Pharmacokinetics

Lecture (1)

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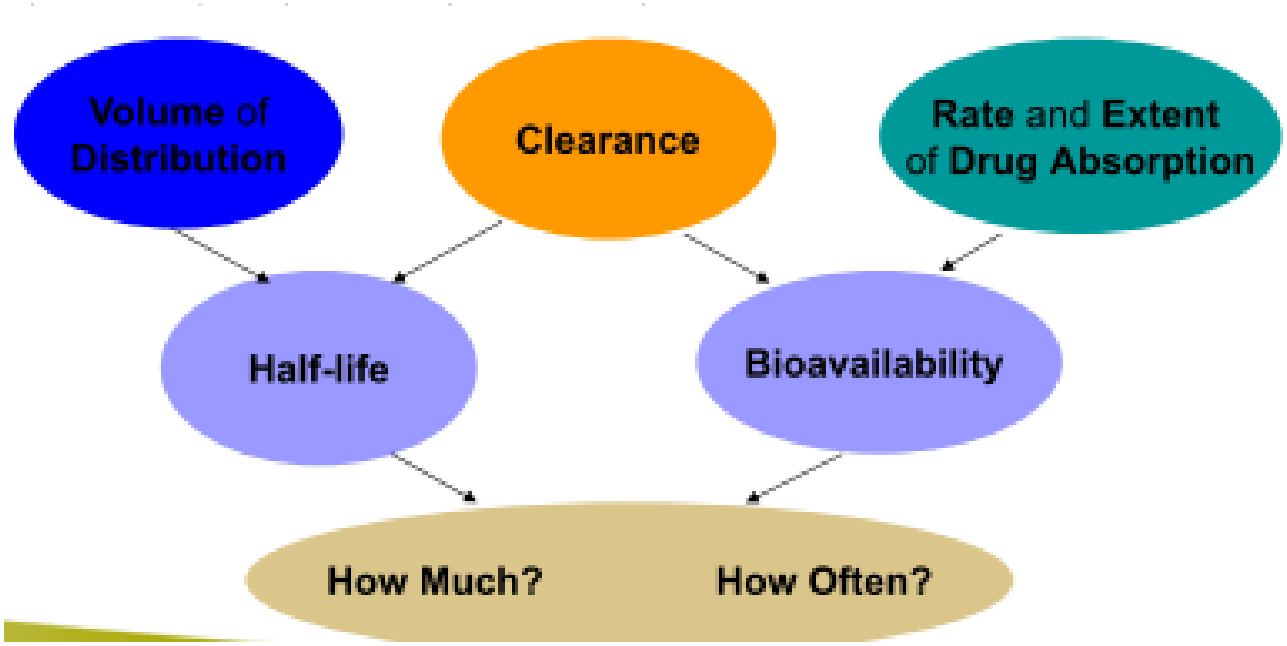
Pharmacokinetics

Pharmacokinetics is the science of the kinetics of drug absorption, distribution, and elimination (i.e., excretion and metabolism). Related terms include drug disposition, ADME, PD, PK/PD, TK, DMPK, DDD&D, Pharmacometrics.

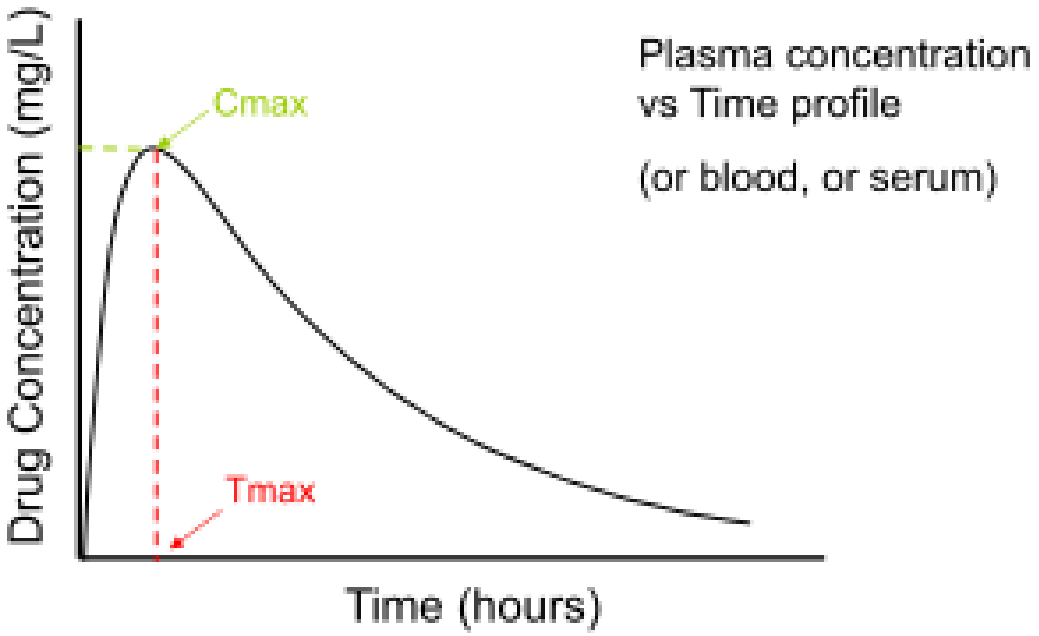


Significance of plasma drug concentrations

- Before therapeutic effect is observed
  - drug in dosage form administered (oral, iv etc)
  - drug is released from dosage form
  - fraction of drug absorbed
  - drug reaches site of action
- Drug must be at the site of action > min effective conc. for a pharmacological response
- For most drugs there is a relationship between the concentration of drug in the plasma and the concentration of drug at the site of action

Pharmacokinetics

Relationship between drug input and the concentration achieved with time.



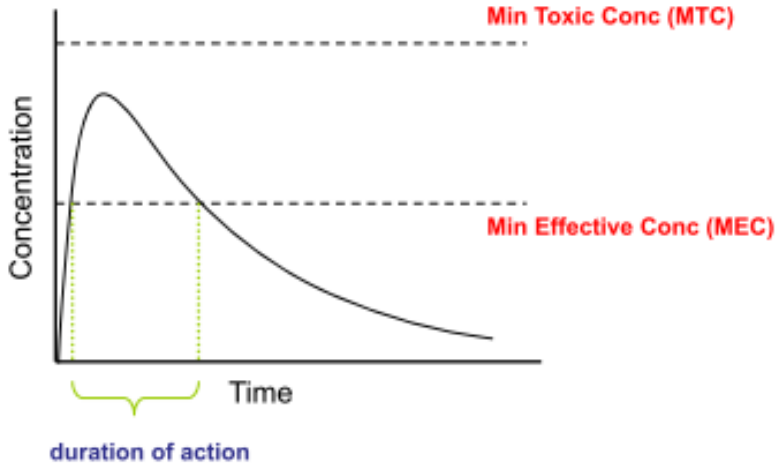
Pharmacokinetics – Bioanalytical measurements

- **Unbound Drug Concentration**

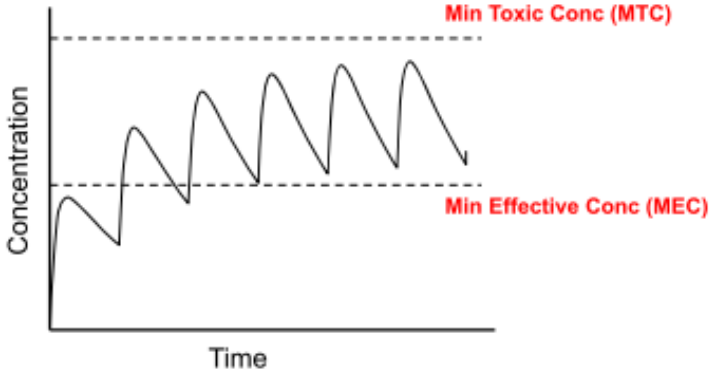
- distribution, elimination and pharmacodynamic responses are dependent upon the unbound concentration.
- Total plasma conc measurements include unbound and bound drug.
- Ratio of unbound to total drug usually does not change, therefore measuring total plasma conc is acceptable.
- But when plasma protein binding is altered it is important to consider the unbound conc i.e. renal or hepatic disease, surgery, pregnancy, burns, concomitant drug administration.

Therapeutic Window

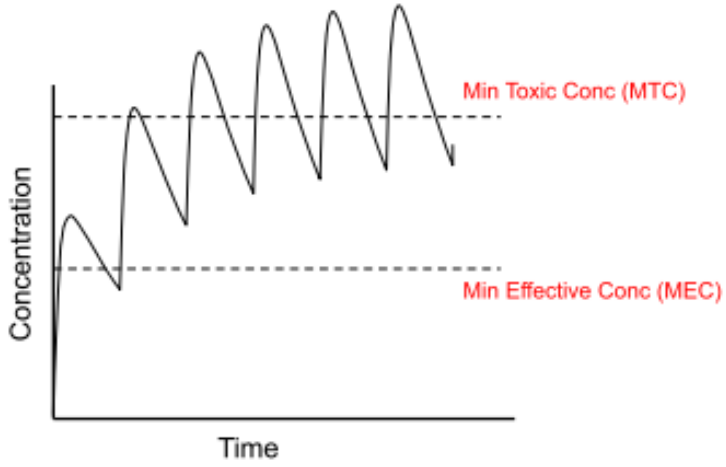
- Single oral dose



- Repeated dose administration – Dosing interval (Tau)



- Understanding PK allows us to avoid this situation



Model Independent PK parameters

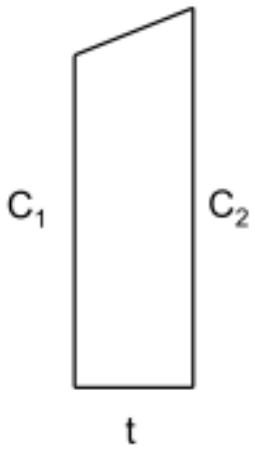
- In PK we use experimentally obtained data to generate a mathematical model that allows future predictions of drug behaviour
- Values obtained for actual, experimental data are more accurate than values obtained from a model
- Model independent parameters:

  AUC, C_{max}, T_{max}

Calculating AUC

The numerical value and the correct units are required in PK calculations

- Trapezoidal rule used to calculate AUC



$$Area = t\left(\frac{C_1 + C_2}{2}\right)$$

Calculating AUC

$$AUC = \left(\frac{C_1 + C_2}{2} \right) \bullet t_2 - t_1$$

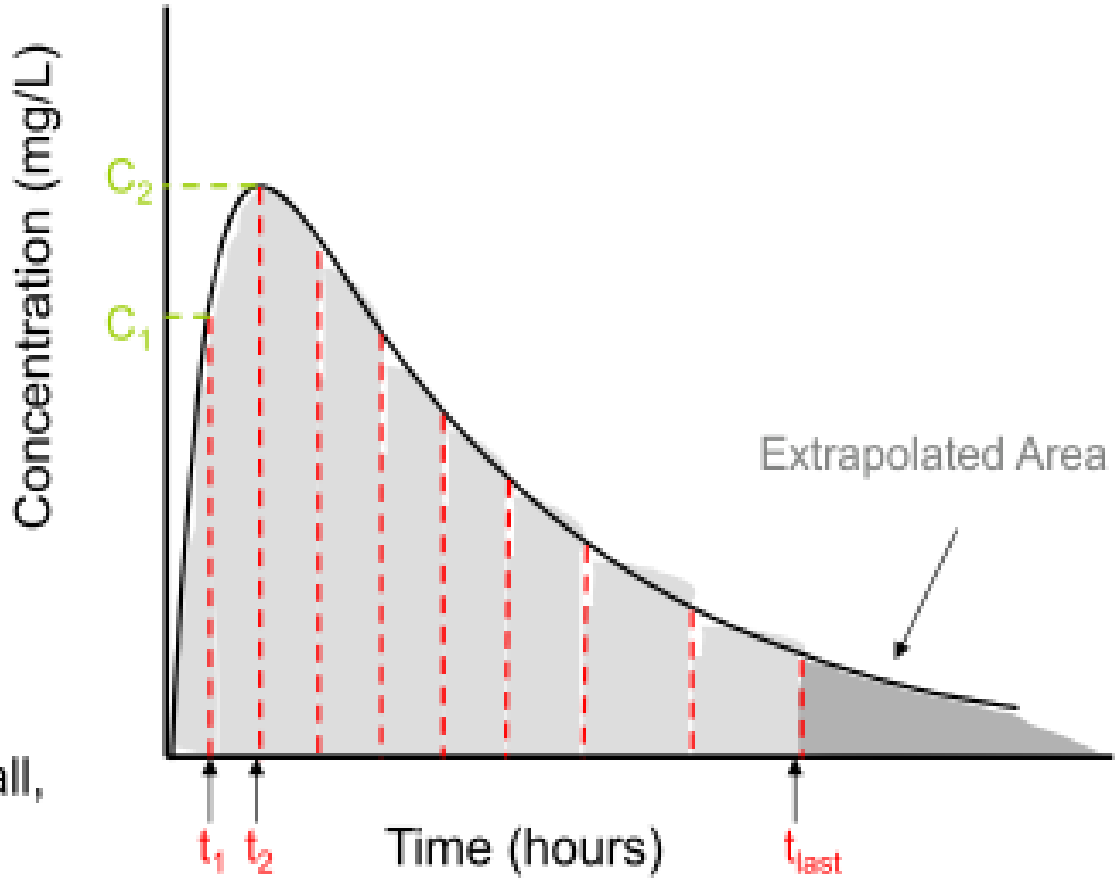
Add AUC from each segment (0 – t_{last})

plus AUC for extrapolated area is:

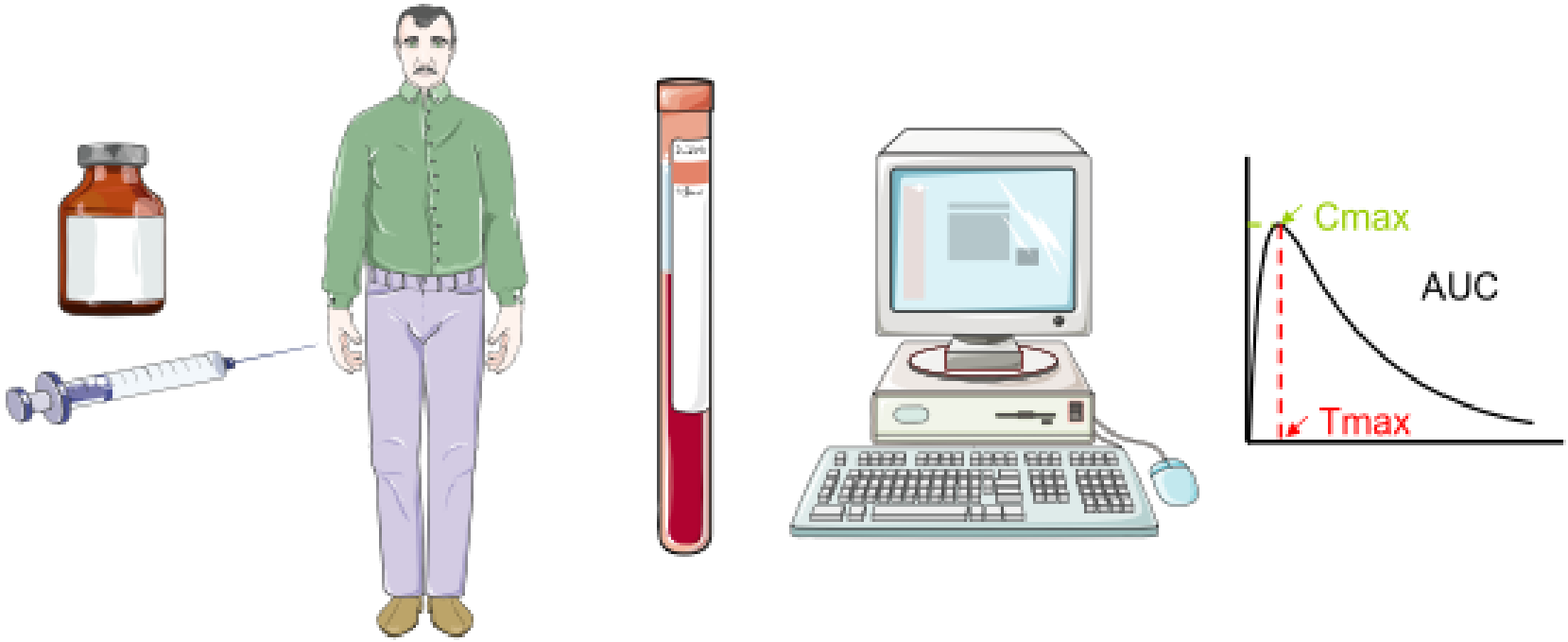
$$AUC_{extrapolated} = \frac{C_{last}}{k}$$

where ***k*** is the terminal elimination rate constant

Ideally, $AUC_{extrapolated}$ is small, < 20% of total AUC



How do we conduct PK studies?



Dose drug (D_o) | Patient | Collect blood samples | Assay for drug content | Construct plasma vs time plot

How do we conduct PK studies?

- **Define AUC, C_{max}, T_{max}**
- **Mathematically model data**
  - predict plasma, urine and tissue [drug]
  - calculate optimal dosage regimens
  - estimate accumulation of drugs or metabolites
  - correlate [drug] with pharmacologic activity
  - evaluate difference in generic formulations
  - describe how physiological change affect ADME
  - explain drug interactions

Types of Models

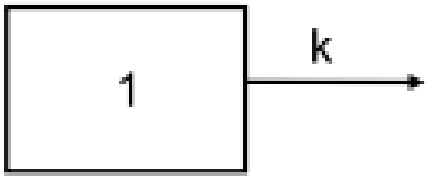
- **Empirical models**
- **Physiologic models**
  - blood flow is responsible for distributing drugs to each organ
  - organ uptake determined by drug binding to tissue
  - actual blood flow rates and tissue volumes are used
  - requires a lot of data to build the model

Types of Models

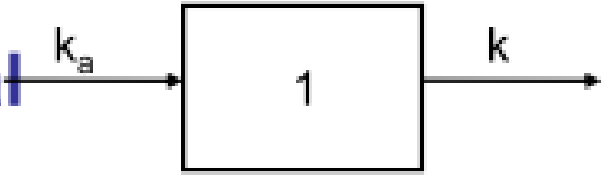
- Empirical models
- Physiologic models
- **Compartmental models**
  - body is simplified to be represented by compartments
  - not real physiologic/anatomic regions
  - each compartment represents a group of tissues with similar blood flow and drug affinity

Types of Models - Compartmental

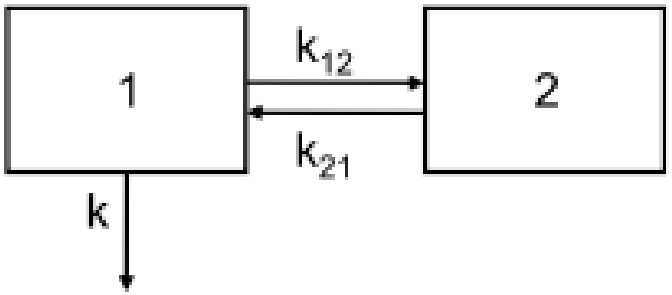
- One compartment – IV



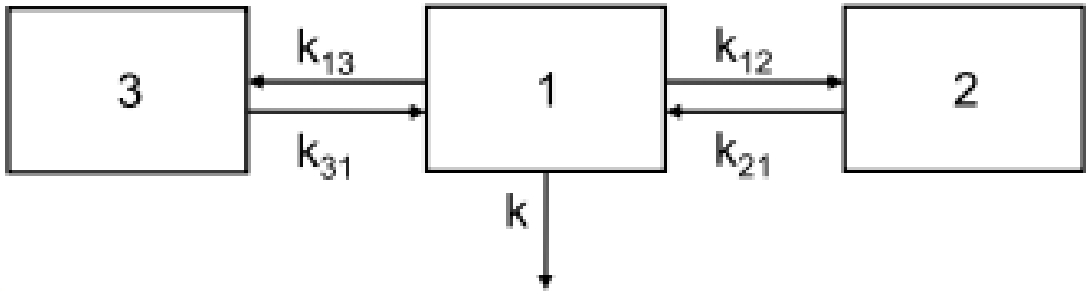
- One compartment – oral



- Two compartment

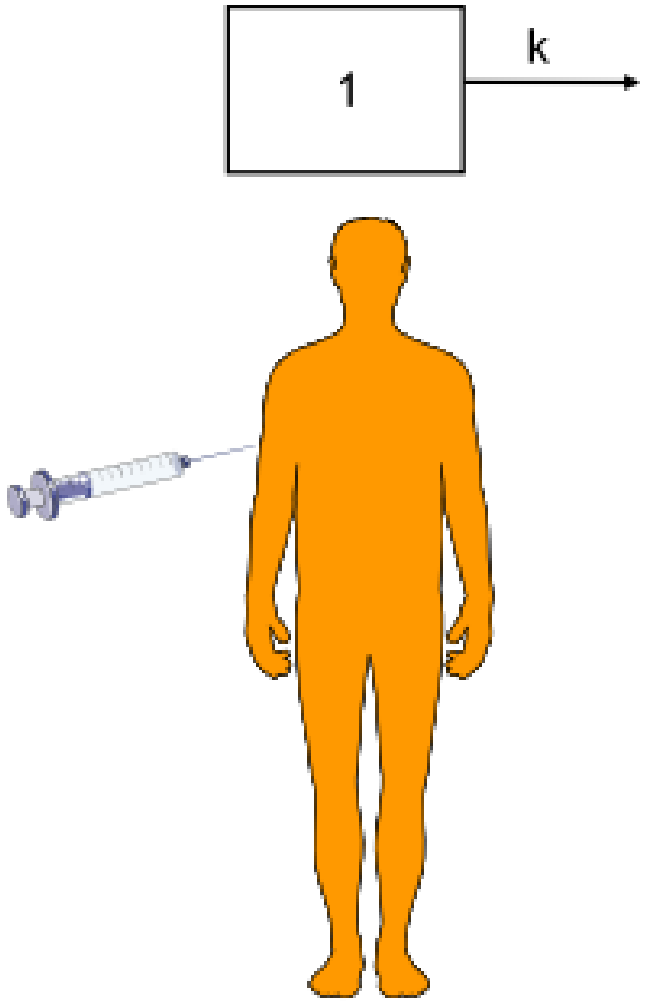


- Three compartment



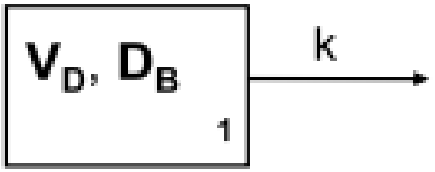
One Compartment Model - IV

- **IV administration**
  - no absorption
  - immediate distribution
  - 100% dose in blood
- **Assumptions**
  1. Drug can enter and leave the body
  2. Body acts as a single, uniform compartment
  3. Drug is mixed instantaneously with blood
  4. Elimination follows first order kinetics



One Compartment Model - IV

- **Pharmacokinetic parameters to define a one compartment model for a *specific* drug**



  - fluid volume of the 'compartment'
  - elimination rate *from* the 'compartment'
- **Knowing the dose (D_B^0) and measuring the concentration allows calculation of these parameters**
- **What is the *rate expression* for this model?**

$$dD_B / dt = -k \cdot D_B$$

- The elimination rate constant, *k*, is a first-order elimination rate constant with units of time^{-1} (eg, hr^{-1} or 1/hr).
- Total removal or elimination of the parent drug from this compartment is effected by metabolism (biotransformation) and excretion. The elimination rate constant represents the sum of each of these processes:

One Compartment Model -IV

- **Elimination Rate Constant (*k*)**
  - In first order elimination the rate of elimination is **dependent** on the amount or concentration of drug present

$$D_B = D_B^0 e^{-kt}$$

  - D_B is amount of drug in the body at time = t
  - D_B^0 is initial amount of drug dosed
  - *k* is elimination rate constant (units are time^{-1} eg hr^{-1})
  - Taking natural logs: $\ln D_B = \ln D_B^0 - kt$
  - OR logs to base 10: $\log D_B = \log D_B^0 - \frac{kt}{2.303}$

One Compartment Model -IV

- **Elimination Rate Constant**

$$D_B = D_B^0 e^{-kt}$$

  - **Cannot** measure the AMOUNT of drug in the body, we **can** measure the CONCENTRATION in plasma
  - For IV admin we *assume* that distribution is *instantaneous*, therefore we *assume* that the amount of drug in the body and the concentration in plasma is related by a proportionality constant that reflects the volume of fluid that the drug is dissolved in i.e. a fixed volume term:

    the APPARENT VOLUME OF DISTRIBUTION

- The *volume of distribution* represents a volume that must be considered in estimating the amount of drug in the body from the concentration of drug found in the sampling compartment. The volume of distribution is also the apparent volume (V_D) in which the drug is dissolved

One Compartment Model -IV

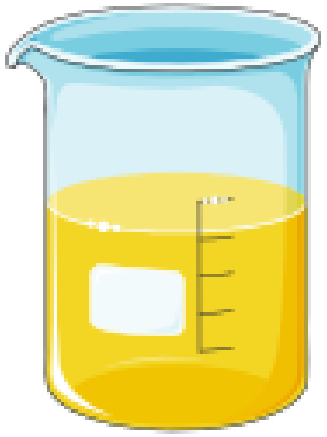
- **Apparent Volume of distribution (V_D)**

  a *proportionality constant* that relates the AMOUNT of drug in the body to the CONCENTRATION that we can measure

Dose: 25 mg

Volume: 200 mL

Conc: 0.125 mg/mL



$$D_B = V_D \bullet C_p$$

$$\therefore V_D = \frac{D_B}{C_p}$$

One Compartment Model -IV

- **Apparent Volume of distribution (V_D)**

Since $D_B = D_B^0 e^{-kt}$ **and** $D_B = V_D \bullet C_p$

we can rearrange the equations to show that:

$$\frac{D_B}{V_D} = \frac{D_B^0}{V_D} e^{-kt}$$

Therefore:

$$C_p = C_p^0 e^{-kt}$$

taking logs

$$\ln C_p = \ln C_p^0 - kt \qquad \log C_p = \log C_p^0 - \frac{kt}{2.303}$$

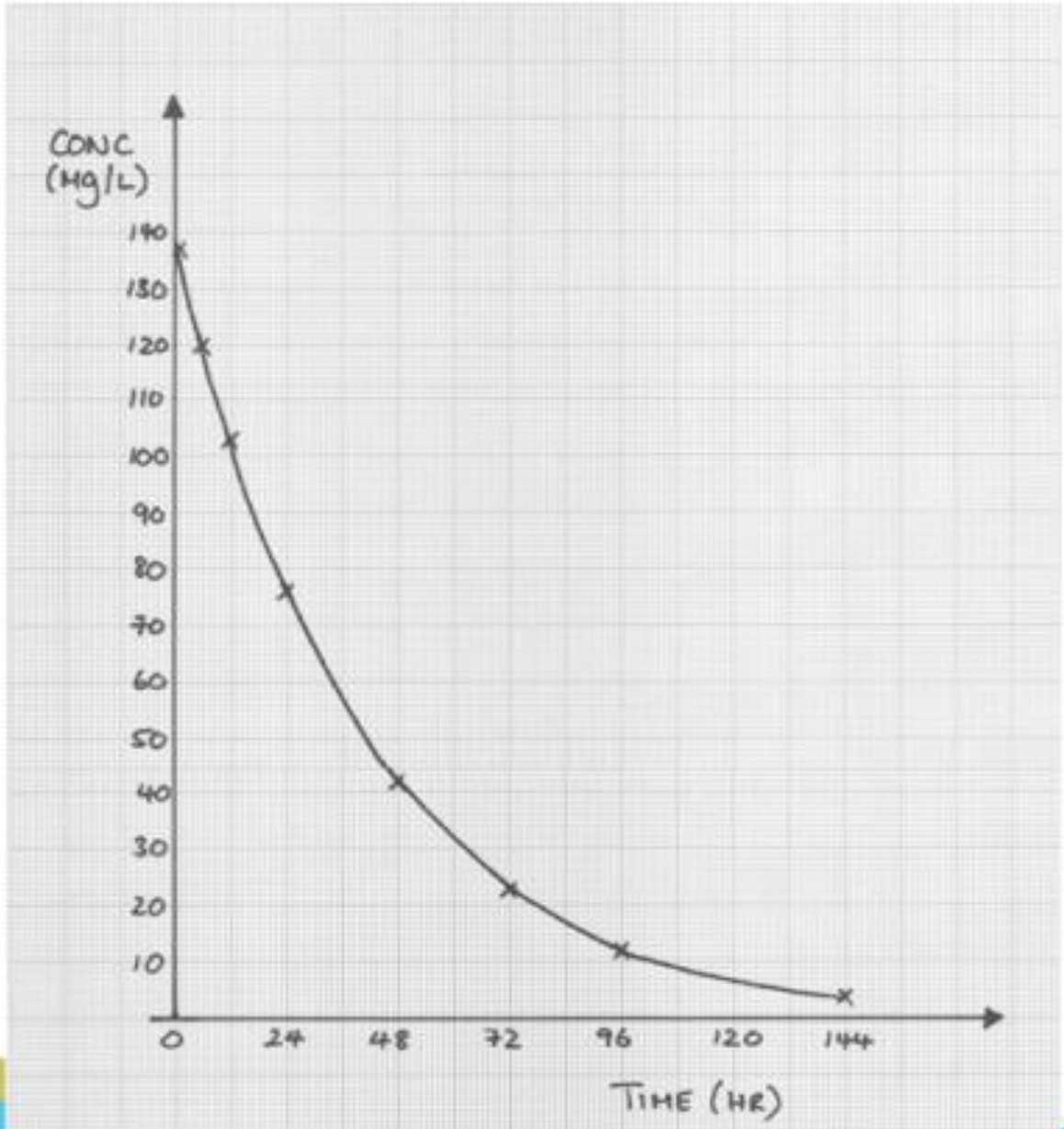
- **One compartment model can be defined with the following equation**

$$C_p = C_p^0 e^{-kt}$$

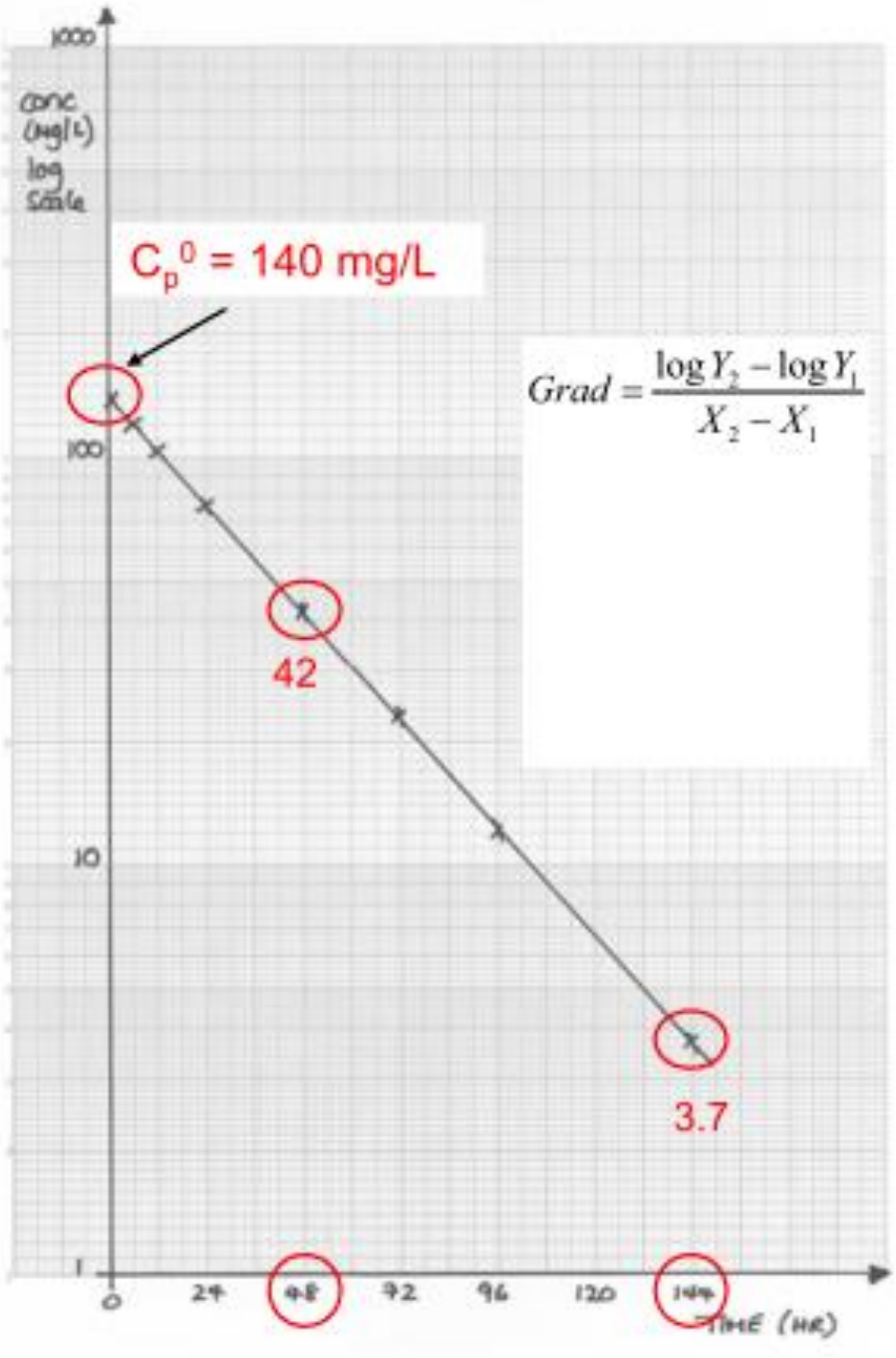
One compartment model - IV

- **Example: Ceftiaxone**
  - 3rd generation cephalosporin (Roche)
  - pneumonia, meningitis, febrile infants, lyme disease
  - 184 mg administered IV to a newborn infant (50 mg/kg)
  - A 1 compartment drug will decline exponentially

Time (hr)	**Plasma Conc** (mg/L)
1	137
6	120
12	103
24	76
48	42
72	23
96	12
144	3.7



linear plot of plasma concentrations vs time



log-linear plot of plasma concentrations vs time

$$\log C_p = \log C_p^0 - \frac{kt}{2.303}$$

Straight line confirms first order relationship

Useful information from plot:

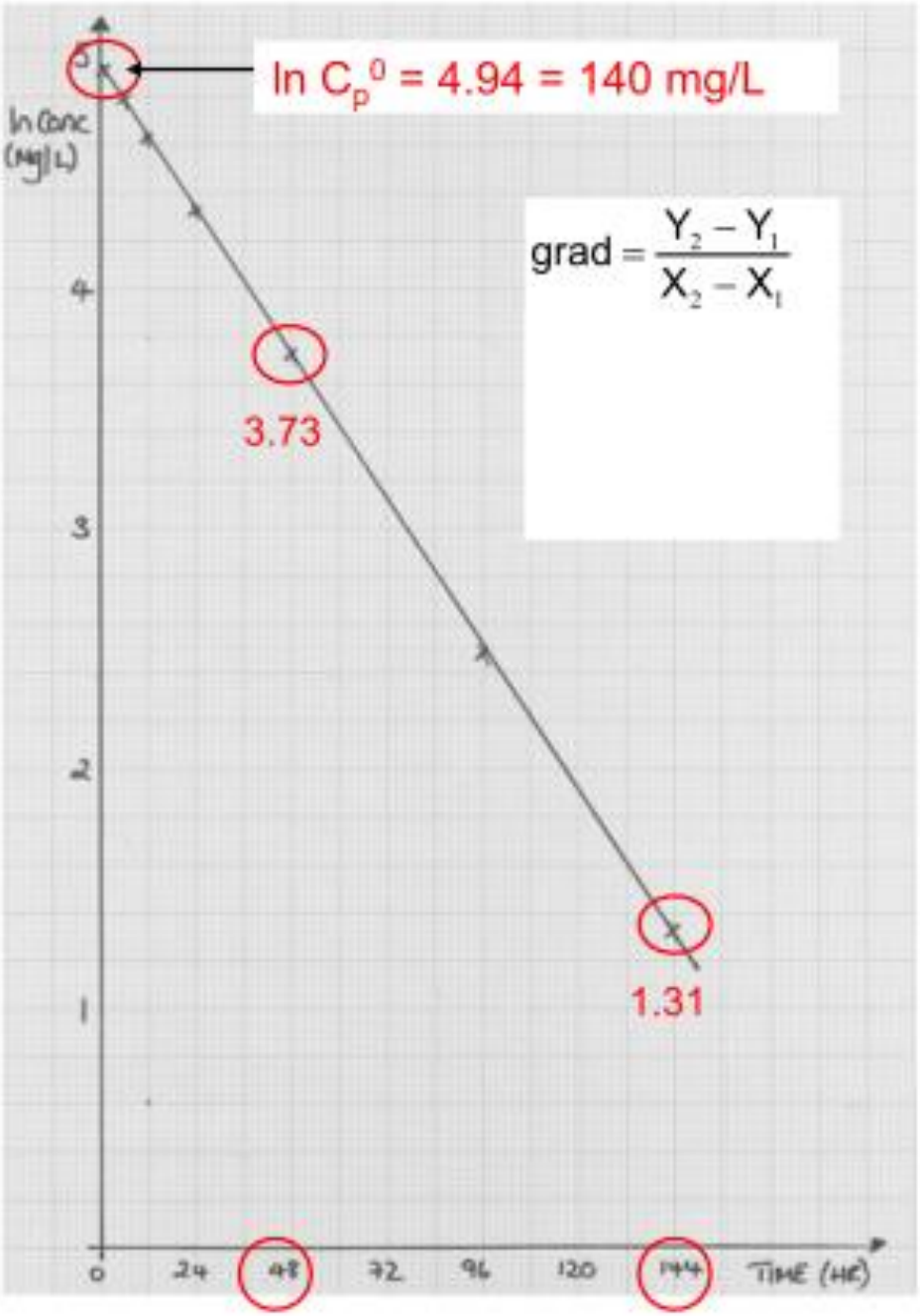
Y-intercept = C_p^0

gradient = -k/2.303

gradient = -0.0109

k = -gradient x 2.303

k = 0.025 h^{-1}



natural log-linear plot of plasma concentrations vs time

$$\ln C_p = \ln C_p^0 - kt$$

Straight line confirms first order relationship

Useful information from plot:

Y-intercept = ln C_p^0

gradient = -k

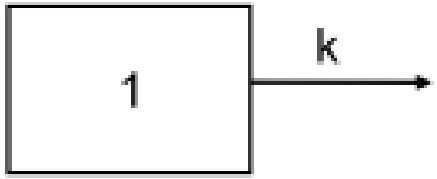
gradient = -0.025

k = 0.025 h^{-1}

$k = \ln(C_1/C_2) / (t_2 - t_1)$

One compartment model – IV ceftriaxone

$$C_p = C_p^0 e^{-kt}$$



- **A one compartment model equation can be written for cephtriaxone**

$$C_p = 140e^{-0.025t}$$

- **Allows for calculation of cephtriaxone plasma concentration any time after IV dose of 50 mg/kg**

Practice Calculation

- Calculate C_B at 6 hours given C_p^0 = 15 mg/L and k = 0.25 hr^{-1}
- The equation: $C_p^t = C_p^0 \times e^{-kt}$

- $C_p = 15 \times e^{-0.25 \times 6} = 15 \times 0.223 = 3.35$ mg/L

Example Calculations

Data: Dose = 500 mg, V = 30 L, k = 0.2 hr^{-1}

Question: C_p at 0, 2, and 4 hours?

Equation: $C_p = (Dose/V_D) \times e^{-kt}$

At zero time $C_p^0 = (Dose/V_D)$

$C_p^0 = 500/30 = 16.7$ mg/L

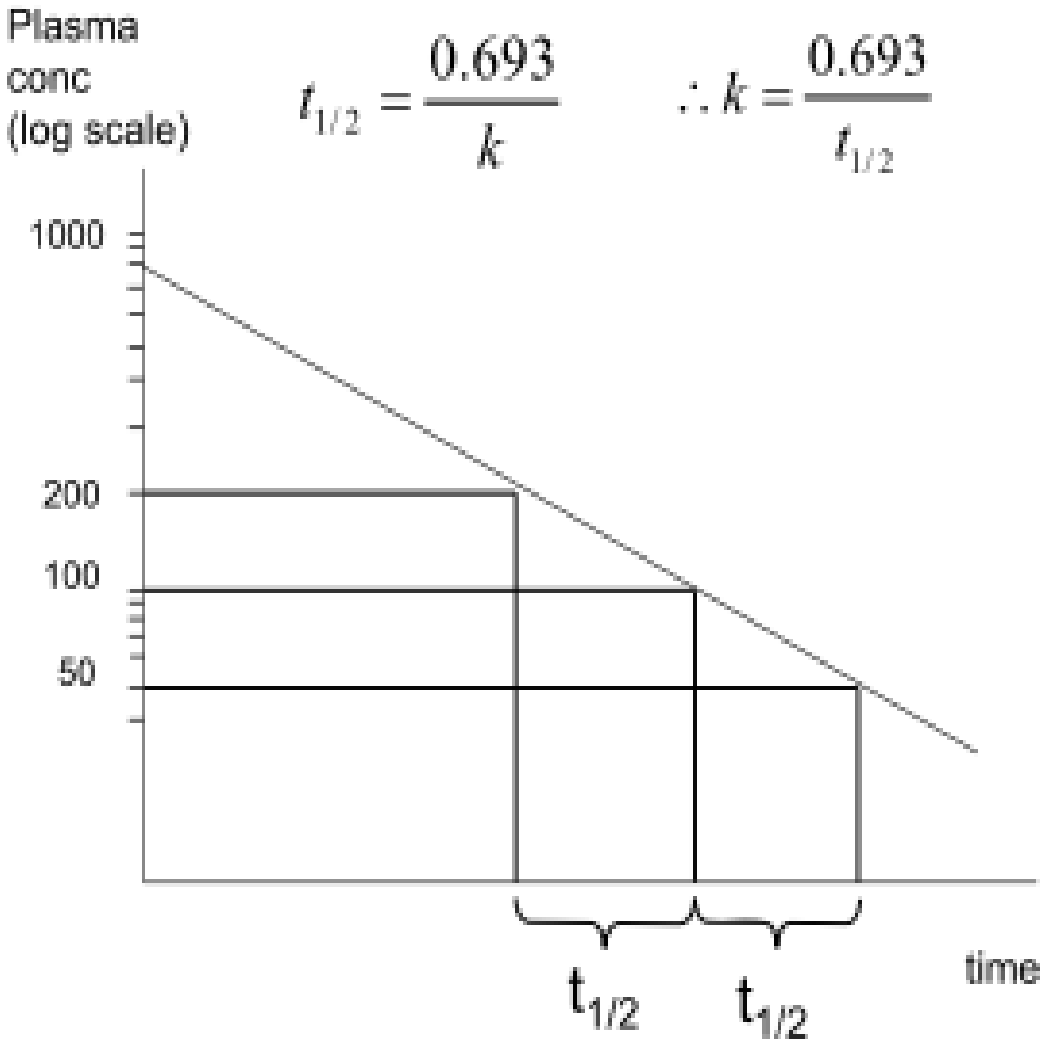
$C_p 2hr = 16.7 \times e^{-0.2x2} = 11.2$ mg/L

$C_p 4hr = 16.7 \times e^{-0.2x4} = 7.5$ mg/L

One compartment model – IV ceftriaxone

- **Data calculation**
  - k, elimination rate constant
  - C_p^0, concentration at t=0
  - half-life can also be calculated
- **Half life:**
  - $t_{1/2}$ is the period of time required for the amount or concentration of a drug to decrease by one half
  - For a first-order reaction $$t_{\frac{1}{2}} = \frac{0.693}{k}$$
- **Biological (elimination) half-life**
  - is the time required for the amount of unchanged drug in the 'body' to be reduced to one half of its value (after input to the body has ceased and distribution equilibrium has been obtained)

Calculation of elimination half-life



Half-life cycles	% of C_p^0 Remaining
1	50
2	25
3	12.5
4	6.25
5	3.125
6	1.563
7	0.78
10	0.098

Calculation of Apparent Volume of Distribution

- V_D is a proportionality constant that related dose (amount) of drug to concentration
- For IV bolus dosing V_D is assumed to be constant with respect to time
- Calculate V_D at any time when the amount of drug in the body and the concentration of drug in the plasma is known
  - this is ONLY known at t=0
  - at t=0, $D_B=D_B^0$ (dose) and $C_p=C_p^0$ (y-axis intercept)

$$V_D = \frac{D_B}{C_p} = \frac{D_B^0}{C_p^0} = \frac{Dose}{C_p^0}$$

Calculation of Apparent Volume of Distribution

- For ceftriaxone

$$V_D = \frac{Dose}{C_p^0} = \frac{184mg}{140mg/L} = 1.3L$$

- The plasma concentration time relationship can be rewritten:

$$C_p = C_p^0 e^{-kt}$$

- since

$$V_D = \frac{Dose}{C_p^0} \qquad \therefore C_p^0 = \frac{Dose}{V_D} \qquad \therefore C_p = \frac{Dose}{V_D} e^{-kt}$$

Calculation of Apparent Volume of Distribution

- For ceftriaxone

$$\therefore C_p = \frac{Dose}{V_D} e^{-kt}$$

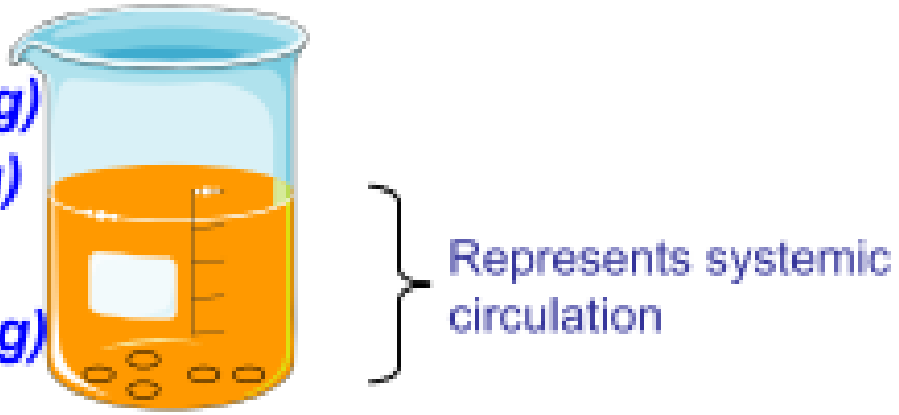
- can be written as:

$$\therefore C_p = \frac{Dose}{1.3} e^{-0.025t}$$

- pharmacist can predict the plasma concentrations of ceftriaxone at any time following any IV dose

Understanding Apparent Volume of Distribution

- Some examples of V_D:
  - Warfarin 8 L ***(0.114 L/kg)***
  - Theophylline 35 L ***(0.5 L/kg)***
  - Quinidine 150 L ***(2.14 L/kg)***
  - Digoxin 420 L ***(6 L/kg)***
  - Imipramine 2100 L ***(30 L/kg)***



- Major determinant of V_D is the relative strength of binding of drug to tissue components as compared with plasma proteins
- i.e. a drug tightly bound by tissues, and not blood, will be held in the tissues and very little will be in plasma so that the drug will *appear* to be dissolved in a large volume…possibly a *very large* volume

Understanding Apparent Volume of Distribution

- Apparent Volume of distribution (V_D) is not necessarily a physiologic value (space)
  - Indicates the amount of drug that has distributed outside the sampling compartment (plasma)
  - If drug does not distribute outside the plasma then V_D will be low
  - If V_D is low it may suggest that drug binds to plasma proteins
  - If drug distributes *easily* from plasma then drug concentrations will be *higher* at extravascular sites and the concentration of drug in plasma will be low i.e V_D will be large
  - If V_D is large then drug may be concentrated at an extravascular tissue site("compartment") i.e. brain, liver, kidneys, myocardial tissue, fat etc

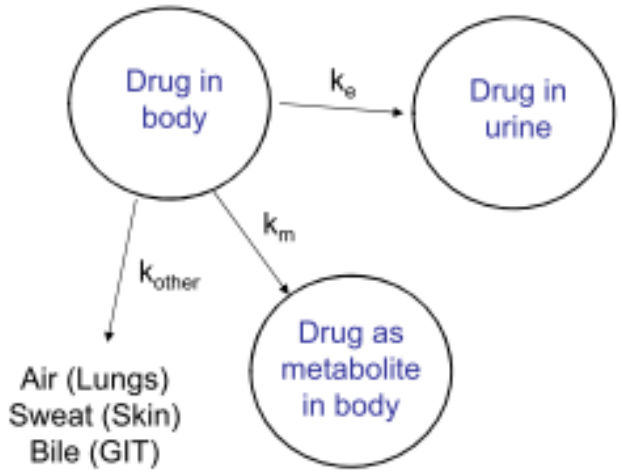
Understanding Apparent Volume of Distribution

- V_D *may* give a 'ball park' indication of the actual (physiologic) distribution volume
  - If plasma volume = 4.5% body weight then a 70 kg person has a plasma volume of 3.15 L
- If V_D is 3-4 L then the drug is likely to be confined to plasma water
  - ***Total extracellular water* = 27%** *of* body weight ***(0.27 L/kg)*** then a ***70 kg*** person has an ECFV of ***~18.9 L***
  - ***Total body water* = 60%** *of* body weight ***(0.6 L/kg)*** then a ***70 kg*** person has a body water volume of ***~ 42 L***
- BUT – it could be a coincidence
- V_D estimates are generally *constant* for each drug, although certain pathologic cases may influence V_D value, i.e. oedema, inflammation, myocardial infarction, hepatic or renal disease, pregnancy

One Compartment Model - Elimination

- Drug elimination is an ongoing process
  - Metabolism/biotransformation
  - Drug excretion through kidneys and other routes
- Elimination is the sum of all events removing parent drug from the body
- Elimination =

  renal excretion + hepatic metabolism + 'other'
- i.e. $k = k_e + k_m + k_{other}$
- Or …$k = k_e + k_{nr}$ (non renal)



One compartment model - Elimination

- $k = k_e + k_{nr}$
- k_e is a first order elimination rate constant for renal excretion
- k_m is a first order elimination rate constant for hepatic metabolism (including first pass)
- k_{other} is a first order elimination rate constant for other elimination route (saliva, lungs, biliary, GIT)
- k_{nr} = is combination of k_{other} and k_m

The **rate of elimination** **changes with changing concentration**

whereas the **elimination rate constant**, for a linear model, is **constant**

Elimination Rate Constant (k)

- 'k' is the overall rate constant describing the first order relationship between the rate of drug elimination and the amount of drug in the body
- k is sometimes called the fractional elimination constant
- If k = 0.1 hr^{-1} then 10% of the amount of drug remaining will be eliminated per hour

Time Interval (hr)	Amount lost during interval (mg)	Amount remaining at end of interval (mg)
0	-	100
0-1	10	90
1-2	9	81
2-3	8.1	72.9
3-4	7.3	63.6

One compartment model - Elimination

- Ratio of elimination rate constants equals the ratio of the amounts of drug eliminated by those routes
- i.e.

$$\frac{k_e}{k} = \frac{\text{amount of drug excreted unchanged in urine}}{\text{total amount of drug eliminated}}$$

$$\frac{k_m}{k} = \frac{\text{amount of drug eliminated by metabolism}}{\text{total amount of drug eliminated}}$$

One compartment model - Elimination

- Back to ceftriaxone example…
- If 60% of administered IV dose is excreted unchanged in the urine what is the renal elimination constant, k_e?

$$\frac{k_e}{k} = \frac{60}{100} = 0.6$$

$$k_e = k * 0.6$$

$$k_e = 0.025 * 0.6 = 0.015 h^{-1}$$

Also known as f_e… the fraction of drug eliminated *unchanged* in the urine

$$\therefore k_e = k * f_e$$

One compartment model – Urinary Excretion Data

- What information is required in order to determine k_e?
- Usually, a pharmacokinetic study is required where urinary excretion data is collected
- $k = k_e + k_m + k_{other}$
- Often k_{other} is ~ 0, $\therefore k_m = k - k_e$
- Urinary excretion data also allows for estimation of k and $t_{1/2}$
- Does not allow for calculation of V_D
- Advantages
  - Non-invasive compared collecting blood samples
  - No need for medical supervision
  - Allows calculation of renal elimination rate constant and estimate of metabolic elimination rate constant

One compartment model – Urinary Excretion Data

- Assume excretion rate is first-order
- k_e is the renal elimination rate constant
- D_u is the amount of drug excreted in the urine

$$\frac{dD_u}{dt} = k_e * D_B$$

- We also know that $D_B = D_B^0 e^{-kt}$
- Therefore $\frac{dD_u}{dt} = k_e * D_B^0 e^{-kt}$
- Equation can be transformed

$$\log \frac{dD_u}{dt} = \frac{-kt}{2.303} + \log k_e D_B^0$$

gradient

intercept

One compartment model – Urinary Excretion Data

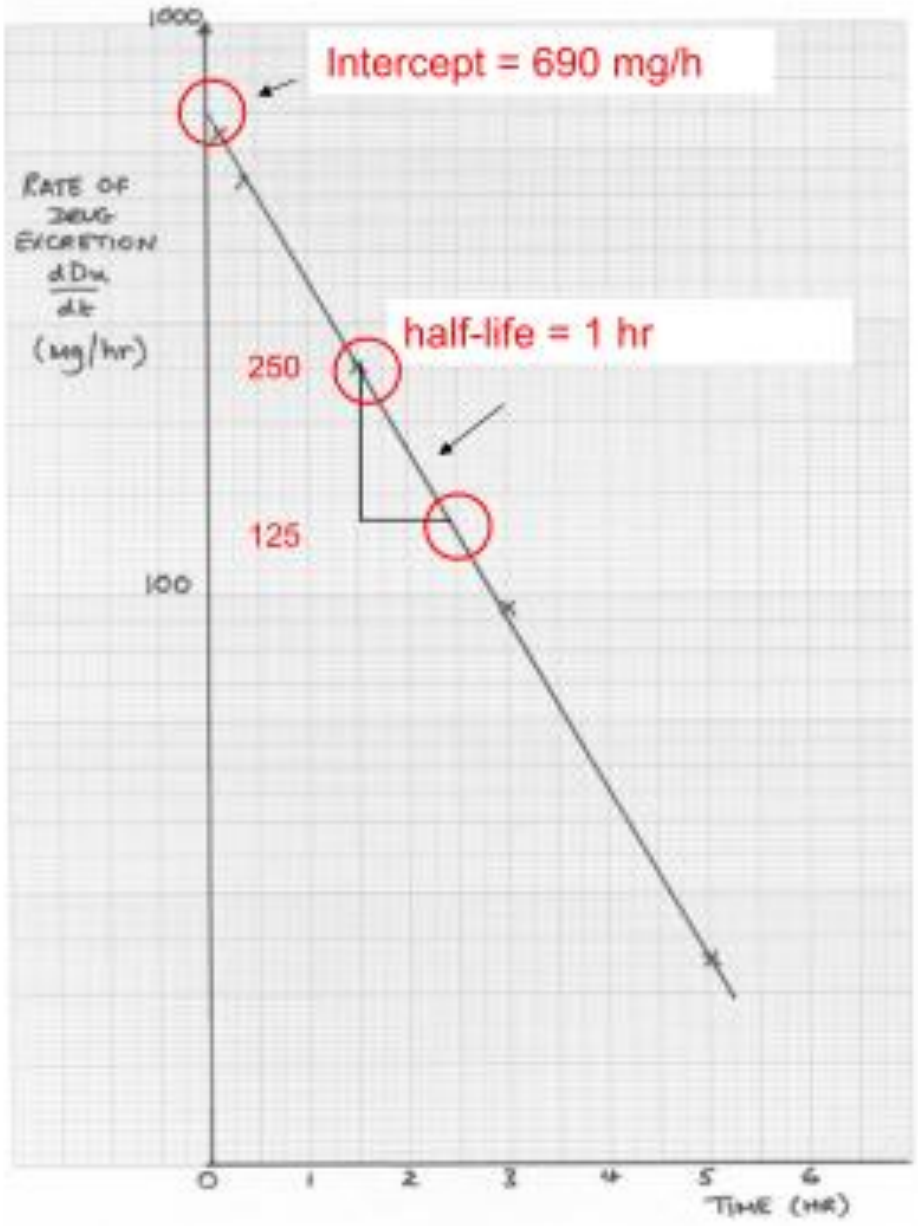
- Plot $\log \frac{dD_u}{dt}$ vs time to get a straightline

- Slope will be = -k/2.303
- Intercept will be = $\log k_e D_B^0$
- If dose (D_B^0) is known we can calculate k_e and k is determined from the slope
- Estimate of non renal elimination rate constant can be determined since $k = k_e + k_{nr}$ then $k - k_r = k_{nr}$

Example – Urinary Excretion Data

- A single IV dose of an antibiotic was given to a 50 kg women at a dose of 20 mg/kg. Urine output was collected over the following 6 hours and assayed for drug content. (Amount of drug in urine (D_u) was determined by drug conc x volume)

Time interval (hr)	Du (mg)	Du/t	Excretion rate (mg/hr)	t* (hr)
0-0.25	160	160/0.25	640	0.125
0.25-0.5	140	140/0.25	560	0.375
0.5-1.0	200	200/0.5	400	0.750
1.0-2.0	250	250/1	250	1.5
2.0-4.0	188	188/2	94	3
4.0-6.0	46	46/2	23	5



$$\log \frac{dD_U}{dt} = \frac{-kt}{2.303} + \log k_e D_B^0$$

Intercept = $\log k_e D_B^0$

$$\therefore \quad ke = \frac{intercept}{dose}$$

$$ke = \frac{690\ mg/h}{1000mg} = 0.69\ h^{-1}$$

Elimination rate constant

$$t_{1/2} = 1\ hr$$

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

$$k = 0.693 \quad h^{-1}$$

Non-renal clearance calculated

$k = k_e + k_{nr}$

$\therefore k_{nr} = k - k_e$

knr = 0.693 – 0.69 = 0.003 hr^{-1}

Example – Urinary Excretion Data

- Drug is almost entirely excreted in the urine
- K_{nr} is very small (0.003 h^{-1})
- Can also calculate k_e using fraction excreted unchanged in urine

$$\therefore k_e = k * f_e$$

- f_e = total amount excreted unchanged in urine/dose
  = 984 mg/1000 mg

$$\therefore k_e = k * f_e = 0.693 * 0.984 = 0.682\ \mathrm{h}^{-1}$$