MULTI- COMPARTMENT MODELS

- Ideally a true pharmacokinetic model should be the one with a rate constant for each tissue undergoing equilibrium.
- Therefore best approach is to pool together tissues on the basis of similarity in their distribution characteristics.
- The drug disposition occurs by first order.
- Multi-compartment characteristics are best described by administration as i.v bolus and observing the manner in which the plasma concentration declines with time.

  The no. Of exponentials required to describe such a plasma level-time profile determines the no. Of kinetically homogeneous compartments into which a drug will distribute.

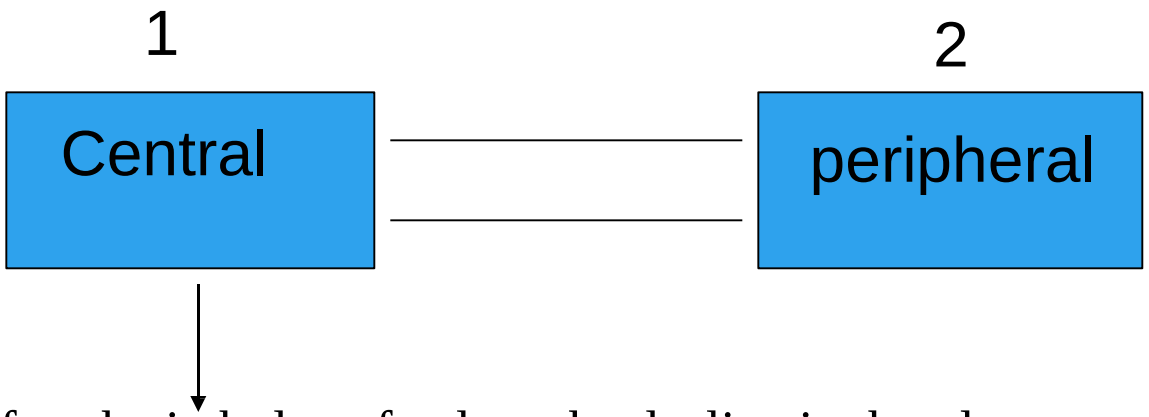
  The simplest and commonest is the two compartment model which classifies the body tissues in two categories :

1. Central compartment or compartment 1
2. Peripheral or tissue compartment or compartment 2.

TWO COMPARTMENT OPEN MODEL-IV BOLUS ADMINISTRATION:

Elimination from central compartment

Fig:



- After the iv bolus of a drug the decline in the plasma conc. Is bi-exponential.
- Two disposition processes- distribution and elimination.
- These two processes are only evident when a semi log plot of C vs. T is made.
- Initially, the conc. Of drug in the central compartment declines rapidly, due to the distribution of drug from the central compartment to the peripheral compartment. This is called distributive phase.

Extending the relationship $X = v_d C$

$$\frac{Dc_c}{Dt} = \frac{K_{21}\, x_p}{v_p} - \frac{K_{12}\, x_c}{v_c} - \frac{K_E\, x_c}{v_c}$$

X= Amt. Of drug in the body at any time t remaining to be eliminated

C=drug conc in plasma

V_d =proportionality const app. Volume of distribution

X_c and x_p=amt of drug in C1 and C2

V_c and v_p=apparent volumes of C1 and C2

$$= \frac{K_{12}\, x_c}{V_c} - \frac{K_{21}\, x_p}{v_p}$$

On integration equation gives conc of drug in central and peripheral compartments at any given time t

$$Cp = \frac{xo}{Vc}\left[\frac{\left(K_{21} - a\right)e^{-at}}{b - a} + \frac{\left(K_{12} - b\right)e^{-bt}}{a - b}\right]$$

Xo = iv bolus dose

- The relation between hybrid and microconstants is given as :

$a + b = K12 + K21 + KE$

$A\ b = K21\ KE$

$Cc = a\ e^{-at} + be^{-bt}$

Cc=distribution exponent + elimination exponent

A and B are hybrid constants for two exponents and can be resolved by graph by method of residuals.

$$A = \frac{X_0}{V_C} \quad \frac{[K_{21} - A]}{B - A} = \frac{C_O\,[K_{21} - A]}{B - A}$$

$$B = \frac{X_0}{V_C} \quad \frac{[K_{21} - B]}{A - B} = \frac{C_O\,[K_{21} - B]}{A - B}$$

C_O = Plasma drug concentration immediately after i.v. Injection

- Method of residuals : the biexponential disposition curve obtained after i. V. Bolus of a drug that fits two compartment model can be resolved into its individual exponents by the method of residuals.

$$C = a\,e^{-at} + b\,e^{-bt}$$

From graph the initial decline due to distribution is more rapid than the terminal decline due to elimination i.E. The rate constant a >> b and hence the term e^{-at} approaches zero much faster than e^{-bt}

$$C = B\,e^{-bt}$$

$$\log C = \log B - \overleftarrow{bt}/2.303$$ C = back extrapolated pl. Conc.

- A semilog plot of C vs t yields the terminal linear phase of the curve having slope –b/2.303 and when back extrapolated to time zero, yields y-intercept log B. The $t^{1/2}$ for the elimination phase can be obtained from equation
- $t^{1/2} = 0.693/b$.
- Residual conc values can be found as-

$$C_r = C - \overleftarrow{C} = ae^{-at}$$

$$\log cr = \log A - \frac{at}{2.303}$$

A semilog plot cr vs t gives a straight line.

$$K_e = \frac{a\ b\ c}{A\ b + B\ a}$$

$$K_{12} = \frac{a\ b\ (b - a)^2}{C_0\ (A\ b + B\ a)}$$

$$K_{21} = \frac{A\ b + B\ a}{C_0}$$

- For two compartment model, K_E is the rate constant for elimination of drug from the central compartment and b is the rate constant for elimination from the entire body. Overall elimination t1/2 can be calculated from b.

Area under (auc) = $\frac{a}{} + \frac{b}{}$

The curve a b

App. Volume of central compartment = $\frac{X_0}{C_0} = \frac{X_0}{K_E\ (AUC)}$

App. Volume of = $V_P = \frac{V_C K_{12}}{}$

Peripheral compartment K_{21}

Apparent volume of distribution at steady state or equilibrium

$$V_{d,ss} = V_C + V_P$$

$$V_{d,area} = \frac{X_0}{B\,AUC}$$

Total systemic clearence= $cl_t = b\ v_d$

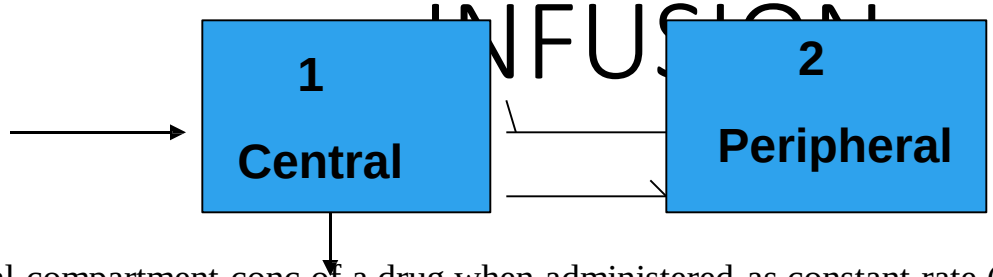
Renal clearence= $cl_r = \frac{dx_u}{Dt} = K_E V_C$

The rate of excretion of unchanged drug in urine can be represented by :

$$\frac{dx_u}{Dt} = K_E A e^{-at} + K_E B e^{-bt}$$

The above equation can be resolved into individual exponents by the **method of residuals**.

TWO – COMPARTMENT OPEN MODEL- I.V. INFUSION



The plasma or central compartment conc of a drug when administered as constant rate (0 order) i.V. Infusion is given as:

$$C = \frac{R0}{VC\,KE}\left[1+\left(\frac{KE - b}{b - a}\right)e^{-at} + \left(\frac{KE - a}{a - b}\right)e^{-bt}\right]$$

At steady state (i.E.At time infinity) the second and the third term in the bracket becomes zero and the equation reduces to:

$$Css = \frac{R0}{Vc\,ke}$$

Now VC KE = vd b

$$Css = \frac{r0}{Vdb} = \frac{r0}{clt}$$

The loading dose $X0,L = css\ vc = \frac{R0}{Ke}$

TWO-COMPARTMENT OPEN MODEL-EXTRAVASCULAR ADMINISTRATION

- First - order absorption :
- For a drug that enters the body by a first-order absorption process and distributed according to two compartment model, the rate of change in drug conc in the central compartment is described by three exponents :
- An absorption exponent, and the two usual exponents that describe drug disposition.

The plasma conc at any time t is

$$C = n\, e^{-kat} + l\, e^{-at} + m\, e^{-bt}$$

C = absorption + distribution + elimination

Exponent exponent exponent

- Besides the method of residuals, ka can also be found by loo-riegelman method for drug that follows two-compartment characteristics.
- Despite its complexity, the method can be applied to drugs that distribute in any number of compartments.

CALCULATING **Ka** using Wagner-nelson method(Bioavailability parameters)

WAGNER-NELSONS METHOD

THEORY: The working equations can be derived from the mass balance equation: Gives the following eqaution with time and mass balance

$$\frac{dA}{dt} = \frac{dX}{dt} + \frac{dU}{dt}$$

- Above equation Integrating gives
- To the equation amount orbed ***VERSUS*** **TIME**

$$A = V \bullet Cp + V \bullet kel \bullet \int_0^t Cp \bullet dt$$

$$\frac{A}{V} = Cp + kel \bullet \int_0^t Cp \bullet dt$$

Amount absorbed up to time t divided by V

kel - AUC from t = 0 up to t = t

WAGNER-NELSONS METHOD

- Taking this to infinity where cp equals 0

$$\frac{A_{max}}{V} = kel \bullet AUC_0^{\infty}$$

- Finally (A_{max} - A), the amount remaining to be absorbed can also be expressed as the amount remaining in the GI, xg
- We can use this equation to look at the absorption process. If, and only if, absorption is a single first order process

$$\left[\frac{A_{max}}{V} - \frac{A}{V}\right] = \frac{Xg^0}{V} \bullet e^{-ka \bullet t}$$

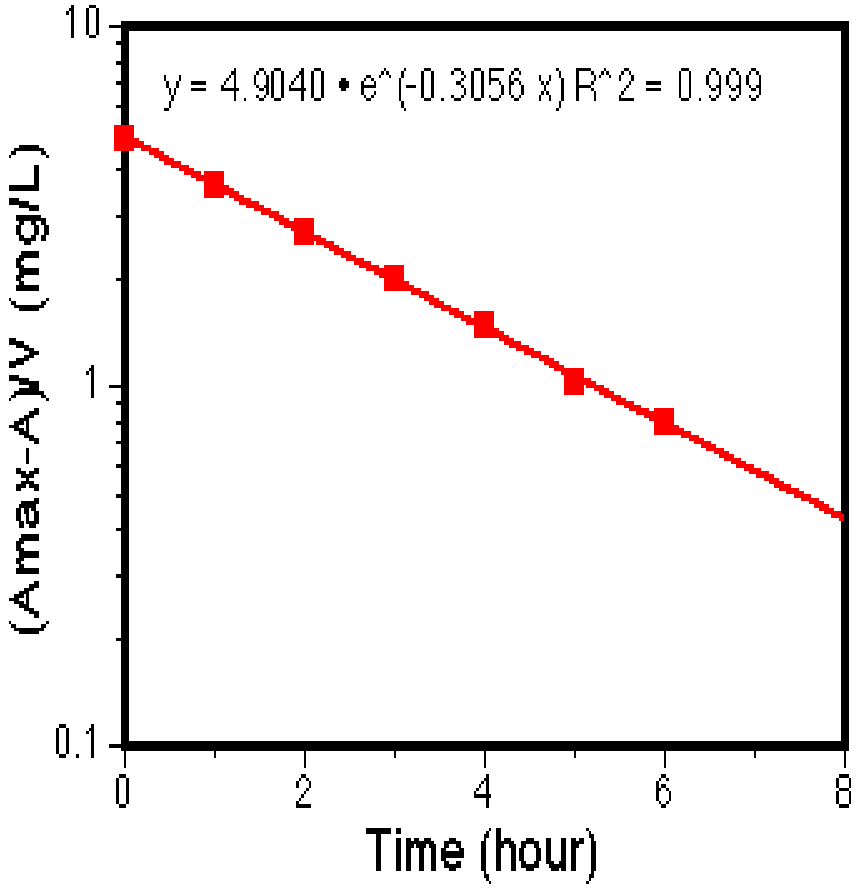
WAGNER-NELSONS METHOD

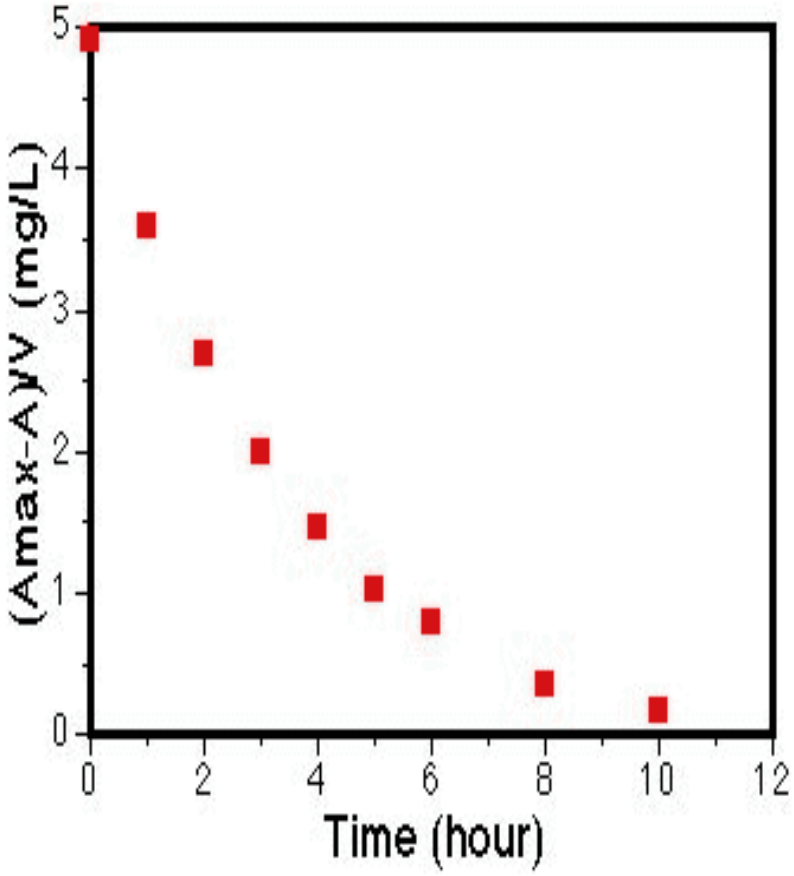
- Example data for the method of wagner-nelson kel (from IV data) = 0.2 hr^{-}

Time (hr)	Plasma Concentration (mg/L)	Column 3 ΔAUC	Column 4 AUC	Column 5 kel * AUC	A/V [Col2 + Col5]	$(A_{max} - A)/V$
0.0	0.0	0.0	0.0	0.0	0.0	4.9
1.0	1.2	0.6	0.6	0.12	1.32	3.58
2.0	1.8	1.5	2.1	0.42	2.22	2.68
3.0	2.1	1.95	4.05	0.81	2.91	1.99
4.0	2.2	2.15	6.2	1.24	3.44	1.46
5.0	2.2	2.2	8.4	1.68	3.88	1.02
6.0	2.0	2.1	10.5	2.1	4.1	0.8
8.0	1.7	3.7	14.2	2.84	4.54	0.36
10.0	1.3	3.0	17.2	3.44	4.74	0.16
12.0	1.0	2.3	19.5	3.9	4.9	-
∞	0.0	5.0	24.5	4.9	4.9	-

WAGNER-NELSONS METHOD

- The data (A_{max}-A)/V *versus* time can be plotted on semi-log and linear graph paper





WAGNER-NELSONS METHOD

- Plotting $(A_{max}-A)/V$ *versus* time produces a straight line on semi-log graph paper and a curved line on linear graph paper. This would support the assumption that absorption can be described as a single first process. The first-order absorption rate constant, ka, can be calculated to be 0.306 hr^{-1} from the slope of the line on the semi-log graph paper.

ADVANTAGES:

- The absorption and elimination processes can be quite similar and accurate determinations of ka can still be made.
- The absorption process doesn't have to be first order. This method can be used to investigate the absorption process.

DISADVANTAGES:

- The major disadvantage of this method is that you need to know the elimination rate constant, from data collected following intravenous administration.
- The required calculations are more complex.

RESIDUAL METHOD OR FEATHERING TECHNIQUE

- Absowhen a drug is administered by extravascular route, absorption is a prerequisite for its therapeutic activity.

- The absorption rate constant can be calculated by the method of residuals.

- The technique is also known as **feathering, peeling** and **stripping.**

φ It is commonly used in pharmacokinetics to resolve a multiexponential curve into its individual components.

φ For a drug that follows one-compartment kinetics and administered extravascularly, the concentration of drug in plasma is expressed by a biexponential equation.

$$C = \frac{K_a F X_0}{V_d (Ka - KE)} [e^{-K_E t} - e^{-K_a t}] \quad (1)$$

If $K_a FX_0/V_d(K_a - K_E) = A$, a hybrid constant, then:

$$C = A\, e^{-K_E t} - A\, e^{-K_a t} \quad (2)$$

- During the elimination phase, when absorption is almost over, $K_a << K_E$ and the value of second exponential $e^{-K_a t}$ approaches zero whereas the first exponential $e^{-K_E t}$ retains some finite value.

- At this time, the equation (2) reduces to:

$$C^- = A e^{-KEt} \quad (3)$$

- In log form, the above equation is:

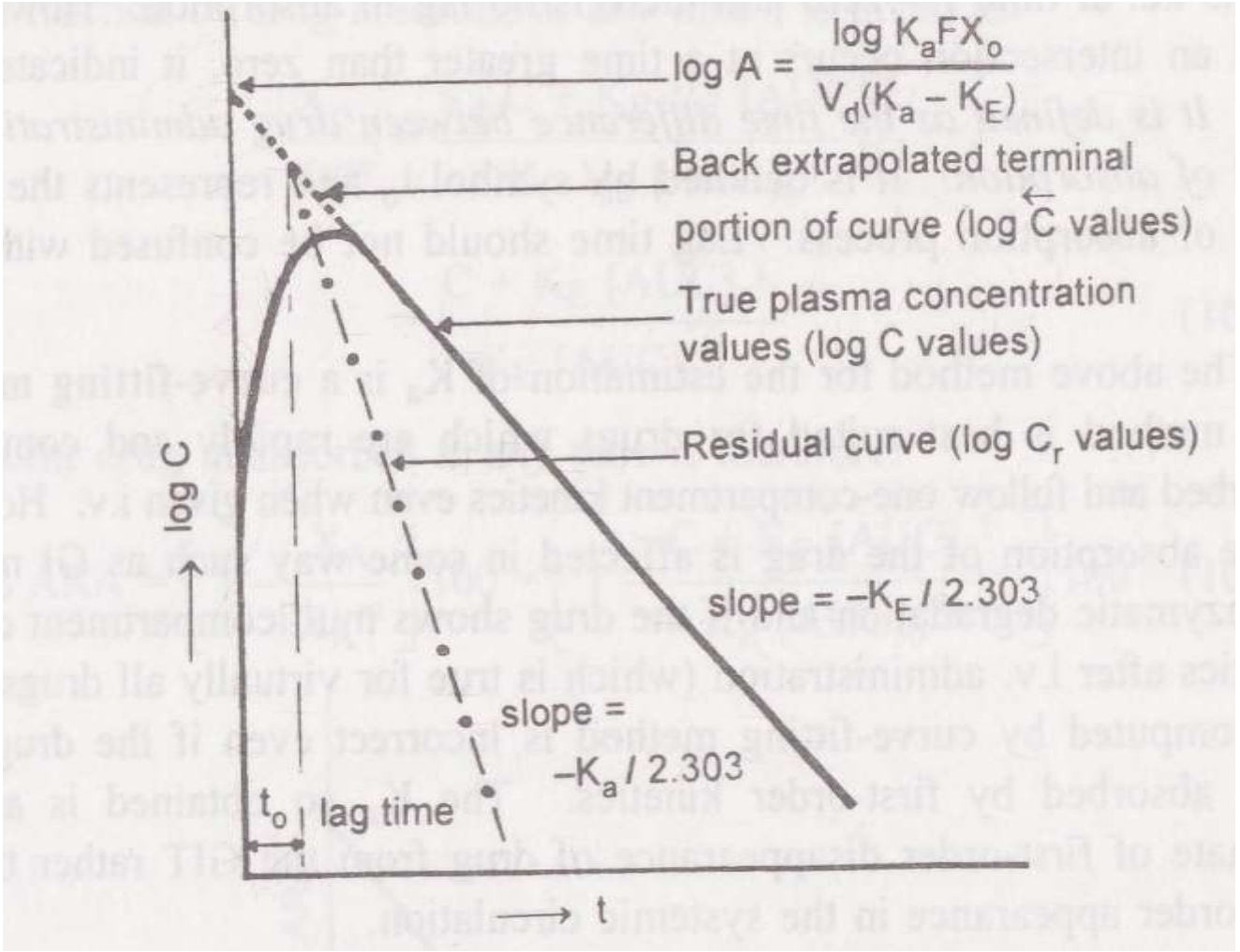
$$\text{Log } C^- = \log A - \frac{KEt}{2.303} \quad (4)$$

Where ,

C^- = back extrapolated plasma concentration values

- A plot of **log C** *versus* **t** yield a biexponential curve with a terminal linear phase having **slope $-K_E/2.303$**

- Back extrapolation of this straight line to time **zero** yields **y-intercept** equal to **log A**.



Plasma conc.-Time profile after oral administration of a single dose of a drug

- Subtraction of true plasma concentration values i.e. equation (2) from the extrapolated plasma concentration values i.e. equation (3) yields a series of residual concentration value C_{τ}.

$$(C^{-} - C) = C_{\tau} = A\, e^{-K_a t} \quad (5)$$

- In log form , the equation is:

$$\log C_{\tau} = \log A - \frac{K_a t}{2.303} \quad (6)$$

φ A plot of ***log*** C_r *versus* ***t*** yields a straight line with **slope** - $K_a/2.303$ and **y-intercept** *log A.*

φ Thus, the method of residual enables resolution of the biexponential plasma level-time curve into its two exponential components.

φ The technique works best when the difference between K_a and K_E is large ($K_a/K_E \geq 3$).

Thanks