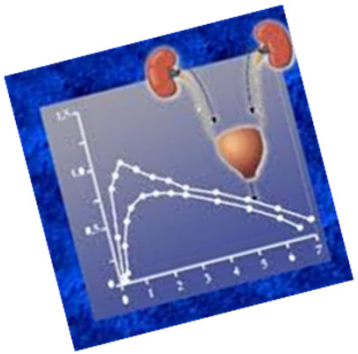
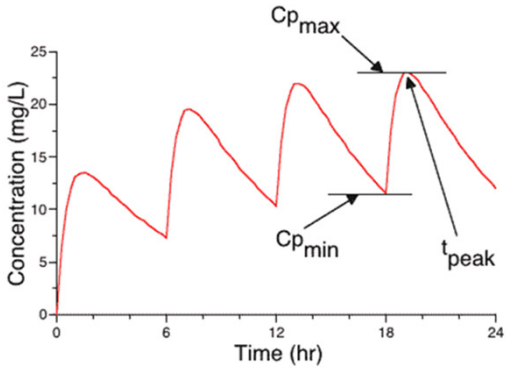


Pharmacodynamics & Pharmacokinetics

Dr. Duncan Cromarty

Block 18



$$C_p = C_0 e^{-kt}$$

“All substances are poisons: there is none which is not a poison. The right dose differentiates a poison and a remedy.”

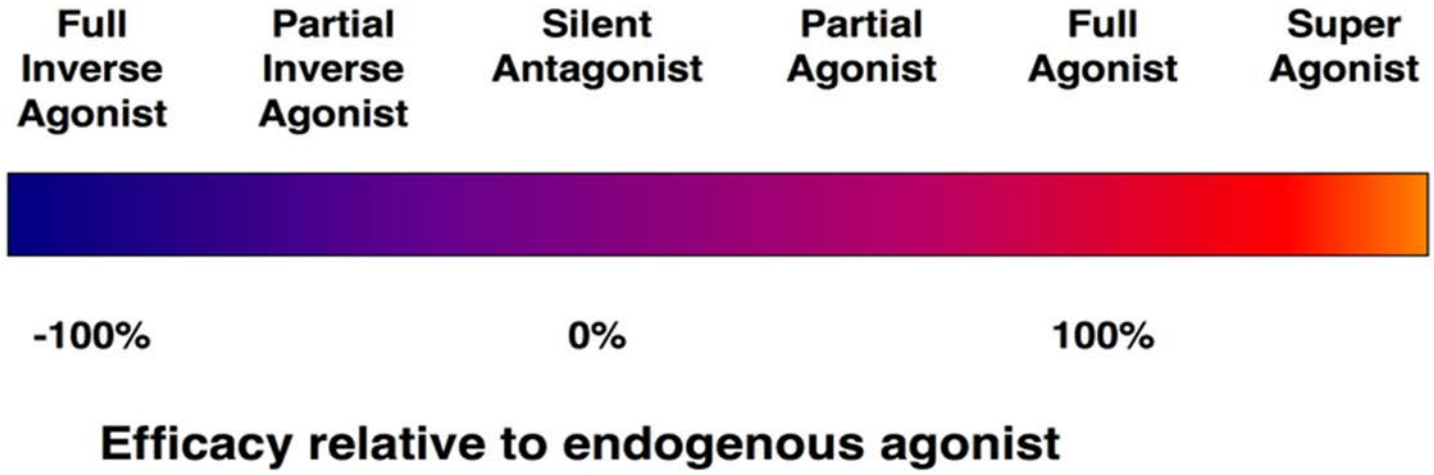
Paracelsus (1493-1541)

Pharmacodynamics

- The effect/s of a drug on living cells
- Mechanism of action of a drug
  - **Activation or inhibition:**
    - Receptors – valsartan, morphine
    - Enzymes - aspirin
    - Transporters – SSRI's - fluoxetine
    - Ion channels - digitalis
    - Direct chemical reaction – antioxidants, detergent

Agonists and Antagonists

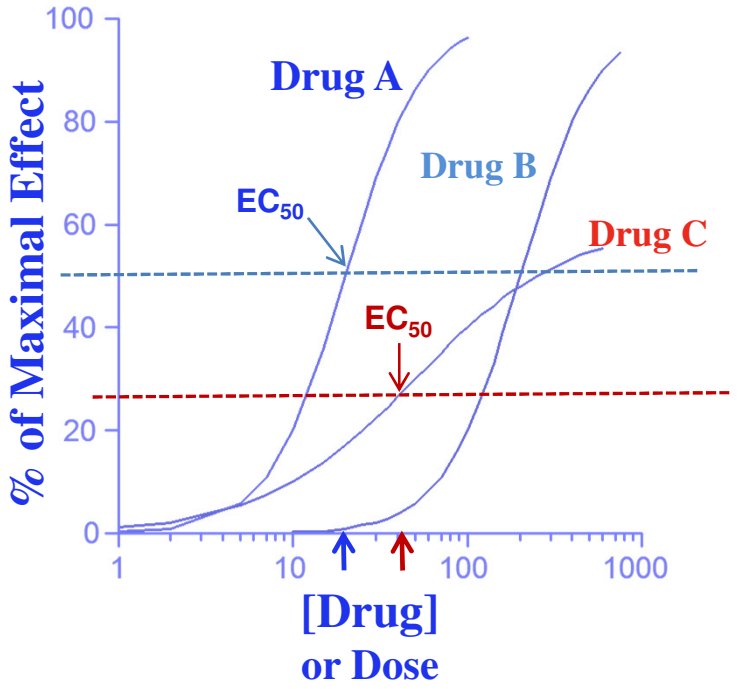
Activators = Agonist
Inhibitors = Antagonist



Efficacy and Potency

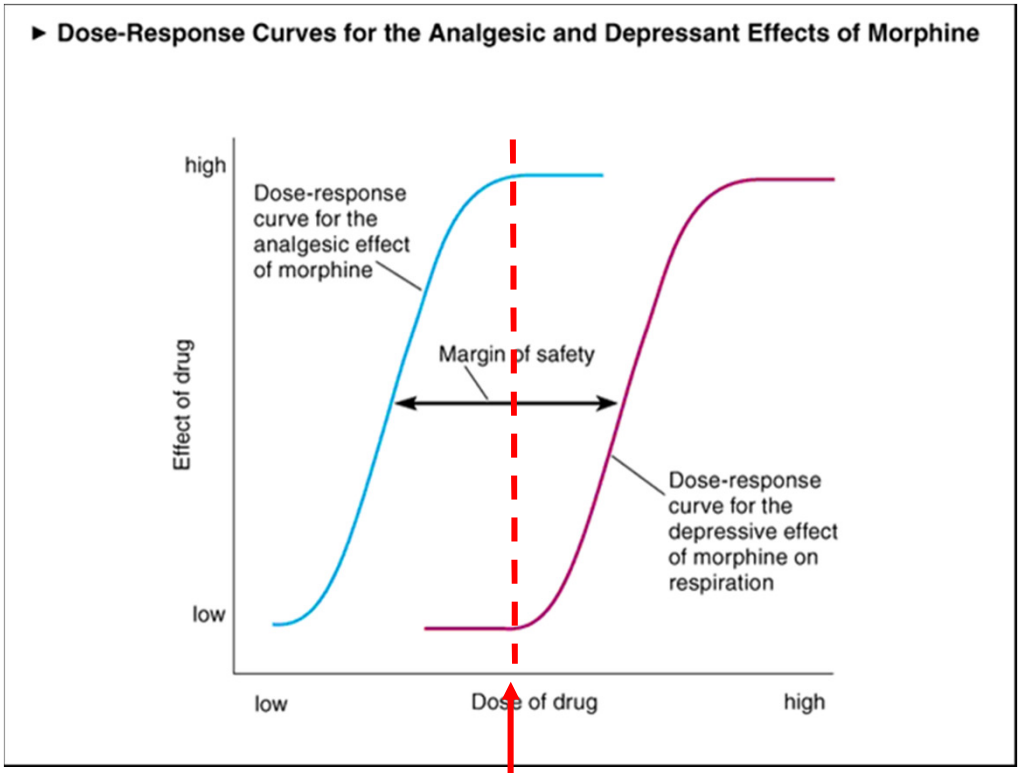
- Therapeutic concentration
- Potency
- Reported as EC_{50} (μM) or

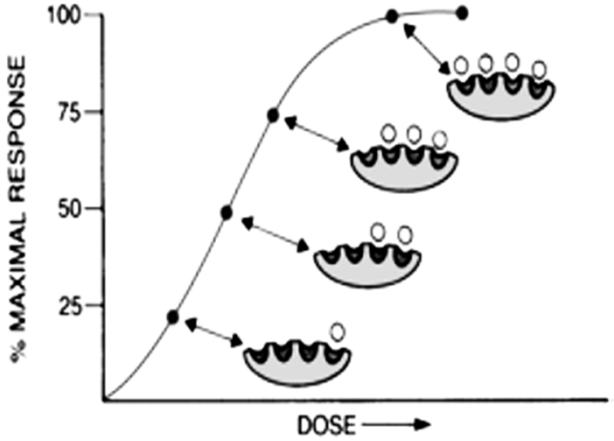
  ED_{50} (mg/kg)
- Affinity
- Selectivity
- Therapeutic index
- Duration of effect



Note the sigmoidal nature of the curves

Effect and Side effect curves





Concentration at which toxic effect is evident

Intrinsic Activity (IA) or Efficacy

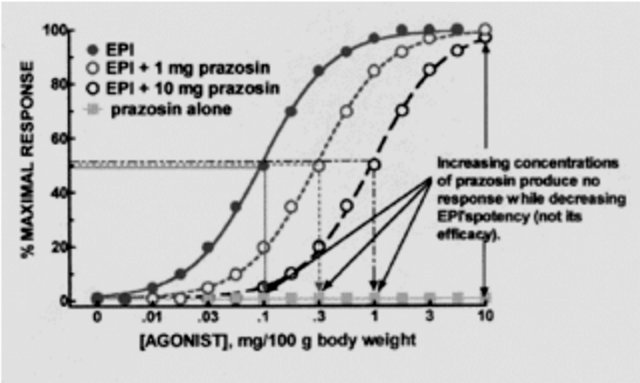
- Drugs ability to generate a measurable effect.
- The extent of the biological effect depends on receptor occupancy by drug.
  - Single receptor triggers full effect
  - Percent of available receptors relates to extent of effect
- **AGONIST** = maximal effect **(IA = 1)**
- **PARTIAL AGONIST** = Sub-maximal effect **(IA < 1)**
- **COMPLETE ANTAGONIST =** Blocks effect (**IA ± 0)**

ANTAGONIST

1. **Competitive**
2. **Biochemical**
3. **Non-competitive**
    - Physiological
    - Allosteric
    - Chemical

Competitive Antagonists

- IA < 10%
- ↑ Affinity for receptor
- May block multiple receptors
- ↑ [Agonist] can displace antagonist
  - e.g. Acetylcholine (agonist) and Atropine (antagonist)

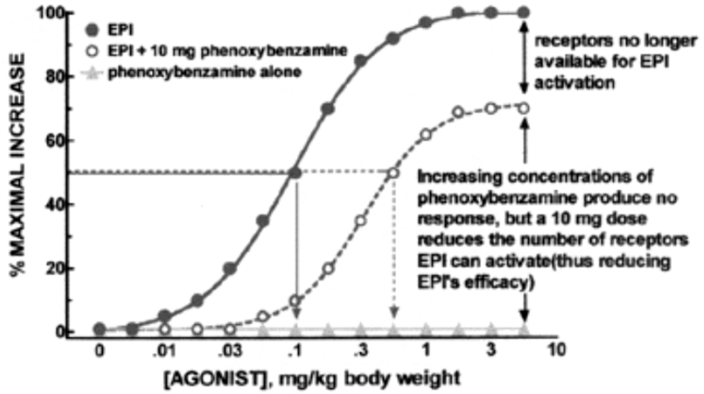


Biochemical

- Drug/drug effect where one drug affects the available concentration of a second drug.
- The antagonist ↓ $[Agonist]_{apparent}$ and drug effect
  - ↑ Biotransformation
  - Competes with agonists transport to receptor
- e.g.
  - Metabolism: Phenobarbital vs. oral contraceptive failure
  - Excretion: Mannitol = ↑ Excretion of drugs

Non-competitive

- **Physiological**
  - Two opposing effect agonists simultaneously active
  - Each one has ↑ affinity of its own receptor
  - ↑ Antagonist has apparent effect of ↓ Agonist
  - Antagonist works on a totally different system with opposing effect to the agonist
  - **IA** = 1
  - e.g.
    - Adrenalin & Histamine
    - Histamine & Omeprazole

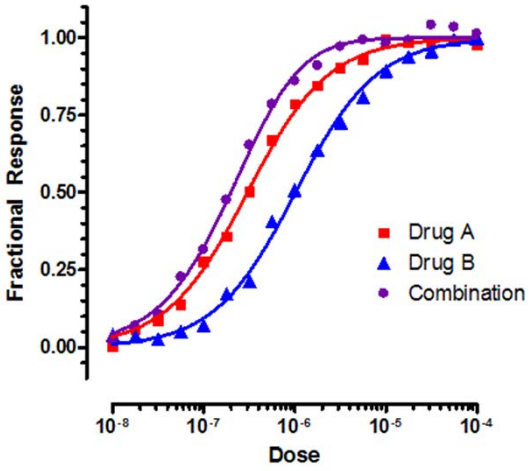


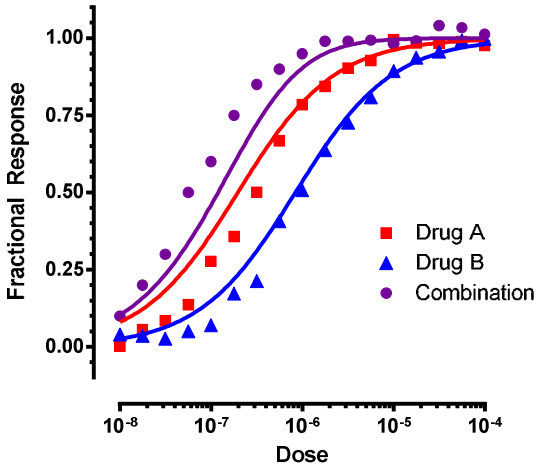
- **Allosteric**
  - The receptor site is altered so that agonist can't bind to it.
  - e.g. Allopuranol

- **Chemical**
  - Chemically binds to agonist:
    - ⬇ [ ] & ⬇ Effect
  - e.g.
    - Heparin & Protamine sulphate
    - Dimercaprol (binds heavy metals)

Additive or synergistic effects

- When two drugs are administered together the total effect may be the sum of the individual effects
- Sometimes the effect of the combination is greater than the expected effect of the individual drugs and this is termed a synergistic effect





Pharmacokinetics

What the body does to the drug

- Mathematical description of the behaviour of drugs after administration
- All calculated from measured plasma concentrations
- Important concepts for dosing

Some pharmacokinetic concepts

- Central compartment = plasma
- All concentrations measured are plasma concentrations
- Initially absorption and elimination take place simultaneously
- Dose and time are the easiest parameters to control
- Most reported values are population averaged data (does not include paediatric or geriatric populations who are the most common users of therapeutic drugs)
- Mathematical models are used to describe the observed changes in plasma concentrations as closely as possible
- Normally start with single rapid bolus dose to assess critical parameters

ADME

Elimination as measured during pharmacokinetic studies
Is a combination of distribution, metabolism and excretion

Definitions & Concepts

• Bioavailability	F
• Elimination half-life	$t_{½}$
• Steady state concentration	C_{ss}
• Volume of distribution	V_d
• Area under the curve	$AUC_{0-\infty}$
• Elimination rate constant	k_{el}
• Clearance rate	Cl
• Maximal plasma concentration	C_{max}
• Time to C_{max}	T_{max}

Bioavailability

Fraction of unchanged drug reaching the systemic circulation after “non IV” administration.

$$F = \frac{[PO]}{[IV]}$$

If same dose given PO results in only 60% of plasma concentration measured for IV administered dose then bioavailability = 60%

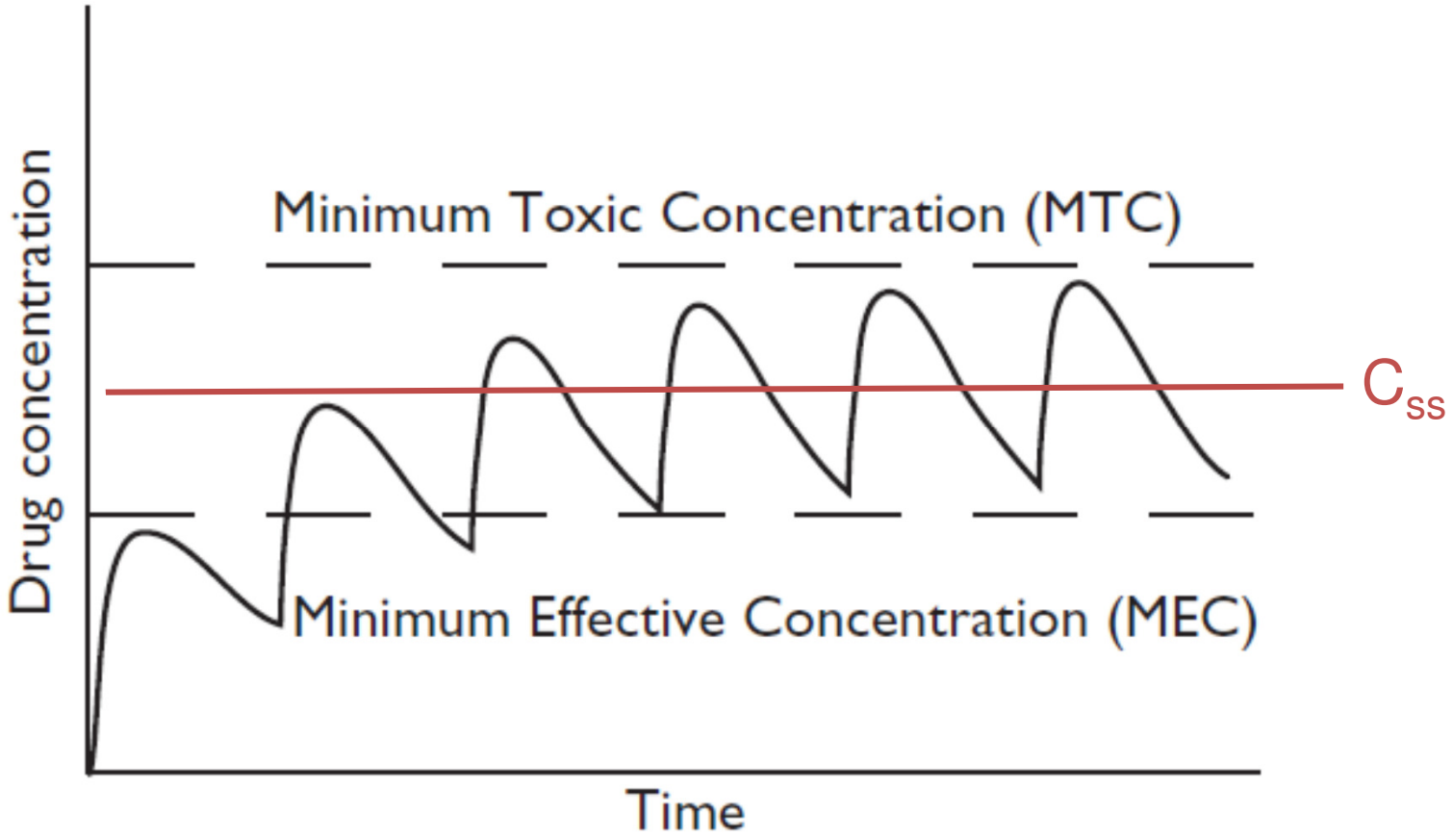
Elimination Half-life ($t_{½}$)

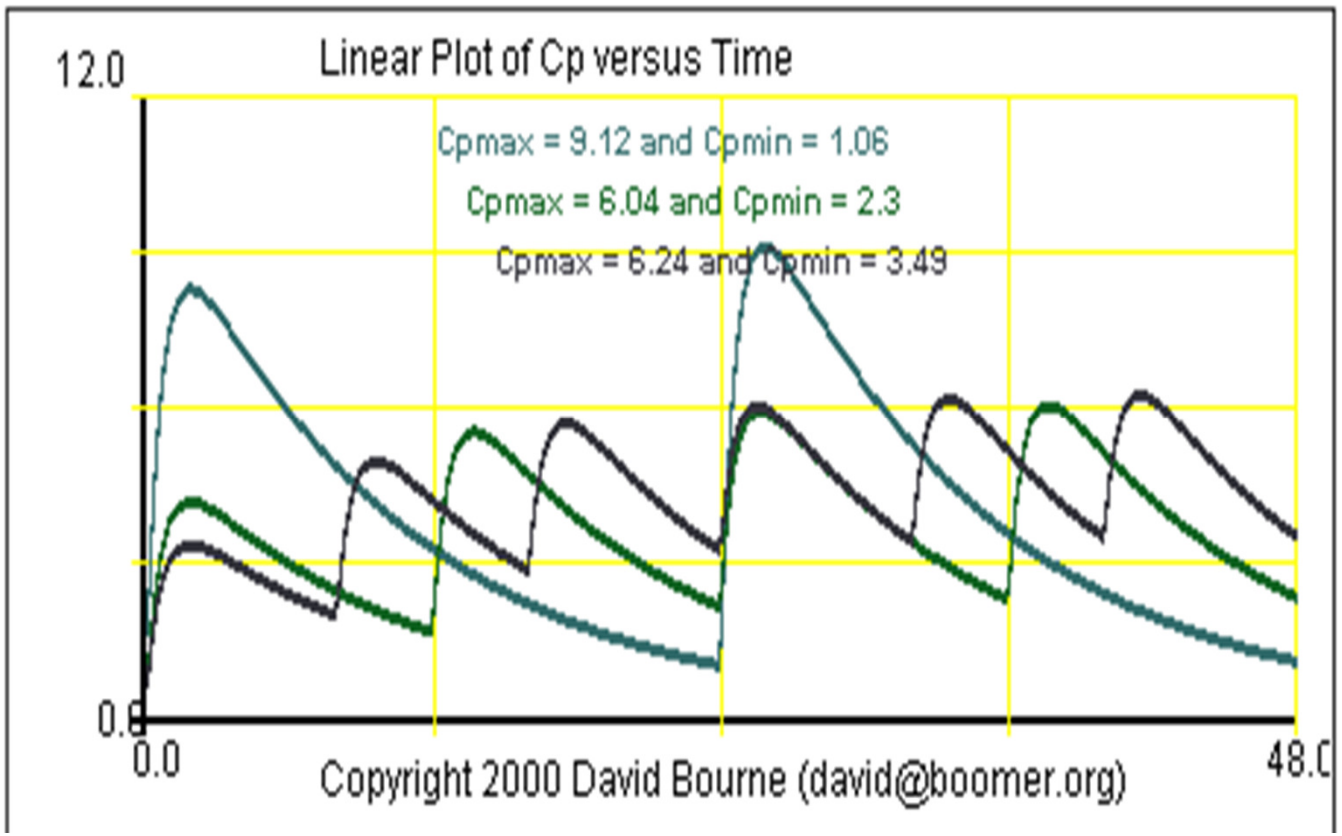
- Time required to decrease the plasma concentration by 50%.
- $t_{½}\alpha$ = distribution half-life (evident in 2 compartment models)
- $t_{½}\beta$ = elimination half-life or terminal half-life

Steady State Concentration (C_{ss})

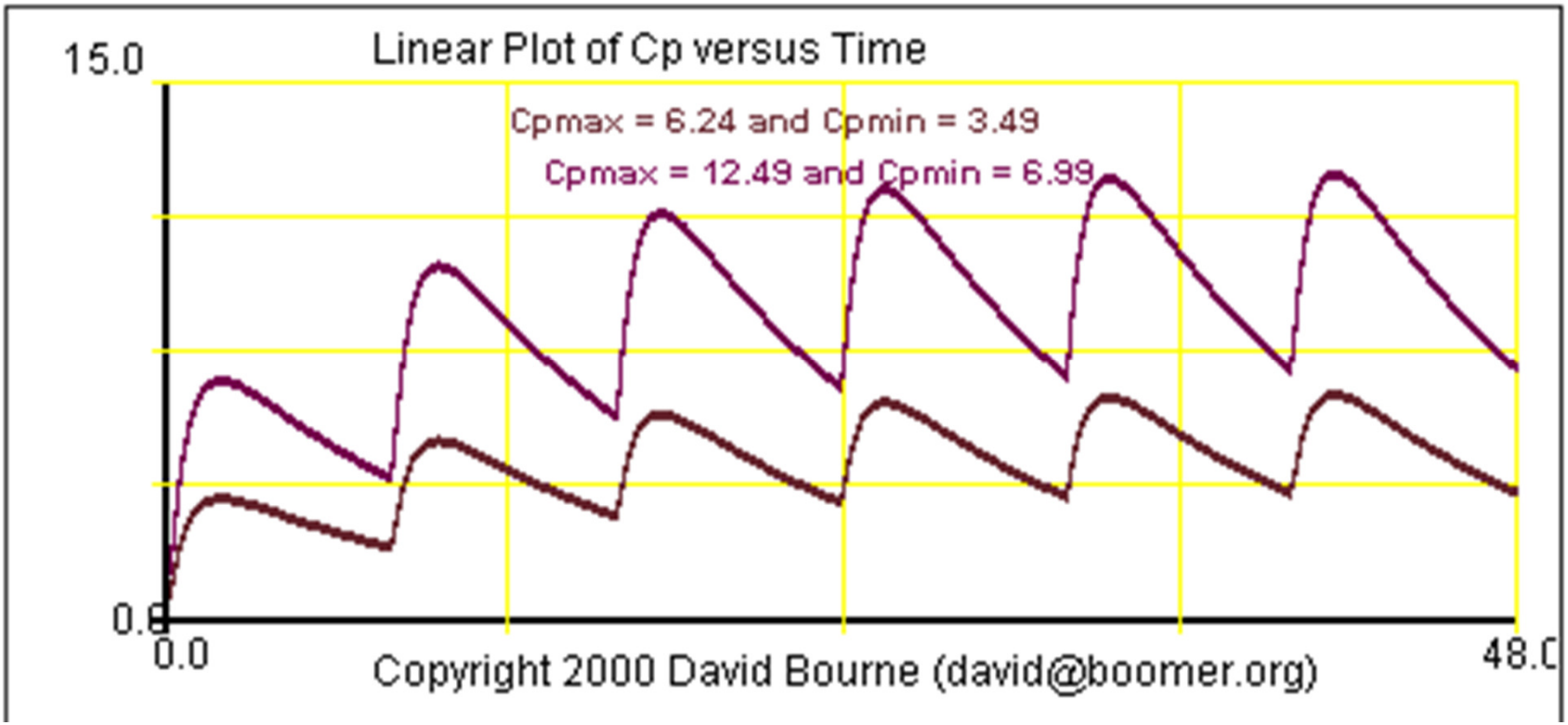
- Average plasma drug concentration during multiple dose regimens.
- ABSORPTION = ELIMINATION (between doses)
- **C_{ss}** ➔ reached after 4-5 x $t_{½}$
- Dose and dosing interval independent
  - These parameters affect the final concentration - not time to C_{ss}
- Skipped doses reduce the C_{ss}

Steady State Concentration (C_{ss})





100 mg 3pd **125 mg bd** **250 mg pd**



100 mg 3pd **200 mg 3pd**

Volume of Distribution (Vd)

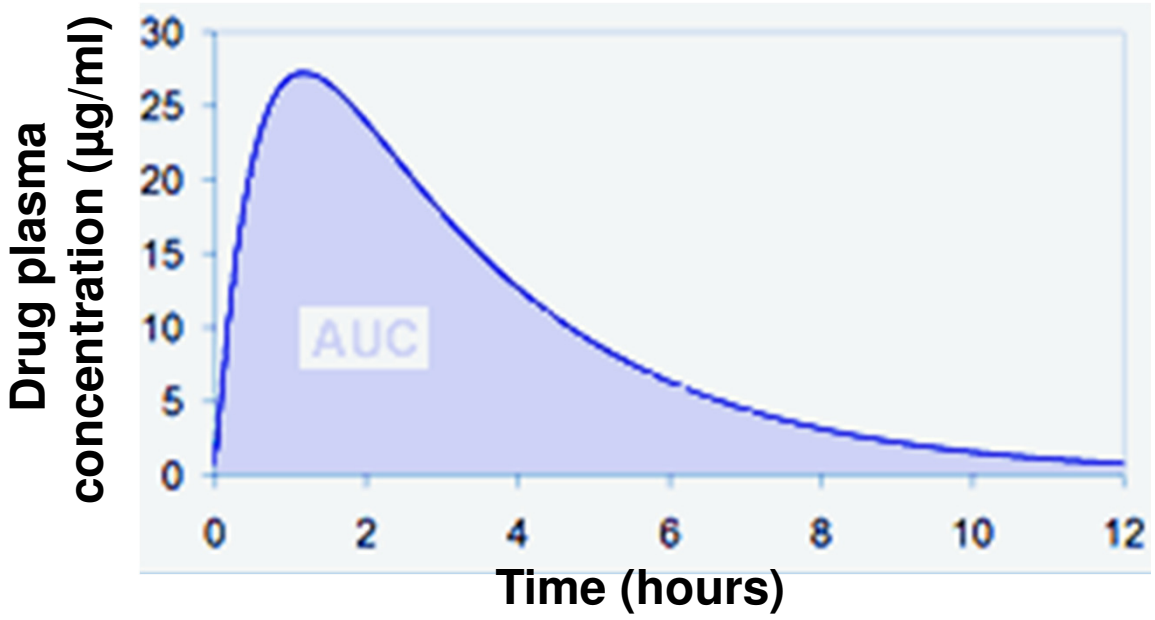
Hypothetical volume of fluid into which the drug dose must be distributed to observe the measured plasma concentration.

$$V_d = \frac{Dose}{C_{p0}}$$

- **BASIC:**
  - Will penetrate cells
  - High V_d
  - Low [plasma]
- **ACIDIC:**
  - Stays in plasma
  - Low V_d
  - High [plasma]

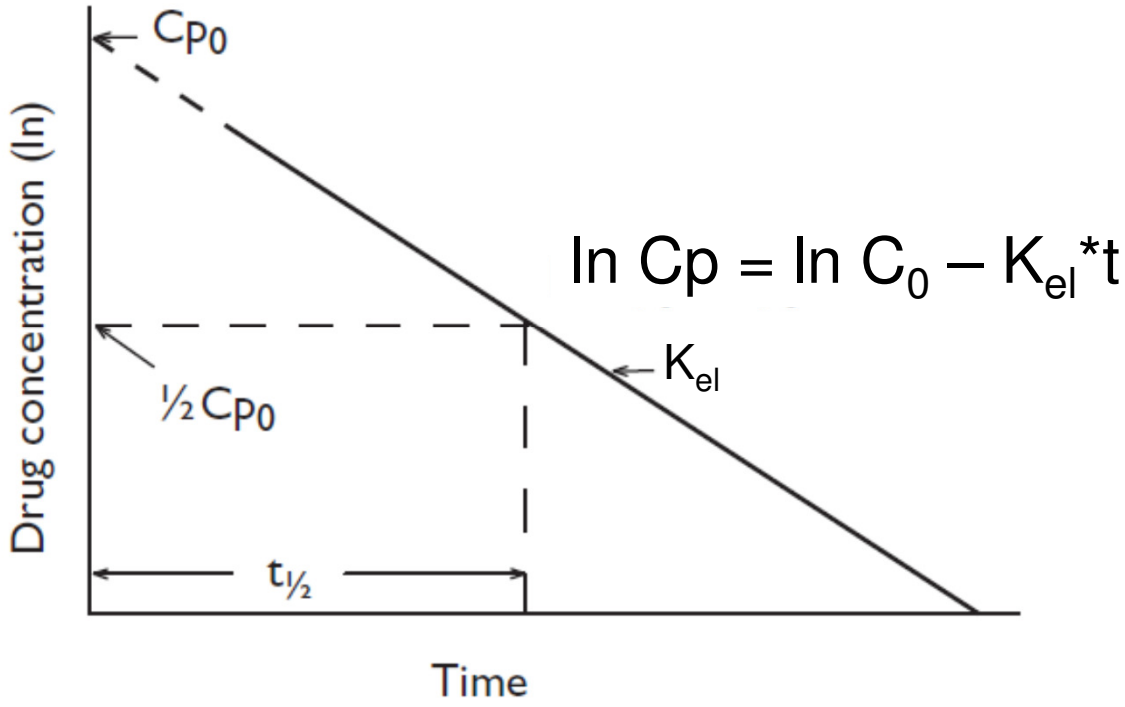
Area under the curve (AUC)

- Measure of the total exposure to the drug
- Can be measured for entire exposure time ($AUC_{0-\infty}$) or between doses (AUC_{0-t})



Elimination rate constant (k_{el})

- Rate at which the drug is eliminated from the plasma
- Sum of distribution, metabolism and excretion



Clearance rate (Cl)

- The volume of plasma irreversibly cleared of drug per unit time

- $$\mathbf{Cl} = \frac{\textbf{Rate of elimination}}{\textbf{Plasma concentration}} = \frac{0.693 * V_d}{t_{1/2}} = \frac{F * Dose}{AUC}$$

- Is a combination of hepatic clearance, renal clearance and other clearance
  - Hepatic maximum = 1500ml/min
  - Renal maximum = 120 ml/min ± GFR

Absorption of Drugs

- Transfer of a drug from its site of administration into the plasma (central compartment).
- Depends on:
  - Route of administration
  - Solubility
  - Physical properties of the drug
  - Disease states affecting absorption

Factors affecting absorption

- Formulation
  - Solids (tablets, capsules)
  - Liquids (p.o., i.v., i.m., s.c., topical, intra-nasal …..)
  - Vapours (lungs)

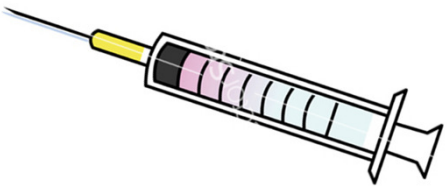
- Physicochemistry of drug (API)
  - Solubility – insoluble drugs have very low bioavailability
  - Molecular size – large molecules are slowly absorbed
  - Lipophilicity – lipophilic drugs diffuse across membranes
  - Polarity – polar drugs need transporters to enter cells
  - Ionisation – traps drugs

Factors affecting absorption ….

- Patient
  - Hydration status
  - Age
  - Gender
  - Lung capacity & function (volatile drugs or metabolites)
  - Pathologies
  - Gastric emptying and transit time
  - Mesenteric blood flow
- Drug/drug or drug/food interactions
  - Food Cyp3A4 activity by grapefruit juice increases drug uptake of CYP3A4 metabolised drugs
  - Concomitant administration of different drugs

Routes of Administration

- **Portal circulation:**
  - Oral
  - Rectal (upper 1/3)
- **Systemic circulation:**
  - Sublingual
  - Percutaneous
  - Transdermal
  - IM, IV, IA
  - Rectal (lower 2/3)
- **Local**
  - Topical
  - Intrathecal



Transport

PASSSIVE TRANSPORT	ACTIVE TRANSPORT
Don’t require energy	Requires energy
Move down [ ] gradient	[ ] gradient not required
	Biological pump mechanisms
	Selectivity and saturable

Distribution

- The reversible movement of a drug out of the plasma into the interstitial spaces (ECF) or target tissues.
- Factors influencing drug distribution:
  - Blood flow
  - Capillary permeability (e.g. BBB)
  - Plasma protein binding
  - Tissue binding
  - Fat solubility of the drug
  - Compartmentalization
    - Placenta & Breast milk

Distribution

- Compartmentalisation
  - Non-compartmental kinetics
  - One compartment kinetics
  - Two compartment kinetics
  - Michaelis Menten kinetics

Distribution

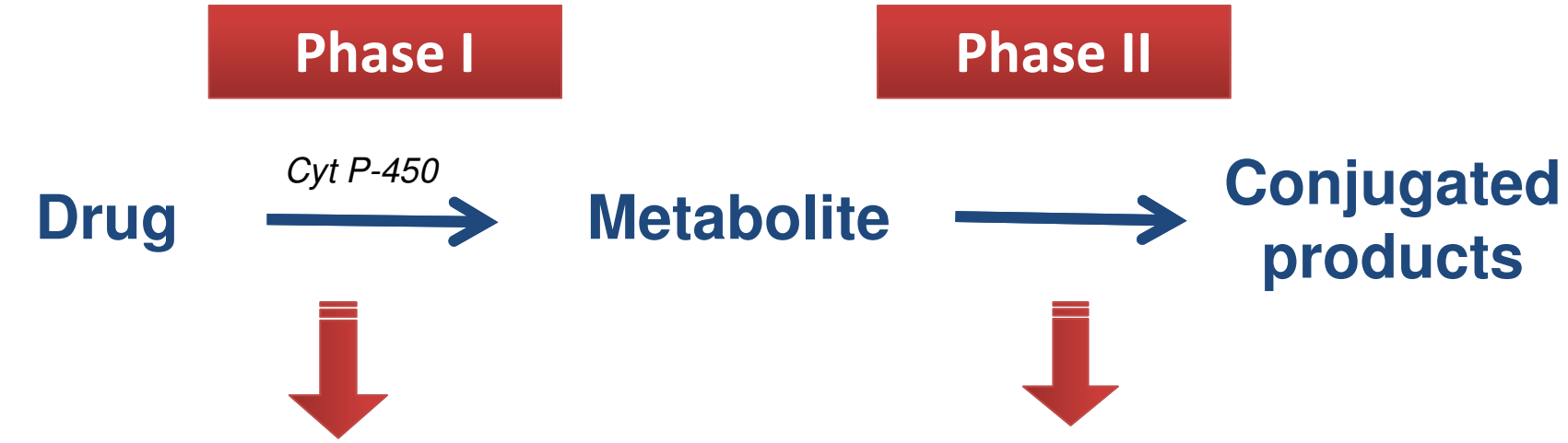
- Main pharmacokinetic parameter is the apparent volume of distribution V_d
- V_d = 4 – 7 litres implies blood retained drug
- V_d = 10 – 17 litres implies extracellular distribution
- V_d = >20 litres implies wide distribution out of plasma
- e.g.

	V (L/Kg)	V (L, 70 kg)	$t_{1/2}$, hr
Warfarin	0.12	8	40
Digoxin	7	490	40
Chloroquine	180	12500	120

Metabolism

- Process of chemical modification through enzymatic activity that may lead to altered of biological activity.
- Phase I and Phase II metabolic processes
- Phase I adds reactive polar handles - membrane bound CYP enzymes of liver
- Phase II conjugates polar molecules to handles - glucuronate, sulphonate, taurine, amino acids
- Also called biotransformation

Metabolism



Metabolic transformation:
CYP P450 enzymes of microsomal fraction
(oxidation, reduction, hydrolysis)

Adds reactive site & makes drug more polar
(-OH)

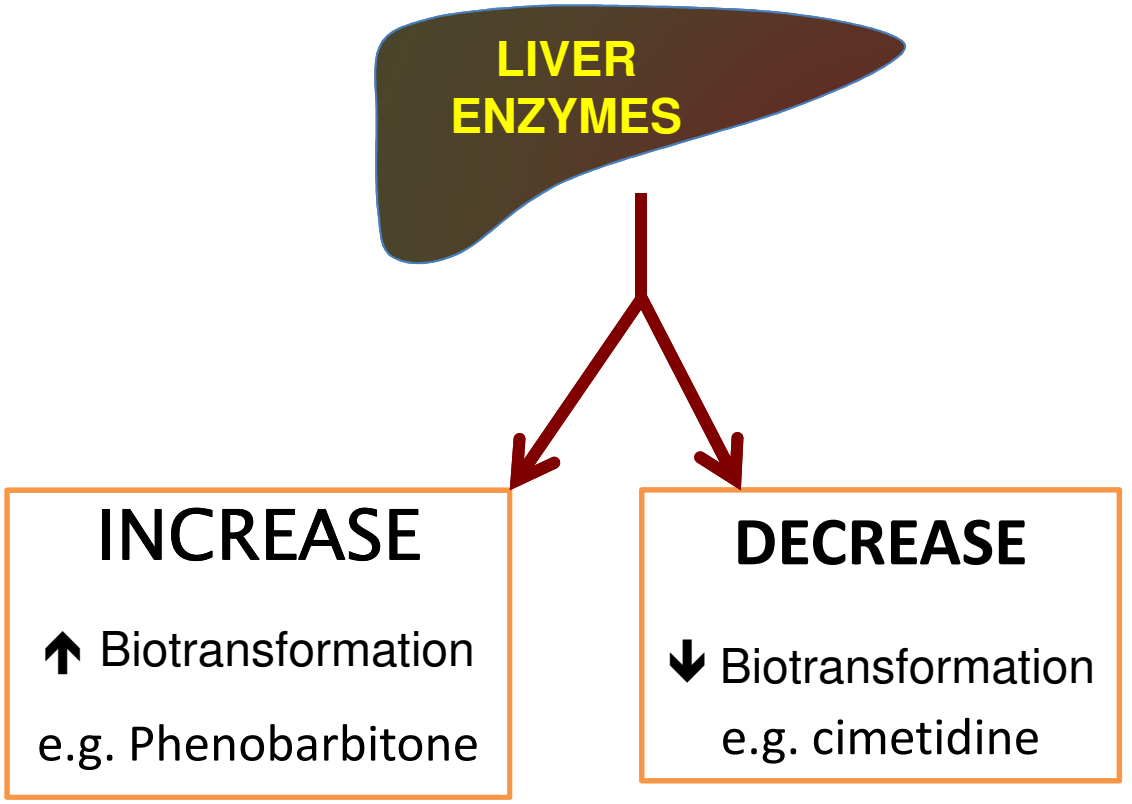
Conjugation reaction:
Cytosolic enzymes add polar group by conjugation to drug
(glucuronic acid, sulphonate ….)

Drug inactivation

↓ Fat solubility; ↑Ionization

Biotransformation/ First pass effect

- Drug is lost by rapid metabolism in liver directly after absorption from the gut due to portal vein drainage of the GIT.
- Very lipophilic drugs often bypass the liver by moving in chylomicrons and the lymph system



Biotransformation

- **Drugs Modified in 3 ways (NB in pharmacogenetics)**
  - Active drug → Inactive metabolite
  - Inactive drug ("pro-drug") → Active metabolite
  - Active drug → Active metabolite
- **Enzymes that mediate biotransformations**
  - Liver microsomal enzymes (fat soluble drugs)
  - Non-microsomal enzymes (H_2O soluble drugs)
    - Mitochondrial
    - Plasma esterases

Excretion

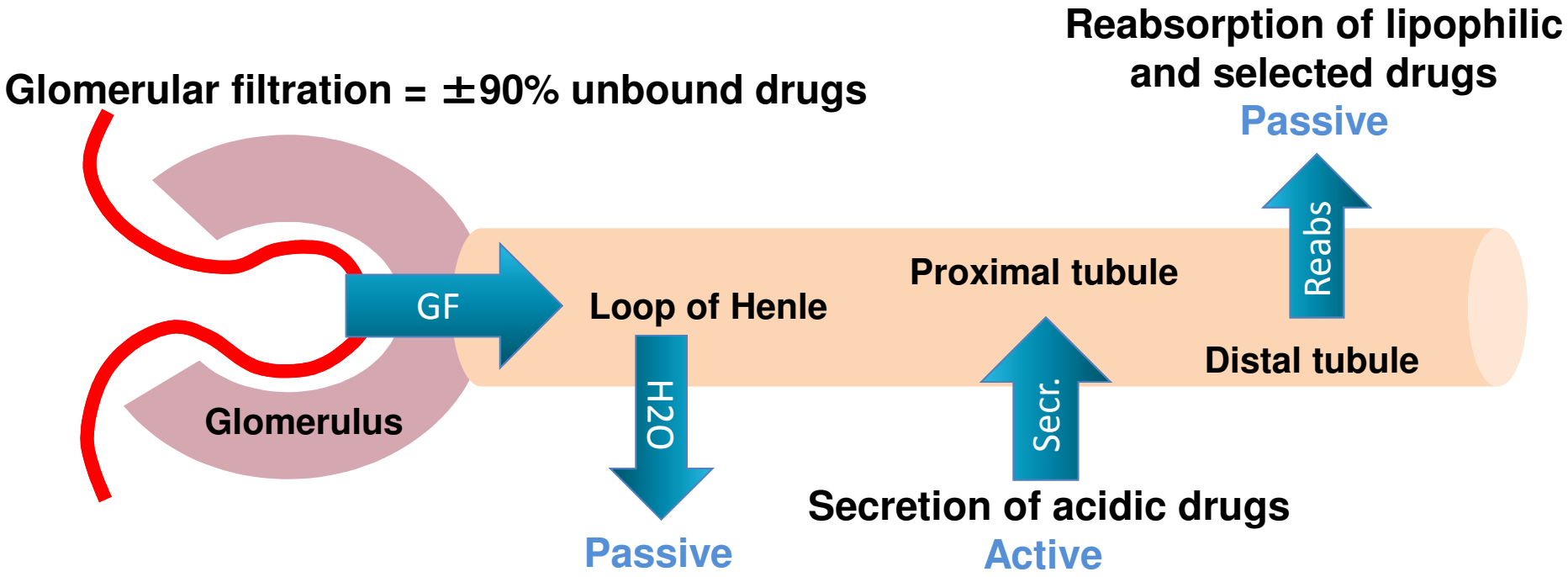
- **<u>Things to remember!</u>**
  - Increased concentration of drug or metabolites at organ responsible for excretion
  - Impaired organ function decreased excretion
  - If intake > elimination = drug accumulates

Routes of Excretion

- Kidneys – most active - Non-volatile drugs
- Liver - bile e.g. cromoglycate, morphine
  - hepatobiliary recycling
- GIT - e.g. Erythromycin
- Sweat - e.g. Bromide
- Tears - e.g. Chloroquine
- Lungs - Volatile drugs
- Saliva
- Breast Milk

Kidney excretion

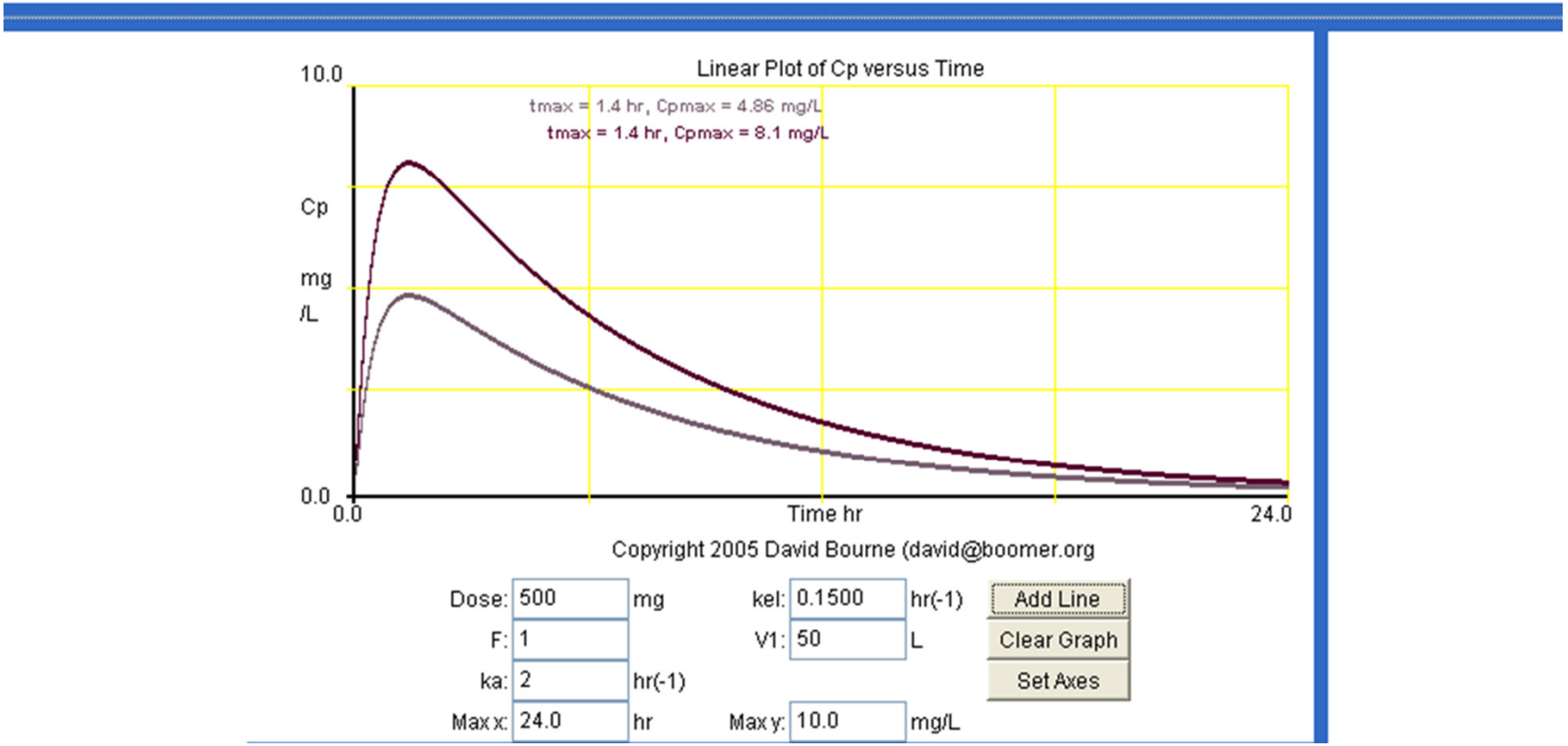
- Most important excretory organ
- Normal loss of function with age
- Excretion influenced by secretion and reabsorption in the tubules



1st ORDER KINETICS	ZERO ORDER KINETICS
More common	Limited examples
Constant fraction (%) eliminated per unit time	Constant amount (mg/h) eliminated per unit time
Dose independent	Dose dependent
Concentration independent	Saturation effect
Exponential [plasma]/time curve plot	Linear [plasma]/time curve plot
	Ethanol, salicylic acid

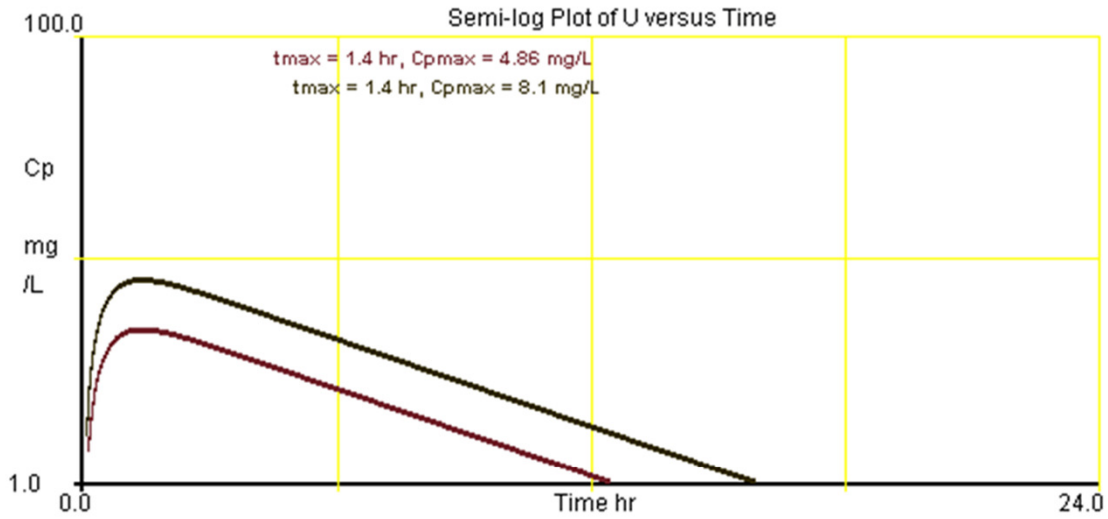
Kinetic plots (Cartesian scale)

Linear Plot of Cp *versus* Time after Oral Administration One Compartment Model

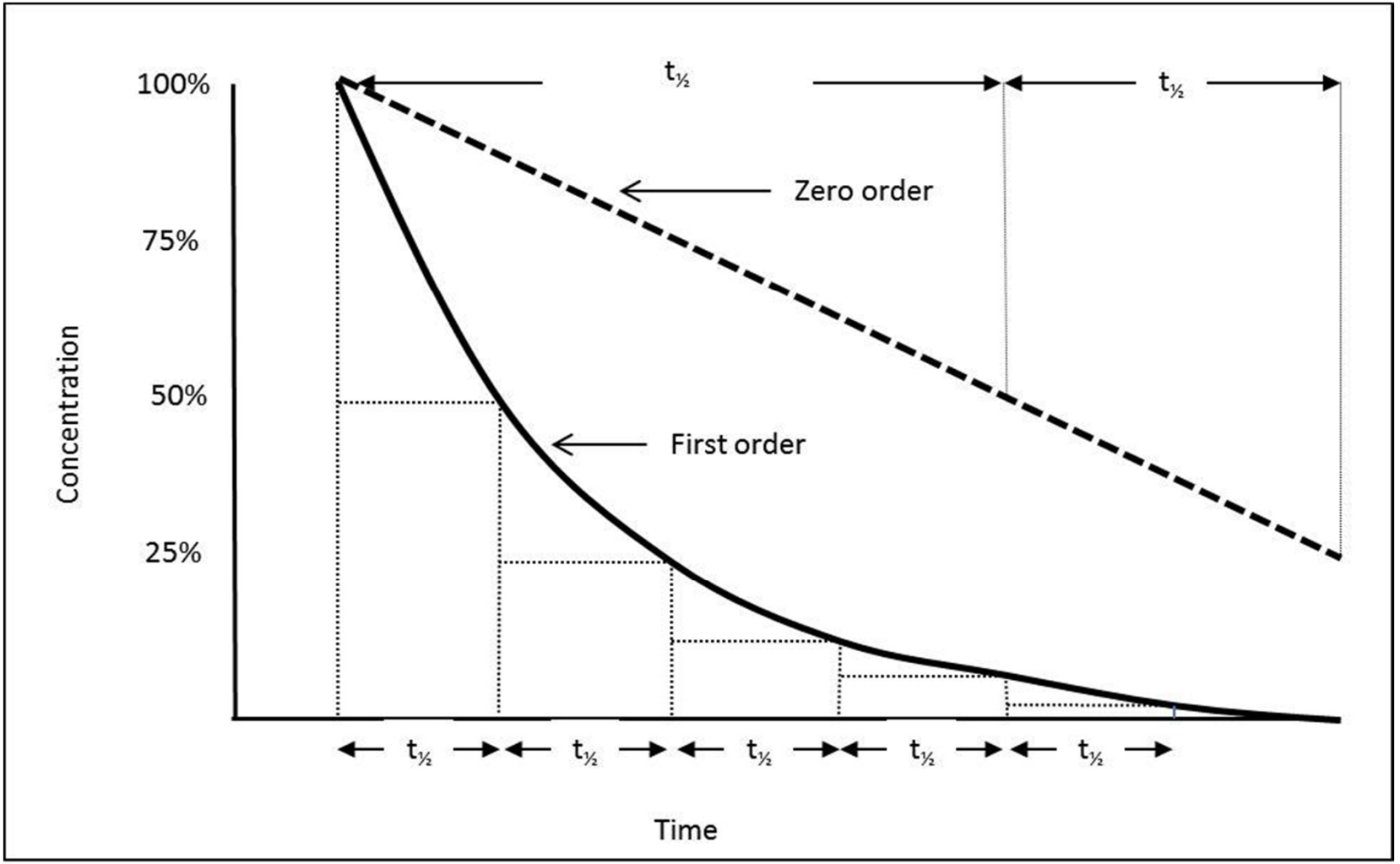


Kinetic plots (semi-log scale)

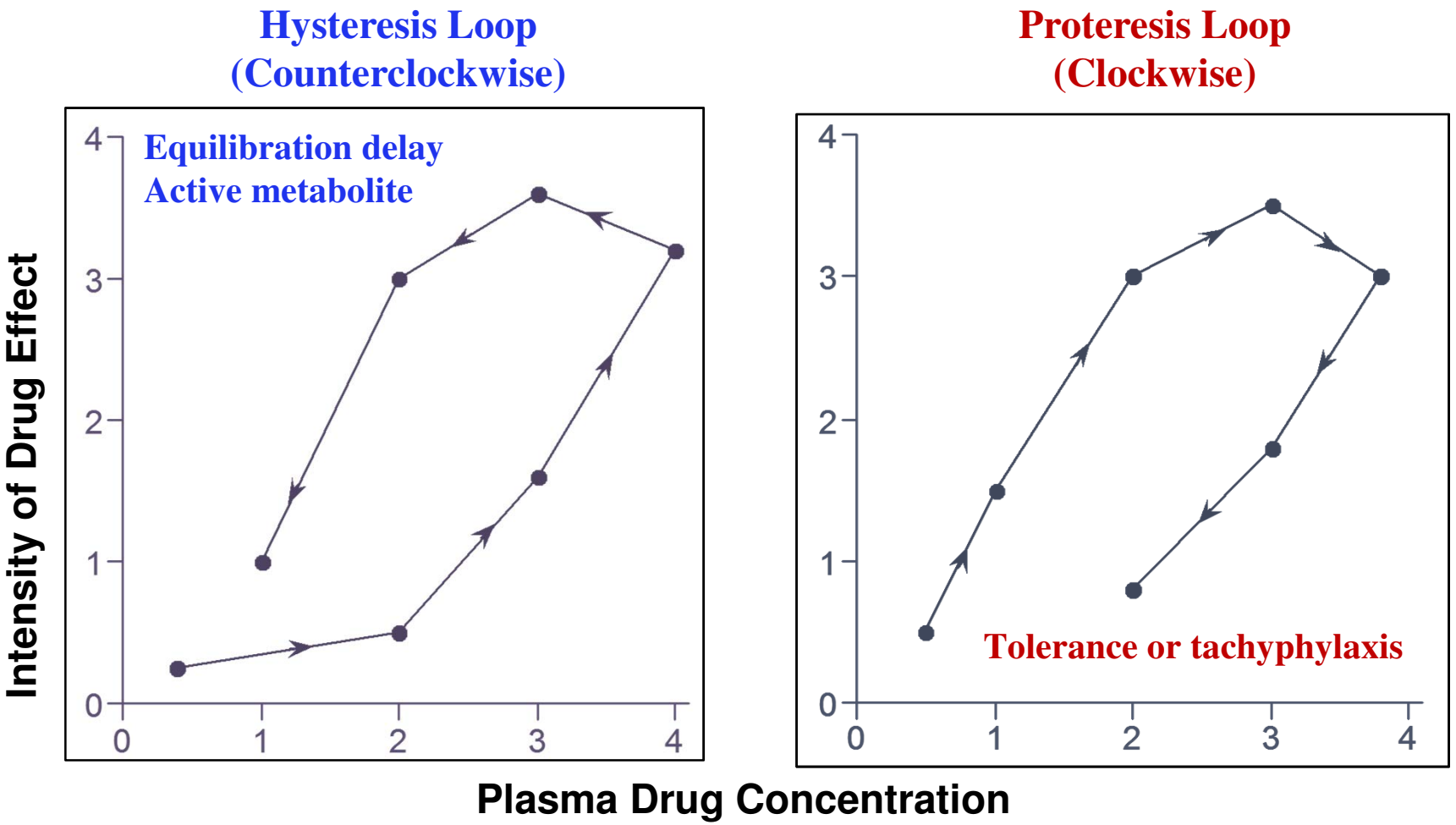
Semi-log Plot of Cp *versus* Time after Oral Administration One Compartment Model



Kinetic plots (0 verse 1st order)



Non-linear effects



Loading dose

- When a therapeutic plasma concentration is required rapidly this can be achieved through an initial loading dose that establishes the desired plasma concentration and avoids the long delay in establishment of $C_{ss.}$
- Often given as IV bolus dose or increasing first dose substantially
- Loading dose can be calculated from the desire maximal plasma concentration and the apparent volume of distribution

$$\textbf{Loading dose} = C_{max} * V_d$$

Bioequivalent drugs

Europe

Two medicinal products are bioequivalent if they are pharmaceutically equivalent or pharmaceutical alternatives and if their bioavailabilities after administration in the same molar dose are similar to such a degree that their effects, with respect to both efficacy and safety, will be essentially the same.

Bioequivalent drugs

USA

The FDA considers two products bioequivalent if the 90% CI of the relative mean C_{max}, $AUC_{(0-t)}$ and $AUC_{(0-\infty)}$ of the test (e.g. generic formulation) to reference (e.g. innovator brand formulation) should be within 80.00% to 125.00% in the fasting state.

Although there are a few exceptions, generally a bioequivalent comparison of Test to Reference formulations also requires administration after an appropriate meal at a specified time before taking the drug, a so-called "fed" or "food-effect" study.

A food-effect study requires the same statistical evaluation as the fasting study.

Pharmaceutically equivalent

Pharmaceutically equivalent if all three criteria are true:

- Have the same active ingredient(s)
- Are of the same dosage form and route of administration
- Have identical in API molar concentration

Pharmaceutically equivalent drug products may differ in:

- Shape
- Release mechanism
- Labelling (to some extent)
- Scoring
- Excipients (including colours, flavours, preservatives)

Supplementary information

The next few slides contain some supplementary information that is important to consider in pediatric and geriatric patients.
This data was obtained from the web based course of Boomer http://www.boomer.org/c/p1/index.html which is an excellent source of information and a good pharmacokinetic reference to access

PK import physiological differences between Neonates and Adults

	Neonate	Adult
Gastric acid output (mEq/10kg/hr)	**0.15**	**2**
Gastric emptying time (min)	**87**	**65**
Total body water (% of body weight)	**78**	**60**
Extracellular water (% of b.wt.)	**44**	**19**
Intracellular water (% of b.wt.)	**34**	**41**
Adipose tissue (% of b.wt.)	**12**	**12-25**
Serum albumin (gm/dL)	**3.7**	**4.5**
Glomerular filtration rate (ml/min/m2)	**11**	**70**

Hilligoss, D.M. (1980) "Neonatal Pharmacokinetics" in `Applied Pharmacokinetics', Evans, W.E., Schentag, J.J., and Jusko, W.J. eds., Applied Therapeutics, page 88

Pediatric Considerations

The physiology determining drug disposition change radically during biological maturation. Therefore drug absorption, distribution, metabolism and excretion are modified extensively throughout infancy and childhood. This means that drug disposition

a) changes during maturation
b) differs from biological norms
c) has large inter-patient variability.

Little data is available for the disposition of drugs in infants as studies in infants and young children are difficult to perform because of ethics and the limited amount of sample which can be collected.
The greatest changes occur in the first year, thereafter dose adjustments can be made based on weight without too many problems.

Pharmacokinetic development of dosage regimens for pediatric patients is often not practical. Dosing based on age, e.g. Young's rule for children older than 2 years is often applied

$$\text{Child Dose} = \frac{\text{age (yr)}}{\text{age (yr)} + 12} \cdot \text{adult dose}$$

Pharmacokinetic changes (pediatric)

Absorption

Infants have a relative achlorhydria; with gastric acid secretions reaching adult levels at age 3.

The bioavailability of acid labile penicillins is increased in newborns.

Delayed gastric emptying and irregular intestinal peristalsis leads to slower absorption of some drugs in infants and young children.

Distribution

Total body water as a fraction of body weight decreases throughout the first year of life. Extravascular fluid is higher at a young age. Distribution volumes expressed as volume per body weight tend to be larger in neonates and decrease during childhood. This has been observed for ampicillin, ticarcillin, and amikacin.

Binding to plasma proteins appears to be less in newborn infants compared with older children and adults. This appears to be true for both acidic and basic drugs.

The presence of competing substances, such as bilirubin in premature infants, complicates the picture.

Metabolism

The various pathways of drug metabolism mature at different rates, and therefore the ability of the newborn to metabolize drugs differs both quantitatively and qualitatively from that of older subjects.

No general rules can be developed and a few examples can illustrate the variety of effects observed.

Caffeine is very slowly metabolized in newborns. During the first month almost no metabolism occurs, with half-lives of about 4 days resulting from renal elimination, normally a minor pathway. Between 3 and 7 months, caffeine is metabolized similarly to adults and the half-lives change to adult values during this period.

For the similar compound theophylline the half-life was 13 to 29 hours for 8 low birth weight infants.

Glucuronidation is quite inefficient at birth, thus chloramphenicol which is normally glucuronidated in adults and has no major alternate metabolic pathway, the overall elimination is much slower in newborns compared with adults.

Sulfate conjugation is well developed at birth thus newborn paracetamol elimination, predominantly sulfation, is not greatly different from that of adult elimination.

For drugs which undergo M-M or saturable metabolism the effect of age is interesting.
For phenytoin, Km is not changed with age, but the maximum metabolism rate, Vm falls progressively with younger patients.

Excretion

Glomerular filtration and renal tubule function in premature infants and newborns is somewhat immature. GFR, normalized for body surface area, increases gradually reaching adult values at about 6 months.

Geriatric Considerations

Although geriatric patients constitute only 11% of the population in North America, they incur 30% of the total costs of drugs. Within the next 30 years these figures are expected to reach 16-18% and 40%, respectively.

Although the elderly are a major group of drug users, most drug studies are performed on patients or volunteers aged 55 years or less.

There is a sevenfold increase in drug toxicities as one ages from 20 to 79 years (from 3% at 20-29 years to 21% at 70-79 years).

Partially this increase is due to multiple medication – drug/drug interactions.

A significant increase in drug toxicities is due to incomplete understanding of changes in the ADME processes of drug disposition with aging.

Physiologic changes with age

	Altered Physiology	Clinical Consideration
Absorption	↓ gastric acid secretion ↑ gastric pH ↓ GI blood flow ↓ pancreatic trypsin ↓ GI motility	Altered dissolution rate, possible decreased absorption rate, time of onset delayed
Distribution		
Body Composition	↓ total body water ↓ lean body weight ↑ body fat (female > male)	Polar drugs tend to have ↓ Vd,lipid-soluble drugs ↑ Vd
Protein Binding	↓ serum albumin ↔ ↑ ∝ 1-GP ↔ ↑ gamma globulin ↔ ↓ RBC binding	↑ free fraction of acidic drugs, ↔ ↓ free fraction of basic drugs
Metabolism	↔ ↓ enzyme induction ↓ hepatic blood flow ↓ hepatic mass ↔ acetylation ↔ ↓ glucuronidation ↔ ↓ mixed function	decreased metabolism and clearance influenced by environmental factors (e.g.smoking,nutrition) oxidation system
Excretion	↓ GFR ↓ renal plasma flow ↓ active secretion	decreased renal clearance, ↑ half-life

Pharmacokinetic changes (geriatric)

Absorption

A number of physiologic changes which potentially alter drug absorption take place. GI motility, pH changes, etc. There has been little evidence, however, to suggest that this is of major consequence.

Reduced absorption in the elderly has been observed for some compounds which are actively absorbed (e.g. galactose, calcium, thiamine, and iron).

The absorption of most drugs by passive processes is not generally affected.

Only t_{max} was reduced for tolbutamide in the elderly versus young.

For other drugs studied, including l-DOPA, metoprolol, propranolol, cimetidine, and digoxin no changes were observed which could be ascribed to absorption alone.

Higher C_{max} values were observed in a number of cases, however, most of these changes could be explained by changes in distribution or clearance.

Distribution

Great changes in body composition occur as the patient ages.
Body fat increases from 15% to 30% and lean body weight decreases in proportion to total body weight.
This should give lower V_d values for drugs which stay in the central compartment, while lipid soluble drugs would have somewhat larger apparent V_d values.
The apparent volume of distribution for diazepam and chlordiazepoxide in the elderly is larger, whereas, the volumes for lorazepam and oxazepam were relatively unchanged. The lipid solubility of the first two drugs is much higher than for the second pair.

Although total plasma protein concentrations remain relatively constant, albumin concentrations are lower in the aged. The fraction of unbound phenytoin increases 25 to 40% in the aged, that would lead to increased clearance. In the case of diazepam it has been found that the percentage unbound could be correlated with age for females, but not in males.

Drug interactions based on protein binding, and other factors, can be more pronounced in the elderly because they tend to be taking more drugs.

Cardiac output in the elderly is reduced, thus distribution to the kidneys and liver are expected to be reduced. For high extraction drugs this could alter the overall elimination of the drug.

Metabolism

The liver is the major organ involved in metabolism and liver blood flow and liver mass tend to decrease with age.

Protein binding also is reduced, especially to albumin.

The third determinant of drug metabolism, intrinsic clearance is quite variable and dependent on the metabolic pathway.

Acetylation appears to be unchanged with age, isoniazid clearance is not altered.

It appears that for some drugs which undergo Phase I metabolism (oxidations, reductions) metabolism reduces with increasing age. Examples are lidocaine, phenytoin, propranolol, theophylline.

For drugs which undergo Phase II metabolism (conjugations) the metabolism does not appear to change greatly with age. E.g. isoniazid (acetylation), temazepam (glucuronidation).

Elimination

With increasing age the glomerular filtration process is reduced by a reduction in kidney size (20%), reduction in the number of nephrons (35%), reduction in the number of functioning glomeruli (30%), and a decrease in renal blood flow (40- 50%).

Serum creatinine is also decreased with age because of the reduced muscle mass. However creatinine clearance as a function of age and dosage adjustments can be made.

Drugs that require dosage adjustments in elderly patients include; the aminoglycosides, digoxin, lithium, methotrexate, quinidine, and the tetracyclines (except doxycycline).

Dosing recommendations in geriatric patients

The effects of age on drug disposition depend on the particular compound in question and the characteristics of the population being studied.

When evaluating geriatric studies **it is important to distinguish between long-term-care patients who are not considered to be healthy and the active who are old (age > 65 years maybe higher) but living in the community.**

Some of the changes ascribed to the elderly may be due to immobility of the patient or an underlying disease or diseases.

Also because of changing body composition between males and females it is often important to distinguish between these groups.

In terms of dosage regimen adjustment, for some drugs, such as the aminoglycosides dose adjustment is progressive with a steady change in creatinine clearance with age reflecting the similar change in the clearance of the drugs under question.