

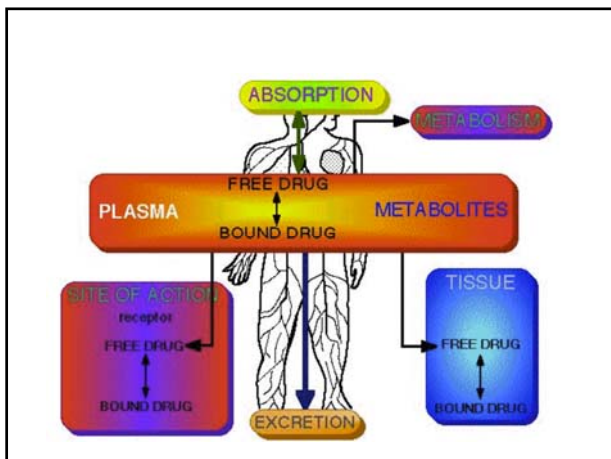
Pharmacokinetics:
Single & Multi-compartment models
Part 1

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What happens to Drugs in the Body
(what the body does to drugs)

Descriptive – “Biopharmaceutics”

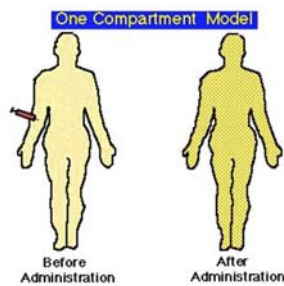
Quantitative – Pharmacokinetics



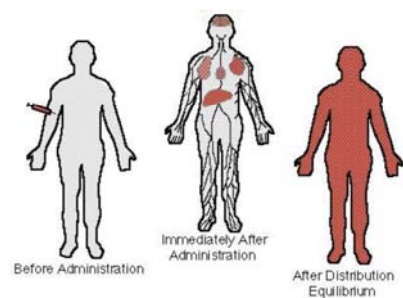
ADME

- Absorption
- Distribution
- Metabolism
- Excretion

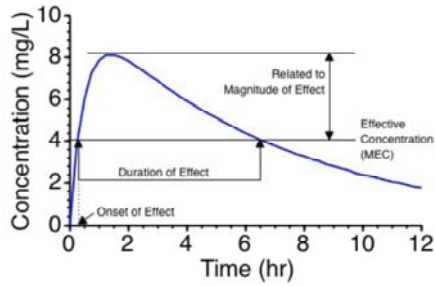
IV bolus dose: one compartment model



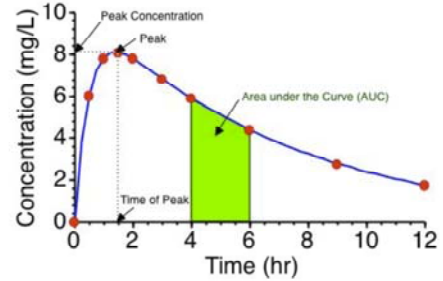
IV bolus dose: two compartment model



Drug effect *versus* time



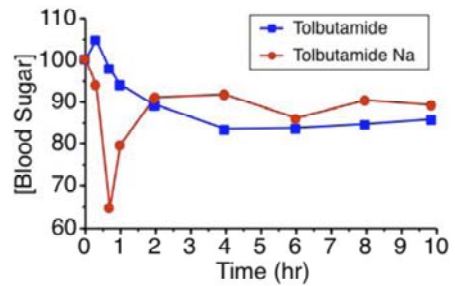
Drug product parameters (depend on formulation & active ingredient)



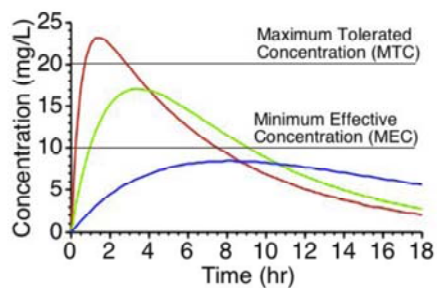
Routes of drug administration

- Intramuscular
- Subcutaneous
- Intravenous
- Intrasyovial
- Intracardiac
- Intrathecal
- Eye
- Nasal
- Ear
- Oral
- Sublingual
- Buccal
- Rectal
- Vaginal
- Urethral
- Topical

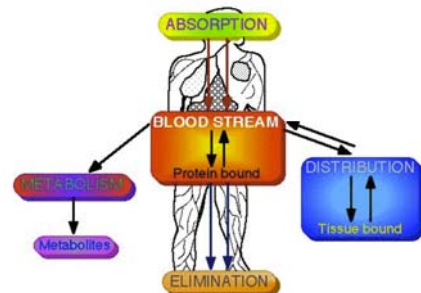
Drug effect & Absorption



Effect of absorption rate constant



ADME



Drug Elimination

Some of the ways the body performs the task of drug elimination

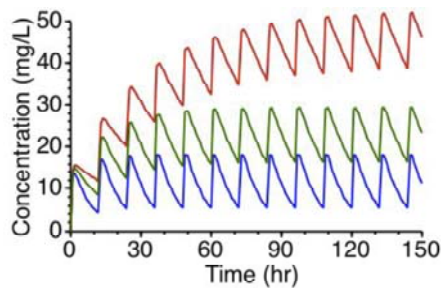
- Conjugation
- Hydrolysis
- Oxidation
- Reduction
- Excretion

Drug Elimination

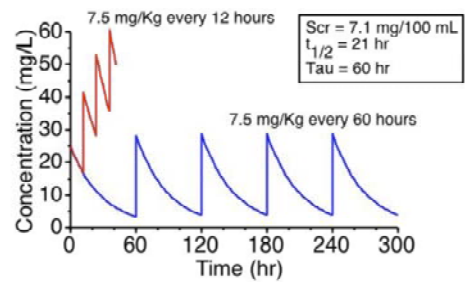
Some of the ways the body performs the **task** of drug elimination

- Conjugation
- Hydrolysis
- Oxidation
- Reduction
- Excretion

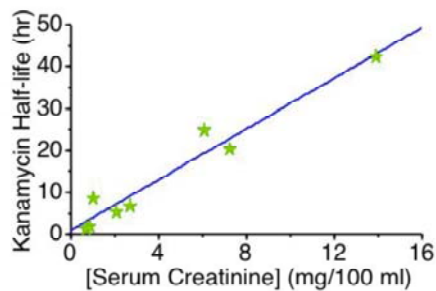
Elimination & Multiple Dose



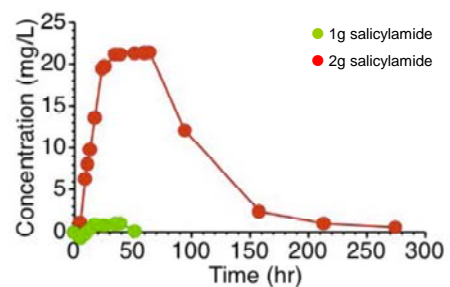
Two dosing regimens with the antibiotic kanamycin



Kidney function affects drug elimination



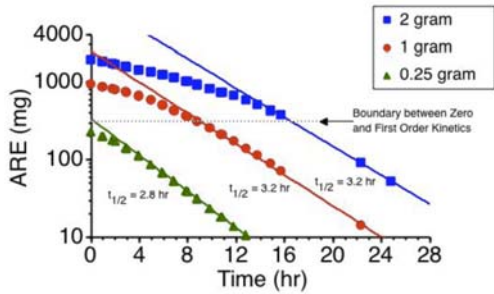
First pass effect



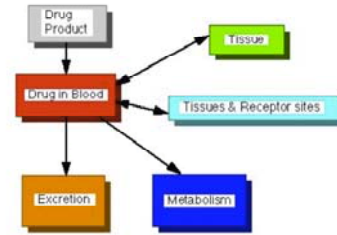
At low dose most of drug is eliminated on first pass (through liver)

Higher dose saturates metabolic enzymes resulting in higher plasma concentration

Aspirin Elimination

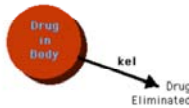


Getting Quantitative - Pharmacokinetics



Pharmacokinetics is the study of drug and/or metabolite kinetics. It is a mathematical description of the rates of drug movement into, within and leaving the body. It includes rates of drug metabolism and biotransformation.

One-Compartment IV Bolus

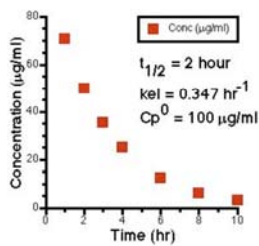


- All the “details” may be complex and involve a number of different processes
- Nevertheless simple mathematical models can approximate the kinetic processes

Assumptions

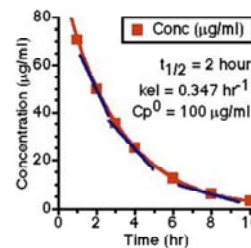
- 1. Body is a Single Compartment
Drug in the blood in rapid equilibrium with drug in extravascular tissue.
- 2. Rapid Mixing
Drug is mixed instantaneously in blood or plasma. Actual times may be minutes, short in comparison to normal sampling times (10s min – hrs)
- 3. Follows first order kinetics
Drug elimination follows first order kinetics

Linear model – 1st order kinetics



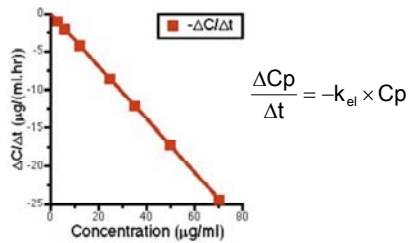
IV bolus injection of drug at t=0. Measure plasma concentration as function of time

Rate of change of concentration versus time ($\Delta C_p/\Delta t$)



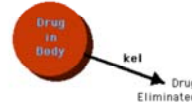
Slope of tangents to curve at each point is a measure $\Delta C_p/\Delta t$

Rate of change of concentration ($\Delta C_p/\Delta t$) against concentration



Linear kinetics is where the graph of $\Delta C_p/\Delta t$ against C_p is a straight line!

Developing the differential equation



$$\frac{\Delta C_p}{\Delta t} = -k_{el} \times C_p$$

as $\Delta t \rightarrow 0$

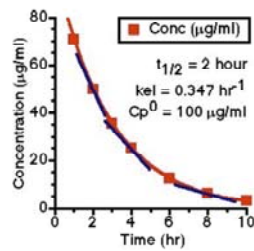
$$\frac{\partial C_p}{\partial t} = -k_{el} \times C_p$$

Integrated Equation

$$\frac{\partial C_p}{\partial t} = -k_{el} \cdot C_p$$

integrating

$$C_p = C_p^0 \cdot e^{-k_{el} \cdot t}$$



Estimating k_{el} and C_p^0 from data

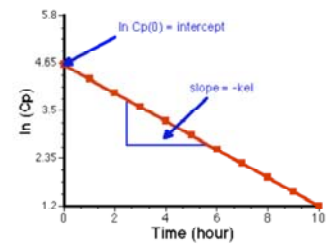
$$C_p = C_p^0 \cdot e^{-k_{el} \cdot t}$$

mono-exponential decay

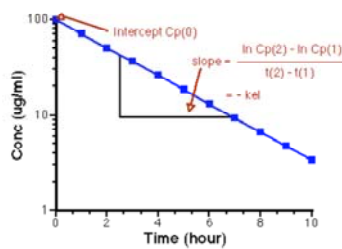
taking natural logs

$$\ln(C_p) = \ln(C_p^0) - k_{el} \cdot t$$

straight line $y = mx + c$



Can use semi-logarithmic scale



Remember to use the correct log button on your calculator!

Natural log function - log base e

"ln (x)" or "log_e (x)"

(e=2.71828.....) John Napier (1550 -1617)

Not the same as log base 10

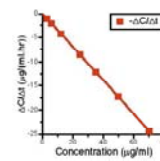
"log (x)" or "log₁₀ (x)"

BUT

$$\ln (x) = 2.302 \log_{10} (x)$$

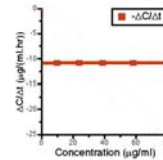
Example values for elimination rate constants

Drug	k_{el} (hr ⁻¹)
paracetamol	0.277
diazepam	0.021
digoxin	0.016
gentamicin	0.347
lidocaine	0.390



First order - rate proportional to C_p

$$\frac{\Delta C_p}{\Delta t} = -k_{el} \times C_p$$



Zeroth order - rate is constant independent of C_p

$$\frac{\Delta C_p}{\Delta t} = -k_{el}$$

Rate of elimination does not increase as C_p increases so can take long time to eliminate even moderate concentrations

Alcoholic interlude – zeroth order kinetics



20 mg/100ml : 4.3mM (effects)
 80 mg/100ml : 17mM (drink drive limit) 0.08%
 500 mg/100ml : 108mM (coma/death)



EC_{50} 200 mM

- Bac calculator
- http://www.drinkdriving.org/drink_driving_information_bloodalcoholcontentcalculator.phpor

Pharmacokinetics of alcohol

Metabolism and excretion

alcohol is metabolised the alcohol dehydrogenase and cytochrome p450 enzymes

85% of that metabolism is in the liver
 up to 15% is done in the stomach

Elimination follows Michaelis-Menten kinetics
 - rate of elimination is independent of concentration

Alcohol metabolism

$$\text{Rate of metabolism} = \frac{V_m \cdot C_u}{K_m + C_u}$$

Table 22-5. Calculated Rate of Metabolism and Clearance of Alcohol as a Function of the Concentration at the Metabolic Site

CONCENTRATION AT SITE (mg/l)	RATE OF METABOLISM* (g/hr)	CLEARANCE ^b (l/h)
7000	9.9	1.4
5000	9.8	2.0
3000	9.7	3.2
1000	9.1	9.1
500	8.3	17
200	6.7	33
100	5.0	50
50	3.3	67
10	0.91	91

*Rate of metabolism = $V_m \cdot C_u / (K_m + C_u)$; $V_m = 10$ g/hr, $K_m = 100$ mg/l.
^bClearance = $V_m / (K_m + C_u)$.

Why zero order kinetics means drinking shots can be dangerous (really)

- A lethal concentration is around 5g/litre. Assuming this is distributed in total body water of volume 42 litres, the lethal dose is approx 210 grams.
- One double measure (50ml) of 40% spirits contains 20ml of alcohol (15 g). If rate of metabolism is 10g/hr, drinking 1 shot per hour exceeds the elimination rate by 5g. Drinking at this rate it would take 2 days to reach a lethal dose.
- BUT what if it was someone's birthday or freshers week and.....

- You drink 4 shots per hour. 4 shots is 60g/hour. This exceeds the metabolic rate by 50g/hour.
-you could reach the fatal dose in 4 hours !!