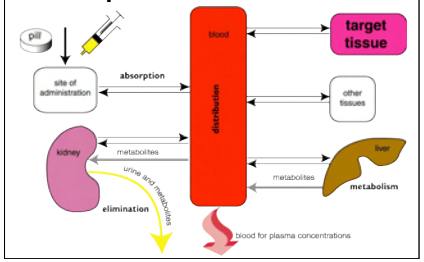
Pharmacokinetics

Distribution

pharmacokinetics

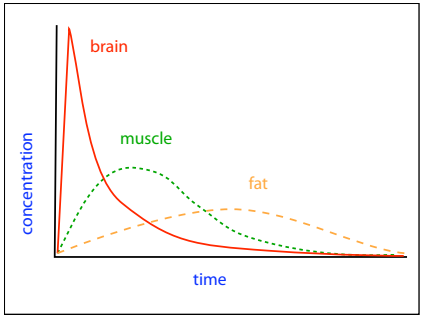


distribution

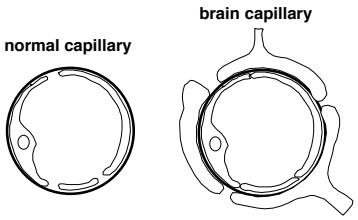
- the movement of drug from the circulation to the tissues and back

distribution

- blood flow
- capillary permeability
  - capillary structure
  - drug structure
  - carrier proteins (efflux pumps)
- protein binding



capillary structure



blood brain barrier

- no access for ionised drugs
  - aminoglycosides
  - penicillins
- lipid soluble drugs rapidly equilibrate and rapidly redistribute
  - anaesthetics
- P glycoprotein pumps many drugs out
  - also cancer cells
  - also bacteria

drug structure

- size
  - most drugs c 200Da
  - peptides c 5,000Da
  - proteins c 50,000 Da
- lipid solubility
  - oil / water partition coefficients

distribution

- blood flow
- capillary permeability
- protein binding

protein binding

- many drugs are bound to albumin
- keeps drugs in circulation
- free drug concentration low
  - only free drug is active

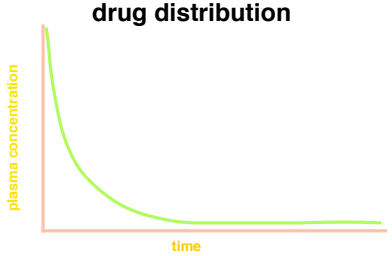
factors affecting protein binding

- other drugs
  - there are usually more binding sites than drug molecules, but if two highly bound drugs are given together, one drug may displace the other resulting in more free (active) drug than expected
  - sulphonamides often saturate binding sites
- hypoproteinaemia
- (body temperature)
- (pH)

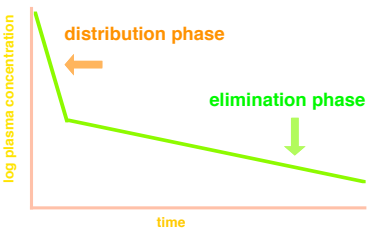
protein binding

- needs phenylbutazone
- may be on warfarin
- may also need surgery
  - thiopentone

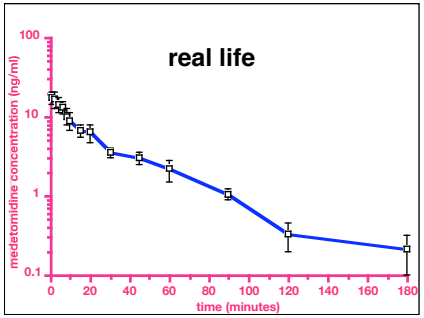
drug distribution

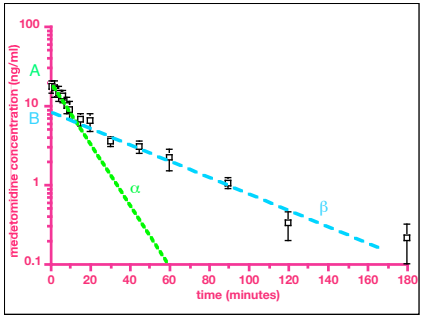


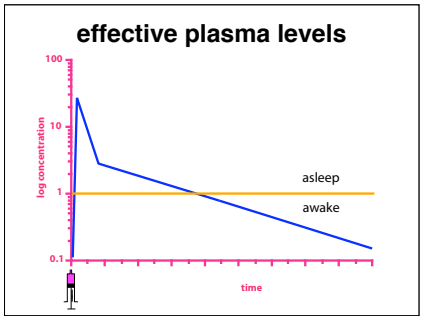
drug distribution

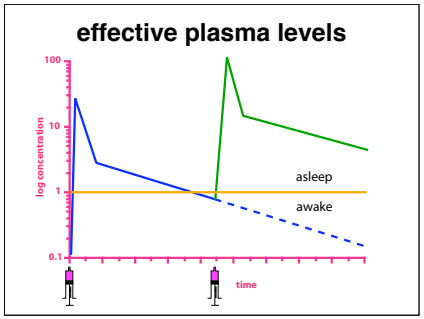


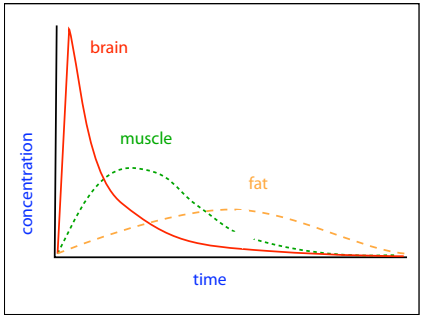
real life



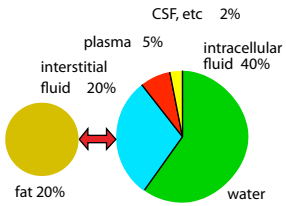

medetomidine concentration (ng/ml)
100
10
1
0.1
A
B
α
β
0
20
40
60
80
100
120
140
160
180
time (minutes)


effective plasma levels
log concentration
100
10
1
0.1
asleep
awake
time


effective plasma levels
log concentration
100
10
1
0.1
asleep
awake
time


brain
muscle
fat
concentration
time

fluid compartments



volume of distribution

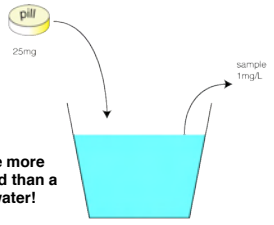
- **Vd is the volume a drug would occupy if it was evenly distributed at the same concentration as in the plasma**

Vd

$$V_d = \frac{Q}{C_p}$$

If 25mg of drug results in a plasma concentration of 1mg/L then V_d = 25/1 = 25L

Vd



- **animals are more complicated than a bucket of water!**

Vd

$V_d C_p = Q$

If Vd = 25L and plasma concentration = 1mg/L, then dose = 25mg

Vd

- Vd does not correspond to any anatomical or physiological compartment
- but - can provide some information on where drug goes

Vd

- heparin - 50 mL/kg ~ plasma volume
- gentamicin - 250 mL/kg ~ ECF volume
- diazepam - 650 mL/kg ~ total body water
- morphine 5 L/kg ~ ?

Vd

- a large Vd implies that the drug is preferentially distributed somewhere - usually to fat - and is unavailable

Vd

- used to calculate doses to achieve target plasma levels
- but
  - individual variation
  - pathology

What would you do?

- epileptic
- fits twice a week
- on phenobarbitone
- 20kg

phenobarbitone

- effective plasma levels 25 - 35μg/mL = ~ 30mg/L
- comes as 30 & 60mg tablets
- completely bioavailable
- Vd 0.75L/kg
- dose?

phenobarbitone dose

$$V_d C_p = Q$$

- Vd = 0.75 x 20 = 15L
- Cp = 30mg/L
- Q = 30 x 15 = 450mg or 22.5mg/kg
- nb. frequency of dosing depends on how quickly the dog gets rid of the drug!!

distribution

- drugs are usually distributed out of the blood to their site of action
- many drugs bind to plasma proteins and are unavailable for action or metabolism
- drugs are not distributed evenly throughout the body - each has a volume of distribution