M.PHARM SEMINAR(2nd SEM)(PHARMACEUTICS)

SUB-BIOPHARMACEUTICS & PHARMACOKINETICS

TOPIC- PHARMACOKINETICS OF IV INFUSION, ONE-COMPARTMENT OPEN MODEL

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CONTENT...

- What is OCOM?
- Why IV infusion?
- Advantages of zero order infusion of drug.
- Model representation.
- Determination of parameters from plasma.
- Infusion equilibrium.
- Infusion plus loading dose.
- Journal review.

OCOM…

- OCOM is the simplest model that represents the body as a single homogeneous system.
- Here, body is open with respect to the drug movement.(Only in highly perfused tissues)
- This model is useful for drugs which rapidly distribute between plasma and other body fluids and tissues upon entry into systemic circulation.

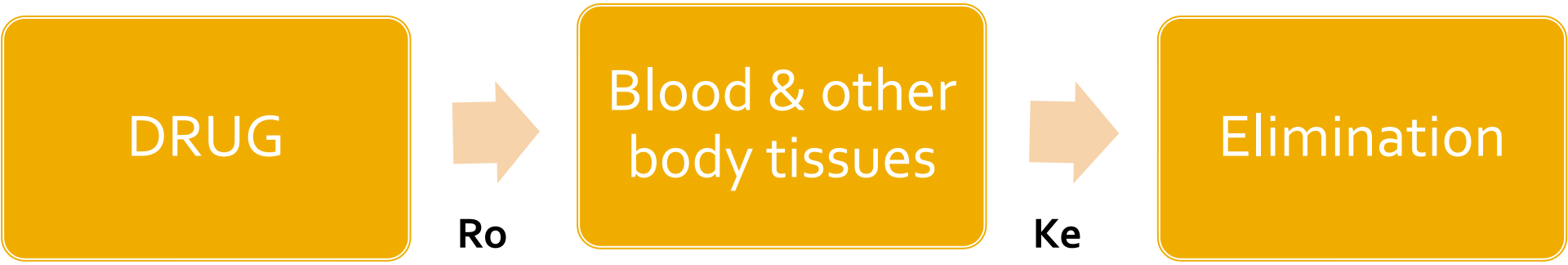
WHY I.V. INFUSION???

- Rapid i.v. injection is unsuitable when the drug has potential to precipitate toxicity or when maintenance of a stable concentration or amount of drug in the body is desired.
- In such situation, the drug is administered at a constant rate by i.v. infusion.
- I.V. drug solution is infused slowly at zero order constant rate(Ro).
- Then drugs get eliminated following 1st order kinetics only after drug infusion has stopped.

Advantages of zero order infusion of drug …

- 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.

MODEL REPRESENTATION…



Ro= Zero order rate of drug infusion
Ke= First order elimination rate constant

DETERMINATION OF PARAMETERS FROM 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 Ro and first order rate elimination , -Ke X:

dx/dt = Ro- KeX 1

(X=amount of drug in the body at any time t remaining to be eliminated.)

- Integration and rearrangement of above equation yields:-

$$X=R_o/K_e(1-e^{-ket}) \ldots..2$$

- Since it is difficult to determine directly the amount of drug in the body X, advantage is taken of the fact that a constant relationship exists in between drug conc in plasma C & X. Thus:

X=VdC

VdC= Proportionality constant(apparent volume of distribution)

CONTD...

Rearranging the eqn we get:-

$$C = R_o/k_e vd(1-e^{-ket}) \ldots\ldots 3$$

$$= R_o/cl_t(1-e^{-ket}) \ldots\ldots 4$$

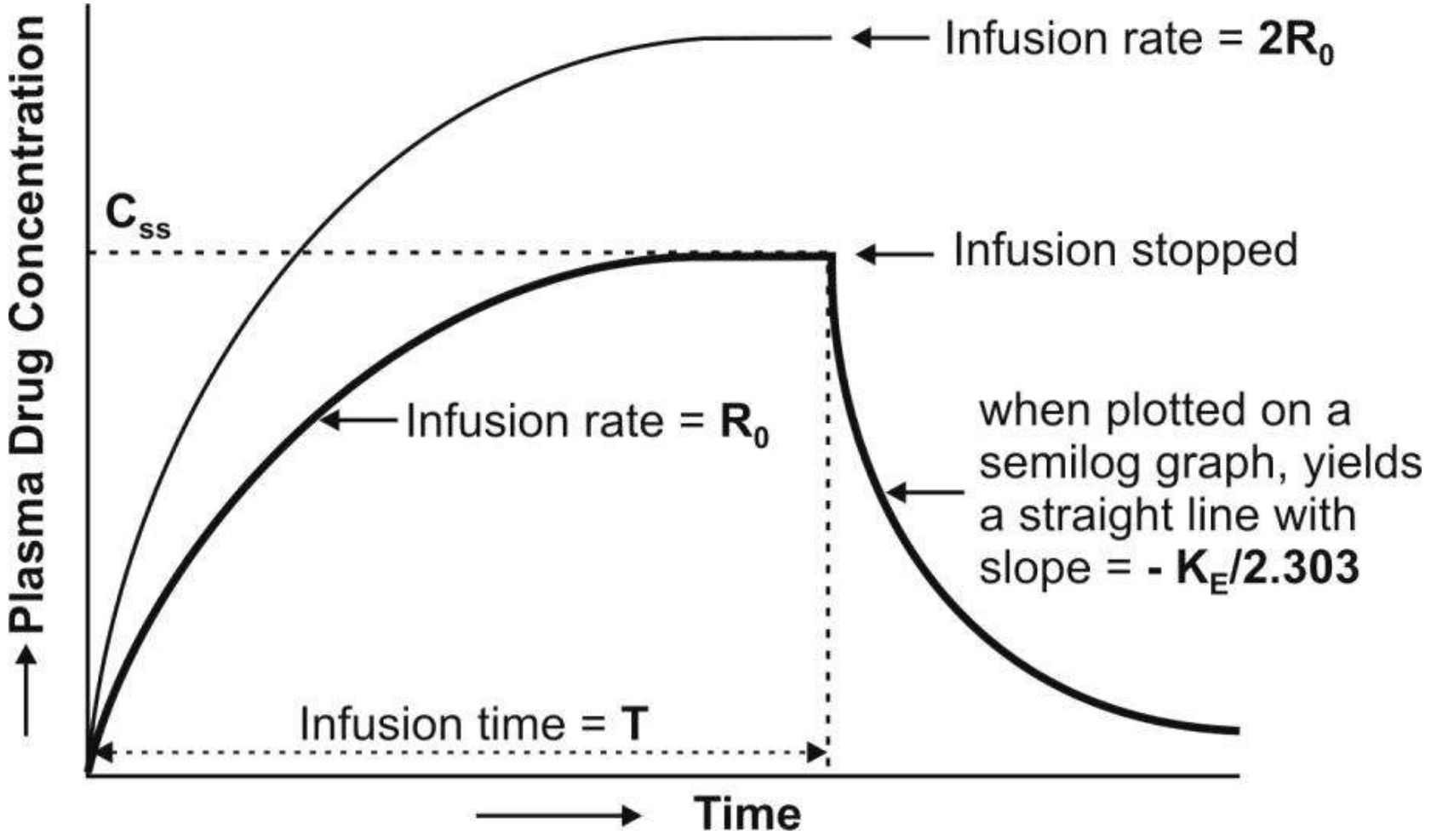
The total body clearance, Clt, also called as total systemic clearance, is an additive property of individual organ clearances.

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

INFUSION EQUILIBRIUM…

- At the start of constant rate infusion, the amount of drug in the body is zero, & hence there is no elimination.
- As time passes, the amount of drug in the body rises gradually(elimination rate is less than the rate of infusion) until a point after which the rate of elimination = rate of infusion i.e. the concentration of drug in plasma approaches a constant value called as steady state or infusion equilibrium.

CONTD...


Plasma Drug Concentration
Infusion rate = 2R0
Css
Infusion stopped
Infusion rate = R0
when plotted on a semilog graph, yields a straight line with slope = - KE/2.303
Infusion time = T
Time

CONTD…

- At steady state, the rate of change of amount of drug in the body is zero. So eqn 1 becomes:-

$$Zero = R_o - k_e x_{ss}$$

$$K_e x_{ss} = R_o \quad \ldots\ldots 5$$

$$C_{ss} = R_o / k_e v_d$$

$$= R_o / cl_t \text{ i.e infusion rate/clearance} \quad \ldots . 6$$

- Xss= amount of drug in the body at steady state.
- Css= amount of drug in plasma at steady state.

CONTD…

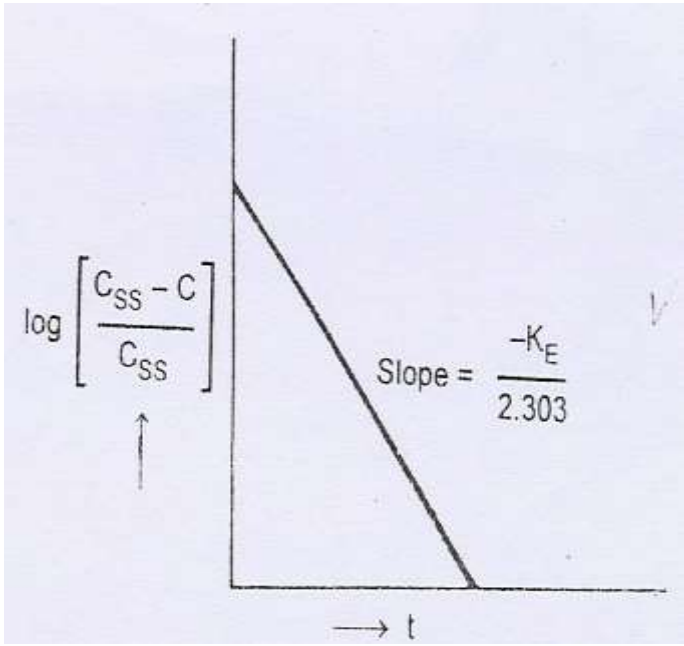
- Substituting the value of $C_{ss} = R_o/cl_t$ in eqn 4:

$$C = c_{ss}(1-e^{-ket}) \ldots\ldots 7$$

Rearrangement yields:

- $$\frac{[C_{ss}-c]}{C_{ss}} = e^{-ket}$$

$$\text{Log}\ \frac{C_{SS}-C}{C_{ss}} = \frac{-k_e t}{2.303} \qquad \ldots 8$$



CONTD...

- The time to reach steady state concentration is dependent upon the elimination half life .
- If n is the number of half-lives passed since the start of infusion ($t/t_{1/2}$), then the eqn 7 can be written as:-

$$C=C_{SS}\,[1-(1/2)^{n}]\ldots..9$$

Half-life	%Remaining	% Css Achieved
1	50	50
2	25	50+25=75
3	12.5	75+12.5=87.5
4	6.25	87.5+6.25=93.75
5	3.125	93.75+3.125=96.875
6	1.562	96.875+1.562=98.437
7	0.781	98.437+0.781=99.218

% of Css attained at the end of a given t1/2.

INFUSION PLUS LOADING DOSE…

- It takes very long time for the drugs having longer half lives before the steady state concentration is reached.(Eg:- Phenobarbital)
- An i.v. **loading dose is given to yield the desired steady-state immediately upon injection prior to starting the infusion.**
- It should then be followed immediately by i.v. infusion at a rate enough to maintain this concentration.

Journal review:-1

Pharmacokinetics of L-arginine following intravenous administration in normal volunteers.

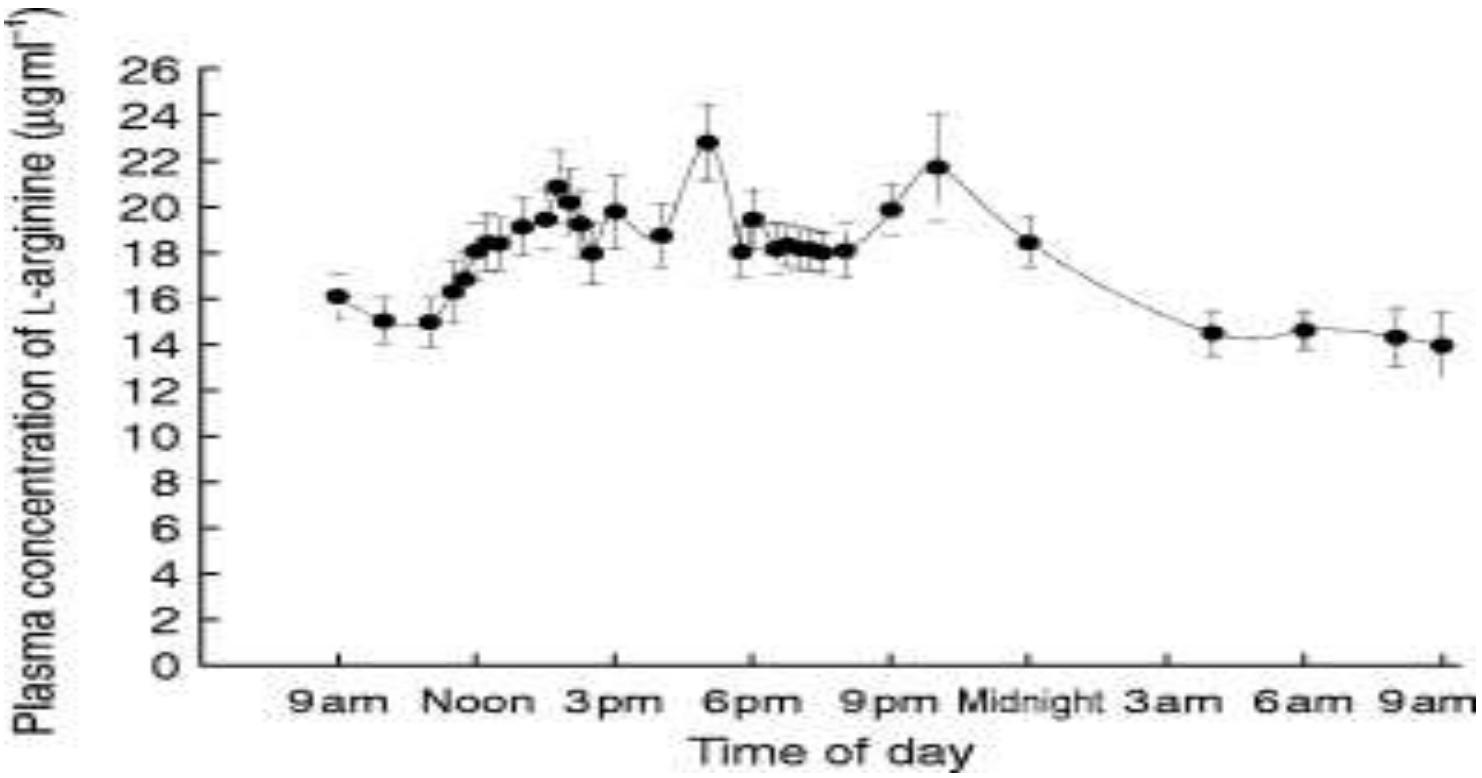
Tangphao O*, Grossmann M1, Chaion S2, Hoffman B3.

- **INTRODUCTION:-**
- This crossover study was designed to examine the pharmacokinetics of single i.v. of l-arginine in healthy volunteers (*n* = 10).
- l-arginine is considered a nutritionally dispensable (or non essential) amino acid in humans.

- **Control study:-**
- In a separate protocol designed to evaluate the effects of a normal diet on plasma l-arginine concentrations, 12 healthy volunteers were admitted to the General Clinical Research Center (GCRC). Blood and urine samples were collected over an 8h period with a diet similar to that given during the pharmacokinetic studies containing normal amounts of proteins and l-arginine. Plasma samples were analysed for l-arginine concentrations and these data were used to interpret the result.

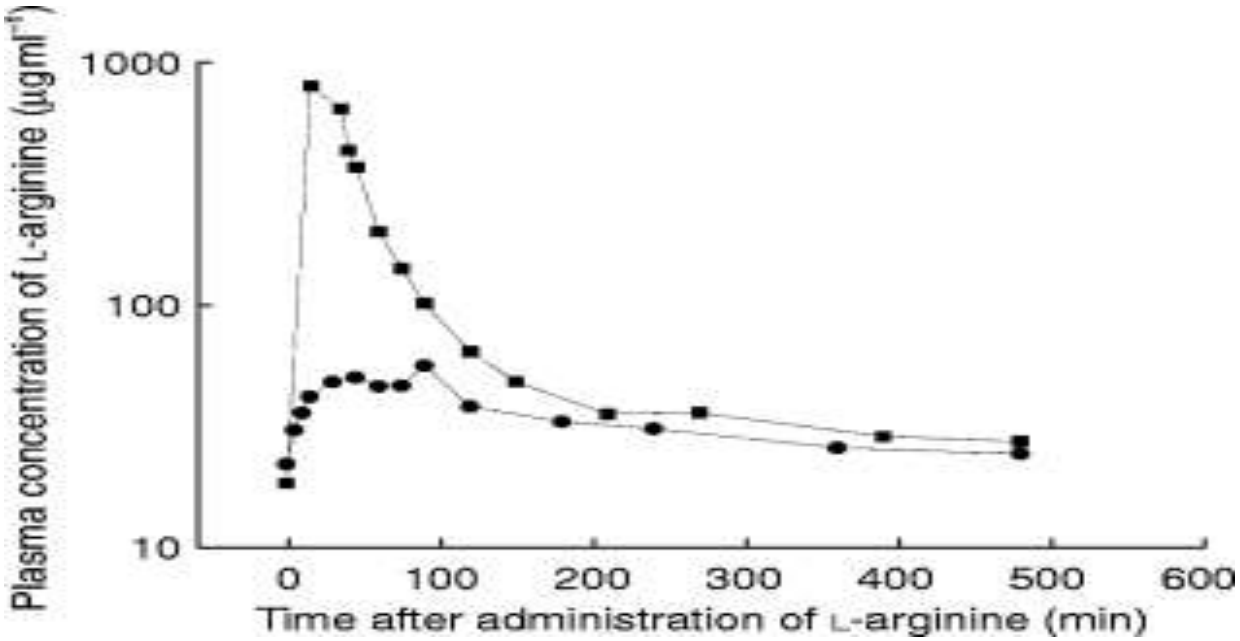
CONTROL STUDY…

- The spontaneous variation of daytime plasma l-arginine concentrations over 8 h (09.00 h to 17.00 h) with a normal diet is shown in Figure 1. The average baseline plasma concentration of l-arginine was 15.1±2.6 μg ml^{-1}



CONTD...

- After the 30 min intravenous infusion, l-arginine plasma concentrations reached a maximum of 1390±596 μg $ml^{-1}$and then declined rapidly (Figure 2). Approximately 5 g l-arginine was excreted into urine after the 30 g intravenous infusion.



RESULT...

- The mean baseline plasma concentration of l-arginine in the control study was 15.1±2.6 μg ml^{-1}. After intravenous administration (30 g over 30 min), the plasma concentration reached 1390±596 μg ml^{-1}. The disappearance of l-arginine appeared biphasic, with an initial rapid disappearance due to concentration-dependent renal clearance followed by a slower fall in plasma concentrations due to nonrenal elimination.

REFERENCE:

- D.M Brahmankar and Sunil. B .Jaiswal, Biopharmaceutics & Pharmacokinetics, Vallabh Prakashan, 1st edition, (1995), page no.239-243.
- Tangphao O et al, Pharmacokinetics of L-arginine following intravenous administration in normal volunteers, British journal of clinical pharmacology, vol:47(3), 1999 march.