

# Pharmacology: General Principles

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**Pharmacology** - “The branch of medicine that deals with the uses, effects, and modes of actions of drugs”. (*The New Shorter Oxford English Dictionary*)

---- *what they do and how they do it*

A **drug** is “*any substance that brings about a biological change or effect on the body*”

Sources of most drugs:

- Plants
- Human-derived proteins/steroids
- Fungi/Bacteria
- Synthetic chemicals
- Recombinant proteins

## A drug can have multiple names

1. Chemical name
  - Compound present in the drug-necessary for chemists who are interested in SAR.
2. Generic name
  - The accepted name of the drug. Is present on all drug labels, publications.
3. Brand name
  - Trademark and copyrighted name given by the company.

## Drug Names

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### Chemical Name:

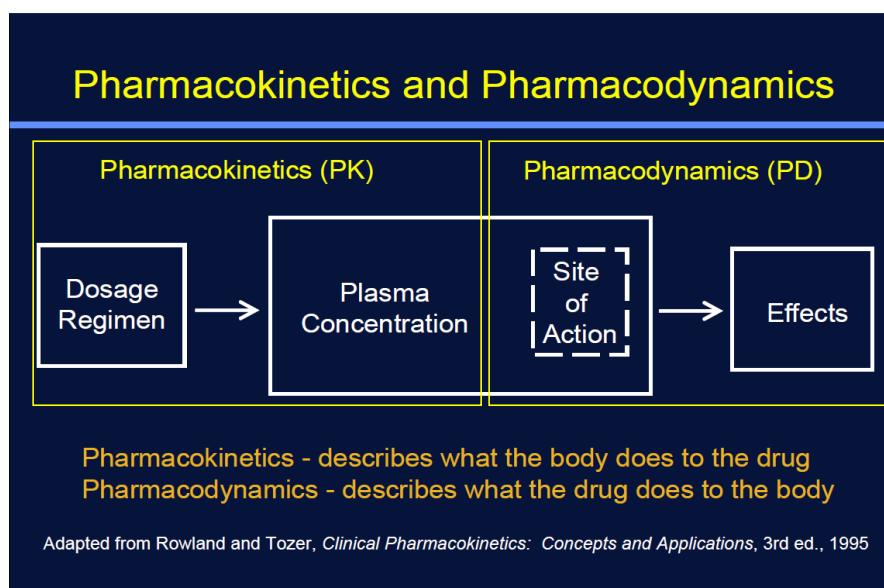
**N[2-[[[5-[dimethylamino, methyl]-2-furanyl]methyl]thio]ethyl]-N'-methyl-2-nitro-1,1-ethylenediamine hydrochloride**

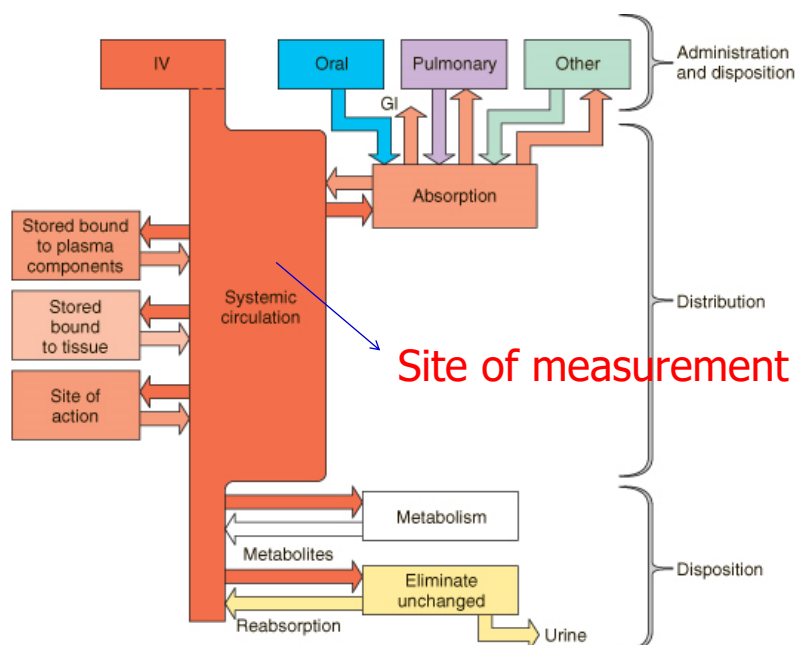
**Generic Name:    ranitidine**

**Trade Name:     Zantac<sup>®</sup>**

## Two disciplines of pharmacology

- Pharmacokinetics: study of what the body does to the drug
  - How does a drug get in? (**Absorption**)
  - Where does it go once it gets there? (**Distribution**)
  - What happens to it? (**Metabolism**)
  - How do you get rid of it? (**Elimination**)
- Pharmacodynamics: study of what the drug does to the body
  - How does it produce an effect?
  - Mechanism of action?





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## Definitions

### □ Absorption

- Process by which drug proceeds from the site of administration to the general circulation within the body

### □ Distribution

- Reversible transfer of a drug between the circulation and various body compartments.
- Note: Any drug that leaves the circulation and does not return has undergone elimination, not distribution

**Definitions****□ Elimination**

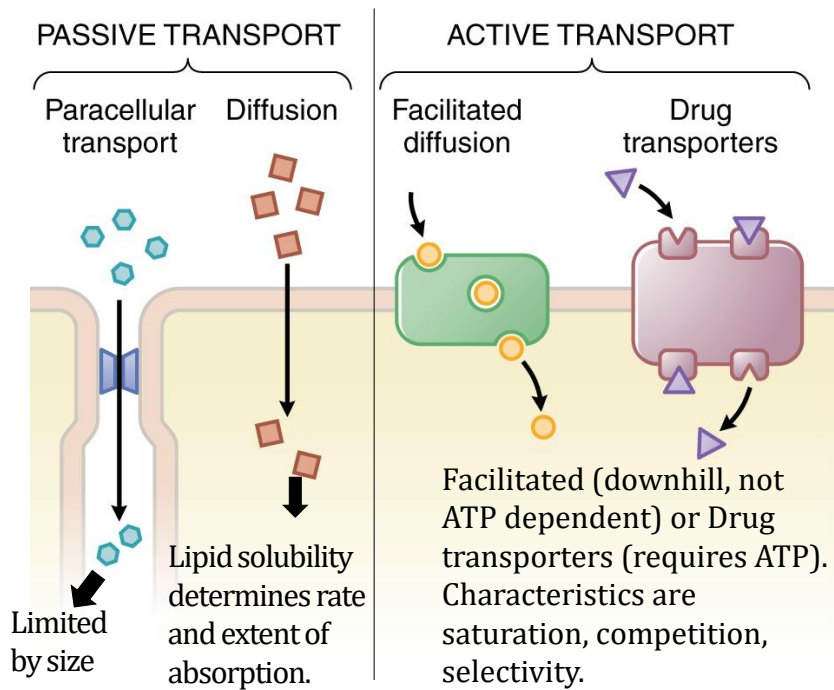
- Irreversible loss of drug from the general circulation
- Elimination = Metabolism + Excretion
- Metabolism- Chemical conversion
- Excretion- Irreversible loss of drug

## Absorption: Basic concepts

For a drug to produce a therapeutic effect, it must be **absorbed** from the site of administration into the bloodstream. Thus, drug molecules must cross a number of biological barriers and membranes (predominantly lipid).

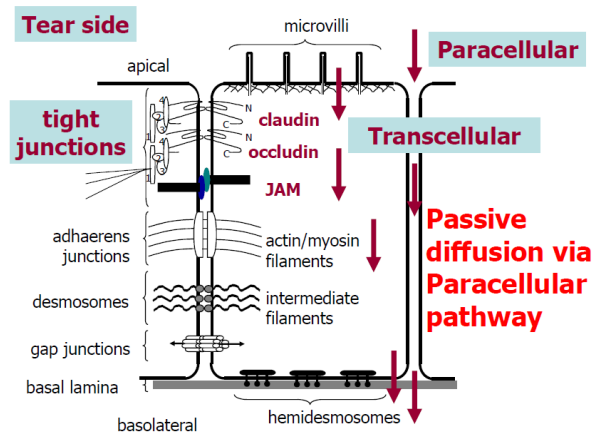
### Mechanisms by which drugs cross lipid membranes are

1. Passive diffusion (**more common**): *Transcellular or paracellular*
2. Carrier-mediated processes: *Facilitated diffusion, Active transport.*
3. Pinocytosis and Endocytosis



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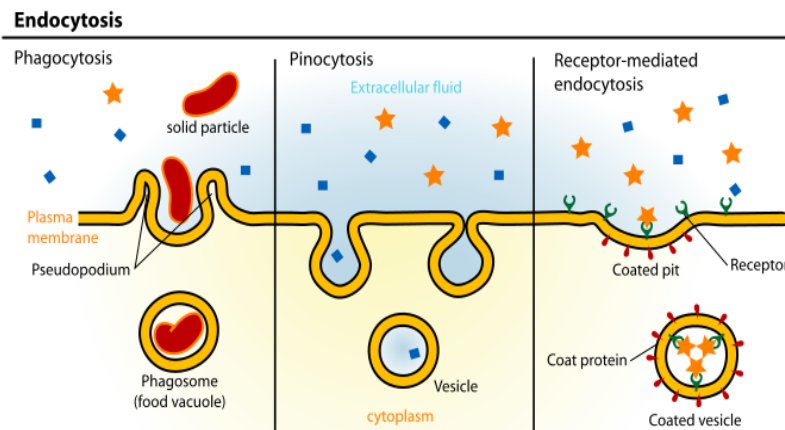
**Paracellular passive transport:**



**Factors influencing the permeability**

- ❑ Nature of cell-cell junctional complex
- ❑ Size of the drug (and not partition coeff)

## Pinocytosis and endocytosis are other mechanisms



Mainly for large molecular weight drugs

## Passive diffusion

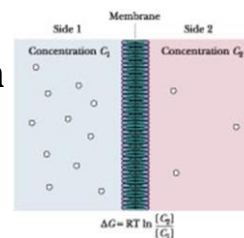
Described by Fick's law of diffusion

**Rate of drug transfer = P.A.DC**

P = Permeability coefficient

A = Surface area of contact

DC = Conc. gradient ( $C_1 - C_2$ ) (driving force)



**P** is a characteristic of both the drug molecule and the membrane barrier; Defined as

$$P = \frac{(\text{Diffusion coef.}) (\text{Partition coef.})}{\text{Membrane thickness}}$$

**Partition coefficient**

- A measure of lipophilicity; a large value of PC indicates higher solubility in lipids. So better absorption.

$$PC = \frac{\text{Conc. of unionized drug in octanol}}{\text{Conc. of unionized drug in buffer}}$$

### Partition coefficients

#### High

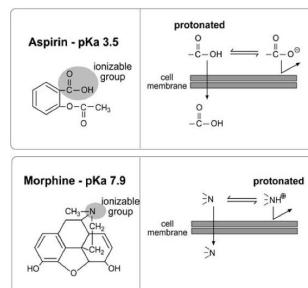
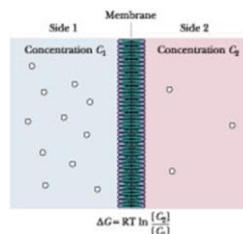
Hydrocarbons  
Anesthetics  
Alcohols  
Lipids  
Many drugs

#### Low

Carbohydrates  
Proteins  
Ionized molecules

## Factors influencing passive diffusion

- Rate of transfer =  $P \cdot A \cdot \Delta C$
- Lipid solubility of a drug is an important determinant of the extent of absorption.
- Unionized molecules (no charge) are lipid soluble, allowing for passive diffusion. Ionized (charged) molecules are not lipid soluble.

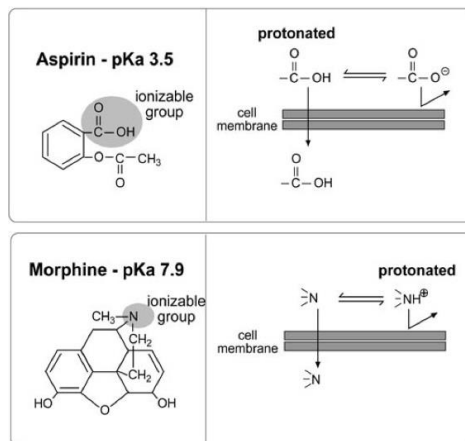


## Factors influencing passive diffusion

- The driving force for transport of a drug between two body compartments is the concentration gradient across the membrane separating the compartments.
- Lipid solubility of a drug is an important determinant of the rate of transfer and the extent of absorption. Drugs that are water soluble or poorly lipid soluble cannot cross the membrane unless they are small (about 200 Da).
- Other factors that influence rate of absorption include surface area and membrane thickness

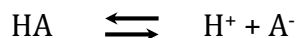
## The degree of ionization of a drug influences passive diffusion

- Most drugs are either **weak acids** or **weak bases**, containing ionizable groups.
- Un-ionized molecules (no charge) are lipid soluble, allowing for passive diffusion. Ionized (charged) molecules are not lipid soluble
- **Extent of ionization is dependent on pH** of the body compartment.



## Absorption of weak acids and bases

- An acid is a proton donor.



The **protonated** form is uncharged and **better absorbed**

- A base is a proton acceptor.



The **protonated** form is charged and **not well absorbed**.

The Henderson-Hasselbach equation can be used to calculate the ratio of uncharged/charged molecules:

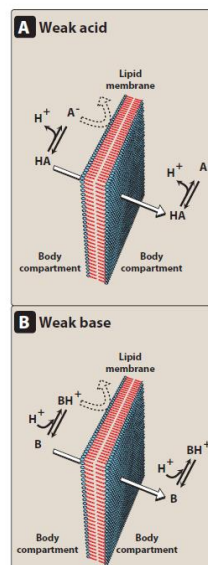
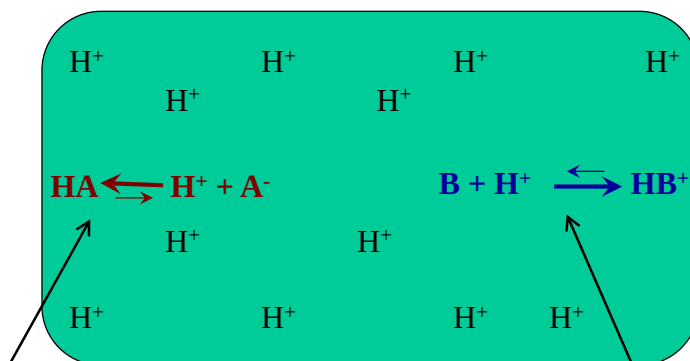


Figure 1.5  
A. Diffusion of the non-ionized form of a weak acid through a lipid membrane. B. Diffusion of the non-ionized form of a weak base through a lipid membrane.

## Influence of pH on ionization

In an acidic medium, e.g. stomach, where there are more protons...



**Weak acid :** More un-ionized in acidic environment. Absorbed better.

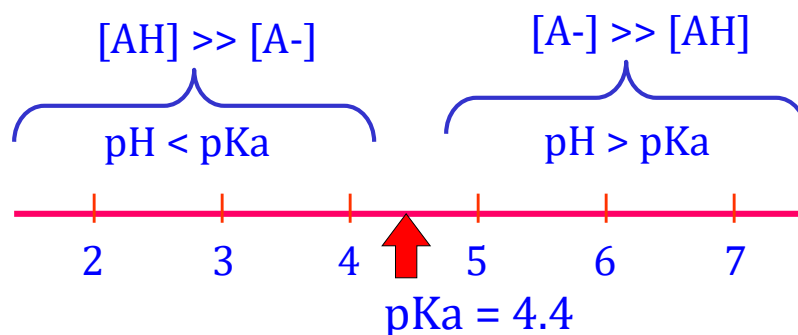
**Weak base:** More ionized in acidic environment. Poorly absorbed

Opposite in an alkaline environment: Weak bases are absorbed better



HH equation for a weak acid

$$\text{pH} = \text{pK}_a + \log [\text{A}^-]/[\text{AH}]$$

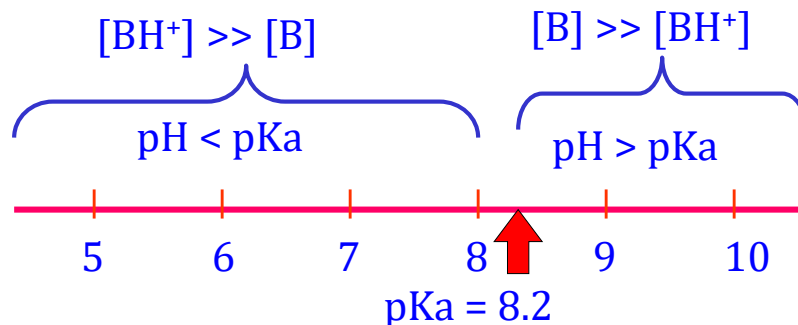


The pKa is defined as the pH at which the drug is half ionized.



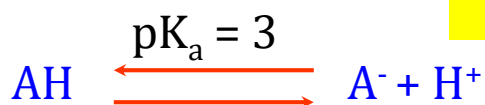
HH equation for a weak base

$$\text{pH} = \text{pK}_a + \log [\text{B}]/[\text{BH}^+]$$



The pKa is defined as the pH at which the drug is half ionized.

## Absorption of aspirin



$$\text{pH} = \text{pK}_a + \log [\text{A}^-]/[\text{HA}]$$

$\text{pH}_{\text{Gastric Juice}} = 1$ , then by HH Eq.,

$$1 = 3 + \log [\text{A}^-]/[\text{AH}]$$

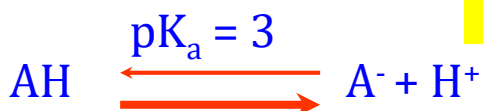
$$\log [\text{A}^-]/[\text{AH}] = -2$$

For  $[\text{AH}] = 1$ ,  $\text{A}^- = 0.01$ .

**In the stomach**

Most of the aspirin is un-ionized, so it gets absorbed

What happens to aspirin in plasma?



$$\text{pH} = \text{pK}_a + \log [\text{A}^-]/[\text{HA}]$$

$\text{pH}_{\text{Plasma}} = 7.0$ , then

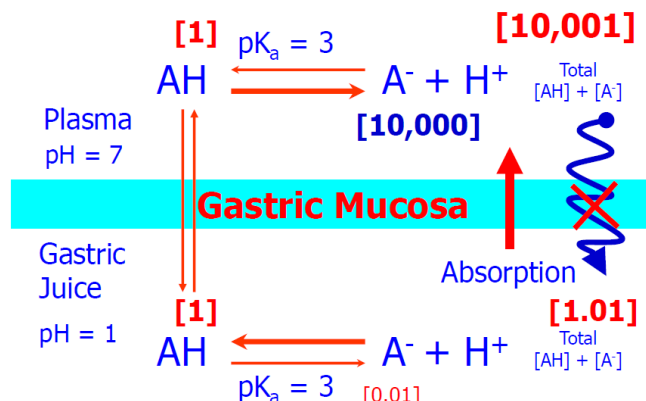
$$7 = 3 + \log [\text{A}^-]/[\text{AH}]$$

$$\log [\text{A}^-]/[\text{AH}] = 4$$

For  $[\text{AH}] = 1$ ,  $\text{A}^- = 10,000$ , so  $\text{A}^- + \text{AH} = 10,001$

Most of the aspirin is ionized, so it stays in plasma.

This is called ion-trapping → Aspirin is unlikely return to STOMACH; it gets trapped in the PLASMA



## Absorption of a drug is influenced by:

1. Physicochemical properties of the drug
  - Molecular size, partition coefficient, degree of ionization (influenced by pH).
2. Nature of the membrane that divides the absorption site from the blood
  - Surface area, tight junctions
3. Local blood flow
4. Route of administration

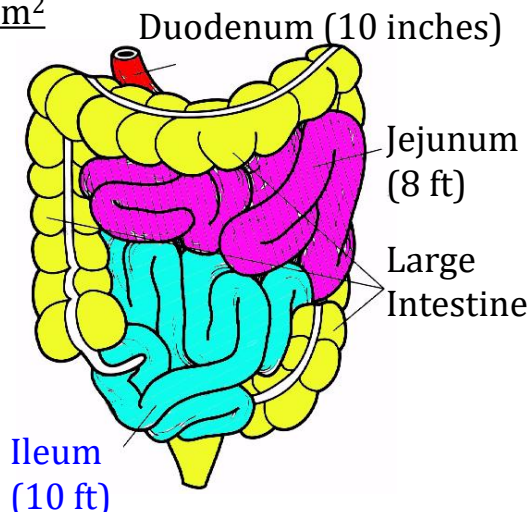
## 2. Surface area at the site of absorption

Small intestine = 200 m<sup>2</sup>

Stomach = 1 m<sup>2</sup>

Rate of drug  
transfer =  $P A DC$   
where

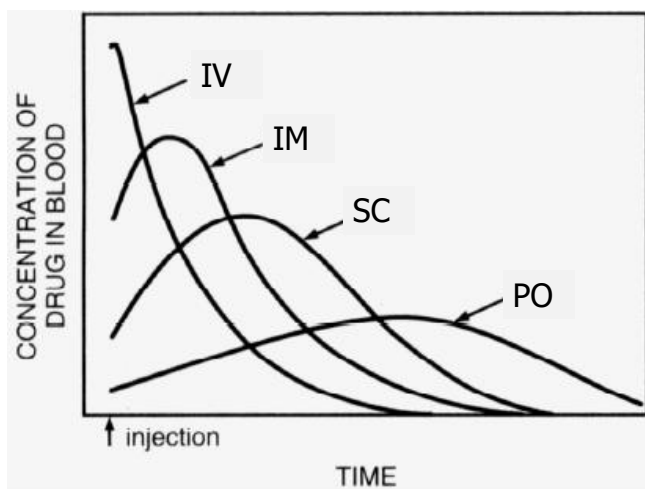
$P$  = Permeability  
coefficient  
 $A$  = Surface area  
 $DC$  = Conc. gradient  
( $C_1 - C_2$ )



## 3. Blood flow at the site of absorption

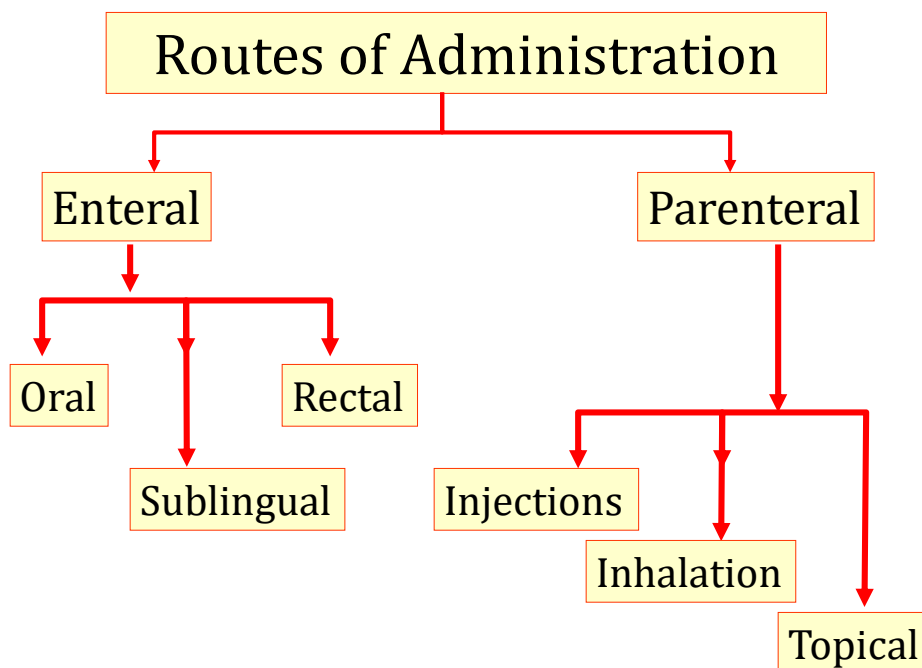
- Perfusion is the rate limiting step for drugs with high partition coefficient.
- Blood flow to some tissues is high and so absorption from these sites is faster.
  - E.g. Lungs, some muscles, small intestine but not skin, adipose tissue

#### 4. Route of administration affects the rate and extent of absorption



#### Factors deciding the choice of the route of drug administration

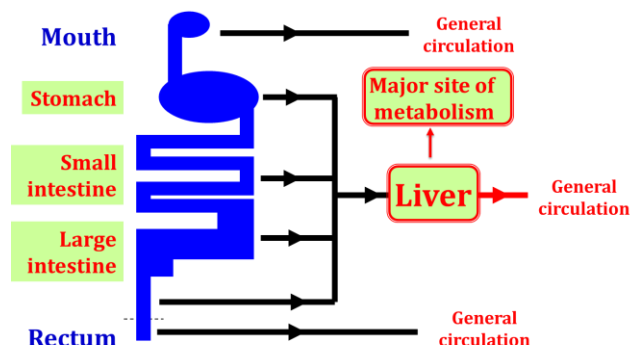
- ❑ **Physico-chemical properties** → whether solid, liquid, or gas, soluble or insoluble, irritant or non-irritant etc.
- ❑ **Type of desired effect** → LOCAL and SYSTEMIC effects?
- ❑ **Rapidity of desired effect** → Oral for routine Tx; IV for emergency Tx
- ❑ **Condition of the patient** → Conscious or unconscious; vomiting or not.



## Factors influencing oral absorption

- Gastric emptying rate (Influenced by food. Consumption of fatty food slows emptying). Surface area (**Small intestine = 200 m<sup>2</sup> Vs stomach = 1 m<sup>2</sup>**)
- Diseases (e.g. diarrhea).
- Drugs such as antacids, PPI, H<sub>2</sub> blockers (change the pH; HIV protease inhibitor, atazanavir + PPI: impaired absorption)
- Binding to other molecules in the gut contents (tetracycline and fluoroquinolones binds to divalent ions).
- Transporter blockade: (grapefruit juice can reduce plasma concentrations of ciprofloxacin, fexofenadine, beta-blockers)
- Too polar to undergo passive diffusion (aminoglycosides)
- Destroyed by stomach acid (e.g. insulin, some penicillin's)
- **“First pass” effect (Drug metabolism)**
- **Efflux due to P-glycoproteins.**

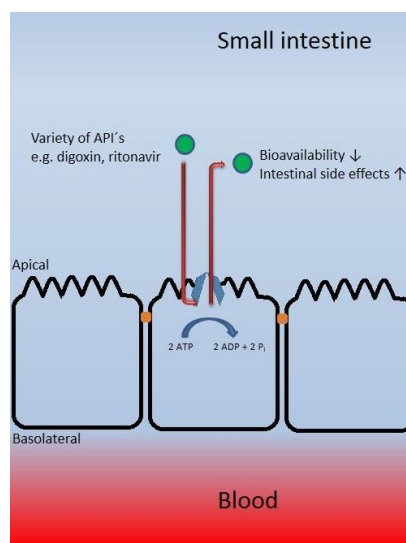
### First pass effect: drugs absorbed orally are initially transported to the liver via the portal vein



- Removal of a drug from portal circulation by metabolic enzymes in the liver so that amount reaching the systemic circulation is less than the amount absorbed across the GI tract. First pass metabolism also happens in the walls of the intestine which is rich in drug metabolising enzymes.
- Many drugs cannot be given ORALLY because of significant first pass effect.

### P-glycoproteins are efflux transporters

- P-glycoproteins **reduce transport of drugs** across the gastric mucosa.
- Not substrate-specific-can bind to different drugs.
- Another source of drug-drug interactions. (Example: Rifampicin and St John's wort induce P-glycoproteins and thereby decrease concentrations of digoxin.)



## A measure of absorption is Bioavailability (F)

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Fraction of the administered drug that reaches the systemic circulation → Signifies extent of absorption and first pass effect

Example: If a 100 mg drug is administered orally and 70 mg is absorbed into blood, then the bioavailability F, is 0.7.

For a dose given intravenously total dose reaches the systemic circulation. Therefore,  $F = 1$ .

### Oral bioavailability

| Drug        | F (%) |
|-------------|-------|
| Gentamicin  | < 5   |
| Verapamil   | 22    |
| Lignocaine  | 35    |
| Propranolol | 36    |
| Digoxin     | 75    |
| Valproate   | 100   |

Poor oral bioavailability can be due to:

- Failure of disintegration or dissolution.
- Chemical, enzymatic or bacterial attack.
- First pass metabolism in gut wall or liver.
- Poor lipid solubility or lack of transporters.
- P-glycoprotein efflux.

## Intravenous Administration

- ❑ **Absorption step is circumvented → No first-pass effect**
- ❑ Immediate effect. Good dosage control, Bolus/cont. infusion, good for highly polar, large molecules and peptides not absorbed upon oral ingestion. Suitable for large volumes.
- ❑ Excellent dosage control, but harder to reverse

## Intramuscular

- ❑ **No first-pass effect**
- ❑ Large volumes compared to SC
- ❑ Rapid absorption compared to oral/SC
- ❑ Absorption can be improved by co-injection of vasodilators

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## Subcutaneous

- ❑ **No first-pass effect**
- ❑ Self administration. Slow release. Can be painful.
- ❑ Drug in suspension or in solution (small doses < 2 mL)
- ❑ Example: Insulin, which is destroyed in the GI tract and in the liver.

## Sublingual

- **Rapid** because of good blood supply
- Lingual vein to superior vena cava  
→ **No first-pass effect**)
- Suitable for small doses, but sometimes inconvenient.
- Examples: Nitroglycerin for angina, ergotamine in eTx of migraine

## Inhalation

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- **Systemic effect**
  - Small lipid soluble molecules, which are absorbed easily across cell linings of the lung (Highly vascularized, large surface area of the alveoli)
  - **No First-pass effect**  
Example: General anesthetics ( $\text{N}_2\text{O}$  and halothane)
- **Local effect**
  - **Act directly on the lung tissue**  
Examples: Bronchodilators, Glucocorticoids

## Transdermal

- ❑ Nicotine Patches
- ❑ Estrogen patches (replace hormones in postmenopausal women)
- ❑ **No First pass effect**

## Rectal for Local/systemic response

- ❑ Drugs in the suppository form
- ❑ Systemic/Vomiting pts; Local/hemorrhoid (i.e., dilatation anorectal vessels)
- ❑ Some first-pass effect, but not much

## Topical Administration (Ocular)

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- ❑ **Most common**, self-administration
- ❑ Non-invasive
- ❑ **Not suitable for posterior structures** (i.e., retina, optic nerve, and vitreous)
- ❑ Not suitable for macromolecules
- ❑ Loss through the nasolacrimal system; reaches systemic circulation
- ❑ Variable bioavailability because only a very small fraction (< 1%) penetrates cornea

## Definitions

### □ Absorption

- Process by which drug proceeds from the site of administration to the site of measurement within the body

### □ Distribution

- Reversible transfer of a drug to and from site of measurement

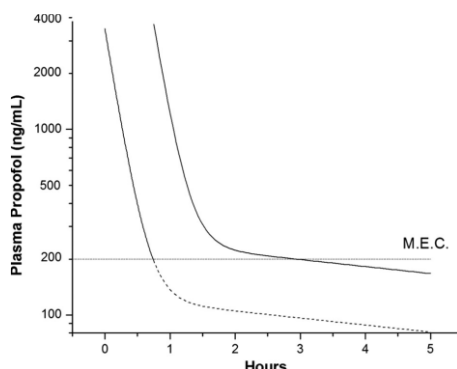
## Distribution

### Factors that influence distribution of drugs from the general circulation to other tissue compartments

1. Size, lipid solubility and ionization (see previous lecture on Absorption)
2. Blood perfusion rate
3. Capillary permeability
4. Binding of drugs to plasma proteins
5. Binding of drugs to tissue components

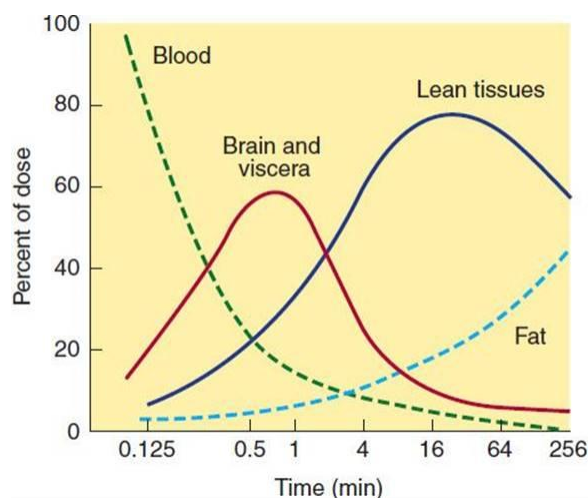
## 2. Blood perfusion rate

- Drugs reach the majority of tissues via the general circulation. Tissues that receive more blood receive more drug initially. Brain, liver, kidneys, lungs > skeletal muscle > fat.



Brain receives propofol rapidly, because it is highly vascularized. After a while, propofol is redistributed from the brain and plasma to other poorly perfused tissues, and then slowly eliminated. A single dose of propofol provides sufficient sedation for short-term procedures.

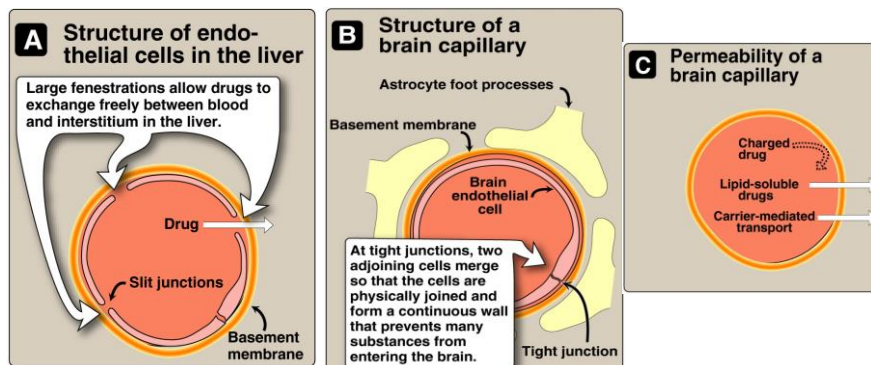
## Propofol Redistribution



Katzung and Trevor Basic and Clinical Pharmacology, 13th Ed. Copyright © 2015 by McGraw-Hill Education

### 3. Capillary permeability

- In liver and spleen, the capillaries are very leaky.
- In other tissues, selective capillary permeability varies
- In brain, tight junctions prevent drugs from entering freely.
  - Only lipophilic drugs diffuse across brain capillaries (unless they are actively transported across).



### 4. Binding to plasma proteins

- Two plasma proteins are of importance: **Albumin** (for drugs that are weak acids),  **$\alpha$ -glycoproteins** (for basic drugs).
- Bound drugs are **NOT pharmacologically active**, **NOT diffusible**, **NOT metabolized**, and **poorly excreted**.
- Drug binding to plasma proteins is reversible. A dynamic equilibrium between free drug and the bound form exists.
- Important in some diseases. (e.g. when albumin levels decrease or  $\alpha$ -glycoprotein levels increase).

## 5. Binding to tissue components

- Many drugs can bind to tissues, including
  - Eye : chlorpromazine to melanin
  - Fat: Thiopental and many more drugs
  - Lung: Anti-histamines
  - Bone: Tetracycline.
- Can serve as a depot.
- Can lead to **abnormal volumes of distribution**.

**A measure of the extent of drug distribution is Apparent Volume of Distribution (V<sub>d</sub>)**

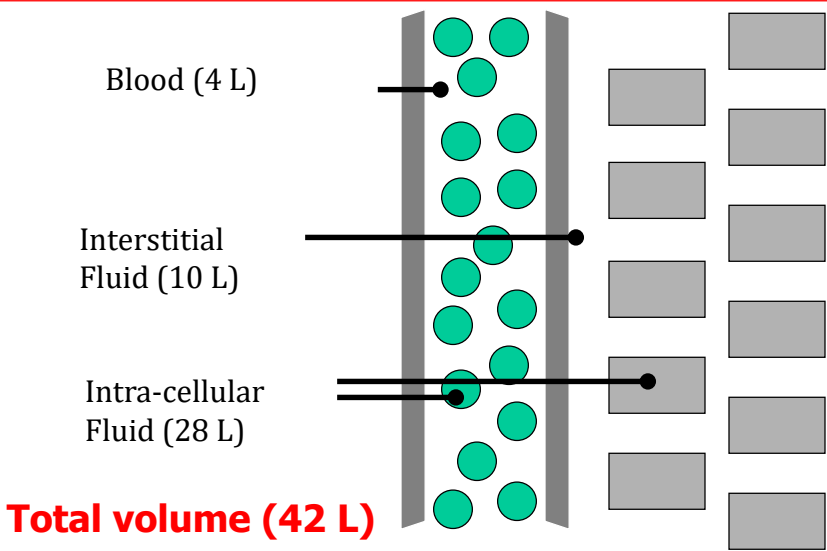
- It is the volume that a drug seems to distribute into. **Not an actual volume!** Only a multiplication factor to convert amounts to concentrations.
- A measure of the tendency of a drug to move out of the blood plasma to some other site.

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

← Total amount of drug (mg)

← Plasma concentration (mg/L)

### Actual Volume of body fluids

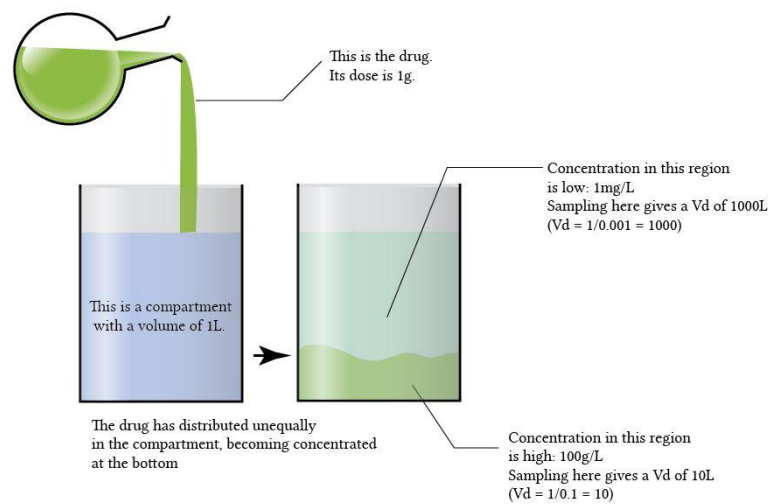
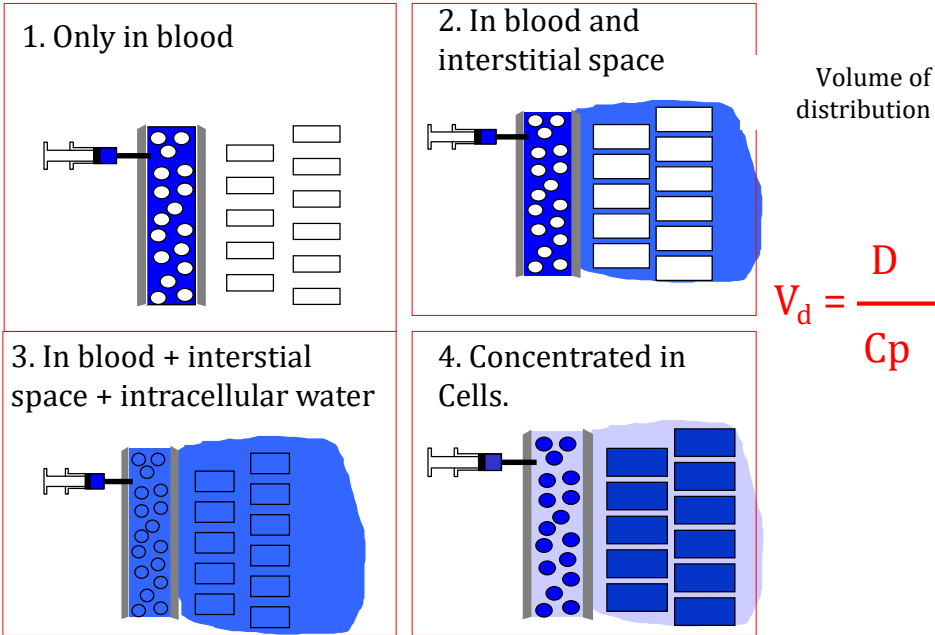


### Volumes of distribution of different drugs

|              |          |
|--------------|----------|
| Warfarin     | 7 L      |
| Gentamicin   | 16 L     |
| Theophylline | 35 L     |
| Cimetidine   | 140 L    |
| Digoxin      | 510 L    |
| Mianserin    | 910 L    |
| Quinacrine   | 50,000 L |

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

Very different from the actual volumes!  
Why? **Because drugs accumulate in tissues**



<https://derangedphysiology.com/main/cicm-primary-exam/required-reading/pharmacokinetics/Chapter%20202/volume-distribution>

## Calculation of Vd.

Vd depends upon body size.

Often quoted as L/kg (Litres per kg body weight)

e.g. Vd for theophylline = 0.48 L/kg

Therefore, for a adult of 60 kgs,  $V_d = 0.48 \text{ L/kg} \times 60 \text{ kg} = 28.8 \text{ L}$

A dose of analgesic (50mg) is administered i.v. and a blood sample is taken shortly afterwards. The initial concentration of analgesic in the blood sample is  $0.85 \mu\text{g.ml}^{-1}$ .

Calculate the volume of distribution of the analgesic (in Litres).

$$\begin{aligned} V_d &= D/C_p \\ &= 50\text{mg} / 0.85 \mu\text{g.ml}^{-1} \\ &= 50,000 \mu\text{g} / 0.85 \mu\text{g.ml}^{-1} \\ &= 58,824 \text{ ml} \\ &= 59 \text{ Litres} \end{aligned}$$

## Calculation of $V_d$

Example: Digoxin in a 70 kg. individual

- Let us say, DOSE = 0.5 mg (IV bolus), then reported initial concentration,  $C_p$  is  $0.714 \mu\text{g/L}$

$$V_d = \frac{0.5 \text{ mg}}{0.714 * 10^{-3} \text{ mg/L}} = 700 \text{ L}$$

- ~16x volume of body fluids ( $\sim 42 * 16$ )
- Why? Because digoxin is lipid soluble and distributes mostly into muscle and adipose tissue

## Volume of distribution ( $V_d$ )

- Drugs of large MW and/or having a tendency to bind to plasma proteins distribute predominantly into plasma. For such drugs, max  $V_d$  = 4 L.
- Drugs of low MW and which are hydrophilic, distribute predominantly into extracellular fluid (i.e., blood + interstitial). For such drugs max  $V_d$  = 14 L.
- Drugs rarely associate exclusively with only one of the fluid compartments. Binding to cellular components such as lipids in adipocytes and cell membranes, proteins within cells and nucleic acids increases  $V_d$ .

## $V_d$ is important for designing the dosing regimen (later)

- It is the only parameter relating the **dose** to the **plasma concentration**
  - Useful for determining the appropriate dose. Knowing  **$V_d$  and the effective plasma concentration** will help figure out the dose to give..
- Together with **Clearance**, it determines the overall elimination rate constant and therefore the half-life of the drug in the body.

## Definitions

### ❑ Elimination

- ❑ Irreversible loss of drug from the general circulation
- ❑ Elimination = **Metabolism** + **Excretion**
- ❑ Metabolism- Chemical conversion
- ❑ Excretion- Irreversible loss of drug

## Drug Metabolism (biotransformation)

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- ❑ Major mechanism for the termination of drug action (↓ **duration of action** & ↓ **intensity of action**)
- ❑ **Liver** is the dominant organ of metabolism, but enzymes are also present in the GI wall, kidneys.
- ❑ Mediated by many enzymes.
- ❑ Enzymes involved in metabolism are distinct from those involved in the metabolism of proteins, carbohydrates, and lipids.
- ❑ Facilitates elimination of drugs; Metabolites are polar; Less renal re-absorption.
- ❑ Metabolites are generally inactive, but not always!

## Metabolism: Two phases

- **Phase I: (activation/detoxification)**
  - Biotransformation reactions: oxidation, reduction and hydrolysis, often mediated by cytochrome P450 class of enzymes
  - Often convert the parent drug to a more polar metabolite, which can then be eliminated by kidney. But not always (prodrugs).
- **Phase II: (detoxification)**
  - Conjugation with glucuronic acid and glutathione; reactions mediated by a variety of transferases.
  - Reactions most often abolish biological activity and add more polarity
  - Very water soluble: Facilitate elimination by kidney.

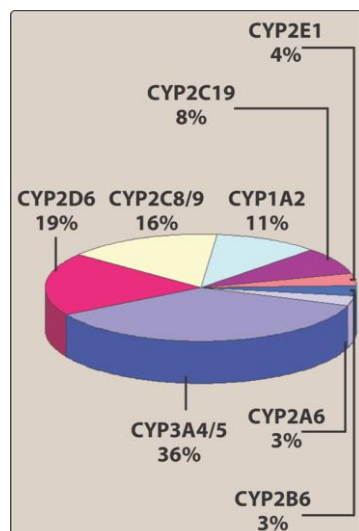
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Not always sequential. Drugs can directly enter into Phase II

## Effects of drug metabolism: Prodrugs

- Conversion of an inactive drug to active drug by action of enzymes involved in drug metabolism
- Examples
  - Cortisone to hydrocortisone
  - Chloral hydrate to trichloroethanol
  - Azathioprine to mercaptopurine
  - Codeine to morphine
  - Clopidogrel to an active metabolite
  - Valacyclovir to acyclovir

## Drugs are metabolized in liver by different CYP450 isozymes



CYP3A4 is also present in the gut wall, leads to metabolism of some drugs such as clonazepam

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## Clinical relevance of drug metabolism

Dose and frequency of administration required to achieve effective therapeutic blood and tissue levels vary in different patients due to:

1. Genetics (polymorphisms in Phase 1 and 2 enzymes)
2. Diet and environmental factors (e.g. grapefruit juice, smoking, exposure to pesticides).
3. Age
  - Fetuses and newborns generally do not metabolize drugs as well as adults.
  - Drug metabolizing activity **decreases** with age.
4. Gut microbiota
5. Liver disease affects metabolism of many drugs.
6. Induction and inhibition of CYP enzymes by drugs.

## CYP450 Polymorphisms –genetic variations in the population

- The most common P450 polymorphism in humans impacts **CYP2D6** expression. ~ 7% to 10% of the Caucasians and 2% to 5% of Africans have a genetic variant that leads to limited activity of CYP2D6.
- CYP2D6 deficient people are slow metabolizers of beta-blockers, neuroleptics, antidepressants and codeine. Increased amphetamine toxicity can occur in patients with decreased CYP2D6 activity.
- CYP2D6 ultra-metabolizers experience excessive sedation and even respiratory depression in response to codeine
- A **CYP2C19** variant allele is associated with increased transcription and thus higher CYP2C19 expression. Such patients can have higher incidence of bleeding while taking clopidogrel (a prodrug).

## Drug metabolism: Important source of drug-drug interactions

### □ Drugs can induce elevation of CYPs

- EtOH induces CYP2E1
- Barbiturates
- Phenytoin - anticonvulsant
- Cigarettes
- Rifampicin
- St John's Wort

### □ Drugs can inhibit CYPs

- Quinidine inhibits CYP2D6
- Chloramphenicol
- Erythromycin
- Grapefruit juice.

Examples of drugs that induce CYP isozymes

| Isozyme: CYP2C9/10                                |                           |
|---------------------------------------------------|---------------------------|
| COMMON SUBSTRATES                                 | INDUCERS                  |
| Warfarin<br>Phenytoin<br>Ibuprofen<br>Tolbutamide | Phenobarbital<br>Rifampin |

| Isozyme: CYP2D6                                         |          |
|---------------------------------------------------------|----------|
| COMMON SUBSTRATES                                       | INDUCERS |
| Desipramine<br>Imipramine<br>Haloperidol<br>Propranolol | None*    |

| Isozyme: CYP3A4/5                                                        |                                                                          |
|--------------------------------------------------------------------------|--------------------------------------------------------------------------|
| COMMON SUBSTRATES                                                        | INDUCERS                                                                 |
| Carbamazepine<br>Cyclosporine<br>Erythromycin<br>Nifedipine<br>Verapamil | Carbamazepine<br>Dexamethasone<br>Phenobarbital<br>Phenytoin<br>Rifampin |

Example of drug induction:CYP3A4 Case

45 y/o C. male with schizophrenia on a stable dose of Haloperidol decanoate 200 mg/month. He developed a seizure disorder and was placed on phenytoin by a neurologist. Within 2 months, the patient had a **worsening of his psychotic symptoms** and required hospitalization. Although baseline haloperidol levels were not obtained, while on phenytoin, it was low (less than 2 ng/ml).

**Mechanism:** CYP3A4 induction by phenytoin decreases haloperidol levels (metabolized by 3A4, other P450s and phase II).

### Example of drug inhibition: Simvastatin-Itraconazole Interaction Vignette

A 52-year-old woman had been taking simvastatin 40 mg once a day for the treatment of hypercholesterolemia for several years, and tolerated the treatment well. Following a diagnosis of onychomycosis, she was prescribed itraconazole 200 mg once a day by her dermatologist for the treatment of the local fungal infection. On the third day following the initiation of itraconazole treatment, the patient developed severe muscle pain and was admitted to hospital with the suspicion of rhabdomyolysis.

**Mechanism:** Simvastatin is metabolized mainly by CYP3A and therefore is susceptible to interactions with CYP3A inhibitors such as itraconazole. Itraconazole increased the peak serum concentrations (C<sub>max</sub>) and total exposure (AUC) of simvastatin by 19-fold.

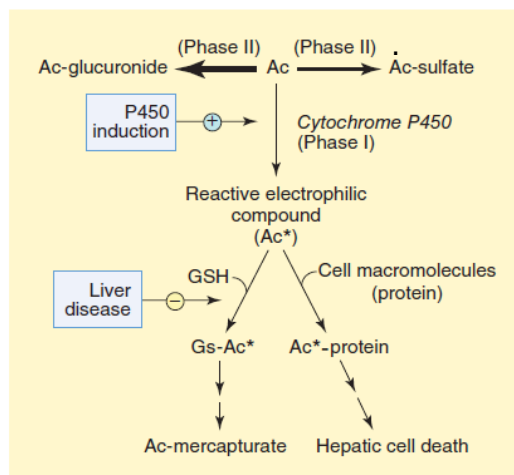
### Many other examples

- Amoxicillin, cephalixin and sulfamethoxazole/trimethoprim can induce bleeding in patients taking warfarin (effect on CYPs and on gut bacteria).
- Antimicrobial therapy with metronidazole, doxycycline or chloramphenicol can be less effective in patients who are on long-term medication with another inducing drug.
- Risk of statin induced myopathy is increased by grapefruit juice, fibrates, niacin, erythromycin, azole anti-fungals and HIV -protease inhibitors, due to inhibition of statin metabolism.
- Metronidazole inhibits the enzyme aldehyde dehydrogenase resulting in nasty symptoms if the patient drinks alcohol

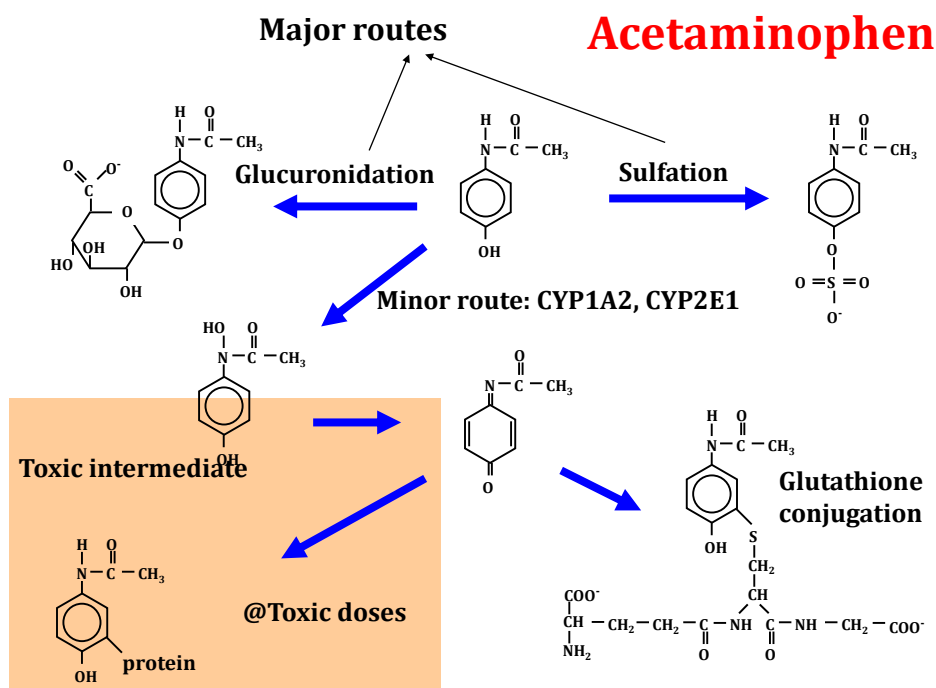
## Acetaminophen toxicity: CYP2E1 Case

A 26-year-old man who has been binge drinking for several years decides to stop. After 2 days of abstaining, he takes **5 tablets of acetaminophen 650 mg**. 48 hours later, he is brought to the ER with **symptoms of hepatitis**.

### Metabolism of Acetaminophen



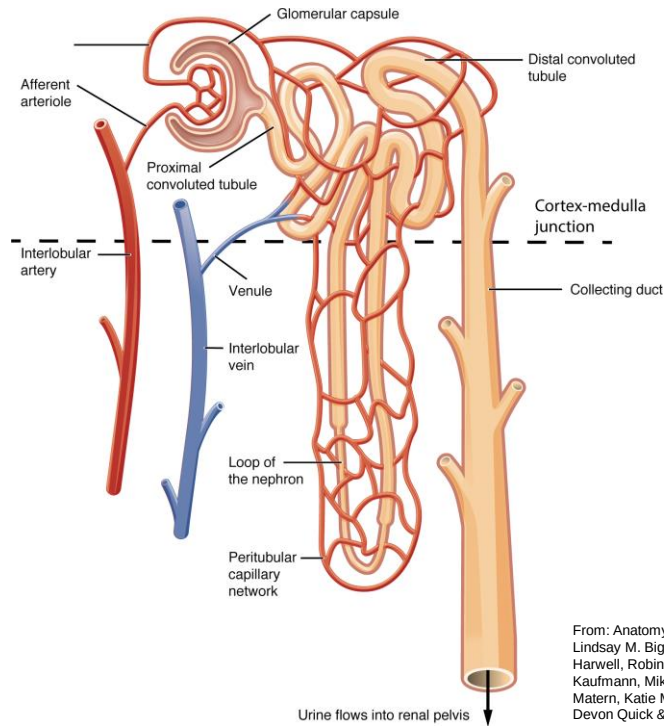
**Mechanism:** Metabolism of acetaminophen (Ac) to harmless conjugates or to toxic metabolites. Ac\* is the toxic, reactive phase I metabolite, N-acetyl-p-benzoquinoneimine. Transformation to Ac\* occurs when hepatic stores of sulfate, glucuronide, and glutathione (GSH, Gs) are depleted or overwhelmed or when phase I enzymes have been induced. Chronic alcoholism induces CYP2E1.



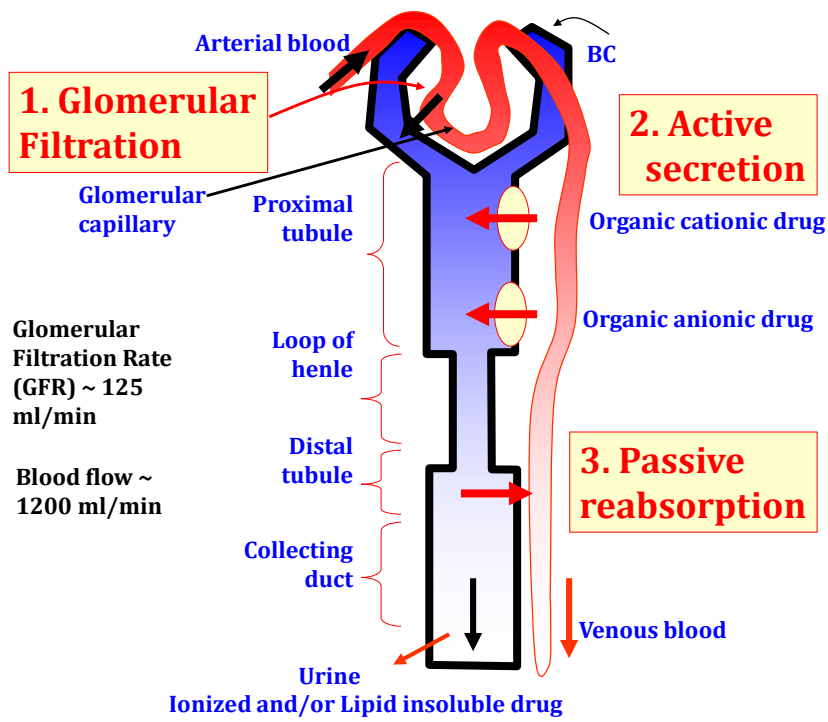
## Routes of Drug Excretion

- ❑ **Renal**
- ❑ GI tract (Biliary and fecal excretion)
- ❑ Pulmonary (e.g. anesthetic gases, alcohol)
- ❑ Tears
- ❑ Milk; important while nursing an infant
  - ➔ Highly lipid soluble drugs appear in milk
  - ➔ Examples: Barbiturates, Salicylates, Morphine, Steroids, Nicotine, Caffeine, EtOH

The functional nephron



Drug elimination by kidney



## Glomerular filtration

- Passive process (Pressure driven)
- Protein-free ultra-filtrate
- Protein bound and large drugs are not filtered (e.g., heparin).
- Rate of filtration is variable  $\sim 125$  mL/min; depends on many factors
- Creatinine clearance used to estimate the glomerular filtration rate (GFR)

## Proximal tubule secretion

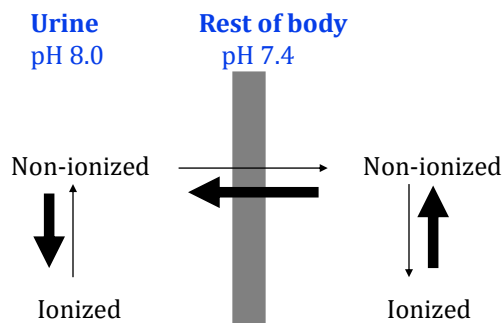
- Active transport of drug from blood to tubule. Is carrier mediated (can saturate!) and ATP dependent.
- Organic cations (e.g. morphine, atrophine) and anions (e.g. acetazolamide) are transported in this manner via different mechanisms.
- Main method by which amoxicillin, cephalixin, acyclovir are eliminated. Dosage adjustments are required if patients has kidney disease
- Potential for drug interactions: Example: Probenecid, an inhibitor of active secretion of organic ions, can block active loss of penicillin and acyclovir, causing increases in antibiotic and antiviral levels in the plasma

## Tubular reabsorption

- Lipid soluble drugs are reabsorbed from tubule to blood, mostly by passive diffusion.
- Highly susceptible to process of metabolism which makes drugs water soluble, which can then be excreted by kidney.
- Influenced by % ionization
  - Weak acids reabsorbed at low pH (i.e., increased urinary pH with sodium bicarbonate leads to increased drug excretion)
  - Weak bases reabsorbed at high pH (i.e., decreasing urinary pH with ammonium chloride leads to increased drug excretion)

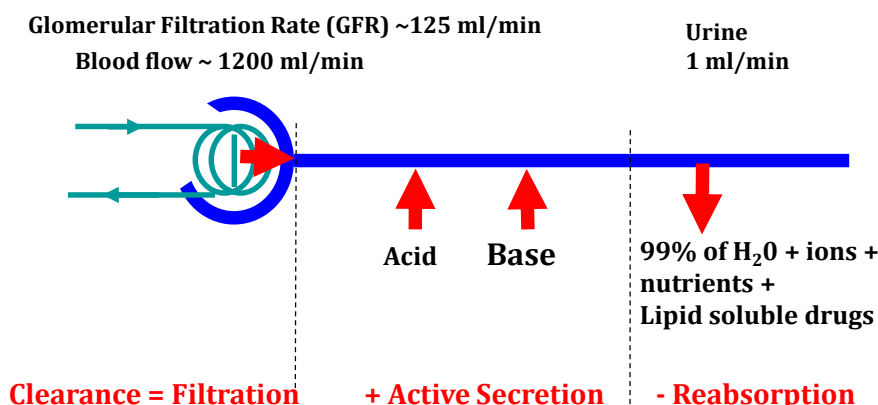
## Example of ion trapping to treat overdose of a weak acid

Urine pH varies (4.5 - 8.0). Sodium bicarbonate may be given to make the urine alkaline



Barbiturate moves into urine - eliminated from body.

## Renal Elimination: summary

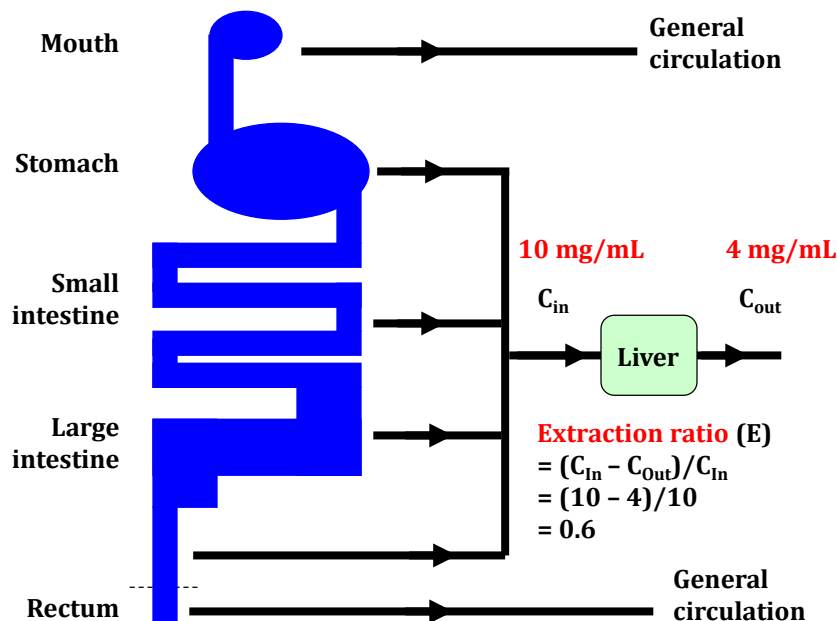


If a drug is solely eliminated from the body by glomerular filtration, and it is not actively secreted or reabsorbed, then it means that kidney is completely able to remove the amount of the drug contained in 125 mls of blood in 1 minute

## Clearance

- It is the **volume of blood** from which a drug is **irreversibly** removed per unit of time. The main parameter that limits the time course of action of drugs. **Units: ml / min (/kg)**
- Assume that the kidney or liver can completely get rid of a drug from 100 mL of blood in 1 hr, then **clearance** = 100 mL/hr.
- The extent to which **clearance** is performed by an organ (i.e. liver or kidney) **cannot exceed blood flow to the organ**.
- Whole body (systemic) clearance of a drug is the sum of clearance of that drug by all organs (e.g. liver, kidney, lungs etc.).

## Blood drainage from G.I.T.

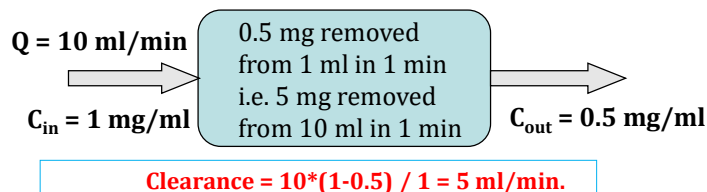


## Clearance

- The clearance (CL) by an organ depends on the blood flow (Q) and can be calculated by the following equation:

$$CL = Q \cdot E = Q(C_{in} - C_{out}) / C_{in}$$

Q is the blood flow,  $C_{in}$  and  $C_{out}$  are the blood concentrations before and after elimination by the organ, and E is the extraction ratio.

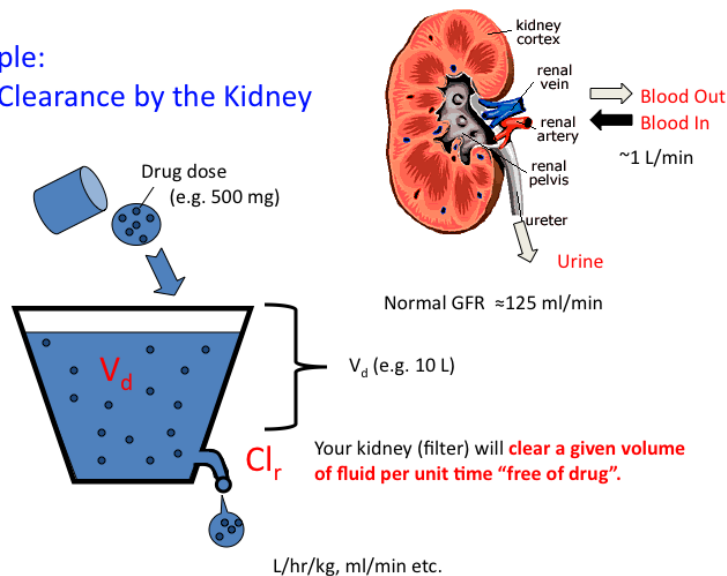


- Clearance of a drug can also be thought of as the rate of elimination normalized to the concentration of drug in plasma.

$$\text{Clearance} = \text{rate of elimination} / \text{plasma concentration}$$

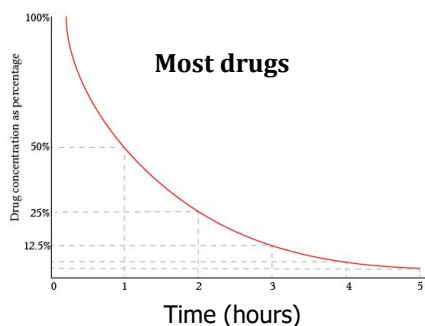
$$\begin{aligned} \text{Rate of elimination} &= Q \cdot C_{in} - Q \cdot C_{out} = Q (C_{in} - C_{out}) \\ &= 10 (1 - 0.5) = 5 \text{ mg / min} \end{aligned}$$

### Example: Drug Clearance by the Kidney



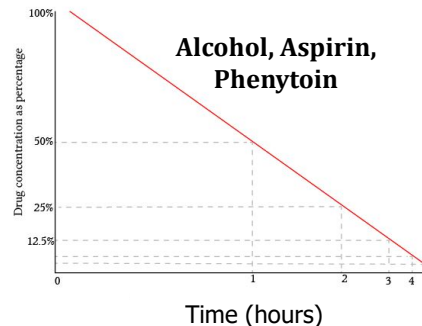
## Kinetics of elimination

### First order kinetics



rate of elimination proportional to plasma concentration. Constant fraction of drug eliminated per unit time. Half-life is independent of plasma drug conc ( $t_{1/2} = 0.693/k$ ).

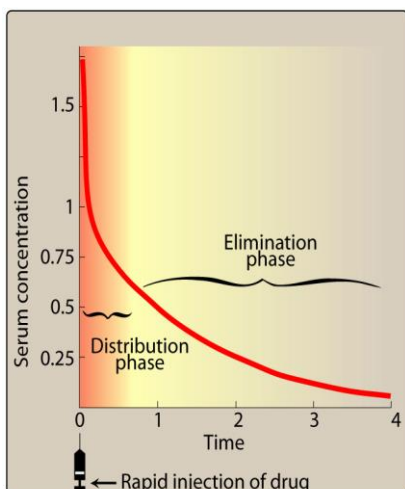
### Zero order kinetics



constant rate of elimination irrespective of plasma concentration. Half-life depends on plasma drug concentration ( $t_{1/2} = C_0/2k$ )

## Kinetics of Elimination

Elimination proceeds with **first order kinetics** for most drugs,  
i.e. rate is proportional to plasma concentration ( $C_p$ )



Rate of elimination  $\propto A$

$$\frac{dA}{dt} = -kA$$

**k** is the **rate constant of elimination**

Substituting for  $A = V_d \cdot C$

$$\frac{dC}{dt} = -kC$$

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

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## First order elimination

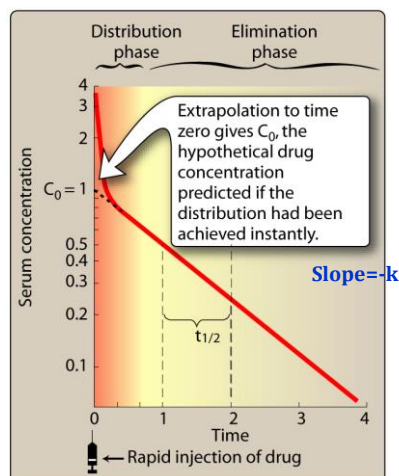
$$C_p = C_o e^{-kt}$$

$$\ln C_p = \ln C_o - kt$$

$$\text{If } t = t_{1/2} \text{ when } C_p = C_o/2$$

$$\ln 2 = kt_{1/2}$$

$$t_{1/2} = 0.693/k$$



$\ln C_p$  vs  $t$  is a straight line.

$C_o$  is the plasma concentration at  $t = 0$  after distribution takes place.

**k** is called elimination rate constant. Units of **k** is  $\text{hr}^{-1}$ .

**$t_{1/2}$**  is the half-life in hrs.

## Example

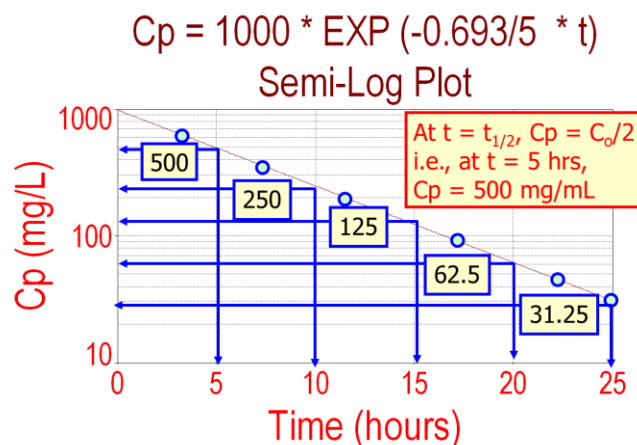
- An individual is given an IV bolus of 200 mg of drug (i.e. dose). Blood samples are drawn and analyzed for drug content. The following concentrations are found:

| <u>Time (hr)</u> | <u>Concentration (µg/L)</u> |
|------------------|-----------------------------|
| 0                | 1000                        |
| 5                | 500                         |
| 10               | 250                         |
| 15               | 125                         |

$$\text{Elimination rate constant (k)} = \text{slope} = \frac{\ln 250 - \ln 125}{10 - 15} = \frac{0.693}{-5} = -0.139/\text{hr}$$

$$\text{Half-life (t}_{1/2}\text{)} = \frac{0.693}{.139} = 5 \text{ hours}$$

### First-order elimination



**Constant fraction of drug eliminated per unit time.**

**By 5 half-lives, 97% of the drug is eliminated**

First Order Elimination

| HALF-LIVES AND PERCENT OF DRUG REMOVED |                             |                           |
|----------------------------------------|-----------------------------|---------------------------|
| ■ NUMBER OF HALF-LIVES                 | ■ PERCENT OF DRUG REMAINING | ■ PERCENT OF DRUG REMOVED |
| 0                                      | 100                         | 0                         |
| 1                                      | 50                          | 50                        |
| 2                                      | 25                          | 75                        |
| 3                                      | 12.5                        | 87.5                      |
| 4                                      | 6.25                        | 93.75                     |
| 5                                      | 3.125                       | 96.875                    |

Constant fraction of drug eliminated per unit time.

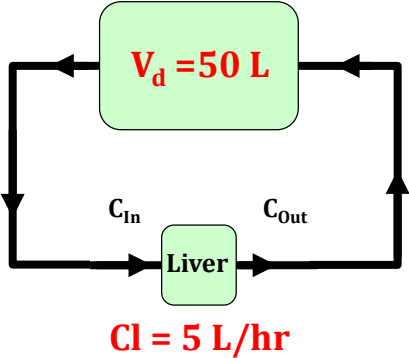
Elimination rate constant & half-life depend on volume of Distribution and clearance

$k = CL/V_d$

→

$t_{1/2} = 0.693 \times V_d/CL$

$k \text{ (1/hr)} = CL \text{ (L/hr)} / V_d \text{ (L)}$



- 5 liters are being cleared of the drug per hour
  - elimination rate constant (i.e. % drug cleared/hour) =  $5 \text{ L hr}^{-1} / 50 \text{ L} = 0.1 \text{ hr}^{-1}$
  - Half-life =  $0.693 \times 50 \text{ L} / 5 \text{ L hr}^{-1} = 6.93 \text{ hrs}$

Zero-Order Elimination

- The metabolic mechanism for most drugs will be saturated only at very high concentrations – doses not commonly used therapeutically.
- But the metabolic capacity for some drugs becomes saturated at concentrations within the therapeutic range: e.g. phenytoin, aspirin, ethanol.
- In a zero-order rate process a constant amount of drug is eliminated per unit of time (e.g., 10 g/hr) because that is the maximum rate of elimination when the pathway is saturated.

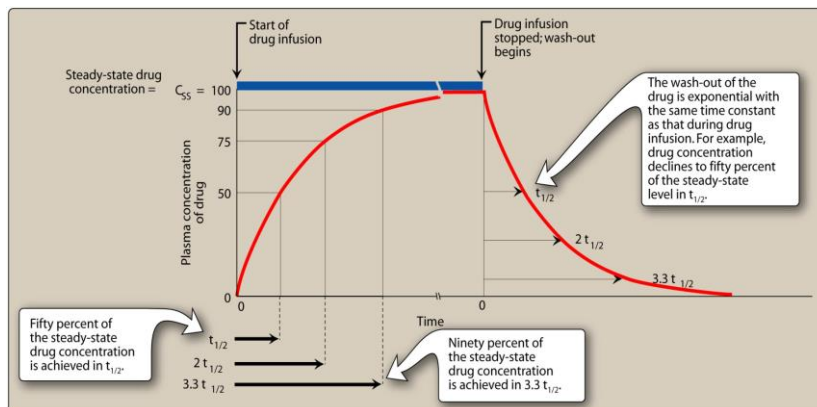
TABLE 2-4.  
First-Order Elimination

| Time after Drug Administration (hours) | Amount of Drug in Body (mg) | Amount of Drug Eliminated Over Preceding Hour (mg) | Fraction of Drug Eliminated Over Preceding Hour |
|----------------------------------------|-----------------------------|----------------------------------------------------|-------------------------------------------------|
| 0                                      | 1000                        | —                                                  | —                                               |
| 1                                      | 880                         | 120                                                | 0.12                                            |
| 2                                      | 774                         | 106                                                | 0.12                                            |
| 3                                      | 681                         | 93                                                 | 0.12                                            |
| 4                                      | 599                         | 82                                                 | 0.12                                            |
| 5                                      | 527                         | 72                                                 | 0.12                                            |
| 6                                      | 464                         | 63                                                 | 0.12                                            |
| 7                                      | 408                         | 56                                                 | 0.12                                            |

TABLE 2-5.  
Zero-Order Elimination

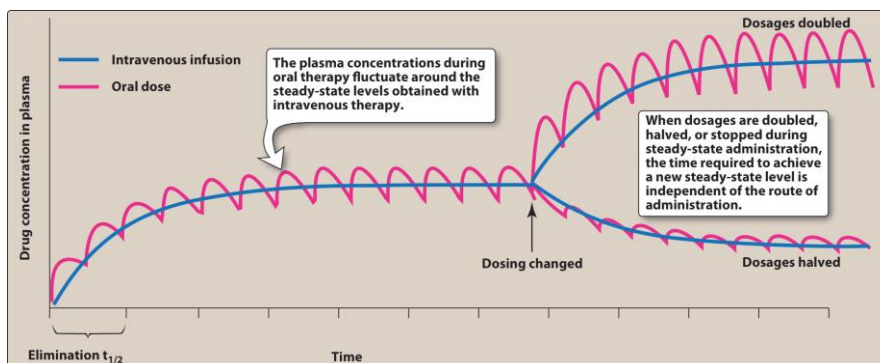
| Time after Drug Administration (hours) | Amount of Drug in Body (mg) | Amount of Drug Eliminated Over Preceding Hour (mg) | Fraction of Drug Eliminated Over Preceding Hour |
|----------------------------------------|-----------------------------|----------------------------------------------------|-------------------------------------------------|
| 0                                      | 1000                        | —                                                  | —                                               |
| 1                                      | 850                         | 150                                                | 0.15                                            |
| 2                                      | 700                         | 150                                                | 0.18                                            |
| 3                                      | 550                         | 150                                                | 0.21                                            |
| 4                                      | 400                         | 150                                                | 0.27                                            |
| 5                                      | 250                         | 150                                                | 0.38                                            |

## Utility of half-life



- 3-5 half-lives to reach steady state after initiation of therapy.
- 3-5 half-lives for the drug to disappear from plasma after cessation of therapy.
- Helps design the dosage regimen for long-term therapy for some drugs.

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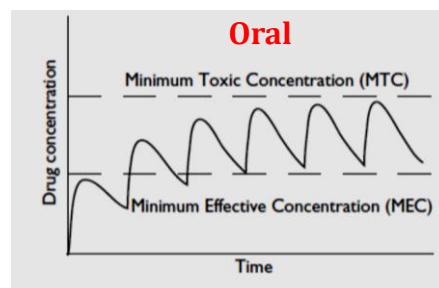
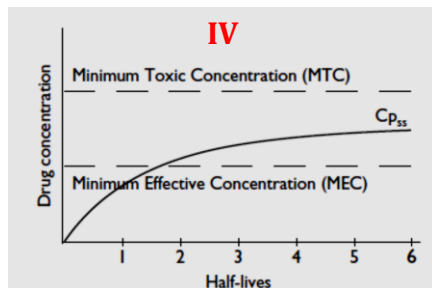
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## Half-life and its clinical significance

- Useful for estimating:
  - time to reach steady state concentration.
  - time for plasma concentration to fall after dosing is stopped.
- Affected by many factors
  - Liver disease (decreased clearance)
  - Kidney disease (decreased clearance)
  - Induction of hepatic drug metabolism (increased clearance)
  - Inhibition of hepatic drug metabolism (decreased clearance)
  - Aging (decreased  $V_d$ , but tricky)
  - Heart disease (decreased clearance)
  - Obesity (increased  $V_d$ )

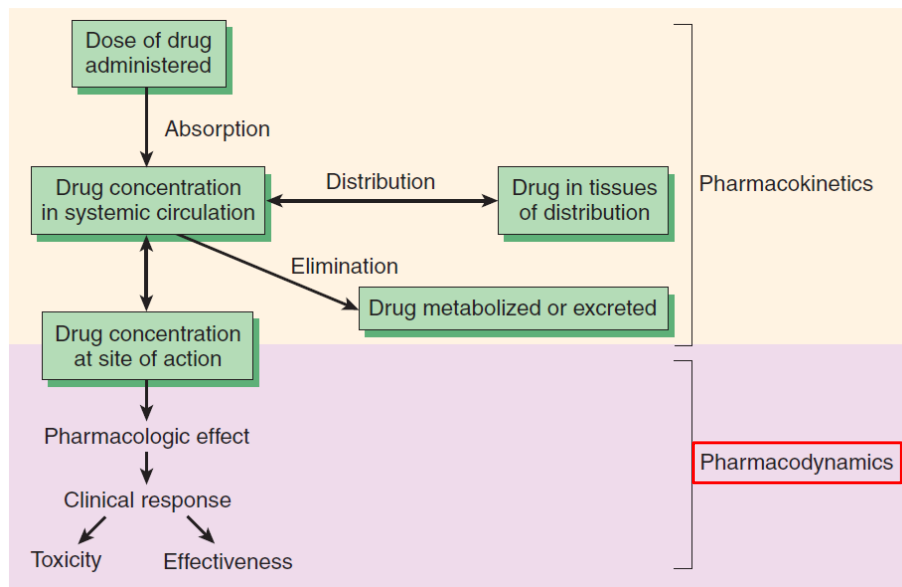
## Design of a rational dosage regimen

- The dosage regimen that should be used in a given situation is described by  $V_d$ ,  $Cl$ , half-life and bioavailability.
- Important to know the therapeutic window: Difference between the minimum effective concentration (MEC) required for a desired response and minimum toxic concentration (MTC).



# Pharmacodynamics

- Receptors
- Dose response relationships



From: Basic and Clinical Pharmacology, 13<sup>th</sup> edition (Eds: Katzung and Trevor). Copyright © 2015 by The McGraw-Hill Education

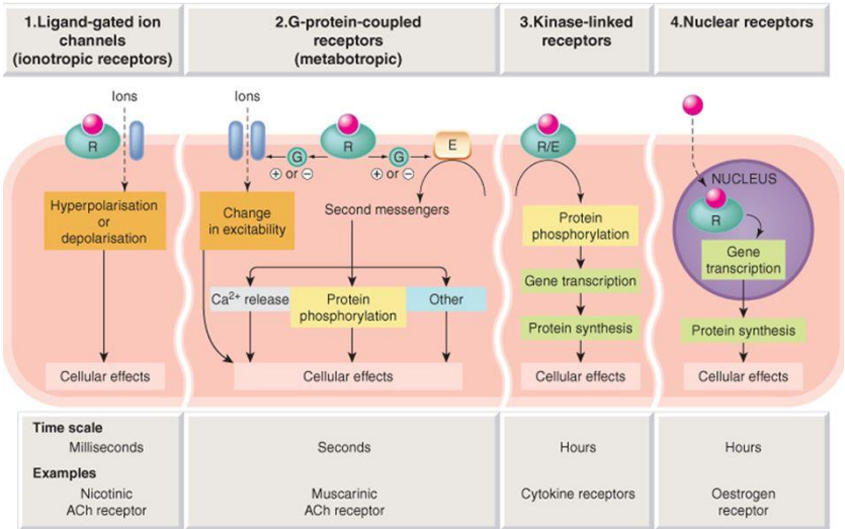
## Therapeutic (and toxic) effects of drugs result from their interactions with specific proteins

- Activation or blockade of the four classes of “receptors”.
  - Many drugs: Oral prednisone given for allergic dermatitis binds to the receptor that binds the hormone cortisol.
- Ion channel blockade
  - anti-arrhythmic agents such as quinidine; local anesthetics such as lidocaine.
- Enzyme inhibition
  - Aspirin. Penicillin, acyclovir
- Inhibition of transporters or structural proteins
  - Proton pump in the stomach: Omeprazole.
- Increase or inhibit release of endogenous transmitter
  - Adrenergic terminals: Amphetamine
- Non-protein mediated:
  - osmotic diuretics, some antacids, chelating agents, adsorbents

## Receptors

- Macromolecules that mediate a biological change upon **binding** of ligand.
- Mediate the actions of hormones, neurotransmitters, growth factors, steroids. Many drugs **bind** to the same receptors used by endogenous agents.
- Are responsible for **selectivity** of drug action. The molecular size, shape, and electrical charge of a drug determine the binding to a particular receptor
- Determine the quantitative relations between dose or concentration of drug and pharmacologic effects

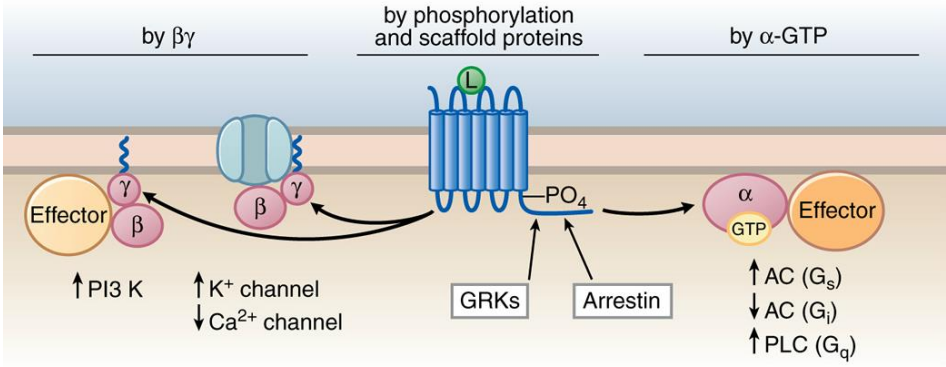
Four main types of receptors mediate the actions of endogenous hormones and many drugs.



| Table 3-1                  |                                         |                                             |                                                                       |                                |
|----------------------------|-----------------------------------------|---------------------------------------------|-----------------------------------------------------------------------|--------------------------------|
| Physiological Receptors    |                                         |                                             |                                                                       |                                |
| STRUCTURAL FAMILY          | FUNCTIONAL FAMILY                       | PHYSIOLOGICAL LIGANDS                       | EFFECTORS AND TRANSDUCERS                                             | EXAMPLE DRUGS                  |
| GPCR                       | β Adrenergic receptors                  | NE, Epi, DA                                 | G <sub>s</sub> ; AC                                                   | Dobutamine, propranolol        |
|                            | Muscarinic cholinergic receptors        | ACh                                         | G <sub>i</sub> and G <sub>q</sub> ; AC, ion channels, PLC             | Atropine                       |
|                            | Eicosanoid receptors                    | Prostaglandins, leukotrienes, thromboxanes  | G <sub>s</sub> , G <sub>i</sub> and G <sub>q</sub> proteins           | Misoprostol, montelukast       |
|                            | Thrombin receptors (PAR)                | Receptor peptide                            | G <sub>12/13</sub> ; GEFs                                             | (in development)               |
| Ion channels               | Ligand-gated                            | ACh (M <sub>2</sub> ), GABA, 5-HT           | Na <sup>+</sup> , Ca <sup>2+</sup> , K <sup>+</sup> , Cl <sup>-</sup> | Nicotine, gabapentin           |
|                            | Voltage-gated                           | None (activated by membrane depolarization) | Na <sup>+</sup> , Ca <sup>2+</sup> , K <sup>+</sup> , other ions      | Lidocaine, verapamil           |
| Transmembrane enzymes      | Receptor tyrosine kinases               | Insulin, PDGF, EGF, VEGF, growth factors    | SH2 domain and PTB-containing proteins                                | Herceptin, imatinib            |
|                            | Membrane-bound GC Tyrosine phosphatases | Natriuretic peptides                        | Cyclic GMP                                                            | Neseritide                     |
| Transmembrane, non-enzymes | Cytokine receptors                      | Interleukins and other cytokines            | Jak/STAT, soluble tyrosine kinases                                    |                                |
|                            | Toll-like receptors                     | LPS, bacterial products                     | MyD88, IAKs, NF-κB                                                    |                                |
| Nuclear receptors          | Steroid receptors                       | Estrogen, testosterone                      | Co-activators                                                         | Estrogens, androgens, cortisol |
|                            | Thyroid hormone receptors               | Thyroid hormone                             |                                                                       | Thyroid hormone                |
|                            | PPARγ                                   | PPARγ                                       |                                                                       | Thiazolidinediones             |

From Goodman and Gilman’s The Pharmacological Basis of Therapeutics, 12<sup>th</sup> Edition.  
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For hormones, binding to receptor is followed by intracellular cascades: examples



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G-proteins coupling to receptors and targets.

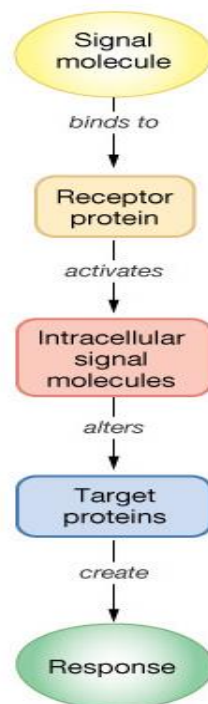
| G-proteins | Targets activated                                                                                                                                                                | Example of receptor involved | Typical effect                                                                                       | Produced by agonists                 |
|------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------|------------------------------------------------------------------------------------------------------|--------------------------------------|
| $G_q$ (+)  | <div>Phospholipase C</div> <div>PIP<sub>2</sub> → IP<sub>3</sub> → DAG</div> <div>Releases Ca<sup>2+</sup> from intracellular stores</div> <div>Activates protein kinase C</div> | H <sub>1</sub> -histamine    | Smooth muscle contraction (↑IP <sub>3</sub> )<br>A variety of effects due to protein phosphorylation | Histamine Ch. 15                     |
| $G_s$ (+)  | <div>Adenylate cyclase</div> <div>ATP → cAMP</div> <div>Activates protein kinase A</div>                                                                                         | $\beta_2$ -Adrenoceptor      | Smooth muscle relaxation (↑cAMP)                                                                     | Adrenaline Ch. 11, salbutamol Ch. 24 |
| $G_i$ (-)  | <div>K<sup>+</sup> channels in cell membrane</div> <div>Increased opening of the channels resulting in hyperpolarisation</div>                                                   | M <sub>2</sub> -muscarinic   | Decreased force of contraction of the heart (↓cAMP)<br>Cardiac slowing                               | Acetylcholine Ch. 10                 |

Fig. 2.2 Examples of G-protein-coupled actions. The pathways are shown for three different G-proteins. IP<sub>3</sub>, inositol triphosphate; PIP<sub>2</sub>, phosphatidylinositol 4,5-bisphosphate.

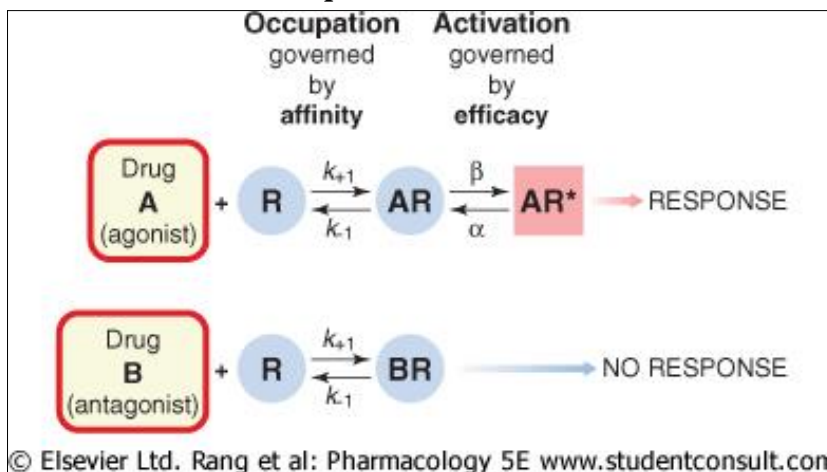
Also G<sub>o</sub> proteins for neurotransmitters in the brain, G<sub>t1</sub> and G<sub>t2</sub> for photons

## Drug effects are mediated by two distinct steps

- Binding to receptor is the first step in the initiation of a biological effect.
- Binding is usually followed by activation of intracellular enzymes or channels, which eventually create the response to a particular hormone.
- These two steps differentiate drugs that are classified as **agonists** or **antagonist**



The two steps are governed by two different parameters.

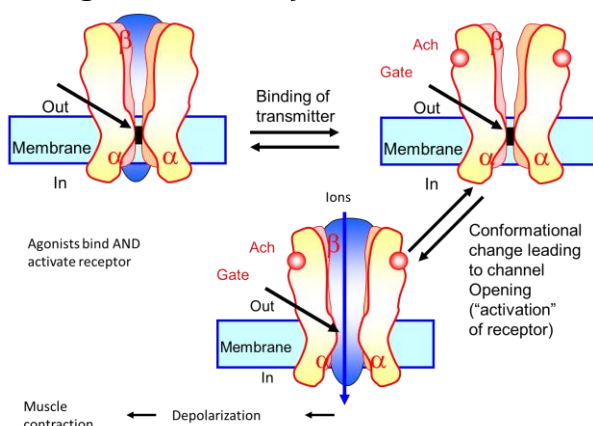


Affinity is a reflection of how tightly a drug binds to the receptor. Determined by binding forces.

Response is **proportional** to fraction of bound receptors.

## Agonists

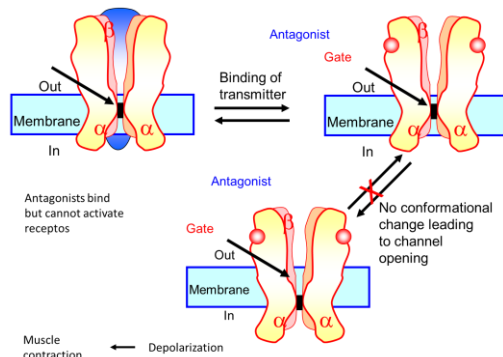
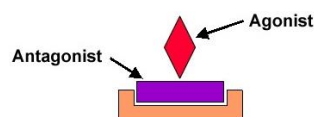
An agonist is a drug (or a ligand) that can bind to a receptor **AND** activate the receptor to elicit a response (e.g. endogenous hormones like epinephrine and exogenous drugs like cortisol).



- Have both affinity and efficacy.
- Different types of agonists exist

## Antagonists

Drugs that bind to the receptor but are unable to activate the receptor. They can be used to block the actions of agonists (e.g. propranolol, timolol to block effects of sympathetic nervous system).



- Affinity but no efficacy.
- Different types of antagonists exist.

## Dose-Response Relationships

- Dose-response relationships are used to classify and compare the effects of different types of agonists and antagonists.
- Magnitude of the pharmacological response to a drug depends on Dose (amount) of drug at receptor site (ADME), fraction of receptors occupied (or bound) by the drug, the nature of the drug (type of agonist).

### Two Approaches

## Dose-Response Relationships

### Dose - Effect

#### ▢ Graded dose-response curve

- Response vs. Dose in a single individual.
- Example: IOP vs. dose. of a glaucoma drug in one patient

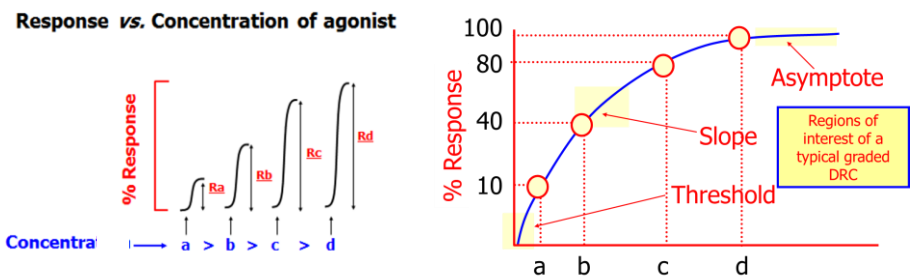
### Dose - Frequency

#### ▢ Quantal dose-response curve

- % Patients responding vs. Dose in a group of individuals; Response is QUANTIZED.
- Example: % Patients reaching a target IOP vs. conc. of a glaucoma drug in a population

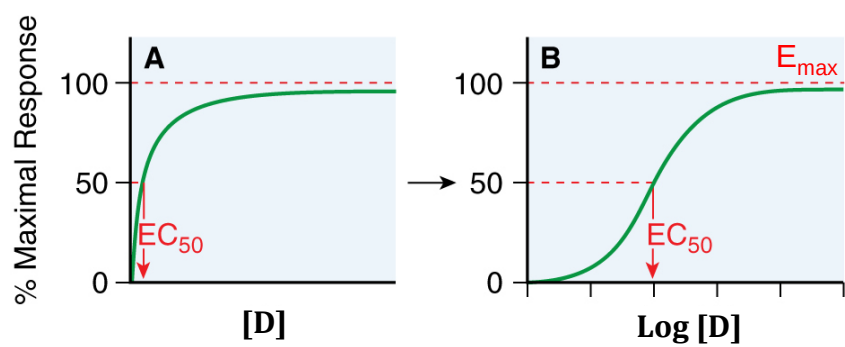
# Graded dose response curve

Relates the drug dose to the degree of pharmacological response (effect) in an individual



Response is graded; as you increase concentration, there is an increase in response till all receptors are bound

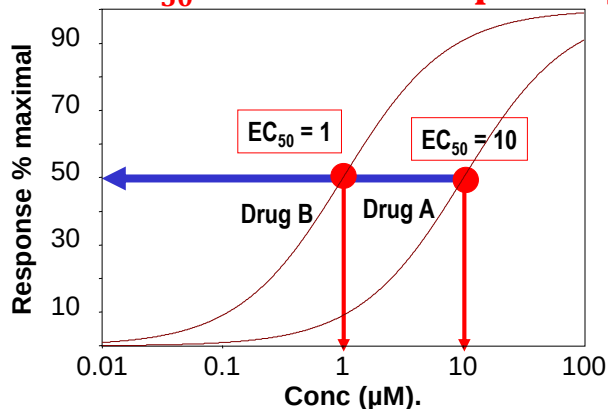
# Graded dose-response curve



$$E = \frac{E_{max} \cdot [D]}{[D] + EC_{50}}$$

$E_{max}$  is the maximum response of the system to the drug.  
 $EC_{50}$  is the concentration of drug that produces a 50 % of the maximum response.

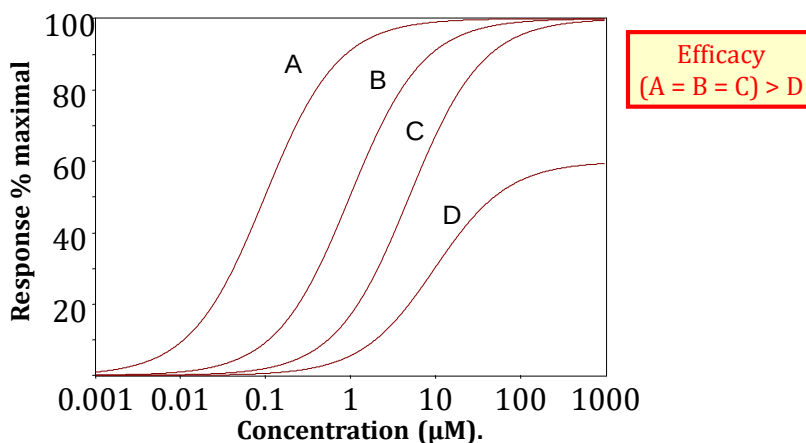
### $EC_{50}$ describes the potency of drug



Drug B (fentanyl) is more potent than Drug A (morphine) at producing analgesia.

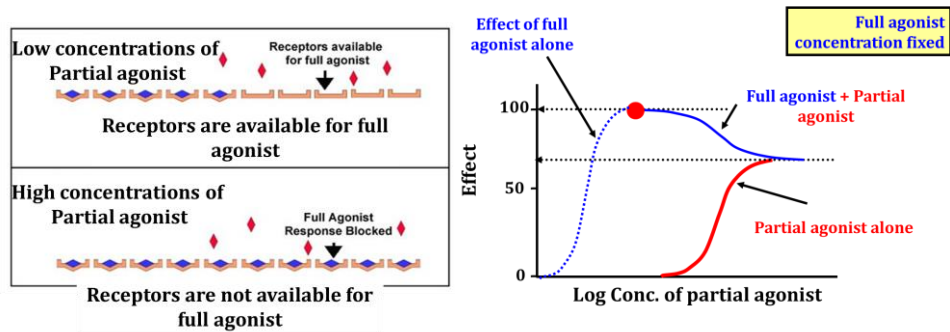
- potency is a measure of how much drug is required to elicit a half-maximal response.
- LOOSELY dependent on the affinity of the drug to the receptor

### $E_{max}$ describes the efficacy of the drug

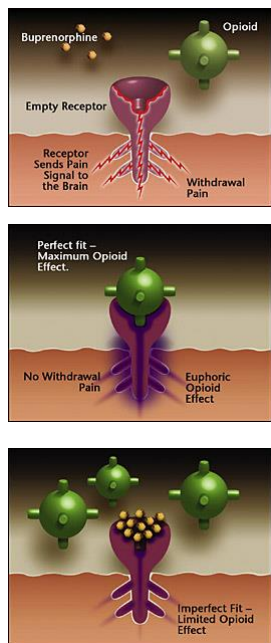


- Efficacy is the “ability” of a drug to activate a receptor to produce a maximal response.. Also referred to as “intrinsic activity”.
- Drugs acting on the same receptor can have different efficacies. Drugs A, B, C are **full agonists**. Drug D is a **partial agonist**

Partial agonists can block the effects of full agonists



A clinically useful property!



Example: Buprenorphine for addiction

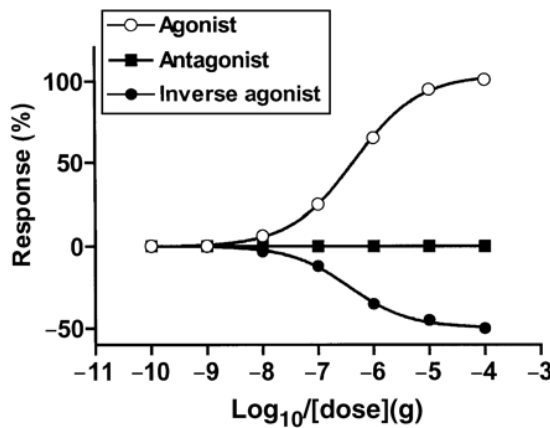
Buprenorphine has a limited opioid effect, and does not cause the intense euphoria seen with full agonists, such as heroin.

Buprenorphine has a higher affinity than morphine/heroin : it competes with and prevents morphine/heroin from binding to the receptor.

Patient should already be in mild to moderate withdrawal from opioid use before administering Buprenorphine.

[http://www.naabt.org/education/buprenorphine\\_treatment.cfm](http://www.naabt.org/education/buprenorphine_treatment.cfm)

## Inverse agonists



Most receptors are functionally silent in the unbound state (in absence of agonist).

However, some receptor systems display constitutive activity, either as a result of over expression or as a result of mutation. These receptors are active in the absence of agonist.

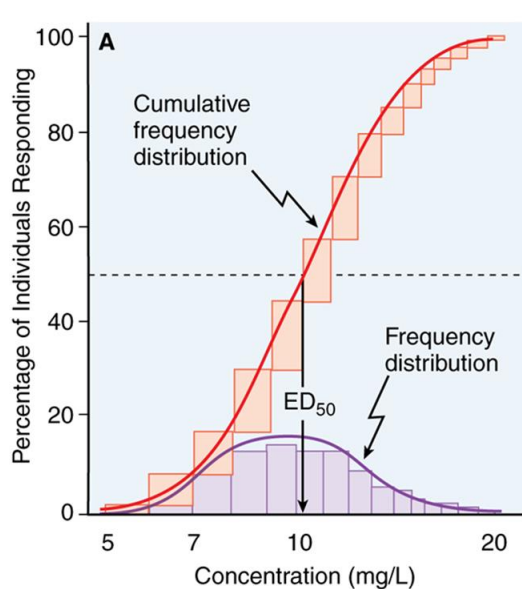
An inverse agonist would inhibit this constitutive activity and, as such, is said to display **negative efficacy**.

•From DG Lambert, Contin Educ Anaesth Crit Care Pain (2004) 4 (6): 181-184

## Drug Antagonism

- Antagonism by receptor blockade
  - Competitive antagonist
  - Non-competitive antagonist
  - Inverse agonists
- Other mechanisms of Antagonism
  - Physiological antagonism
  - Chemical antagonism
  - Pharmacokinetic antagonism

Quantal dose-response curves

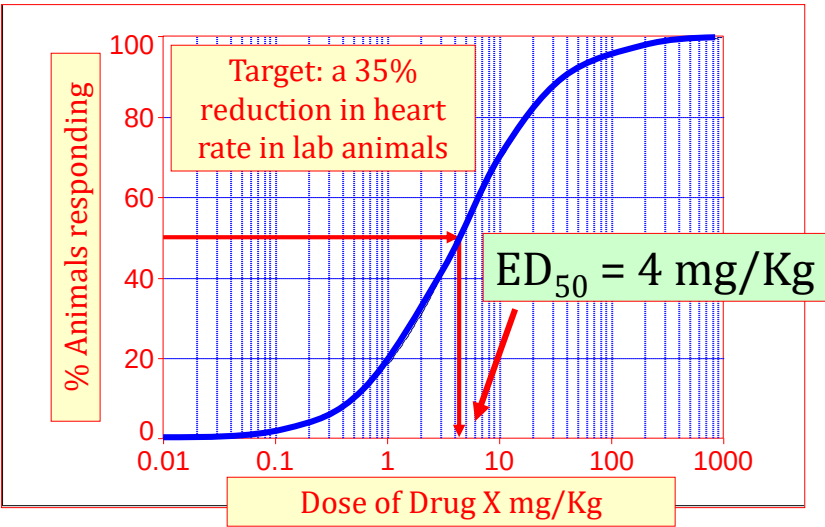


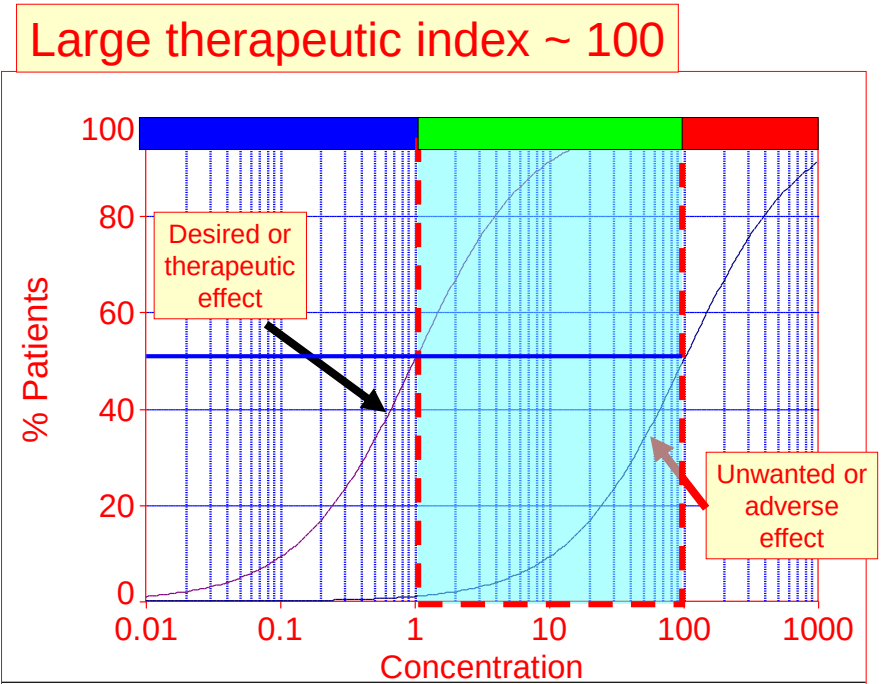
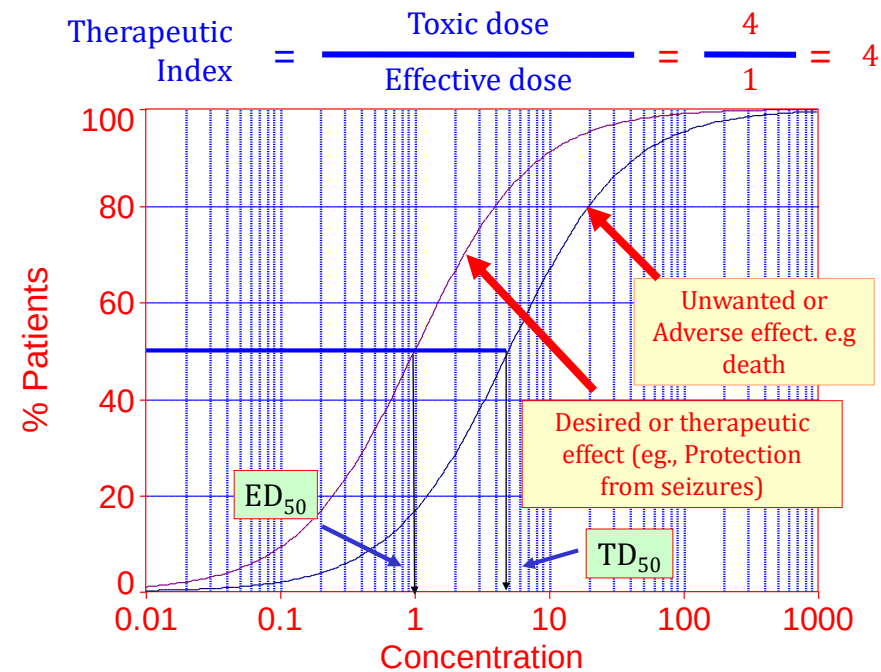
Different doses of a drug are given to 100 people and the concentration that produced a quantal response is determined.

Frequency distribution  
Each bar shows the number of people responding to that dose; excludes people responding to lower doses

Cumulative frequency - each bar shows the number of people responding to that dose and to lower doses - at 20 mg all 100 people respond

Quantal DRC based on all-on-none responses  
(Effective dose)





$$\text{Therapeutic Index} = \frac{\text{Toxic dose (TD}_{50}\text{)}}{\text{Effective dose (ED}_{50}\text{)}}$$

- A measure of a drug's safety margin. Large value indicates a wide margin between doses that are effective and doses that are toxic
- Examples: Warfarin has a narrow index (~2). Penicillin has a large therapeutic window (10x).
- Instead of TD<sub>50</sub>, could use also Lethal dose (LD<sub>50</sub>).

## Pharmacodynamic effects and interactions during therapy

- Reduction in receptor density can occur in response to constant or continuous exposure to an agonist (**down-regulation**).
  - Significance: Tolerance (PT). Rapid onset of PT is called tachyphylaxis
- Increase in receptor density can occur in response to constant exposure to an antagonist (**up-regulation**).
  - Leads to apparent “receptor supersensitivity”. Example: Exacerbation of ischemic cardiac disease upon sudden withdrawal of  $\beta$ -blockers
- Combined treatment with multiple drugs can lead to interactions due to modification of the action of one drug at the target site by another drug, independent of a change in its concentration. Can be synergistic, or antagonistic.

| Table 1. Examples of Common Additive/Synergistic Pharmacodynamic Drug-Drug Interactions                                                                                                                                                                                        |                                                                                 |                                        |                                                                                                                          |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------|----------------------------------------|--------------------------------------------------------------------------------------------------------------------------|
| Substance/Class A                                                                                                                                                                                                                                                              | Substance/Class B                                                               | Possible PD Effect/Outcome             | Mechanism(s)                                                                                                             |
| ACEi/ARBs                                                                                                                                                                                                                                                                      | Potassium-sparing diuretics: spironolactone, eplerenone, amiloride, triamterene | Hyperkalemia                           | Inhibition of aldosterone release plus aldosterone receptor antagonism or reduction of renal tubular potassium secretion |
| NSAIDs                                                                                                                                                                                                                                                                         | Warfarin, phenprocoumon                                                         | Increased bleeding risk                | Inhibition of vitamin K–dependent clotting factors plus inhibition of platelet aggregation                               |
| SSRIs                                                                                                                                                                                                                                                                          | NSAIDs                                                                          | Increased bleeding risk                | Dual-pathway inhibition (serotonin and thromboxane A <sub>2</sub> ) of platelet function                                 |
| SSRIs                                                                                                                                                                                                                                                                          | Triptans; opioids; MAOIs                                                        | Serotonin syndrome                     | Additive serotonin reuptake inhibition                                                                                   |
| Nitrates                                                                                                                                                                                                                                                                       | PDE <sub>5</sub> Inhibitors                                                     | Acute drop in blood pressure, collapse | Additive cGMP elevation by increased formation (nitrates) and reduced clearance (PDE <sub>5</sub> i)                     |
| Tricyclic antidepressants                                                                                                                                                                                                                                                      | Antipsychotics/neuroleptics                                                     | Anticholinergic syndrome               | Additive anticholinergic effects                                                                                         |
| ACEi indicates angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; MAOIs, monoamine oxidase inhibitors; NSAIDs, nonsteroidal anti-inflammatory drugs; PD, pharmacodynamics; PDE, phosphodiesterase; SSRIs, selective serotonin reuptake inhibitors. |                                                                                 |                                        |                                                                                                                          |

Hermann et al., The Journal of Clinical Pharmacology, (2018); 00(0) 1-13

| Table 2. Examples of Common Antagonistic Pharmacodynamic Drug-Drug Interactions                                                                                                     |                                                     |                                                                                                 |                                                                                                                                                                                                                                                                                                                                                          |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------|-------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Substance/Class A                                                                                                                                                                   | Substance/Class B                                   | Possible PD Effect/Outcome                                                                      | Mechanism(s)                                                                                                                                                                                                                                                                                                                                             |
| Warfarin                                                                                                                                                                            | Vitamin K                                           | Reduced anticoagulatory warfarin effect                                                         | Functional antagonism of warfarin-mediated vitamin K epoxide reductase inhibition by vitamin K supplementation                                                                                                                                                                                                                                           |
| ACEi/ARBs                                                                                                                                                                           | NSAIDs                                              | Reduced antihypertensive ACEi/ARB effects                                                       | Reduction in glomerular perfusion by reduced local prostaglandin E <sub>2</sub> synthesis with corresponding reactive renin secretion.<br>NSAID-mediated sodium and water retention.<br>Elevated intrarenal aldosterone concentrations by inhibition of UGT2B7-mediated aldosterone glucuronidation (PK DDI with an endogenous substrate!) <sup>47</sup> |
| Antidiabetic drugs                                                                                                                                                                  | Glucocorticosteroids                                | Attenuation of antidiabetic effects                                                             | Glucocorticoid-mediated inhibition of a number of steps in the insulin signaling network through several different mechanisms, resulting in direct actions of glucocorticoids on muscle, liver, and other tissues <sup>48</sup>                                                                                                                          |
| Levodopa                                                                                                                                                                            | Antipsychotics/neuroleptics, eg. haloperidol        | Attenuation/abolition of L-dopa effect                                                          | Dopa-receptor antagonism                                                                                                                                                                                                                                                                                                                                 |
| Macrolide antibiotics                                                                                                                                                               | Drugs with capability for QTc-interval prolongation | Exaggerated QTc-prolongation, life-threatening ventricular arrhythmia (Torsade de Pointes, TdP) | Cardiac ion channel inhibition                                                                                                                                                                                                                                                                                                                           |
| ACEi indicates angiotensin-converting enzyme inhibitor; ARBs, angiotensin receptor blockers; NSAID, nonsteroidal anti-inflammatory drug; PD, pharmacodynamics; PK, pharmacokinetic. |                                                     |                                                                                                 |                                                                                                                                                                                                                                                                                                                                                          |

Hermann et al., The Journal of Clinical Pharmacology, (2018); 00(0) 1-13

## Clinical Selectivity: Beneficial versus Toxic Effects of Drugs

**No drug causes only a single, specific effect**

Beneficial and Toxic Effects can be

- A. Mediated by the same receptor-effector mechanism
  - bleeding caused by anticoagulant therapy; hypoglycemic coma due to insulin
- B. Mediated by identical receptors but in different tissues or by different effector pathways
  - glucocorticoid hormones
- C. Mediated by different types of receptors (anti-histamines)
- D. Allergic or idiosyncratic reactions or unpredictable effects:

## Drug effects

- 1. Beneficial effects (therapeutic).
- 2. Adverse effects
  - Can range to mild to severe
  - Can be reversible, but irreversible in other cases
  - Cannot always be avoided (E.g. diamox use in glaucoma)
  - Can be predictable or unpredictable

## Predictable adverse drug reactions:

- **Dose dependent (related to drug's actions).**
  - morphine causes respiratory depression in addition to analgesia.
  - An oral hyperosmotic agent will aggravate CHD in addition to reducing IOP.
  - An oral antibiotic can kill beneficial bacteria in the gut leading to infectious colitis
- Occurs in normal patients.
- Low therapeutic Index, a frequent cause (e.g. Warfarin)
- Drug-Drug interactions
- Prescribing mistakes.

## Unpredictable adverse drug reactions

- Non-dose dependent ADR (not related to drugs' actions)  
(EXAMPLE: Penicillin)
- Allergic or idiosyncratic reactions
- Types of allergic reactions
  - Type I - immediate, anaphylactic (IgE)
    - e.g., anaphylaxis with penicillins
  - Type II - cytotoxic antibody (IgG, IgM)
    - e.g., methyldopa and hemolytic anemia
  - Type III - serum sickness (IgG, IgM)
    - e.g., procainamide-induced lupus
  - Type IV - delayed hypersensitivity (T cell-mediated)
    - e.g., contact dermatitis

## **Predicting drug interactions is important for the clinician**

- Could be life threatening.
- Can range in severity.
  - Minor (example: effects of furosemide can be enhanced by hydralazine, but not to a significant extent)
  - Moderate (rifampin + isoniazid can lead to hepatotoxicity; monitoring or lower dose).
  - Severe (ketoconazole + cisapride leads to ventricular arrhythmias).
- Pharmacokinetic or Pharmacodynamic in nature.

## **Factors that can influence treatment outcome**

- Drug-Drug interactions (can range in severity)
- Age (very young and very old)
- Pregnancy (risk to fetal development)
- Diseases – can alter a drug's absorption, distribution, metabolism or elimination.
- Hereditary factors – slow metabolizers
- Low Therapeutic Index, a frequent cause of adverse effects.
- Prescribing mistakes and compliance