 min x 24/24 hr = 0.12 mg/24 hr

Loading dose

- Single/few quickly repeated doses — Attain target conc. Rapidly
- $Lnan\,in\,g\ \ cIone \longrightarrow \frac{Tor\,get\ C\,y\,X\,V}{}$
- Loading dose depends ONLY on V
- NOT on CL or t_1t_2
- Target Cl Of digoxin = 0.9 ng/ml; V_d = 496 L; F=0.7
- Loading dose = 0.9 X 496 / 0.7 = 638 kg or 0.625 mg

TABLE 3ß Summary of Key Pharmacokinetic Relationships	
Initial concentration	$\frac{\text{Loading dose}}{\text{Volume of distribution}}$
Steady-state concentration =	$\frac{\text{Fraction absorbed} \times \text{Maintenance dose}}{\text{Dosing interval} \times \text{Clearance}}$
Elimination half-life	$\frac{0.693 \times \text{Volume of distribution}}{\text{Clearance}}$

Thank You