Principles of Pharmacodynamics & Pharmacokinetics

Pharmacokinetics:
Single & Multi-compartment models
Part 1

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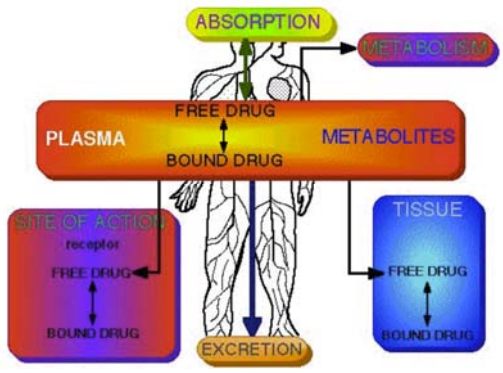
What happens to Drugs in the Body (what the body does to drugs)

Descriptive – "Biopharmaceutics"

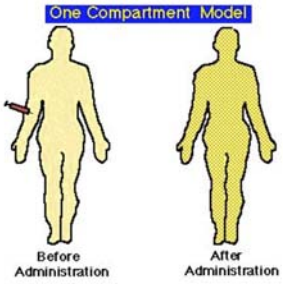
Quantitative – Pharmacokinetics



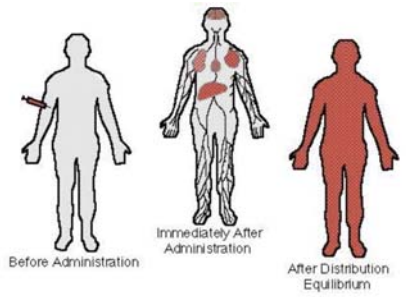
ADME

- Absorbtion
- Distribution
- Metabolism
- Excretion

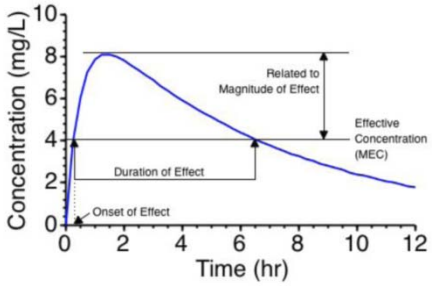
IV bolus dose: one compartment model



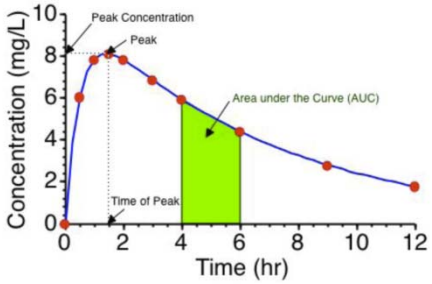
IV bolus dose: two compartment model



Drug effect *versus* time



Drug product parameters
(depend on formulation & active ingredient)



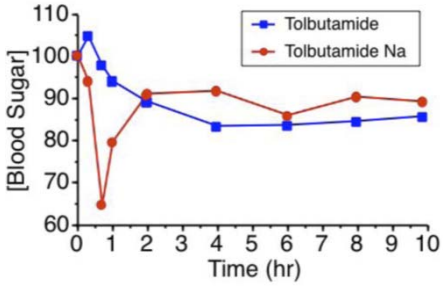
Routes of drug administration

Intramuscular
Subcutaneous
Intravenous
Intrasynovial
Intracardiac
Intrathecal

Eye
Nasal
Ear
Oral
Sublingual
Buccal

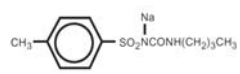
Rectal
Vaginal
Urethral
Topical

Drug effect & Absorption



Orinase Diagnostic®

tolbutamide for injection, USP



DESCRIPTION

ORINASE DIAGNOSTIC Sterile Powder contains tolbutamide sodium which is a white to off-white, practically odorless, crystalline powder, having a slightly bitter taste. It is freely soluble in water, soluble in alcohol and in chloroform, very slightly soluble in ether.

CLINICAL PHARMACOLOGY

The prompt decrease in blood glucose in normal individuals is associated with a prompt increase in serum insulin levels, as determined by immunoassay, which rise from a fasting mean value of 19 μU per mL to a peak mean value of approximately 40 μU per mL (range 27 to 89) 20 minutes after injection. In patients with functioning islet cell adenoma, tolbutamide sodium has a marked and prolonged blood glucose lowering effect associated with an excessive, prompt rise in serum insulin (118 to 1,055 μU/mL), resulting in a marked and prolonged blood glucose effect (Figure 1).

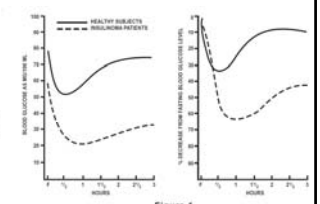
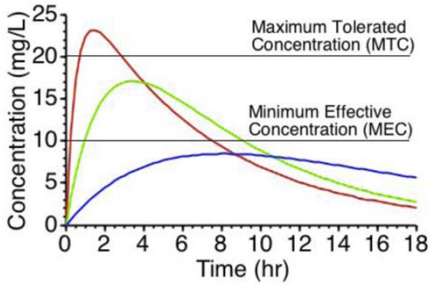


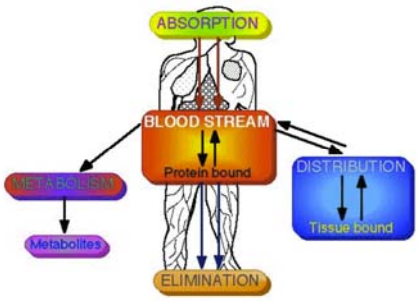
Figure 1

Effect of intravenous injection of ORINASE DIAGNOSTIC on blood glucose in healthy subjects and insulinoma patients.

Effect of absorption rate constant

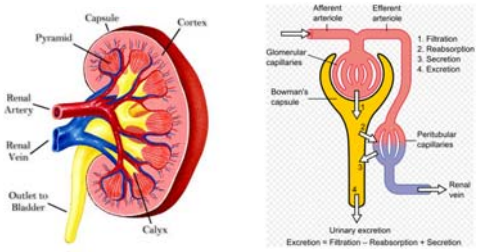


ADME



Drug Elimination

Most drugs are eliminated in urine after passing through kidneys



Drug Elimination

Drug or metabolites must be soluble in urine !

Drug Elimination

Chemical modification may be necessary

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

- Conjugation
- Hydrolysis
- Oxidation
- Reduction
- Excretion

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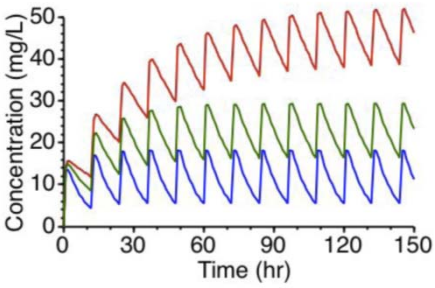
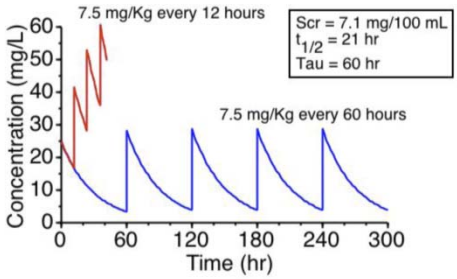
Elimination & Multiple Dose

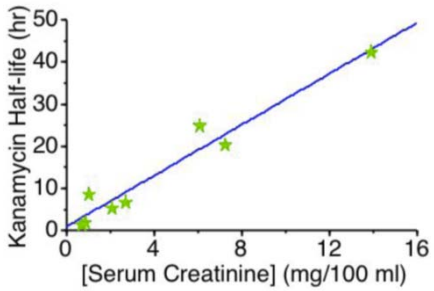


Two dosing regimens with the antibiotic kanamycin



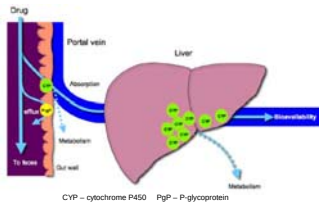
- Excretion in urine is a major route of elimination of drugs and metabolites
- Renal function affects drug elimination
- Renal function tests are important clinically
- (may be confounded if liver disease also present)

Renal disease affects drug elimination

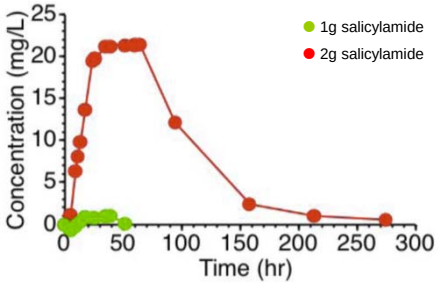


First pass effect

- Oral route of administration
  - Gut
  - Hepatic portal vein
  - Liver
  - Enzymes
    - Gut
    - Bacterial
    - Hepatic
  - Liver may metabolise most of drug before it reaches rest of circulation



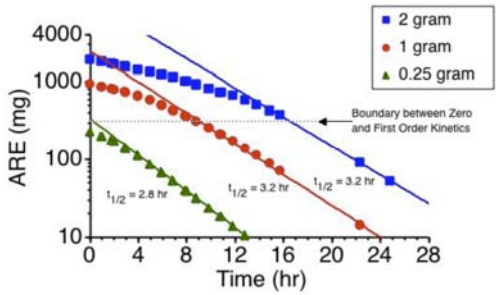
First pass effect



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

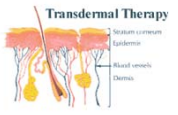
Higher dose saturates metabolic enzymes resulting in higher plasma concentration

Aspirin Elimination

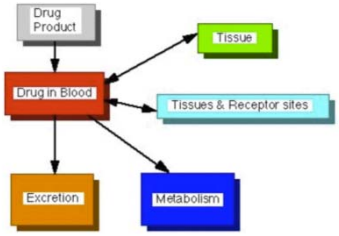


Routes that avoid first pass effect

- Intravenous
- Intra-muscular
- Sublingual
- Inhalation
- Intranasal
- Suppository



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.

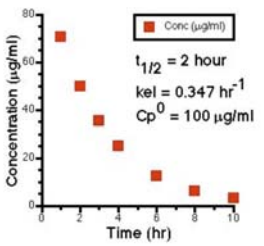
One-Compartment IV Bolus

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

Assumptions

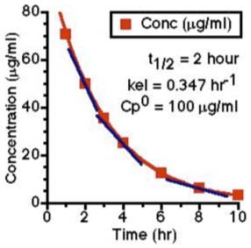
- 1. Body is a Single Compartment
  - Drug in the blood in rapid equilibrium with drug in extravascular tissue.
- 2. Rapid Mixing
  - Drug is mixed instantaneously in blood or plasma.
  - Actual times may be minutes, short in comparison to normal sampling times (10s min – hrs)
- 3. Follows first order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

Linear model – 1st order kinetics



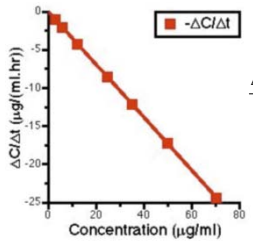
IV bolus injection of drug at t=0. Measure plasma concentration as function of time

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



Slope of tangent to curve at each point is a measure $\Delta Cp/\Delta t$

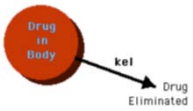
Rate of change of concentration (ΔCp/Δt) against concentration



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

Linear kinetics is where the graph of ΔCp/Δt against Cp is a straight line !

Developing the differential equation



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

as $\Delta t \to 0$

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

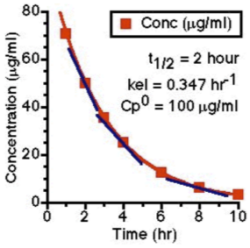
Integrated Equation

1st order differential equation

$$\frac{\partial Cp}{\partial t} = -k_{el} \bullet Cp$$

- solution is

$$Cp = Cp^0 \bullet e^{-k_{el} \bullet t}$$



Estimating k_{el} and Cp^0 from data

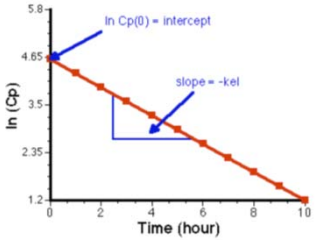
$$Cp = Cp^0 \bullet e^{-k_{el} \bullet t}$$

mono-exponential decay

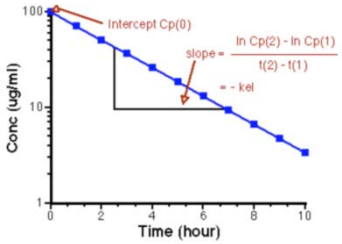
taking natural log

$$\ln(Cp) = \ln(Cp^0) - k_{el} \bullet t$$

straight line y = mx + c



Can use semi-logarithmic scale



Remember to use the correct log button on your calculator !

Natural log function or log base e

"ln (x)" or "$\log_e$ (x)"

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

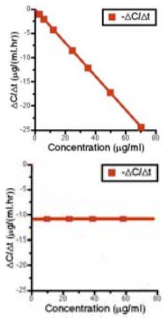
Not the same as log base 10

"log (x)" or "$\log_{10}$ (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 Cp

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

Zeroth order - rate is constant independent of Cp

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

Rate of elimination does not increase as Cp 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 by 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

$$\text{Rate of metabolism} = \frac{Vm \cdot Cu}{Km + Cu}$$

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[a] (g/hr)	CLEARANCE[b] (l/hr)
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

[a]Rate of metabolism = $Vm \cdot Cu/(Km + Cu)$; $Vm = 10$ g/hr, $Km = 100$ mg/L.
[b]Clearance = $Vm/(Km + Cu)$.

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 !!