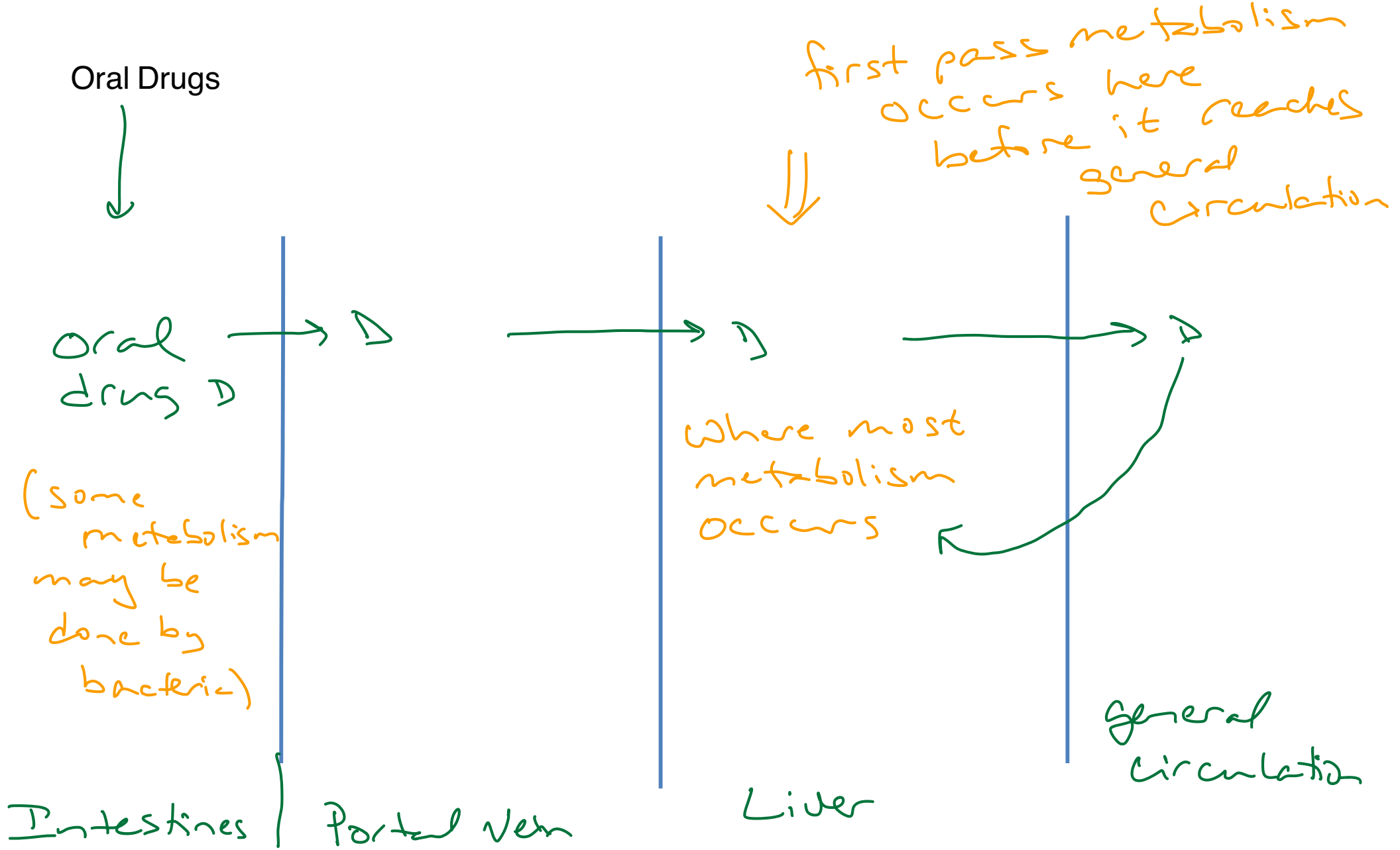
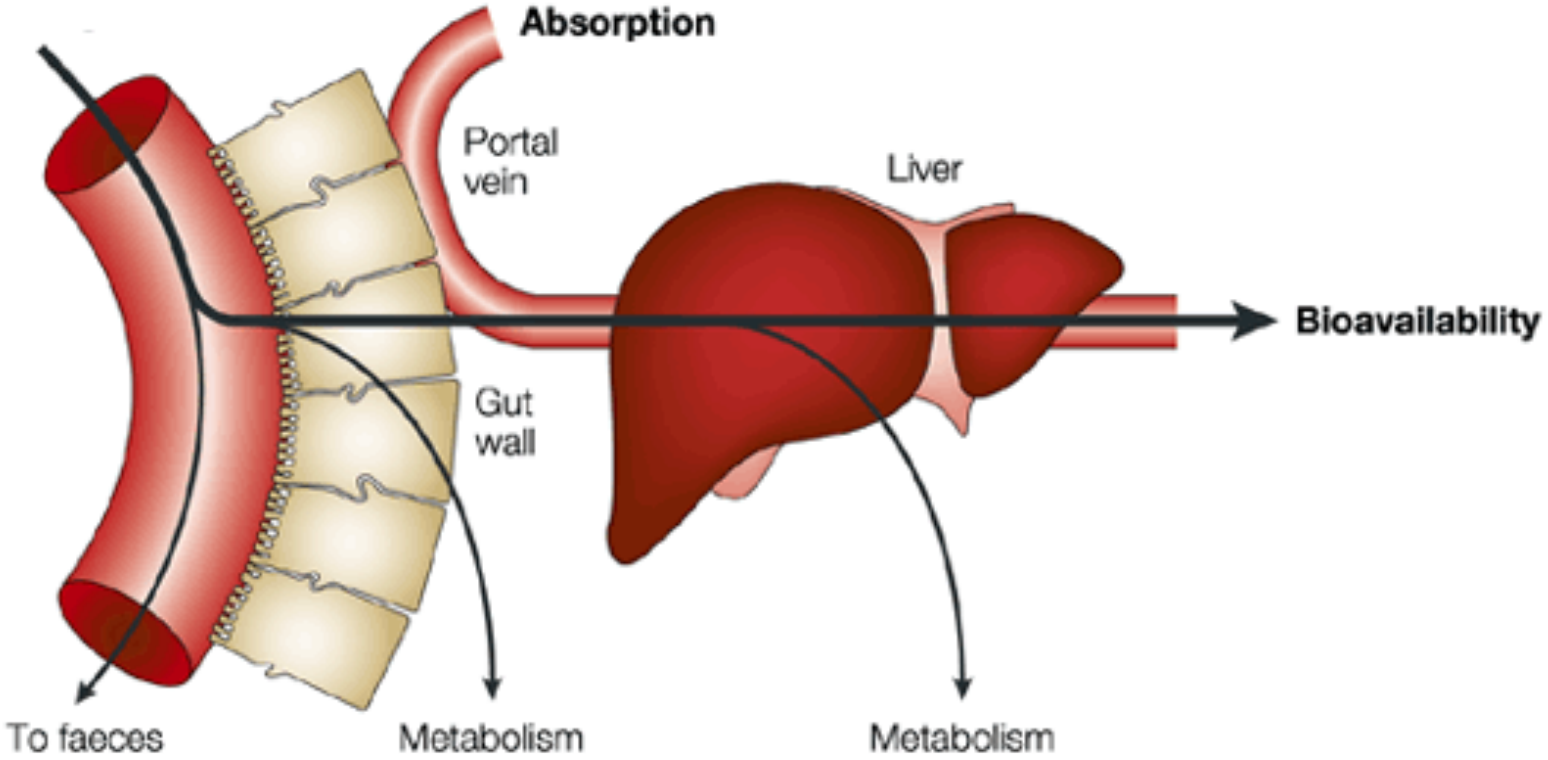
Drug Metabolism

ADMET

general goal is to convert xenobiotics into compounds easier to excrete

- foreign to body
- not endobiotic


Oral Drugs
first pass metabolism occurs here before it reaches general circulation
oral drug
(some metabolism may be done by bacteria)
Where most metabolism occurs
Intestines
Portal Vein
Liver
General circulation



Nature Reviews | Drug Discovery

Pharmacokinetics

- Study of the time course of a drug in the body

- how it enters, moves through, gets out

Pharmacodynamics

- study of the relationship between drug concentration and pharmacologic effects

Pharmacokinetic Parameters:

1) apparent volume of distribution
V_D

2) clearance

3) bioavailability

4) half life $t_{1/2}$

L liberation (dissolution + disintegration)

A bsorption — movement from site of administration to general circulation

Relate to Bioavailability

D istribution — movement from intra vascular to extravascular space

M etabolism — transformation

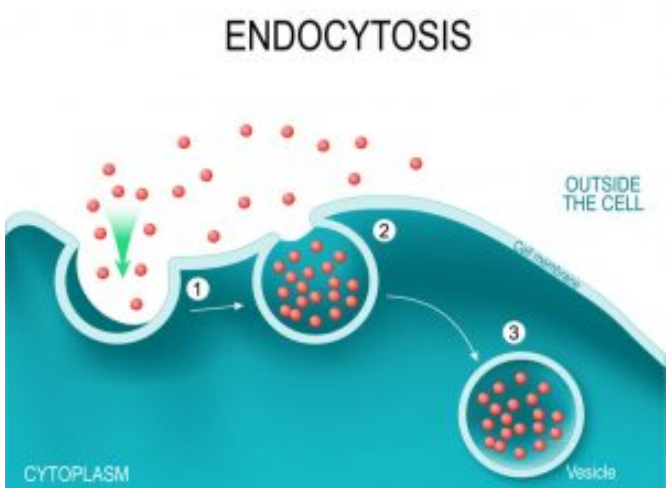
E xcretion — elimination of drug or it's metabolites

T oxicity

3 Ways for a Substance to Cross a Lipid Barrier: Transport

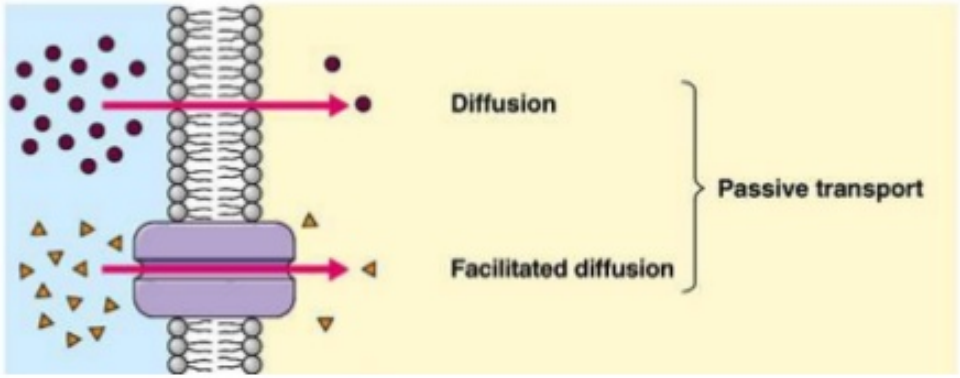
Transport proteins

3 Ways for a Substance to Cross a Lipid Barrier: Endocytosis



good for large polar stuff

3 Ways for a Substance to Cross a Lipid Barrier:



Fick's Law of Diffusion

- concentration gradient
- hydrophobicity

diffusion coefficient

$$\frac{dq}{dt} = -DA\frac{dc}{dx}$$

rate of diffusion

concentration gradient

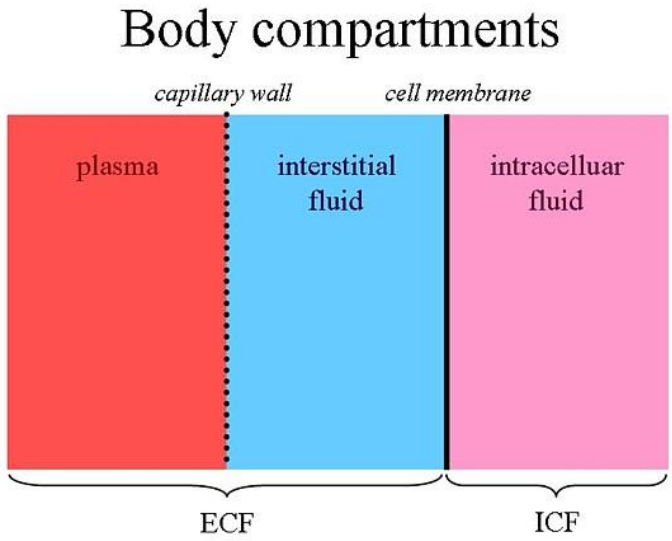
membrane surface area

Distribution → after absorption drug is distributed to interstitial + intra cellular fluid

Plasma ↑ blood fluid

Interstitial ↑ between cells

Intracellular ↑ in cells

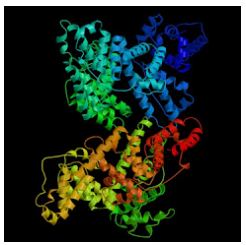


Highly perfused organs: liver, kidneys, heart, lungs

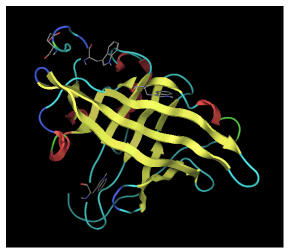
where conc. is initially highest

takes longer to get to muscle, skin etc.

Plasma Proteins



Albumin = major for acidic drugs



α-acid glycoprotein good for basic drugs

Plasma Proteins

Saturation – a really large dose of drug can bind all possible sites then have a rapid increase in plasma conc

Competition – drugs can compete for binding
drugs can displace one another

Disease States hypoalbinemia – decreased albumin levels

V_D Volume of distribution

V_{app} apparent volume of distribution

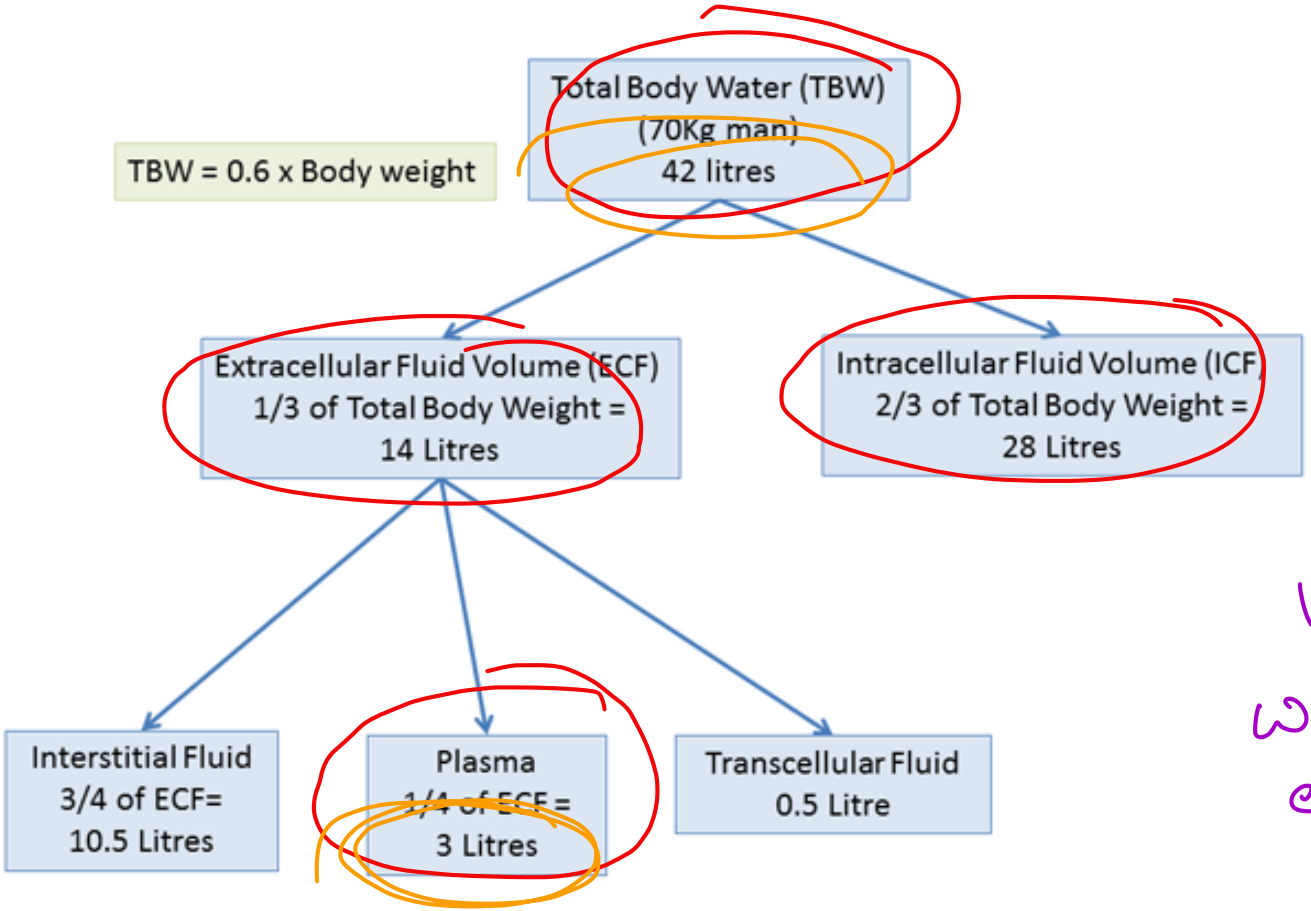
* the volume you would need to account for the dose

$$V_{app} = \frac{\text{dose}}{\text{C plasma conc.}}$$

Large V_{app}

low conc. in plasma

drug is probably in fatty tissue or on plasma proteins



Vdrp can be much higher than this because of drug in other places

We can use Vdrp to see where a drug ends up

Examples…..

Amphetamine

$V_{app} = 20\,L$

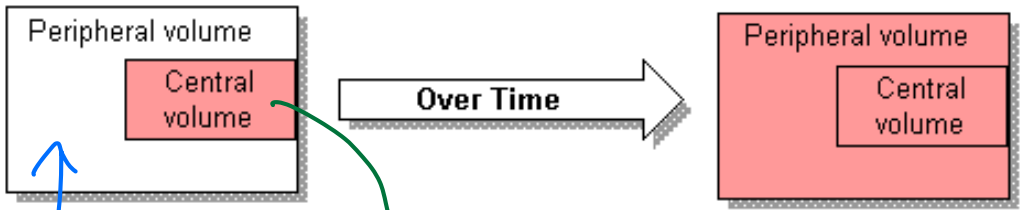
Warfarin

$V_{app} = 8\,L$

Diazepam

$V_{app} = 80\,L$

Two compartment model



peripheral tissues

V_t

Central compartment

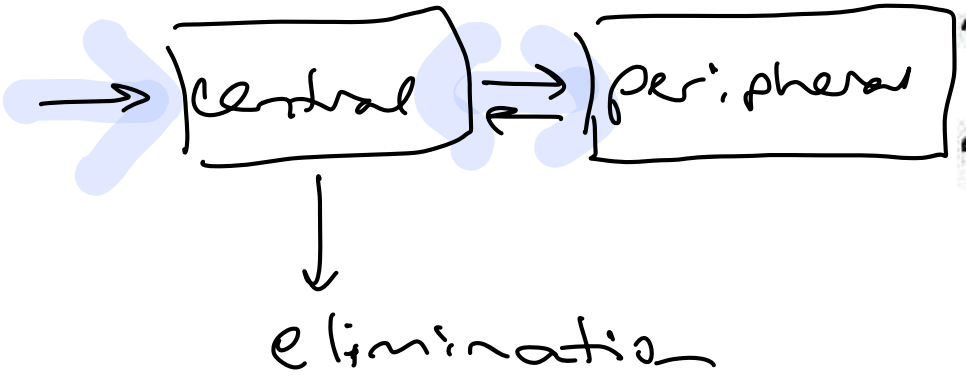
heart, lungs, live

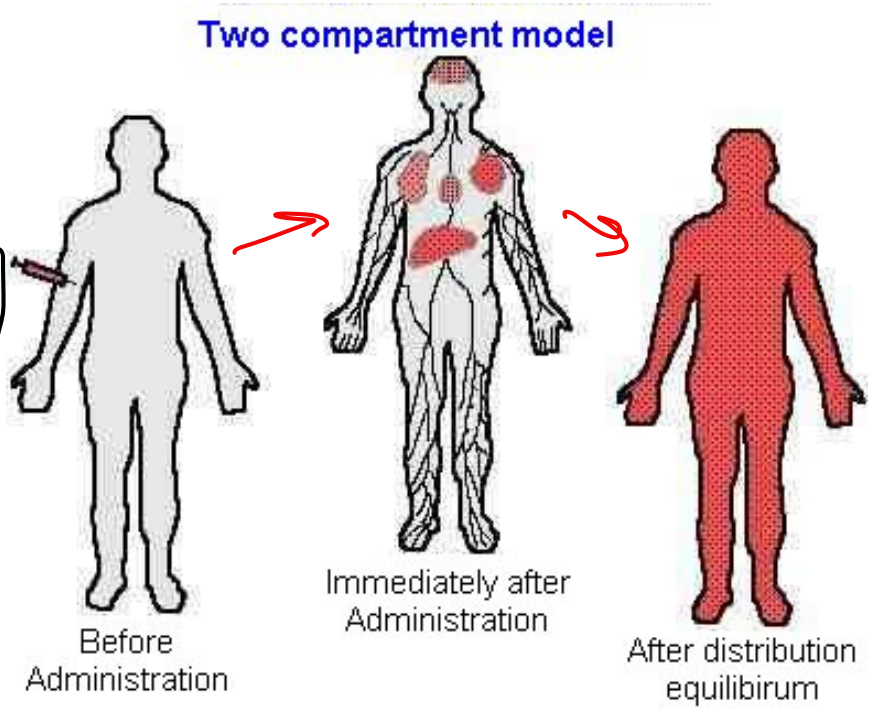
V_c

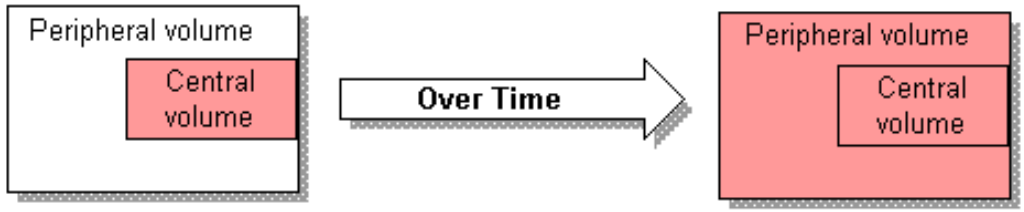
Distribution

$V_t + V_c = V_{app}$

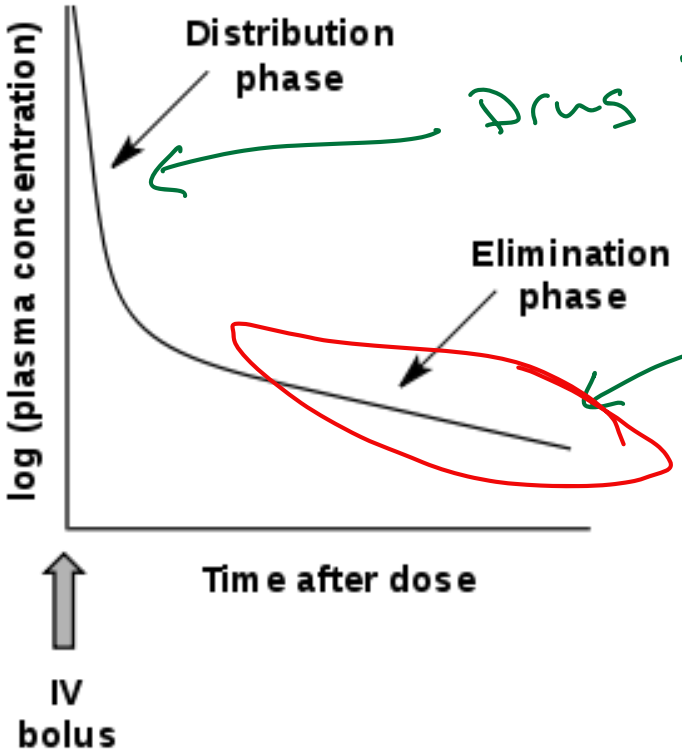
Two Compartment Model







Two Compartment model produces Biphasic Plot

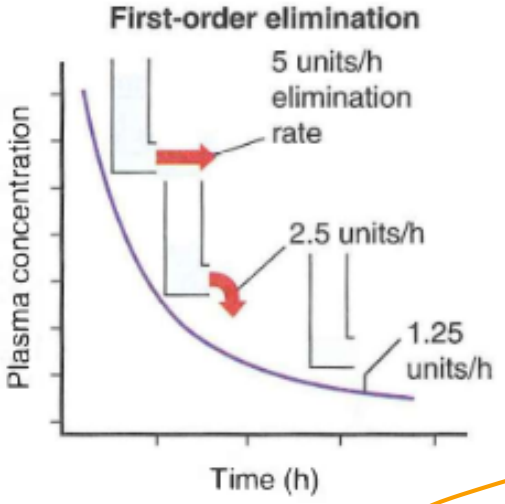


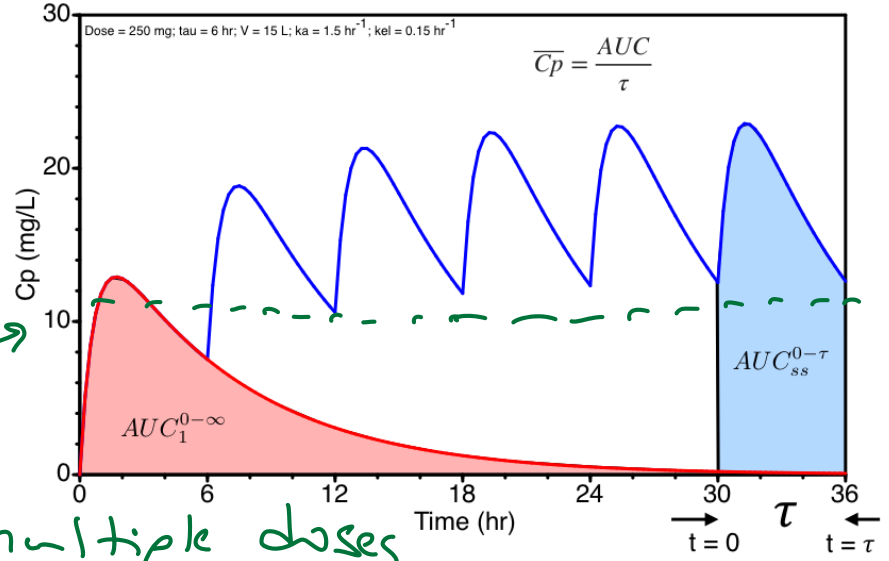
Drug in process of net movement C → P

Drug being eliminated

this is 1st order kinetics part we use to find $t_{1/2}$

multiple dosing events





Can take multiple doses to reach a steady state where we have therapeutic

Can calculate a loading dose if you know desired plasma conc. and Vapp

$Amt = (V_{app})(\text{target conc.})$

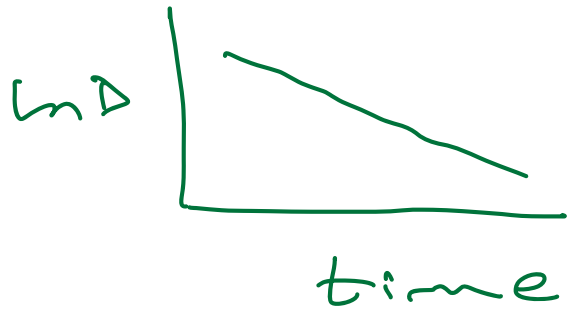
theophylline
V_{app} 35L
10 mg/L = [D]

$LD = 35L \times \frac{10mg}{L} = 350mg$

First Order Elimination

$$\ln D = \ln D_0 - kt$$

y = $\ln D$, int = $\ln D_0$, x = t



Time	[drug] blood	[drug] removed	Fraction eliminated	ln D
0	1000	0	0	6.90776
1	800	200	0.20	6.6846
2	640	160	0.20	6.4615
3	512	128	0.20	6.2383

$y = -0.2231x + 6.9078$

$k = .2231$ rate constant

what is $t_{1/2}$?

$$t_{1/2} = \frac{.693}{k}$$

$$k = \frac{.693}{t_{1/2}}$$

$$t_{1/2} = \frac{.693}{.2231} = 3.10$$

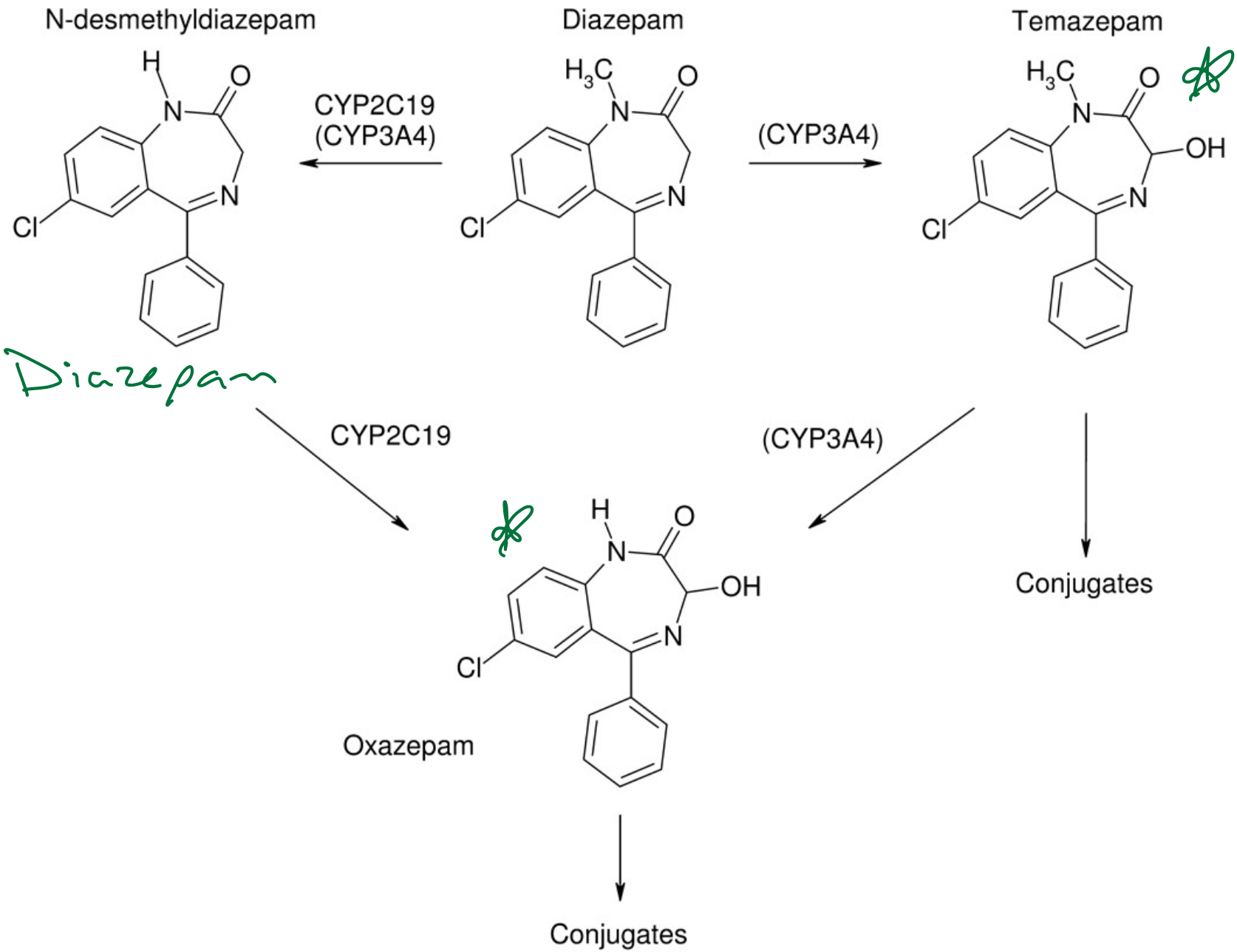
Essential Equations to do Pharmacokinetic Modeling

C_p = plasma concentration of drug in central compartment.

1. One compartment model: $C_p = C_0 e^{-K_e t}$
2. Two compartment model: $C_p = Ae^{-at} + Be^{-bt}$
3. Three compartment model: $C_p = Ae^{-at} + Be^{-bt} + Ce^{-ct}$

Parameters Needed to do Pharmacokinetic Modeling

1. One compartment: C_0, K_e
2. Two compartment: A, B, a, b
3. Three compartment A, B, C, a, b, c

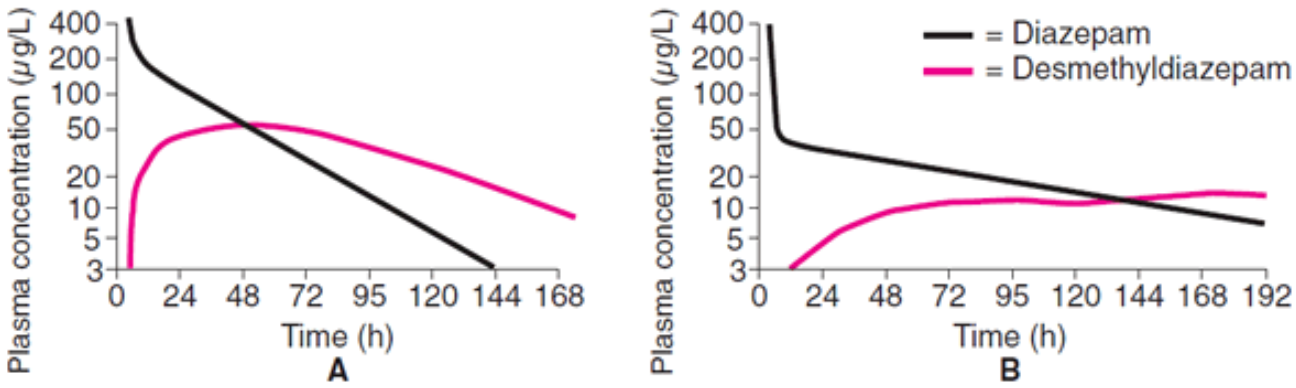

N-desmethyldiazepam
Diazepam
Temazepam
CYP2C19
(CYP3A4)
(CYP3A4)
Diazepam
CYP2C19
(CYP3A4)
Conjugates
Oxazepam
Conjugates

$V_{App} = 80L$

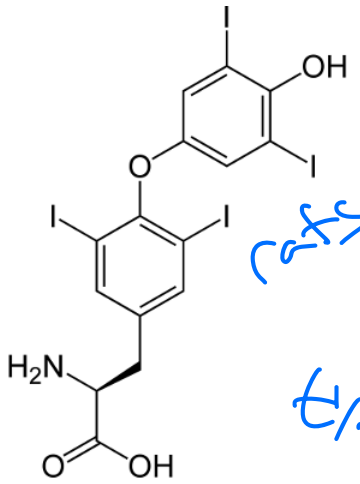
$LD_{50} = 30mg/kg$ $\quad ED_{50} = 0.25/kg$

TI?

$$TI = \frac{30}{.25} = 120$$



Levothyroxine



$V_D = 11-15\,L$

rats: LD_{50} 20 mg/kg $TI = \frac{20}{.3} = 67$

ED_{50} 0.3 mg/kg

$t_{1/2} = 7.5$ days $K = \frac{.693}{7.5}$

If max [D] = 0.033 mg/L

what is [D] at 2 weeks? $K = 0.0924$

$\ln D = -Kt + \ln D_0$

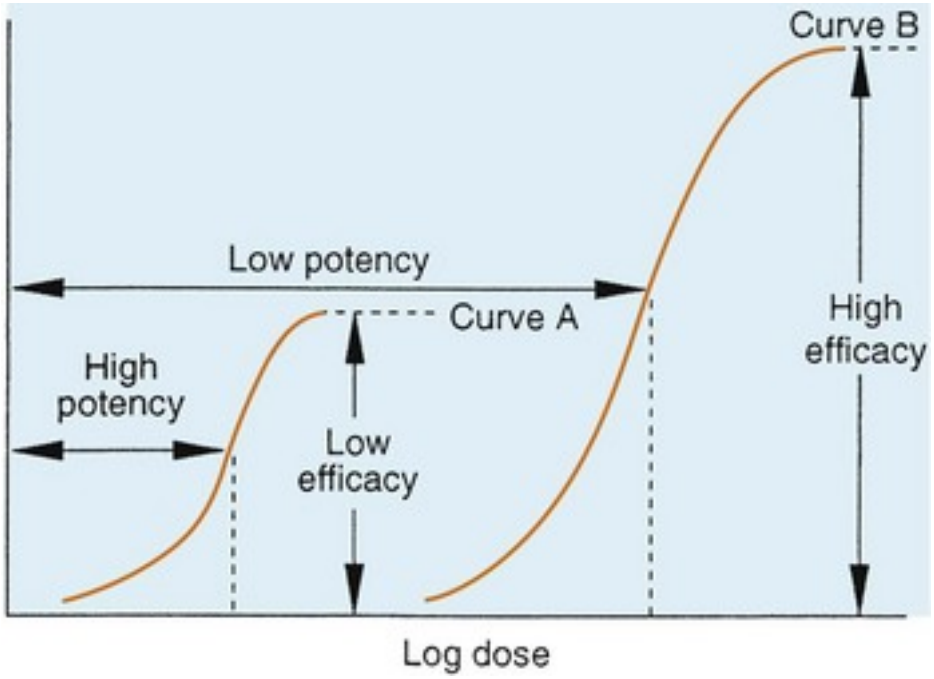
$\ln D = -(0.0924)14 + \ln(0.033)$

$D = 0.00905$

If [D] = 0.033 mg/L $V_{app} = 12\,L$

What is loading dose

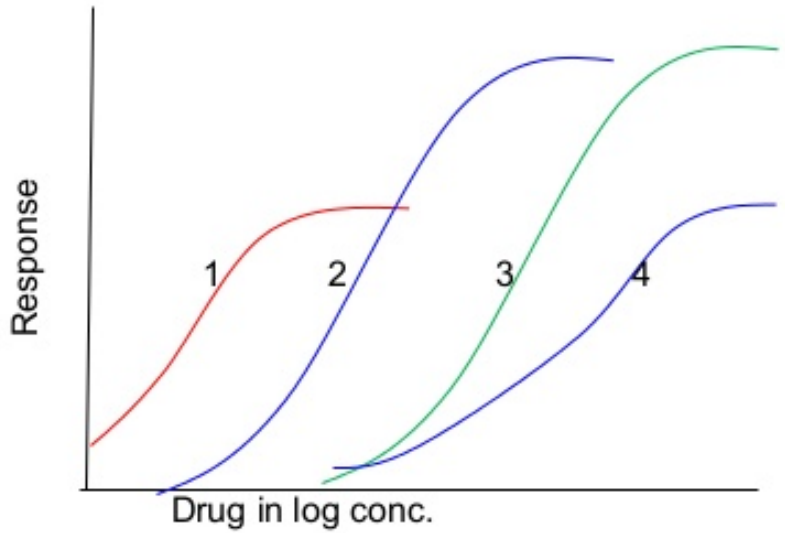
$12L \times .033\frac{mg}{L} = .396\ mg$



Potency – EC_{50} needed to get a certain effect

Efficacy – ability to get a full effect


effect
A
B
C
Conc.


Response
1
2
3
4
Drug in log conc.

Dosing

How Much

How Fast

Dosing Considerations

1. Oral Administration

2. Age, sex, race, diet, environment

3. Weight, body fat%

4. Time of dosage

5. Other drugs

Chemical Equivalence

Bioequivalence

Therapeutic Equivalence