ONE COMPARTMENT OPEN MODEL

I.V. Administration of Drug

GITAM
(DEEMED TO BE UNIVERSITY)
(Estd. u/s 3 of the UGC Act, 1956)
VISAKHAPATNAM • HYDERABAD • BENGALURU
Accredited by NAAC with A+ Grade

Dr. Suvendu Kumar Sahoo
Assistant Professor
GITAM Institute of Pharmacy
GITAM Deemed to be University
Visakhapatnam- 530045

ONE COMPARTMENT OPEN MODEL

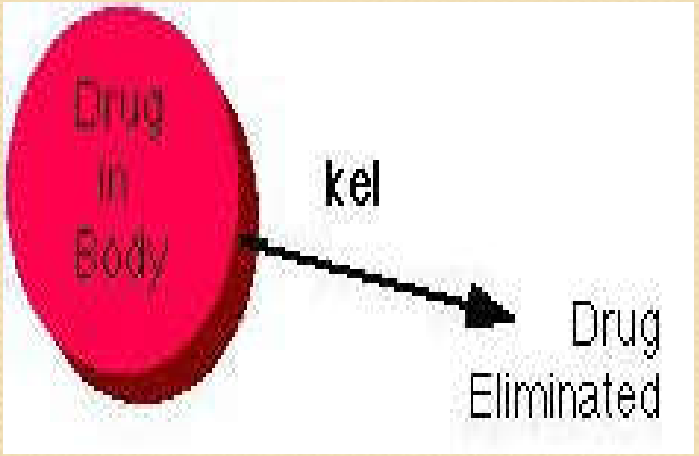
- The body is considered as a single, kinetically homogeneous unit.
- This model applies only to those distributes rapidly throughout the body.
- Drugs move dynamically in an out of this compartment
- Elimination is first order (monoexponential) process with first order rate constant.
- Rate of input (absorption) > rate of output

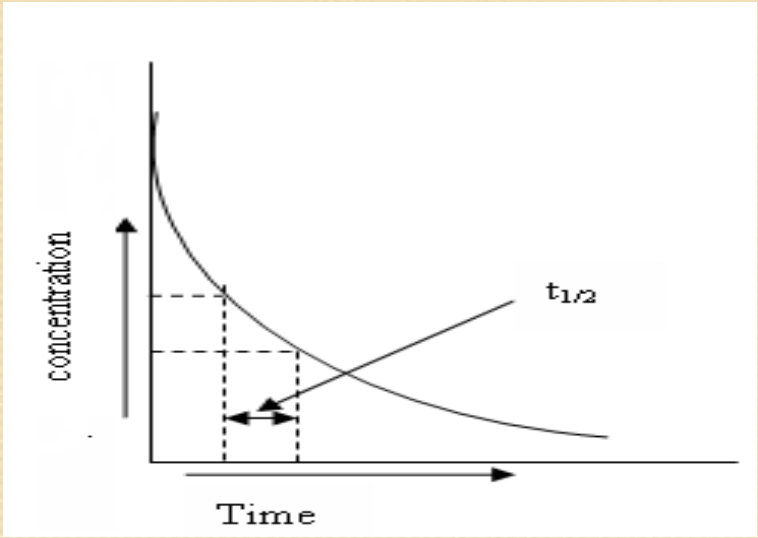
Depending on rate of input, several one compartment open models are :

1. One compartment open model, i.v. bolus administration
2. One compartment open model, continuous i.v. infusion.
3. One compartment open model, e.v. administration, zero order absorption.
4. One compartment open model, e.v. administration, first order absorption

INTRAVENOUS BOLUS ADMINISTRATION

- When drug is given in the form of rapid i.v. injection it takes about one to three minutes for complete circulation and therefore the rate of absorption is neglected.





$$\frac{dX}{dt} = \text{Rate In} - \text{Rate Out}$$

$$\frac{dX}{dt} = -\text{Rate Out}$$

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

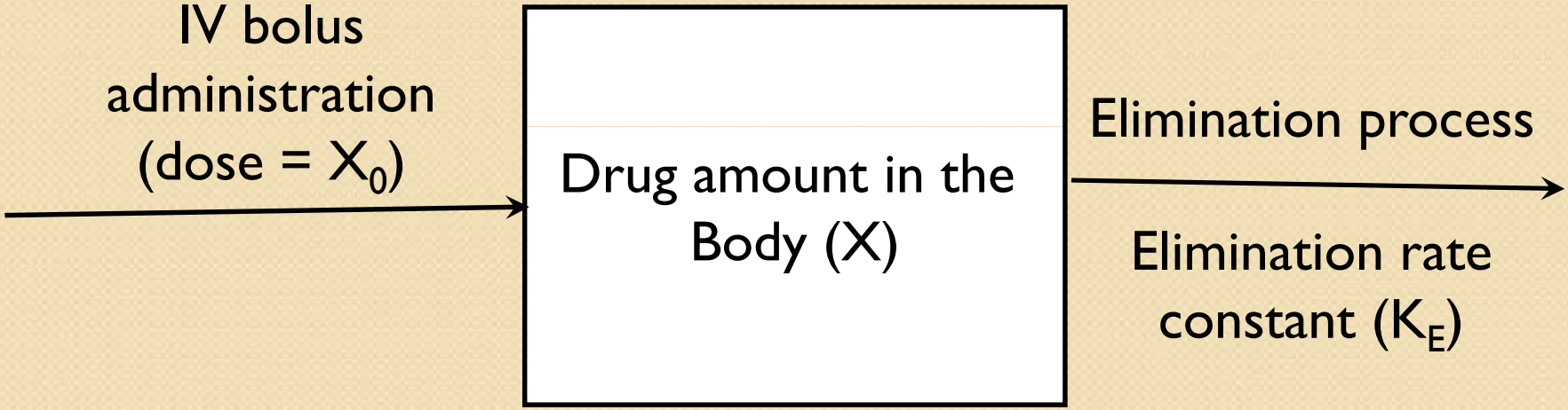
K_E =first order overal elimination rate constant

X= amt of drug remaining in the body at any time

I.V. BOLUS ADMINISTRATION

i) Plasma level data

ii) Urinary excretion date



Estimation of pharmacokinetic parameters

I.V. Bolus – Unchanged drug in Blood/ Plasma

Elimination rate constant:

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

The times course of drug in the body is obtained by rearrangement and integrating above equation

$$\int_{X_o}^{X} \frac{dX}{X} = \int_{0}^{t} -K_E dt$$

$$|\ln X|_{X_o}^{X} = -K_E |t|_0^t$$

$$\ln X \quad \ln X_0 = \quad K_E(t \quad 0)$$

$$\ln X = \ln X_0 - K_E t$$

Equation can be written in exponential form as

$$X = X_0 e^{-K_E t}$$

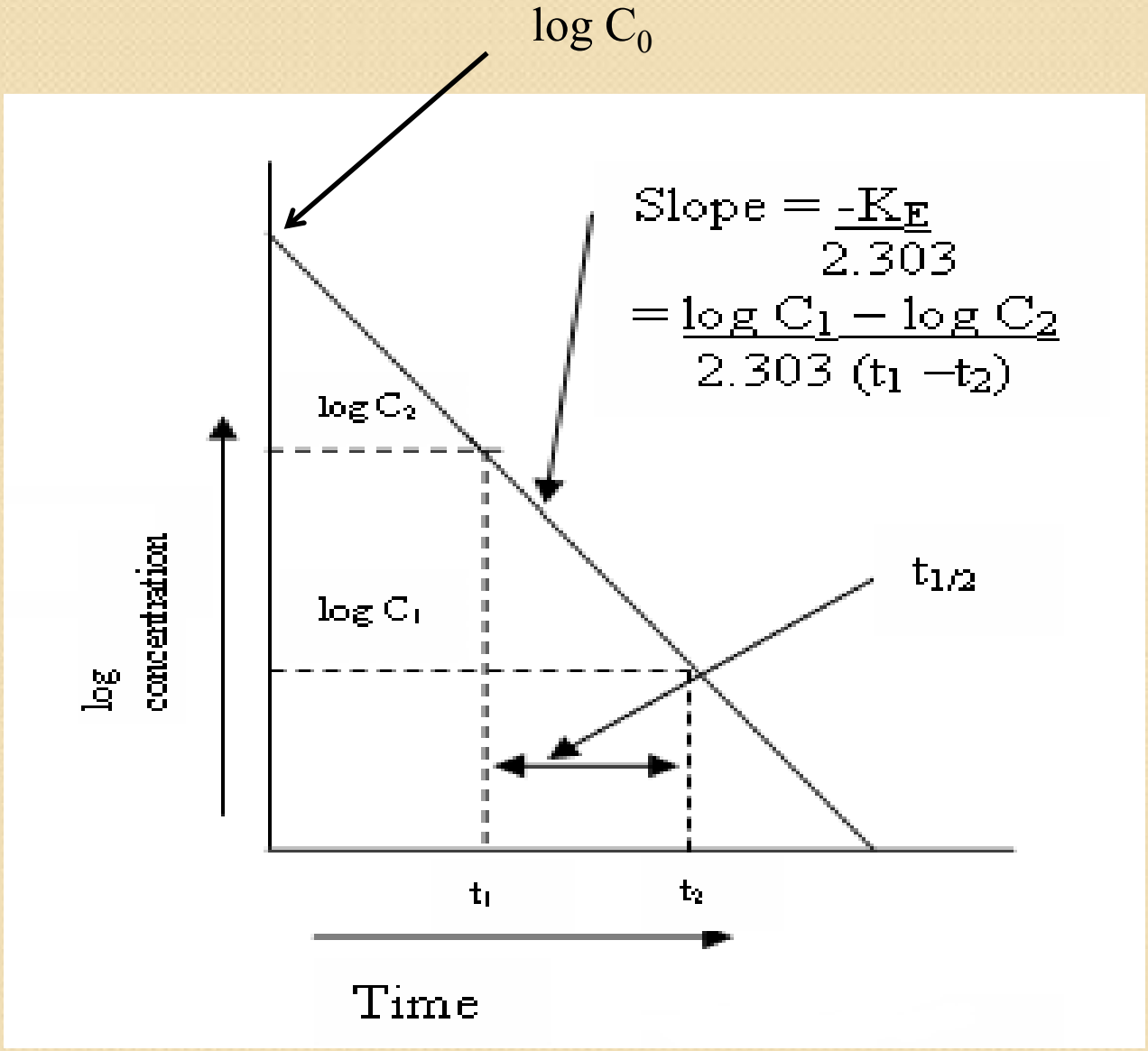
Transforming equation into logarithm form we get,

$$\log X = \log X_0 - \frac{K_E t}{2.303}$$

As

$$X = V_d C$$

$$\log C = \log C_0 - \frac{K_E t}{2.303}$$


log C_0
Slope = $\frac{-K_E}{2.303}$
$= \frac{\log C_1 - \log C_2}{2.303\ (t_1 - t_2)}$
log C_2
log C_1
log concentration
$t_{1/2}$
t_1
t_2
Time

Elimination Half - Life:

- It is defined as time taken for the amount of drug in the body as well as plasma concentration to decline by half or 50% of its initial value.
- It is expressed in hours or minutes

$$\log C = \log C_0 - \frac{K_E t}{2.303}$$

By rearranging above equation

$$\log \frac{C_0}{C} = \frac{K_E t}{2.303}$$

When $C_0/C = 2$, then $t = t_{1/2}$

$$\log 2 = \frac{K_E t}{2.303}$$

$$K_E t_{1/2} = \log 2 \times 2.303 = 0.301 \times 2.303 = 0.693$$

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

For first order processes (as described and derived as above) this time is independent of concentration.

Half life is secondary parameter that depends upon the primary parameters clearance and volume of distribution according to following equation,

$$t_{1/2} = \frac{0.693 V_d}{Cl_T}$$

Area Under the Curve

$$[AUC]_0^{\infty} = \frac{C_0}{K_E}$$

Apparent Volume of Distribution:

V_d = amt of drug in the body/ plasma drug conc.

$$V_d = X/C$$

For drugs given as i.v. bolus ,

$$V_d = \frac{X_0}{C_0} = \frac{\text{i. v. dose}}{C_0}$$

Clearance

Clearance is defined as the theoretical volume of body fluid containing drug from which the drug is completely removed in a given period of time.

Rate of elimination α Plasma drug concentration

or

$$\frac{dX}{dt} \propto C_p$$

$$\frac{dX}{dt} = Cl_T . C_p$$

$$Cl_T = \frac{dX/dt}{C_p} = \frac{\text{Rate of elimination}}{\text{Plasma drug concentration}}$$

Clearance

Total amount of the drug eliminated from the body in infinite time is obtained by integrating the equation with respect to time in between t = 0 and t = α

$$\int_0^\infty dX = Cl_T \int_0^\infty C_p dt$$

Total amount eliminated

$$= Cl_T [AUC]_0^\infty \qquad \text{since} \int_0^\infty C_p dt = [AUC]_0^\infty$$

Total body clearance

$$Cl_T = \frac{\text{Total amount of drug eliminated}}{[AUC]_0^\infty}$$

In case of i.v. injection (bolus), total drug eliminated is equal to the administered dose (X_0)

$$Cl_T = \frac{X_0}{[AUC]_0^\infty}$$

$$X_0 = V_d.C_0 \quad \text{and} \quad [AUC]_0^\infty = \frac{C_0}{K_E}$$

$$Cl_T = \frac{V_d C_0}{C_0/K_E}$$

$$Cl_T = V_d K_E$$

Volume of fluid cleared of drugs in a unit time

Total Body Clearance

It is estimated by dividing the rate of elimination by each organ with the concentration of drug presented to it.

Renal clearance

$$Cl_R = \frac{\text{Rate of elimination by kidney}}{C}$$

Hepatic clearance

$$Cl_H = \frac{\text{Rate of elimination by liver}}{C}$$

Thus , Cl_T is also called as total systemic clearance, is an additive property of individual organ clearances. It is represented as:

$$Cl_T = Cl_R + Cl_H + Cl_{others}$$

ORGAN CLEARANCE

- Rate of elimination by an organ = Rate of Presentation to organ (input) – Rate of exit from organ (output)

- Rate of presentation = Organ blood flow × Entering Conc.
  (Input) = $Q.C_{in}$

- Rate of Exit = Organ blood flow × Exiting Conc.
  (Ouput) = $Q.C_{out}$

- Rate of elimination = $Q.C_{in} – Q.C_{out}$
  (Rate of extraction)
  = $Q(C_{in} – C_{out})$

suvendukumar.sahoo@gitam.edu

ORGAN CLEARANCE

$$\frac{\text{Rate of extraction}}{C_{in}} = Cl_{organ} = \frac{Q(C_{in} - C_{out})}{C_{in}} = Q \times ER$$

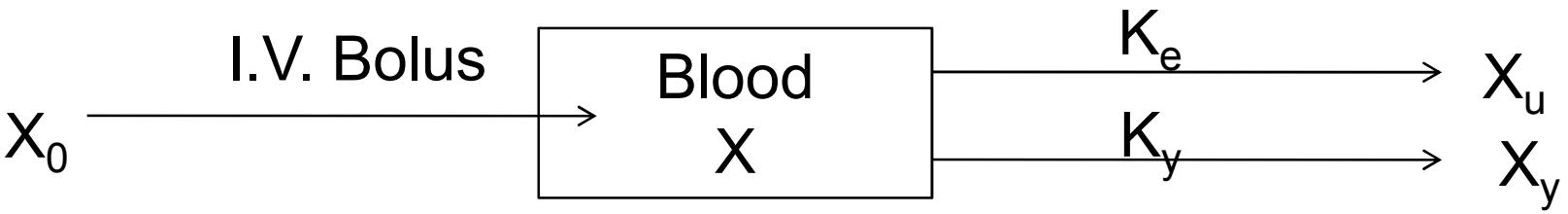
- ER = Extraction ratio
- value ranges from zero (no elimination) to one (complete elimination)

- Based on ER values drugs can be classified as:
  - Drugs with high ER = above 0.7
  - Drugs with intermediate ER = between 0.7- 0.3
  - Drugs with low ER = below 0.3
- ER is an index of how efficiently the eliminating organ clears the blood flowing through it of drug.

suvendukumar.sahoo@gitam.edu

Estimation of pharmacokinetic parameters

I.V. Bolus – Unchanged drug in Urine



$$K_E = K_e + K_y$$

- Excretion rate method
- Sigma-minus method

X_u = Cumulative amount of unchanged drug excreted in urine

suvendukumar.sahoo@gitam.edu

1. Excretion rate method

- The rate of appearance of unchanged drug in urine is

$$\frac{dX_u}{dt} \propto X$$

$$\frac{dX_u}{dt} = K_e X$$

$$X = X_0 e^{-K_E t}$$

- In i.v. bolus

$$\frac{dX_u}{dt} = K_e X_0 e^{-K_E t}$$

- Applying logarithm

$$\log \frac{dX_u}{dt} = \log K_e X_0 - \frac{K_E t}{2.303}$$

suvendukumar.sahoo@gitam.edu

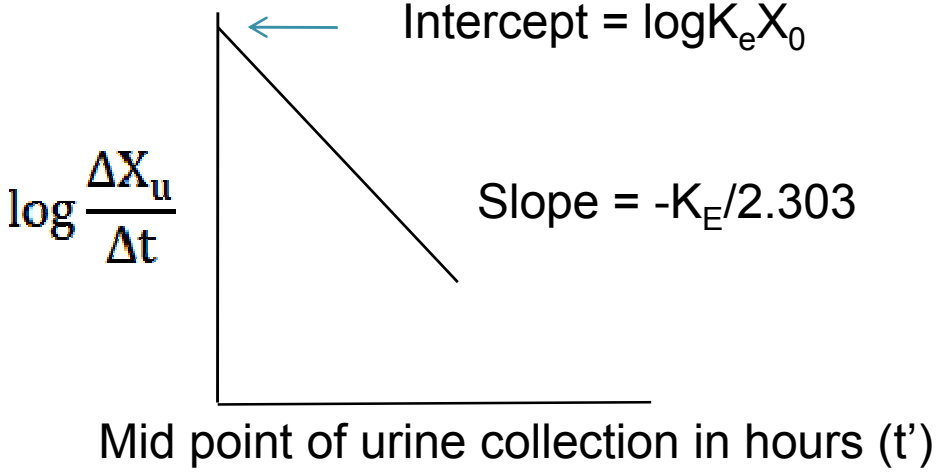
dX_u/dt = instantaneous rate of excretion

Experimentally, average excretion rate, $\Delta X_u/\Delta t$

- The assumption that

  $\Delta X_u/\Delta t \approx dX_u/dt$ at the mid point of urine collection period (t')

$$\log \frac{\Delta X_u}{\Delta t} = \log K_e X_0 - \frac{K_E t'}{2.303}$$



suvendukumar.sahoo@gitam.edu

2. Sigma-minus method

- No assumption of $\Delta X_u/\Delta t \approx dX_u/dt$

$$\frac{dX_u}{dt} \propto X$$

$$\frac{dX_u}{dt} = K_e X$$

- In i.v. bolus

$$X = X_0 e^{-K_E t}$$

$$\frac{dX_u}{dt} = K_e X_0 e^{-K_E t}$$

- On integrating $\int_0^t dX_u - \int_0^t (K_e X_0 e^{-K_E t}) dt$

suvendukumar.sahoo@gitam.edu

$$|X_u|_0^t = K_e X_0 \frac{|e^{K_E t}|_0^t}{-K_E}$$

$$X_u^t - X_u^0 = K_e X_0 \left(\frac{e^{-K_E t}}{-K_E} + \frac{e^0}{K_E}\right)$$

$$X_u^t - 0 = K_e X_0 \left(\frac{1}{K_E} - \frac{e^{-K_E t}}{K_E}\right)$$

$$X_u^t = \frac{K_e X_0}{K_E}(1 - e^{-K_E t})$$

- Total amount of unchanged drug that will excreted

$$\int_0^\infty dX_u = \int_0^\infty (K_e X_0 e^{-K_E t})dt$$

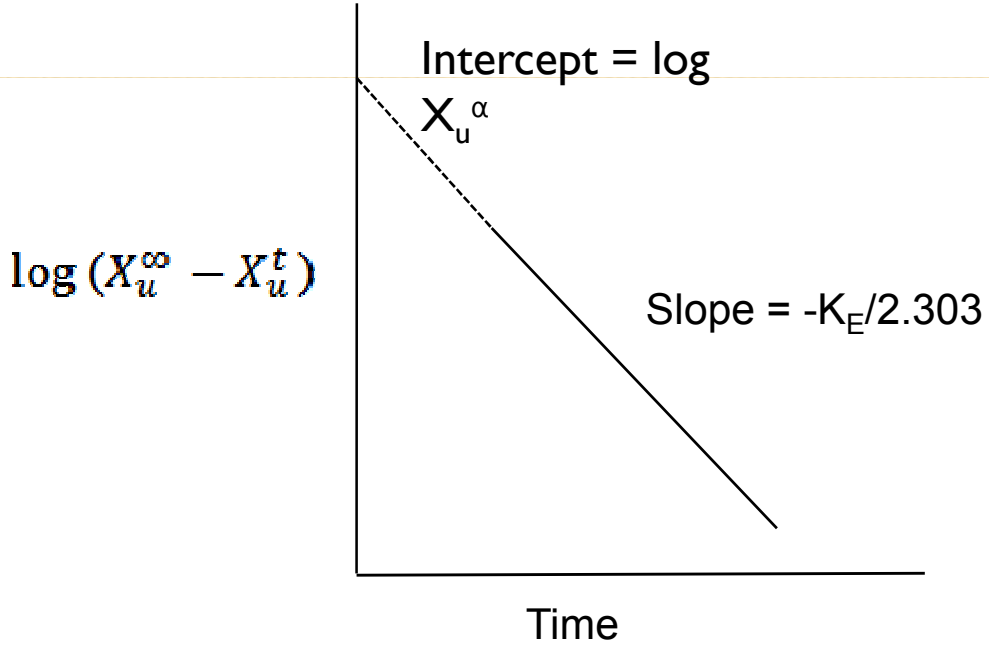
$$X_u^\infty = \frac{K_e X_0}{K_E}$$

suvendukumar.sahoo@gitam.edu

$$X_u^t = X_u^\infty \left(1 - e^{-K_E t}\right)$$

$$X_u^\infty - X_u^t = X_u^\infty \, e^{-K_E t}$$

$$\log\left(X_u^\infty - X_u^t\right) = log X_u^\infty - \frac{K_E t}{2.303}$$



suvendukumar.sahoo@gitam.edu

$$\text{Slope} = -K_E/2.303$$

$$K_E = \text{Slope} \times 2.303$$

$$t_{1/2} = 0.693/K_E$$

$$\text{Intercept} = \log X_u^{\infty}$$

$$X_u^{\infty} = \text{Antilog (Intercept)}$$

$$X_u^{\infty} = \frac{K_e X_0}{K_E}$$

$$K_e = \frac{K_E X_u^{\infty}}{X_0}$$

suvendukumar.sahoo@gitam.edu

Renal excretion as a fraction of total excretion

- In case of I.V. bolus, f_e is fraction of I.V. dose excreted unchanged in urine

$$f_e = \frac{\text{Total drug excreted unchanged}}{\text{I. V. dose}} = \frac{X_u^\infty}{X_0}$$

- f_e ranges between 0 to 1
- If f_e value is low, urinary excretion is a minor pathway of drug elimination
- f_e= 1; renal excretion is only route of elimination

suvendukumar.sahoo@gitam.edu

Renal Clearance

$$\frac{dX_u}{dt} = Cl_R C$$

$$Cl_R = \frac{dX_u/dt}{C}$$

In practice, renal clearance is estimated by dividing the average urinary excretion rate $\Delta X_u/dt$, by plasma concentration of drug, C, at the mid point of the urine collection period, t'.

$$Cl_R = \frac{\Delta X_u/\Delta t}{C \text{ at } t'}$$

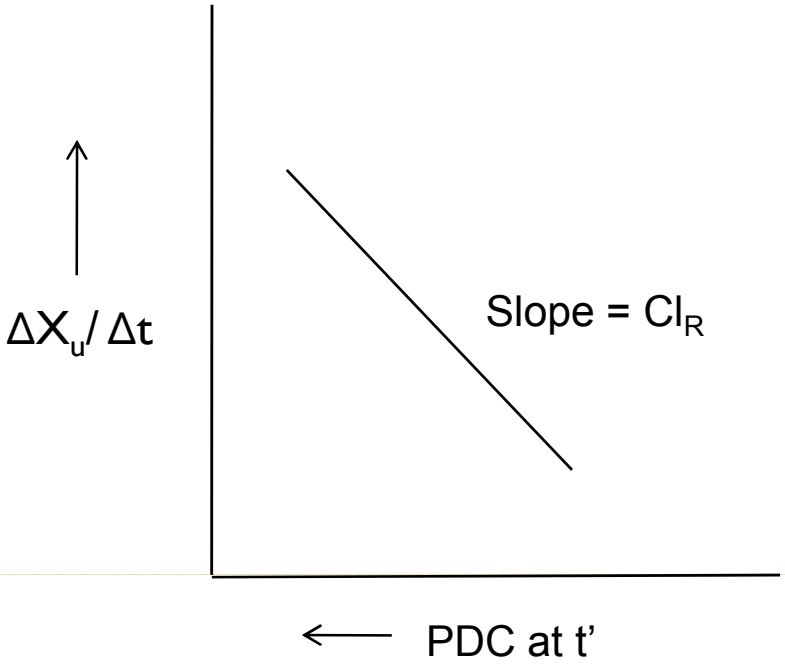
But we know that, $\Delta X_u/\Delta t = K_e X$

$$Cl_R = \frac{K_e X}{C \text{ at } t'}$$

But $X/C = V_d$

So $Cl_R = K_e . V_d$

suvendukumar.sahoo@gitam.edu



$$\frac{dX_u}{dt} = Cl_R C$$

- But $Cl_R = K_e . V_d$

$$\frac{dX_u}{dt} = K_e V_d C$$

suvendukumar.sahoo@gitam.edu

$$\int_{t_1}^{t_2} dX_u = K_e V_d \int_{t_1}^{t_2} C.dt$$

$$|X_u|_{t_1}^{t_2} = K_e V_d \int_{t_1}^{t_2} C.dt$$

$$|X_u|_{t_1}^{t_2} = K_e V_d [AUC]_{t_1}^{t_2}$$

- On integration from time zero to infinity

$$\int_{0}^{\infty} dX_u = K_e V_d \int_{0}^{\infty} C.dt$$

$$|X_u|_{0}^{\infty} = K_e V_d \int_{0}^{\infty} C.dt$$

suvendukumar.sahoo@gitam.edu

$$X_u^\infty - 0 - K_e V_d \int_0^\infty C.\,dt$$

$$X_u^\infty = K_e V_d \int_0^\infty C.\,dt$$

$$K_e V_d = Cl_R = \frac{X_u^\infty}{\int_0^\infty C.\,dt} = \frac{X_u^\infty}{[AUC]_0^\infty}$$

$$V_d = \frac{X_u^\infty}{K_e [AUC]_0^\infty}$$

But we know,

$$X_u^\infty = \frac{K_e X_0}{K_E}$$

Or

$$\frac{X_u^\infty}{K_e} = \frac{X_0}{K_E}$$

suvendukumar.sahoo@gitam.edu

On substituting

$$V_d = \frac{X_0}{K_E [AUC]_0^\infty}$$

$$V_d K_E = \frac{X_0}{[AUC]_0^\infty}$$

$$Cl_T = \frac{X_0}{[AUC]_0^\infty}$$

suvendukumar.sahoo@gitam.edu

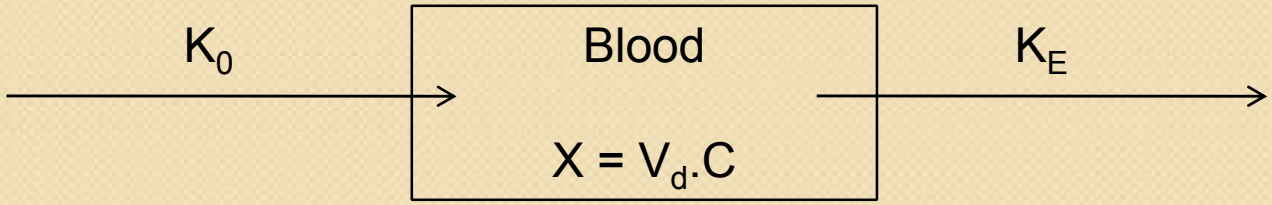
Intravenous Infusion:

Rapid i.v. injection is unsuitable when the drug has potential to precipitate toxicity or when maintenance of a stable concentration or amount of the drug in body is desired. In such a situation , the drug is administered at a constant rate (zero ordered) by i.v. infusion.

Advantages of zero order infusion of drug include

- Ease of control of rate of infusion.
- Prevents fluctuating maxima and minima plasma level. This is desired especially when the drug has a narrow therapeutic index.
- Other drugs, electrolytes and nutrients can be conveniently administered simultaneously by the same infusion line in critically ill patients.

I.V. infusion – Unchanged drug in Blood/Plasma



At any time during infusion, the rate of change in amt. of drug in the body, dX/dt is the difference between the zero order rate of drug infusion, K_0 and first order rate elimination, $K_E X$

$$\frac{dX}{dt} = K_0 - K_E X \quad \ldots. (1)$$

Since, $X=V_dC$ the above equation can be transformed into concentration terms,

$$\frac{dC}{dt} = \frac{K_0}{V_d} - K_E C \quad \ldots.. (2)$$

Rearranging eqⁿ (2) and multiplying it with $e^{K_E t}$, we get

$$\frac{dC}{dt} e^{K_E t} + K_E C e^{K_E t} = \frac{K_0}{V_d} e^{K_E t} \quad \ldots\ldots (3)$$

Integrating equation (3) between limits of t=0 to t=t, and on simplification we get

$$C e^{K_E t} = \frac{K_0}{V_d}\left(\frac{e^{K_E t}}{K_E} - \frac{1}{K_E}\right) \quad \ldots\ldots (4)$$

Dividing eqⁿ (4) by $e^{K_E t}$ and on simplifying

$$C = \frac{K_0}{V_d K_E}\left(1 - e^{-K_E t}\right) \quad \ldots\ldots (5)$$

$$X = \frac{K_0}{K_E}\left(1 - e^{-K_E t}\right) \quad \ldots\ldots (6)$$

Theoretically, a steady state level is reached after an infinitely long infusion time.

In clinical practice, the plasma drug level within the 95% to 99% plateau level is considered to be steady state level.

The steady state drug concentration in plasma can be determined from the eq^{n} (5) by setting time equal to infinity.

As

$$e^{-K_E \infty} = 0$$

so we get

$$C_{ss} = \frac{K_0}{V_d K_E} \quad \ldots\ldots (7)$$

Since V_d & K_E are constants for a drug, C_{ss} is directly proportional to the infusion rate of the drug, K_0.

An increase in rate of infusion will NOT shorten the time to reach the steady state drug concentration, but a higher steady state drug level will be obtained.

Thus infusion rate decides the steady state drug concentration, and biological half-life determines the time to reach that level.

Since V_d & K_E are constants for a drug, C_{ss} is directly proportional to the infusion rate of the drug, K_0.

Alternative method

At steady state

Rate of input = rate of output

so dC/dt = 0

and

$$\frac{dC}{dt} = \frac{K_0}{V_d} - K_E C$$

$$\frac{K_0}{V_d} - K_E C_{ss} = 0$$

$$C_{ss} = \frac{K_0}{V_d K_E}$$

Plasma drug concentration at any time during I.V. infusion can be written as

$$C = C_{ss}\left(1 - e^{-K_E t}\right) \quad \ldots\ldots (8)$$

suvendukumar.sahoo@gitam.edu

Elimination Half-life

$$C = C_{ss}\left(1 - e^{-K_E t}\right)$$

$$C = C_{ss} - C_{ss}e^{-K_E t}$$

$$C_{ss}e^{-K_E t} = C_{ss} - C$$

$$e^{-K_E t} = \frac{C_{ss} - C}{C_{ss}}$$

$$\log\left[\frac{C_{ss} - C}{C_{ss}}\right] = \frac{-K_E t}{2.303}$$

$$K_E = \frac{2.303}{t}\log\left[\frac{C_{ss}}{C_{ss} - C}\right] \quad \ldots\ldots(9)$$

$$t_{1/2} = \frac{0.693}{K_E} \quad \ldots\ldots(10)$$

Post infusion – Plasma concentration of Drug

The rate of change of plasma concentration after stopping infusion

$$\frac{dC}{dt} = -K_E C \quad \ldots\ldots(11)$$

C = conc. of drug when I.V. infusion is stopped

If the infusion is stopped after reaching plateau level, then C is nothing but C_{ss}.

$$\frac{dC}{dt} = -K_E C_{ss} \quad \ldots\ldots(12)$$

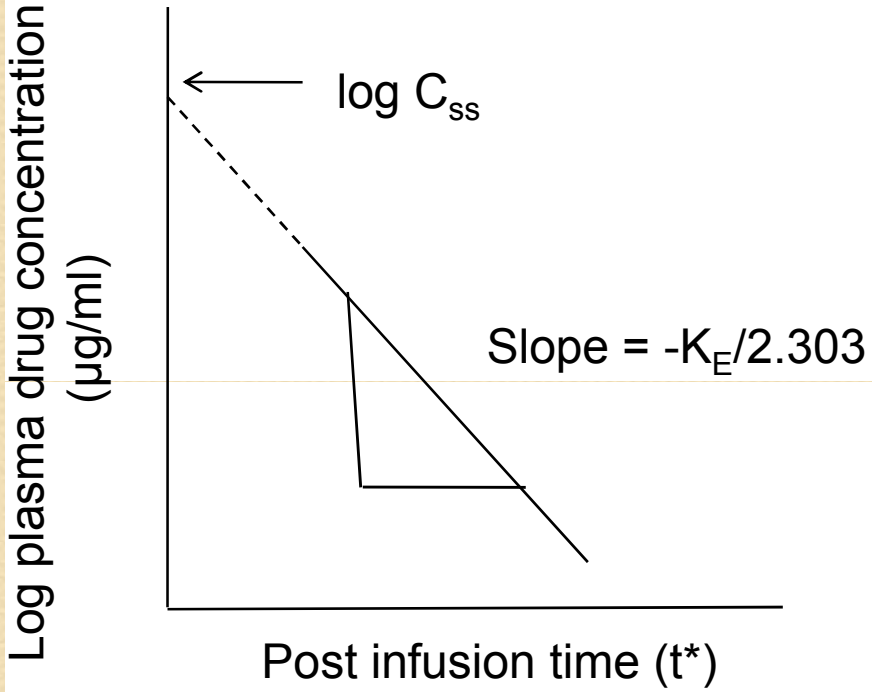
Integrating the eq^n (12)

$$C = C_{ss} e^{-K_E t^*} \quad \ldots\ldots(13)$$

suvendukumar.sahoo@gitam.edu

Taking logarithm

$$\log C = \log C_{ss} - \frac{K_E t^*}{2.303} \quad \ldots\ldots(14)$$



suvendukumar.sahoo@gitam.edu

If the infusion is stopped before reaching steady state level, the post infusion concentration of the drug in plasma is calculated as

$$C = \left[\frac{K_0}{V_d K_E}\left(1 - e^{-K_E t}\right) e^{-K t^*}\right] \quad \ldots\ldots(15)$$

t = duration of infusion

t* = duration after infusion is stopped

suvendukumar.sahoo@gitam.edu

I.V. infusion – Unchanged drug in urine

$$\frac{dX_u}{dt} = K_e X \qquad \ldots\ldots(16)$$

$$x = \frac{K_0}{K_E}\left(1 - e^{-K_E t}\right) \qquad \ldots\ldots(6)$$

$$\frac{dX_u}{dt} = \frac{K_e K_0}{K_E}\left(1 - e^{-K_E t}\right) \qquad \ldots\ldots(17)$$

$$\int_0^t dX_u = \frac{K_e K_0}{K_E} \int_0^t \left(dt - e^{-K_E t} dt\right)$$

$$x_u^t - 0 = \frac{K_e K_0}{K_E}\left[t - \left(\frac{e^{-K_E t}}{K_E} + \frac{1}{K_E}\right)\right]$$

suvendukumar.sahoo@gitam.edu

$$X_u^t = \frac{K_e K_0}{K_E} t - \frac{K_e K_0}{K_E^2} + \frac{K_e K_0}{K_E^2} e^{-K_E t}$$

$$X_u^t = \frac{K_e K_0}{K_E} t - \frac{K_e K_0}{K_E^2}(1 - e^{-K_E t}) \quad \ldots\ldots(18)$$

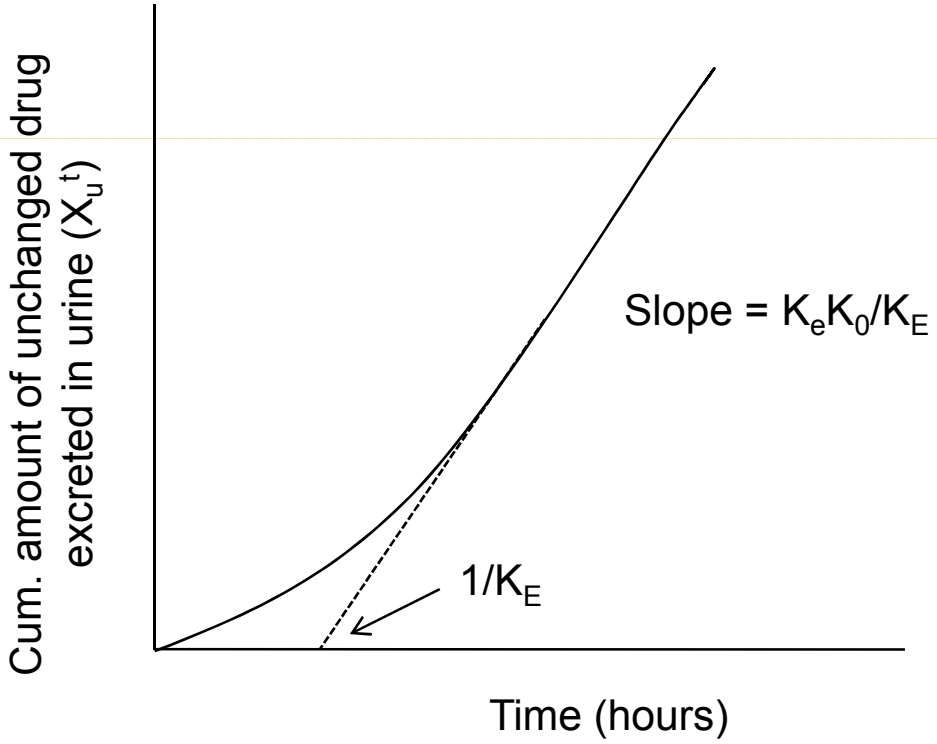
A steady-state level is reached after 5 half-lives of the drug, the term $e^{-K_E t}$ approaches zero.

$$X_u^t = \frac{K_e K_0}{K_E} t - \frac{K_e K_0}{K_E^2} \quad \ldots\ldots(19)$$

$$X_u^t = \frac{K_e K_0}{K_E}\left(t - \frac{1}{K_E}\right) \quad \ldots\ldots(20)$$

suvendukumar.sahoo@gitam.edu

The plot of cum. amount of drug excreted versus time should be a curve until steady state is reached and become linear after steady state is reached



suvendukumar.sahoo@gitam.edu

At steady state, the rate of excretion of drug is constant. Extrapolation of linear segment of the curve to $X_u = 0$ yield an intercept of $1/K_E$.
The slope of the line is $K_e K_0/K_E$

$$X_u^t = \frac{K_e K_0}{K_E}\left[t - \frac{1}{K_E}\left(1 - e^{-K_E t}\right)\right] \quad \ldots\ldots(21)$$

suvendukumar.sahoo@gitam.edu