MIDW 125

Introduction to Pharmacology, Pharmacodynamics and Pharmacokinetics

January 6-13, 2015

Welcome and introduction

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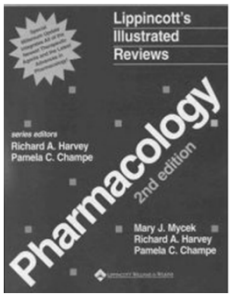
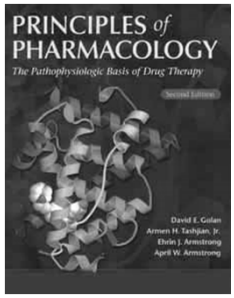
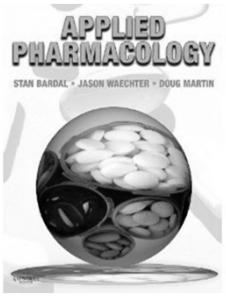
No set office hours – happy to meet anytime

Send me an email to make arrangements

*Additional *optional* pharmacology texts*







All on reserve at Woodward library

Overview of next 3+1 lectures

Part 1: Introduction
What are drugs?

Part 2: Pharmacodynamics
What do drugs do to the body?

Part 3: Pharmacokinetics
What does the body do to drugs?

Part 4: Drug Dosing
How do we design drug dosing regimens?

Part 1: Introduction to Pharmacology

Some definitions

What is Pharmacology? ***pharmakon = drug***
logos = the study of

∴ **Pharmacology = the study of drugs**
→ ***what*** **they do and** ***how*** **they do it**

≠ Pharmacy: the health profession that deals with the preparation and dispensing of (prescription) medications

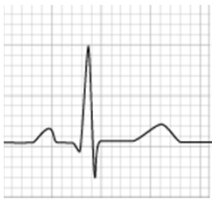
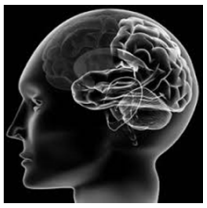
"Drug" has many definitions

Webster's Dictionary:

"a substance intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease"

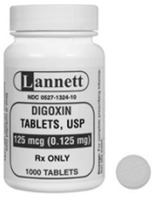
More broadly:

"any substance that brings about a biological change or effect on the body"

Drugs come from many sources

Plants

Foxglove ⟶ Digoxin

Animals


Pregnant mare urine

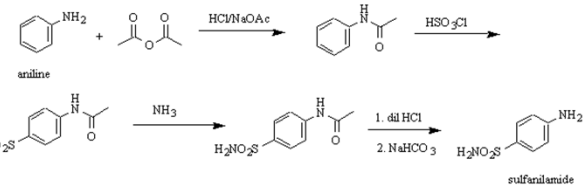
↓

Premarin®

Drugs come from many sources

Minerals – *Lithium*

Synthetic – *Sulfa drugs*



Natural ≠ Safe!

Strict rules urged for energy drinks

Health Canada examining approach to high-caffeine products

BY SHARON KIRKEY
POSTMEDIA NEWS
AND TRACY SHERLOCK
VANCOUVER SUN

MARK VAN MANEN/PNG
Sasha Goundar (left), Nathan Martyn and Ashley Yasinsky delight in their daily energy drink before hitting the beach Monday in Vancouver. The Canadian Medical Journal says energy drinks deliver enough of a drug to cause intoxication.

"Caffeine-loaded energy drinks have now crossed the line from beverages to drugs delivered as tasty syrups," the Canadian Medical Association Journal says.

~Vancouver Sun, July 27, 2010

Vitamin drinks could cause harm

Some have too-high levels of vitamin A; Health Canada must act, experts warn

- Health Canada's recommended daily intake of retinol for women is 700 mcg
- One 547mL Fuze Vitalize bottle contains 3000 mcg
- Increased risk of liver damage
- **Potentially harmful for pregnant women – increased risk of birth defects**

~Vancouver Sun, January 24, 2011

One drug…many names

1. Chemical Name:

Identifies the chemical elements and compounds that are found in the drug – most important to chemists, pharmacists and researchers who work with the drug at a chemical level.

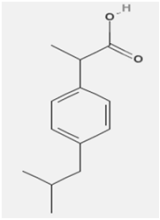
2. Generic or Non-proprietary Name:

The universally accepted name of a drug. It appears on all drug labels, resource guides and publications. Generic names often follow similar patterns for drugs of the same class or mechanism. *(ex: lido<u>caine</u>, pro<u>caine</u>)*

3. Brand or Trade or Proprietary Name:

The copyrighted and trademarked name given by the drug company – restricts the use of the name.

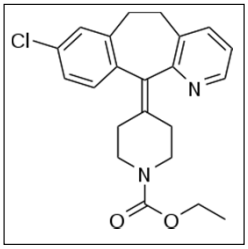
One drug…many names



Chemical name: (±)-2-(*p*-isobutylphenyl) propionic acid

Generic name: Ibuprofen

Brand names: Advil®, Motrin®



Chemical name: Ethyl 4-(8-chloro-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-ylidine)-1-piperidinecarboxylate

Generic name: Loratadine

Brand name: Claritin®

Pharmacology has 2 arms

Pharmacodynamics

"what the drug does to the body"

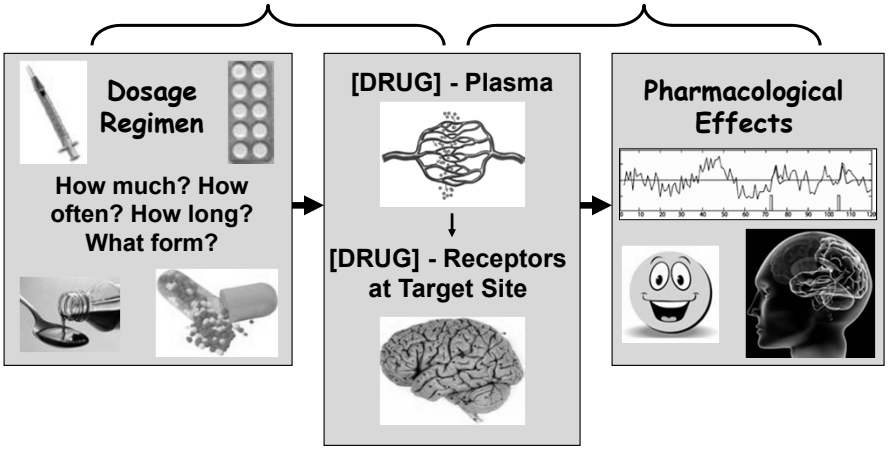
- **the study of the effect(s) of drugs on body processes**

Pharmacokinetics

"what the body does to the drug"

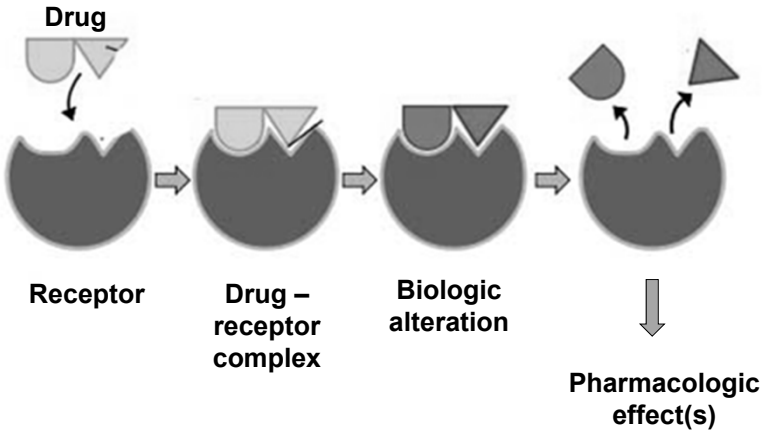
- **the study of the movement of drugs in the body (how it reaches and leaves its site of action and at what concentration)**

The PK – PD relationship



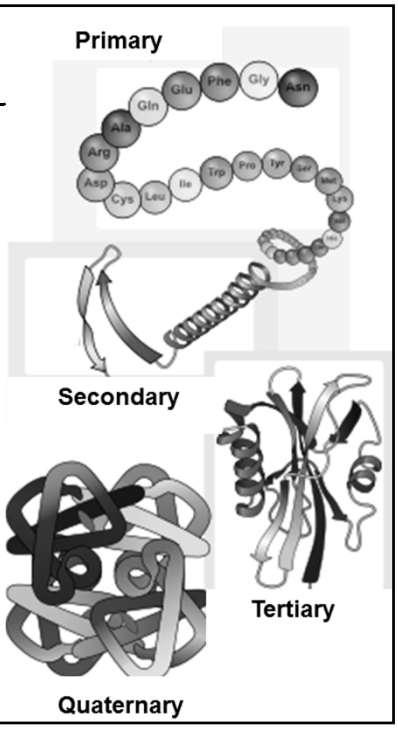
Part 2: Pharmacodynamics

Simplification of drug action



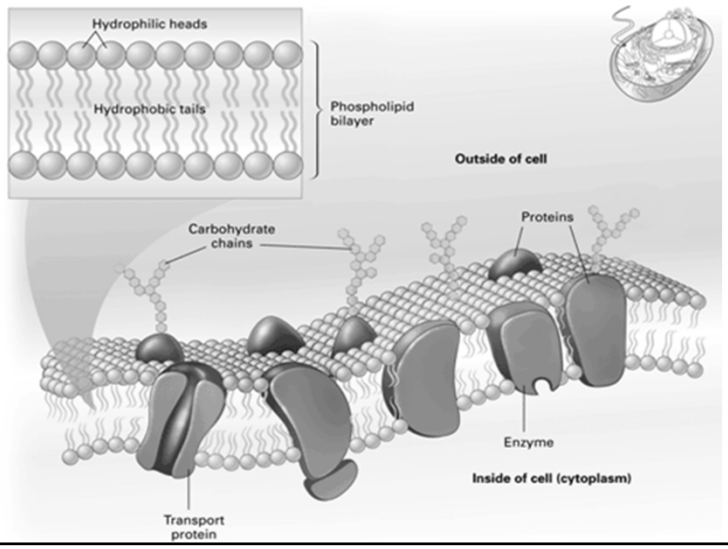
What are receptors?

- **Receptors are macromolecules that mediate a biological change following ligand (drug) binding**
- **Most receptors are proteins with:**
  - **1° aa sequence**
  - **2° regular sub-structures**
  - **3° 3-D structure**
  - ***sometimes* 4° multi-protein complexes**



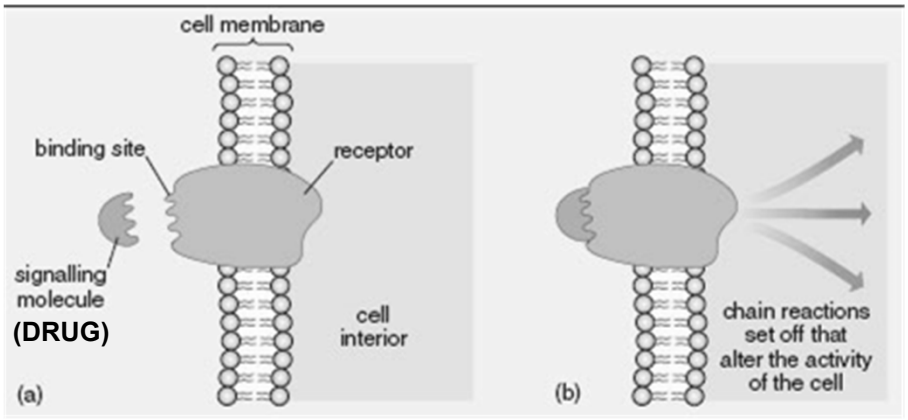
Where are receptors?

- **Receptors are located on the surface of or within cells**



The drug-receptor complex

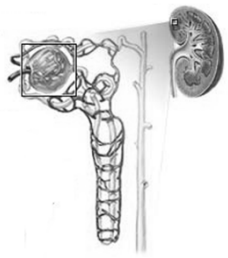
- **Van der Waals forces, hydrogen and ionic bonds in the active (binding) site typically mediate formation of the drug-receptor complex → receptor affinity**



An exception to the rule

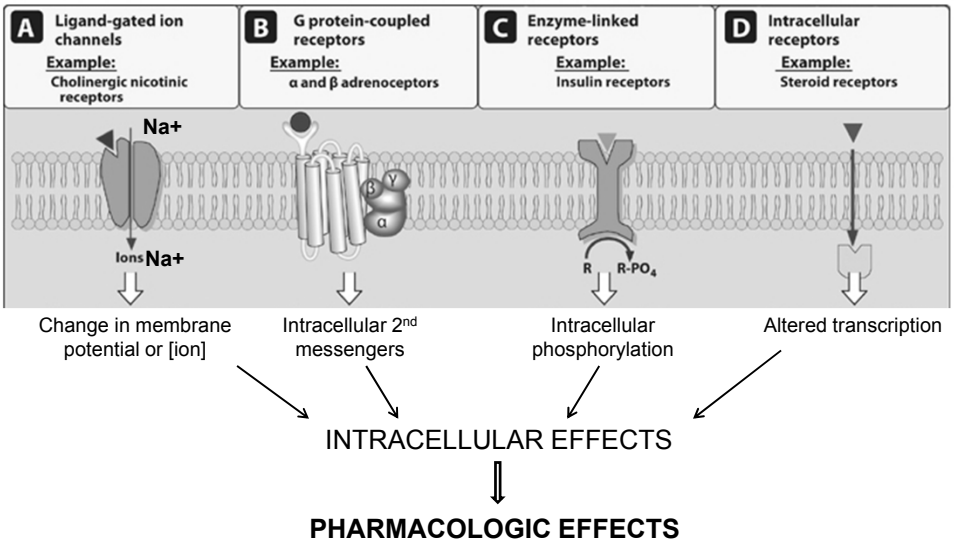
- **a few drugs work via non-receptor mechanisms, for example:**

<u>Antacids</u> - purely chemical basis via acid neutralization in the stomach



<u>Osmotic diuretics</u> - promote urine excretion by altering water flow in the kidney *independent* of receptors

There are 4 main classes of receptors



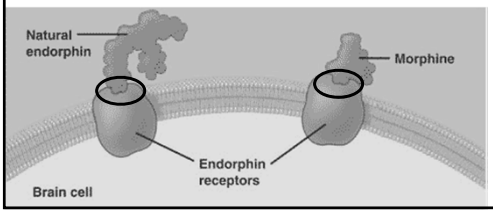
What binds to the receptors?

- **Most receptors have naturally occurring (endogenous) molecules that bind to them**
- **Exogenous (foreign) molecules can be designed to bind to the same receptor ⇒ rational drug design**

Example ~

Endorphins (endogenous)
Morphine (exogenous)
} ***Bind opiate receptors in brain*** ⟶

EUPHORIA



Drugs can be agonists

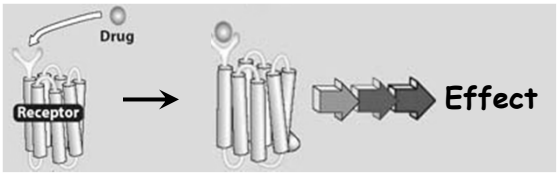
AGONISTS have:

1. **AFFINITY for the receptor** ***(they bind to it)***
2. **INTRINSIC ACTIVITY** ***(binding elicits a response)***

Agonists can be either

1. **Endogenous** ***(ex: adrenalin)***
2. **Exogenous** ***(ex: dobutamine)***

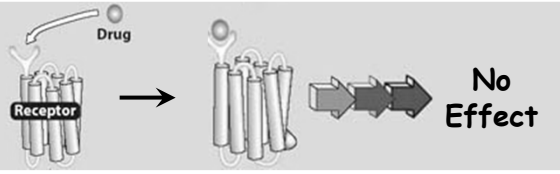
} **Both ↑**  **rate**



Drugs can be antagonists

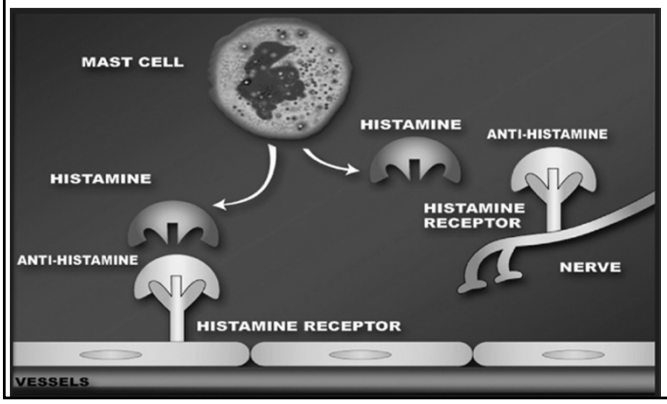
ANTAGONISTS ***(aka receptor blockers or inhibitors)***

1. **have AFFINITY** ***(bind the receptor)***
2. **LACK intrinsic activity** ***(no response)***



Antagonist example

Claritin®: an antagonist that blocks histamine receptors → allergy treatment



Pharmacologic effects – side effects

"A drug without side effects isn't really a drug"

Side Effects/Adverse Effects

Mild, tolerable, subside on their own ***(ex: GI disturbances)***

Potentially life-threatening & sustained ***(ex: seizures)***

Risks vs benefits must be carefully weighed → Therapeutic Index

Side effect or not? A matter of perspective

"may cause drowsiness"

When taken for seasonal allergies

⇓

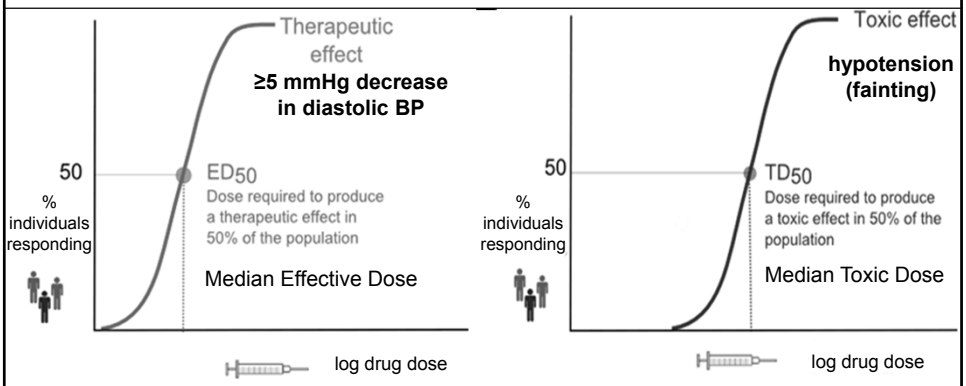
When taken as a sleep aid

⇓

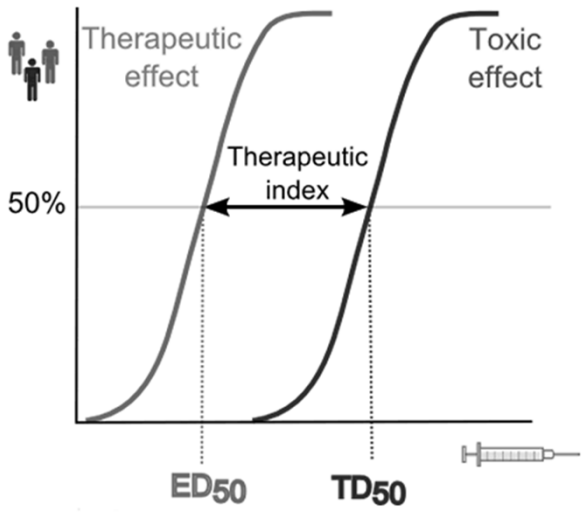
⇓

The pharmacologic effect is related to dose

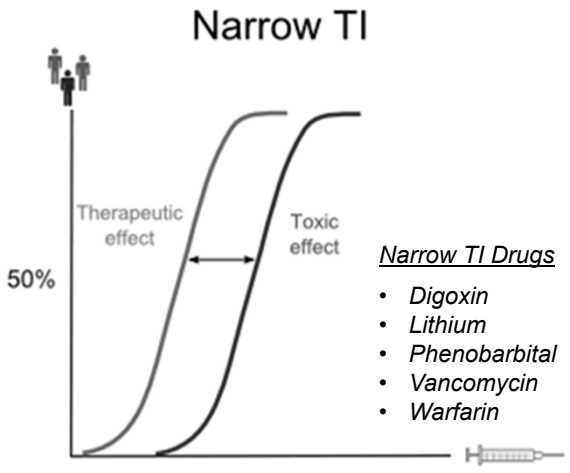
Drug dose-response curves



Therapeutic index: a measure of drug safety



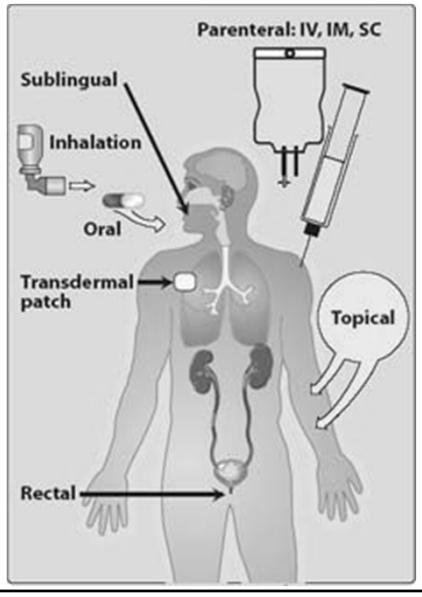
Therapeutic index: a measure of drug safety



Narrow TI Drugs

- *Digoxin*
- *Lithium*
- *Phenobarbital*
- *Vancomycin*
- *Warfarin*

Routes of drug administration



Which route to use? 3 factors to consider

1.

- size, water vs lipid solubility, pH stability

2.

- consciousness, ability to follow instructions, age, other medications

3.

- urgency of situation, local vs systemic effects

Enteral administration (systemic effect)

- **involves the gastro-intestinal (GI) tract**
  - *oral (po) – most common*
  - *sublingual (sl)*
  - *rectal (pr)*

Advantages: convenient, inexpensive, safe

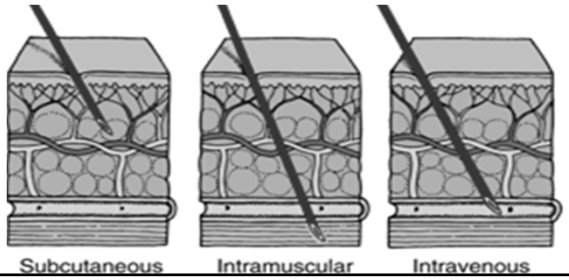
Disadvantages: possible1st-pass metabolism, pH stability, variable absorption

Parenteral administration (systemic effect)

- **does not involve the GI tract (usually injections)**
  - *intravenous (iv)*
  - *subcutaneous (sc, subQ)*
  - *intramuscular (im)*

<u>Advantages:</u> immediate – no absorption (iv), avoids stability concerns, unconscious OK

<u>Disadvantages:</u> discomfort, potential for infection



Other routes

Inhalational (systemic or local effect)

- *metered dose inhalers, general anesthetics, nasal decongestants*

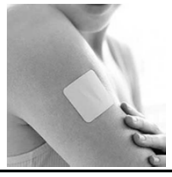


Topical (local effect)

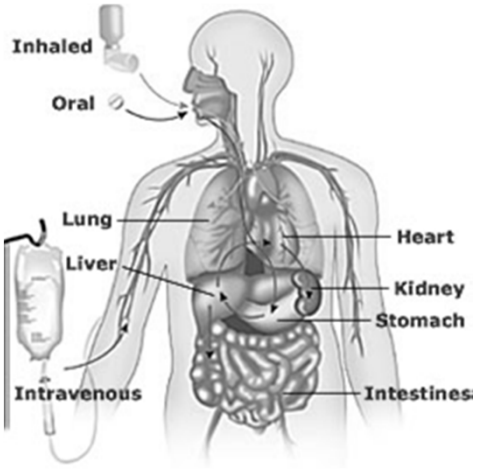
- *cream, ointment, drops*


Transdermal (systemic effect)

- *patch*



The drug is now in the body…what next?

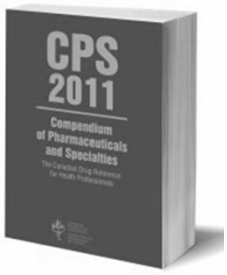


"Pharmacokinetics"

Part 3: Pharmacokinetics

Claritin monograph

What words or phrases in the drug monograph are unfamilar to you?

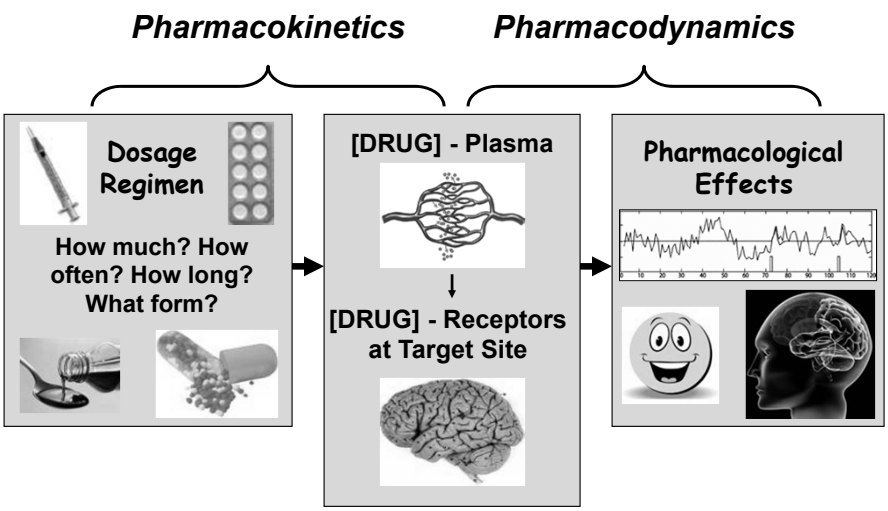


Source: Compendium of Pharmaceuticals and Specialties (CPS)

Claritin monograph

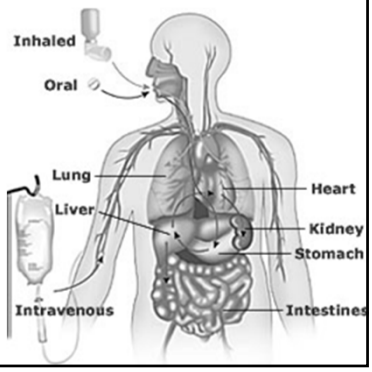
- **pharmacokinetics**
- **elimination**
- **half-life**
- **C_{max}**
- **T_{max}**
- **steady state**
- **bioavailability**
- **active metabolite**
- **unchanged drug**
- **conjugated drug**
- **clearance**

The PK – PD relationship



Pharmacokinetics – the ADME processes

A	**gets drug into the blood**
D	**where it goes in the body**
M	**what happens to it**
E	**how it gets out**

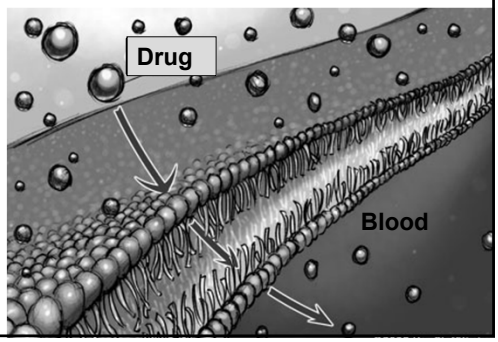


Absorption

- **The movement of drug from site of administration into the <u>blood</u> → occurs by ***<u>passive diffusion</u>***

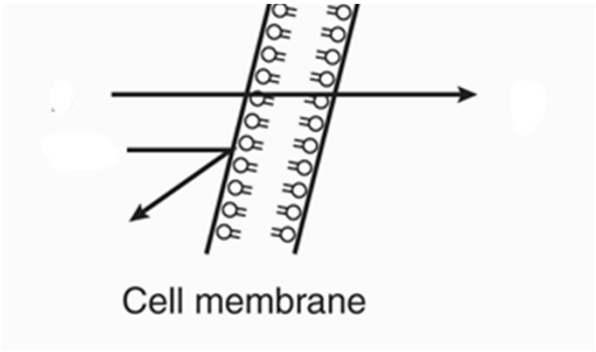
<u>Influencing Factors:</u>

- **concentration gradient (hi → low)**
- **drug size (must be less than 1 kDa)**
- **lipid solubility / pH**



Membrane permeability – effect of lipid solubility

- **Only uncharged, hydrophobic drugs can passively diffuse across lipid bilayers (membranes)**



Membrane permeability – effect of pH

- **Most drugs are weak acids or weak bases – exist in equilibrium between protonated & unprotonated, charged & uncharged species**

weak acid drug	weak base drug
$HA \leftrightarrows H^+ + A^-$	$B + H^+ \leftrightarrows BH^+$

- **pH of environment and pKa of drug dictate which of the two forms predominates**

Weak acid and weak base drugs

Total weak acid drug = HA + A^- =

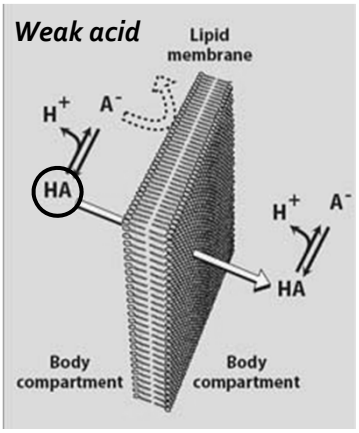
99%	1%
50%	50%
12%	88%

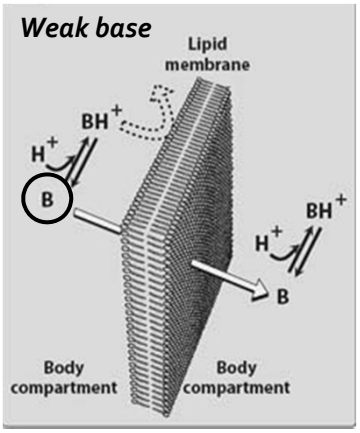
Total weak base drug = BH^+ + B =

99%	1%
50%	50%
12%	88%

Membrane permeability – effect of pH

- **Only the uncharged (unionized) species will cross the membrane *(ie be absorbed)***





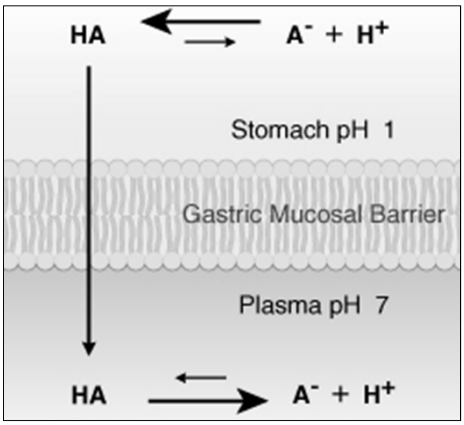
Predicting absorption/diffusion

- **We can use the Henderson-Hasselbalch equation to predict the extent to which this will occur**

$$pH = pKa + \log \left[\frac{\text{unprotonated form}}{\text{protonated form}} \right]$$

Practice calculation 1

Piroxicam is a weak acid (pKa=1.8) that is used to relieve arthritic pain. How much of it will diffuse across the gastric mucosal barrier and into the blood (plasma) when taken orally?



Practice calculation 2

The first dose provides temporary pain relief but also causes stomach upset. The person decides to take a 'Tums' with her next dose.

After this her stomach is no longer upset, but now her pain won't go away. Why?

(Tums raises the stomach pH by 2 units)

Bioavailability (fraction absorbed, F)

- **the fraction of drug that reaches systemic circulation unchanged**

$$F = \frac{\text{amount of drug in systemic circulation}}{\text{amount of drug administered}}$$

What can you do to ensure a drug is 100% bioavailable (F=1)?

- non-iv dosage recommendations take fractional absorption into account
- useful for comparing routes of administration

Question…

When comparing the iv vs po routes of administration, which would require a larger dose of the same drug in order to achieve the same effect? Why?

How does the drug know where to go?

drug circulates throughout body in the blood

↓

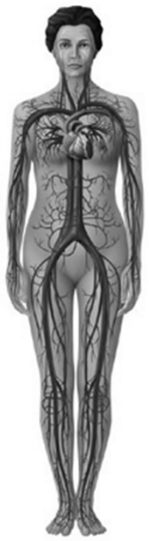
encounters receptors for which it has affinity

↓

binds

⇓

pharmacological response

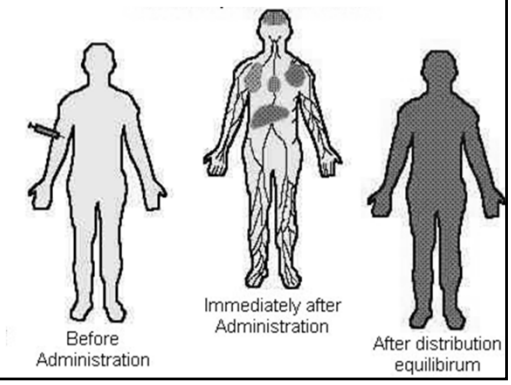


Distribution

- **The process by which drug reversibly leaves the bloodstream**
  - drug moves between body compartments
  - drug reaches the site of action (receptors)

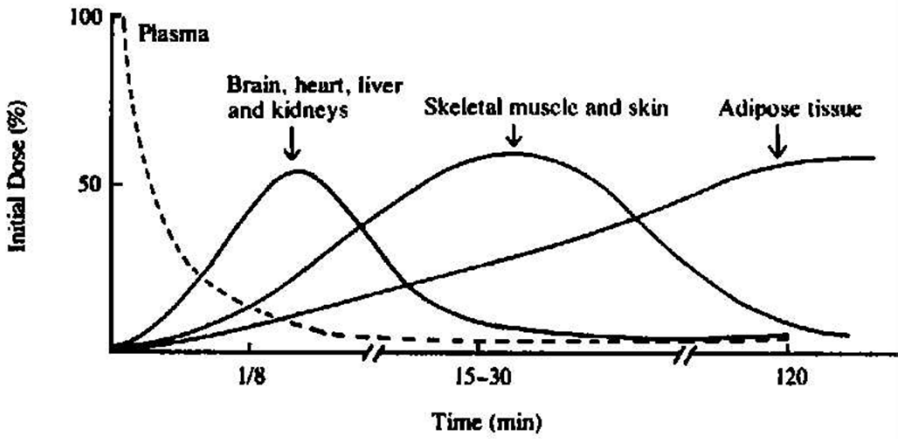
Influencing Factors:

☑ conc. gradient
☑ drug size
☑ lipid solubility / pH
→ blood flow
→ protein binding



Distribution – effect of blood flow

- Drug is delivered to tissues in relation to perfusion



Distribution – effect of protein binding

- Drugs reversibly bind plasma (blood) proteins
  (protein + drug ⇆ drug-protein complex)

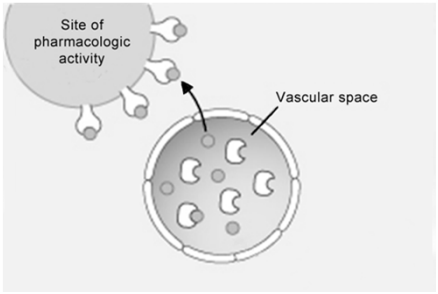
- Proteins are large – sequester (trap) drug in blood
  ∴ drug can't distribute to target receptors
  ∴ protein bound drug is pharmacologically <u>inactive</u>

- Concentration of free drug in blood ↓
  ∴ less pharmacologically active drug

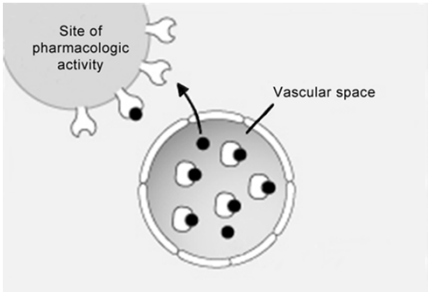
Most drug dosing regimens take protein binding into account BUT there are situations where protein profiles are altered (pregnancy; disease) and dosing needs to be adjusted

Effect of protein binding

Weakly protein bound drug



Highly protein bound drug



Volume of distribution (V_d)

- Administration: dose or amount *(mg, μg)*
- Plasma analysis: concentration *(mg/L, μg/mL)*

$$\text{Concentration} = \frac{\text{dose}}{V_d}$$

Which volume do we use?

Volume of distribution (V_d)

There are several physiological fluid compartments into which hydrophilic drugs can distribute

Total body water (TBW)
= 70kg x 1L/kg x 0.6 = 42L

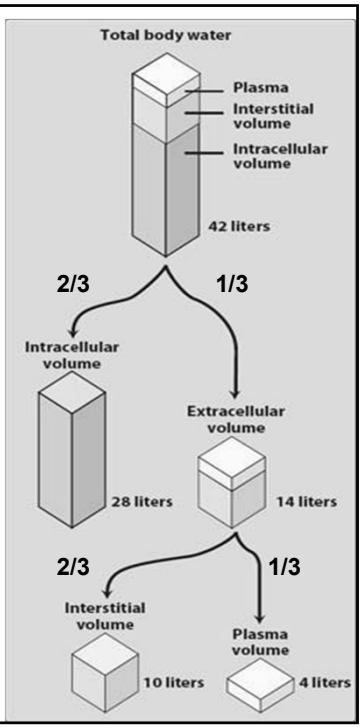
- 70kg: hypothetical PK man
- 1L/kg: density of water
- 0.6: body ~60% water

Examples:

Heparin = 3L → Plasma

Gentamicin = 18L → ECF

Ethanol = 38L → TBW



A clinical example

A 30mg dose of the antidepressant Nortriptyline is administered to a patient iv and a plasma concentration of 25μg/L is subsequently measured.

What is the volume of distribution of this drug?

A clinical example ~ solution

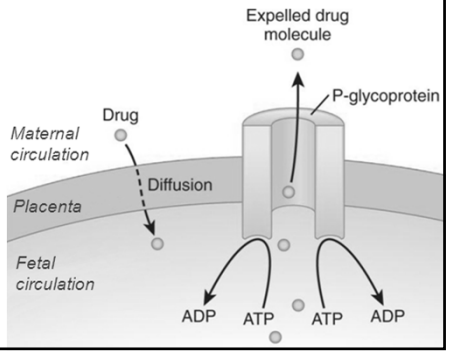
What is volume of distribution?

- NOT a real, physiological volume but rather a *proportionality constant* that relates the amount of drug in the body to its concentration in the blood
- The magnitude of Vd indicates the extent of drug distribution in the body, but not the location

Large Vd (>42 L):	drug distributes outside blood and body fluids into tissues
Small Vd (≤42 L):	drug has limited distribution, typically restricted to blood or physiological fluids

Distribution notes in pregnancy

1. **Plasma protein levels are DECREASED in pregnancy ~ *what affect will this have on drug activity?***
2. **The placenta is NOT a barrier to drug transport – small (<500 Da) MW, lipophilic, un-ionized drugs passively diffuse**
3. **P-glycoprotein (Pgp) drug transporter pumps drugs from <u>fetal to maternal side</u>**



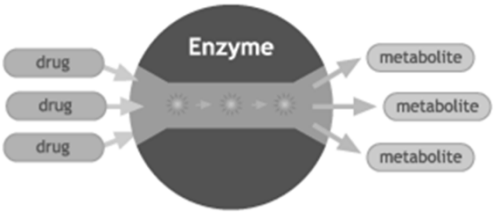
Metabolism

➢ **the irreversible biotransformation of drug**

- makes it <u>more polar</u> to ↑ renal (urinary) excretion

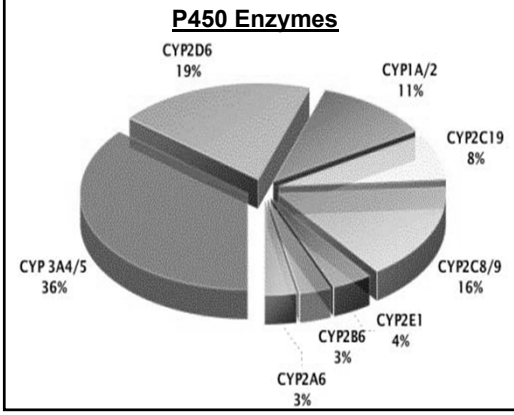
Occurs primarily in the liver via 2 (usually sequential) enzyme-catalyzed processes:

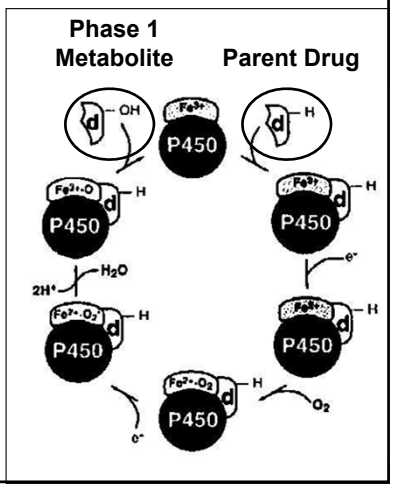
- **Phase I *oxidation/reduction/hydrolysis***
- **Phase II *conjugation***



Phase I: cytochrome P450 enzymes

A superfamily of related enzymes that add on or uncover small polar groups (–OH, –NH_2, –COOH) to ↑ water solubility





P450 enzyme induction and inhibition

- **some P450 enzymes can be induced or inhibited by other drugs, foods, pregnancy or disease**

Induction: ↑ metabolic activity of enzymes
∴ [Drug] ***(ex: alcohol)***

Inhibition: ↓ metabolic activity of enzymes
∴ [Drug] ***(ex: grapefruit juice)***

- **Primary cause of drug interactions**
- **Requires drug dosing to be increased or decreased**
- **P540 enzyme profile changes in pregnancy:**

↑ in CYP 2D6, 3A4 and 2C9 ↓ in CYP 1A2 and 2C19

Practice problem

Relative to a <u>non-pregnant</u> woman, how would drug dosing need to be altered (↑ or ↓) for the following drugs in pregnancy:

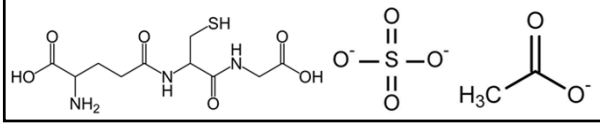
1. **Erythromycin (metabolized by Cyp3A4)**
2. **Omeprazole (metabolized by Cyp2C19)**
3. **Paroxetine (metabolized by Cyp2D6)**
4. **Ibuprofen (metabolized by Cyp2C9)**
5. **Caffeine (metabolized by Cyp1A2)**

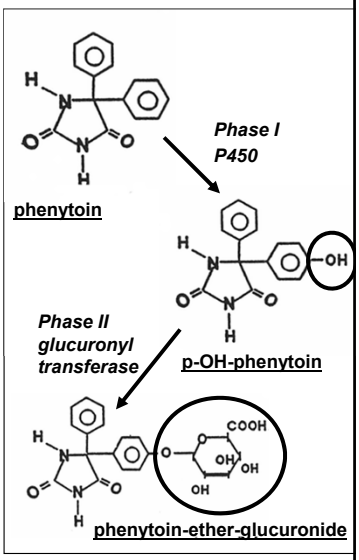
Phase II: conjugative enzymes

Mediated by various non-P450 liver enzymes

- **covalently add large, polar, endogenous molecules to Phase I metabolite**
- **ensures that metabolite is ready for excretion**

(glucuronide, glutathione, sulfate, acetate, amino acids etc)

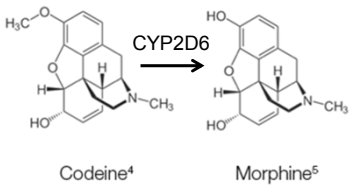




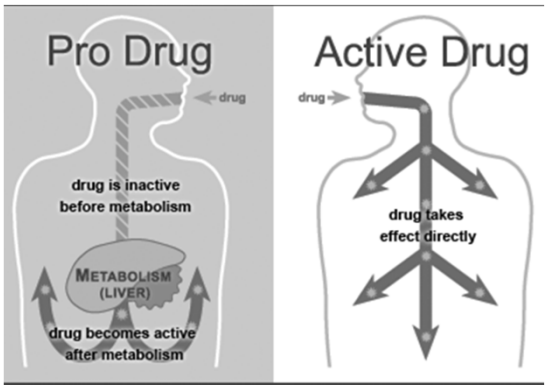
Drug metabolism

- **usually *inactivates* the drug**
- **is required to *activate* <u>prodrugs</u>**

Metabolite + Receptor
≠ MR complex

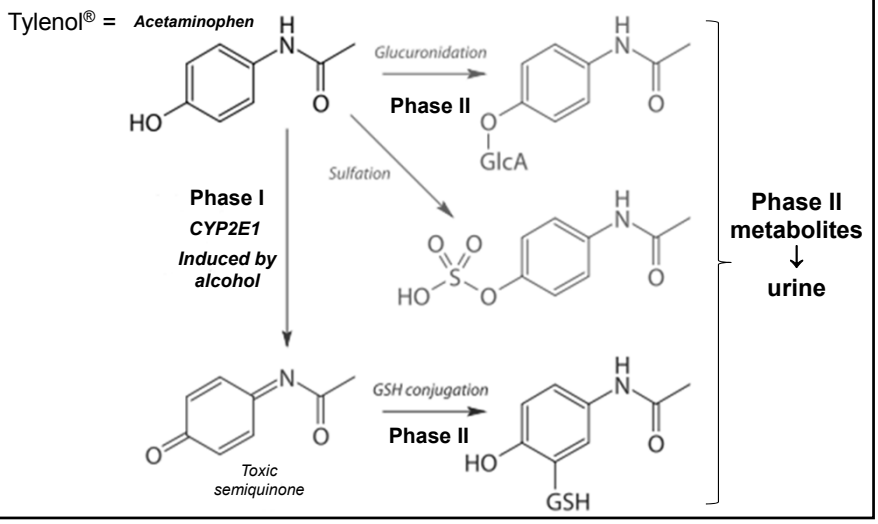


Codeine[4] Morphine[5]



Drug metabolism

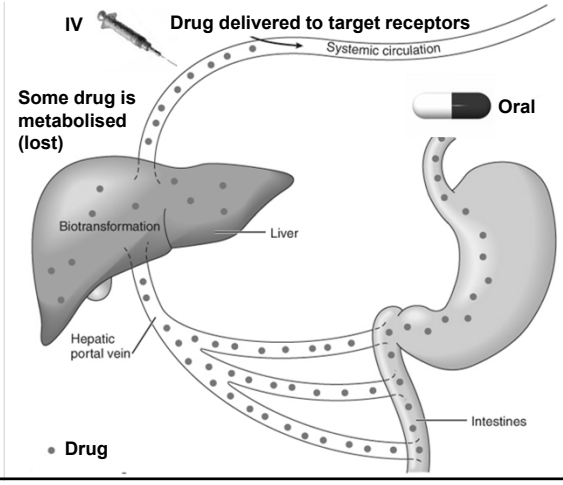
- **may be *harmful* if the metabolite(s) are toxic**



First pass metabolism

Most drugs absorbed from the GI tract are delivered to the liver <u>before</u> reaching the systemic circulation

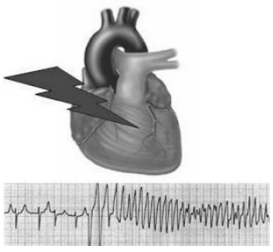
∴ oral doses > iv doses to account for loss due to metabolism



Drug metabolism in the gut

Some drugs undergo significant metabolism by bacterial enzymes in the gut *(ex: digoxin)*

What effect might a course of antibiotic therapy have in a person taking digoxin?



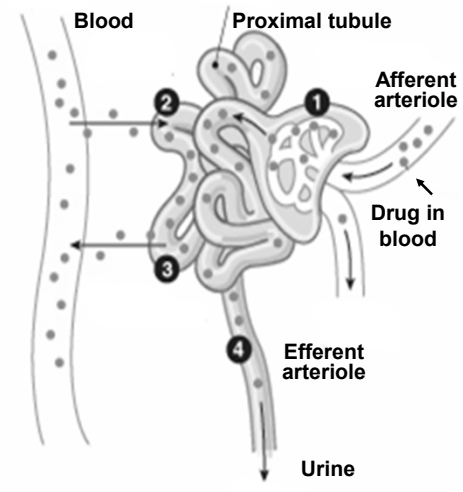
Metabolism notes in pregnancy

1. **P450 enzymes are altered in pregnancy (see previous)**
2. **The placenta is capable of metabolizing drugs, but this is of little relevance to the mother *(ie it does not significantly impact the maternal drug concentration)***
3. **However, placental metabolism can protect the fetus from drug exposure (some P450 and conjugation)**
4. **The fetal liver is capable of metabolizing drugs by <u>oxidation</u> reactions only (all other enzymes are not yet developed)**

Excretion – kidney (renal excretion)

- **The irreversible loss of drug from the body**

1. **<u>Passive Glomerular Filtration</u>**
   diffusion of small drugs <20kDa
2. **<u>Active Tubular Secretion</u>**
   transport systems for large drugs
   **Pgp acts here*
3. **<u>Passive Tubular Reabsorption</u>**
   concentration gradient may drive uncharged drug back into blood
   **urine pH is key*



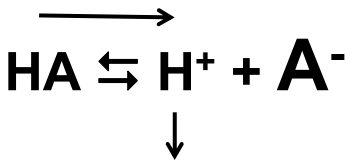
Absorbed or Excreted?

Weak acid: $HA \rightleftharpoons H^+ + A^-$

Weak base: $B + H^+ \rightleftharpoons BH^+$

Changing urine pH to treat an overdose

- **increasing urine pH shifts equilibrium to promote excretion of weak acid drugs** ***(ex: aspirin)***
  - **iv sodium bicarbonate raises pH from 6-8**



Ionized form is water soluble .: excreted in urine

*Remember: ↑ pH = ↓ $[H^+]$

Changing urine pH to treat an overdose

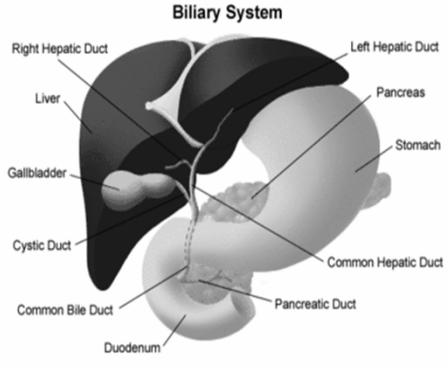
How would you modify the urine pH to treat an overdose of a weak base drug?

$$B + H^+ \leftrightarrows BH^+$$

Excretion – bile/feces (aka biliary excretion)

- **Drugs and/or metabolites actively secreted into biliary tract – delivered to duodenum via common bile duct **Pgp acts here***

- **Carrier-mediated process ∴protein binding & ionization are not limiting factors**



Excretion – breast milk

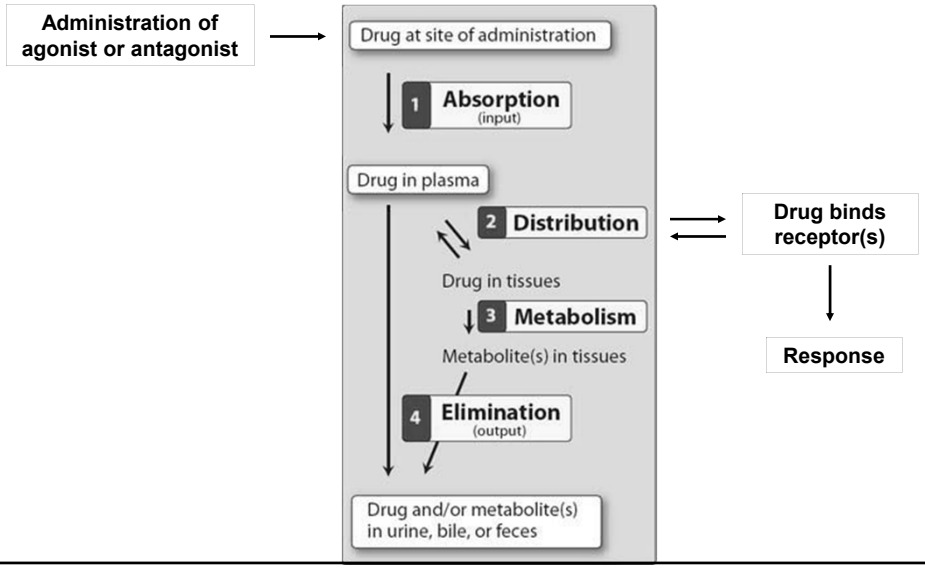
1. **Breast milk is a relatively minor route of drug excretion from mother's perspective**

2. **Potentially significant for nursing baby**

3. **Breastmilk pH < plasma *(7.2 vs 7.4)***
   → what group of drugs will concentrate (be trapped) in breastmilk – weak acids or bases?

4. **Drugs of concern: CNS depressants, sedatives, anticancer drugs**

Summary



CLARITIN®
Schering

Loratadine

Histamine H_1-Receptor Antagonist

Pharmacology: Loratadine is a long-acting tricyclic antihistamine with selective peripheral H_1-receptor antagonistic activity. It exhibits a dose-related inhibition of the histamine-induced skin wheal and flare response in humans which is rapid in onset, is apparent at 2 hours and persists throughout the 24-hour observation period. Single oral doses up to 160 mg and repeat daily doses of 40 mg for up to 13 weeks were well tolerated with the incidence of sedation and dry mouth being no different from placebo.

Pharmacokinetics: ^{14}C-loratadine is rapidly absorbed reaching C_{max} values (4.7, 10.8 and 26.1 ng/mL) at 1.5, 1.0 and 1.3 hours for the 10, 20 and 40 mg dose, respectively. The loratadine elimination half-life (t½ β) ranged from 7.8 to 11 hours. Descarboethoxyloratadine, the major active metabolite, reached C_{max} values (4.0, 9.9 and 16.0 ng/mL) at 3.7, 1.5 and 2.0 hours after a dose of 10, 20 and 40 mg, respectively. Its t½ β ranged from 17 to 24 hours. The accumulation indices, calculated by C_{max} and the area under the curve (AUC) ratios, did not change after the 5th day, indicating little or no accumulation of either loratadine or its metabolite after a multiple once per day dosage regimen. The t½ β at steady-state levels for loratadine and its metabolite were 14.4 and 18.7 hours, respectively, similar to that reported following a single oral dose.

The confidence intervals for C_{max} and $AUC_{0-\infty}$ are within the 80 to 125% range indicating that the Claritin Rapid Dissolve Tongue Tablets were bioequivalent with respect to the active metabolite descarboethoxyloratadine.

After administration of a single 10 mg dose of loratadine as either the Rapid Dissolve Tongue Tablet, a conventional tablet, or the syrup formulation (1mg/mL), peak plasma concentrations of loratadine and its metabolite were achieved at approximately 1 and 2 hours, respectively; mean elimination half-life of the active metabolite ranged between 19 and 21 hours. See Tables I and II.

Since loratadine is extensively metabolized there was a high inter-subject variability in the plasma drug concentrations. Hence, the percent coefficient of variation (CV) of the pharmacokinetic parameters was large.

Following administration of 10 mg of loratadine once daily for 10 days as either a Rapid Dissolve Tongue tablet or a conventional tablet, plasma concentrations of loratadine and its active metabolite were at steady state by day 5 with both formulations. Mean peak plasma concentrations (T_{max}) of loratadine and its metabolite in both formulations were attained at 1.3 hours; peak to trough fluctuations observed for the Rapid Dissolve Tongue tablet and the conventional tablet were similar with respect to loratadine and its metabolite. Mean elimination half-life of the active metabolite was 20 hours for both formulations. See Table III.

Table I—Claritin

Mean (n=18) Pharmacokinetic Parameters for Loratadine and Descarboethoxyloratadine [(Claritin Rapid Dissolve Tongue 10 mg Tablet vs Claritin 10 mg Tablet (Conventional)]

	Mean (%CV[a])			
	Claritin Rapid Dissolve Tongue 10 mg Tablet		Claritin 10 mg Tablet (Conventional)	
Parameter	Loratadine	DCL[b]	Loratadine	DCL[b]
C_{max} (ng/mL)	2.56 (83)	3.72 (53)	2.11 (90)	3.66 (45)
T_{max} (h)	1.14 (72)	1.97 (129)	1.00 (34)	1.97 (98)
$AUC_{0-\infty}$ (ng·h/mL)	6.14 (100)	49.1 (50)	4.64 (106)	48.4 (44)

[a]Coefficient of variation.
[b]DCL: Descarboethoxyloratadine.

Table II—Claritin

Mean (n=18) Pharmacokinetic Parameters for Loratadine and Descarboethoxyloratadine (Claritin Rapid Dissolve Tongue 10 mg Tablet vs Claritin Syrup 1 mg/mL)

	Mean (%CV[a])			
	Claritin Rapid Dissolve Tongue 10 mg Tablet		Loratadine Syrup (1 mg/mL)	
Parameter	Loratadine	DCL[b]	Loratadine	DCL[b]
C_{max} (ng/mL)	2.65 (193)	3.46 (44)	3.62 (150)	3.65 (35)
T_{max} (h)	1.00 (30)	1.42 (39)	0.86 (44)	0.94 (17)
$AUC_{0-\infty}$ (ng·h/mL)	6.33 (201)	40.8 (29)	10.1 (147)	38.8 (27)

[a]CV: Coefficient of variation.
[b]DCL: Descarboethoxyloratadine.

Table III—Claritin

Loratadine, Administered as Either Claritin Rapid Dissolve Tongue 10 mg Tablet or Claritin 10 mg Tablet (Conventional Tablet) to Healthy Subjects Once Daily for 10 Days

	Mean (%CV[a])					
	Loratadine			DCL[b]		
	Day 5	Day 7	Day 10	Day 5	Day 7	Day 10
Parameter	Claritin Rapid Dissolve Tongue 10 mg Tablet					
C_{max} (ng/mL)	3.79 (83)	3.35 (73)	4.04 (80)	4.65 (58)	4.69 (68)	4.69 (73)
AUC(r)[c] (ng.h/mL)	12.0 (76)	11.2 (75)	12.2 (71)	71.9 (88)	82.1 (93)	72.9 (103)
	Claritin 10 mg Tablet (Conventional tablet)					
C_{max} (ng/mL)	3.12 (77)	3.43 (64)	3.81 (67)	4.56 (63)	5.12 (68)	4.60 (81)
AUC(r)[c] (ng.h/mL)	10.6 (67)	11.6 (61)	11.3 (64)	75.4 (94)	85.0 (99)	73.5 (114)

[a]CV: Coefficient of variation.
[b]DCL: Descarboethoxyloratadine.
[c]Area under the plasma concentration-time curve from time 0 to 24 h (for day 10, using concentration time points matching those on days 5 and 7).

Table IV—Claritin

Adverse Experiences Reported in Adult Patients

Claritin Tablets, 10 mg Once Daily vs Placebo and Comparatives

Number (%) of Adult Patients Reporting Frequently Occurring (>2% of Loratadine-treated Patients) Adverse Experiences in Adults Possibly or Probably Related to Treatment: Patients Treated with Claritin, Placebo and Comparatives

Adverse Experience	Loratadine 10 mg once daily N=1 241	Placebo N=1 652	Clemastine 1 mg b.i.d. N=687	Terfenadine 60 mg b.i.d. N=506	Astemizole 10 mg once daily N=342
Fatigue	54 (4)	62 (4)	62 (9)	17 (3)	22 (6)
Headache	97 (8)	104 (6)	32 (5)	40 (8)	26 (7)
Dry mouth	49 (4)	32 (2)	22 (3)	15 (3)	2 (1)
Dryness in nose	9 (<1)		6 (<1)	3 (<1)	
Sedation*	99 (8)	101 (6)	151 (22)	41 (8)	50 (15)

*Reported as somnolence, sleepiness, drowsiness, lethargy, slow or "drugged feeling."

In a single-dose, 2-way cross-over study with Claritin Rapid Dissolve Tongue Tablets, food increased the AUC of loratadine and descarboethoxyloratadine by 90% and 6%, respectively. Food decreased the mean C_{max} of loratadine and descarboethoxyloratadine by 9% and 15%, respectively. The time to peak plasma concentration (T_{max}) of loratadine and descarboethoxyloratadine were delayed by approximately 2.4 and 3.7 hours, respectively, when food was consumed prior to administration of Claritin Rapid Dissolve Tongue Tablets.

In a single-dose, randomized, 2-way cross-over study with 10 mg Claritin Rapid Dissolve Tongue Tablets in 24 subjects, under fasting condition, the mean AUC(tf) and C_{max} values were increased by 84% and 30%, respectively, when administered without water compared to administration with water, demonstrating that bioavailability was not attenuated when Claritin Rapid Dissolve Tongue Tablet was dissolved on the tongue and subsequently swallowed without concomitant consumption of a liquid. The bioavailability of descarboethoxyloratadine was not different when administered without water.

Approximately 82% of the ^{14}C-loratadine dose is excreted in the urine (40%) and feces (42%) over a 10-day period. Approximately 27% of the dose is eliminated in the urine during the first 24 hours largely in the conjugated form. Unchanged drug is present only in trace quantities in the urine and the active metabolite descarboethoxyloratadine represents only 0.4 to 0.6% of the administered loratadine dose.

In 2 randomized, multicentre, double-blind, placebo-controlled, parallel group studies, performed in patients with seasonal allergic rhinitis, the safety and efficacy of Claritin Rapid Dissolve Tongue Tablets and the conventional Claritin tablets vs placebo were evaluated. Claritin Rapid Dissolve Tongue Tablets administered as 10 mg once daily for 15 days, were significantly more effective than placebo in reducing physician-evaluated and patient daily-assessed total combined, total nasal, and total non-nasal symptoms in patients with seasonal allergic rhinitis. Claritin Rapid Dissolve Tongue Tablet had a clinical effect comparable to or greater than conventional Claritin tablet. Both of the drugs were safe and well tolerated in this patient population. From clinical studies conducted on healthy individuals with allergic rhinitis, no clinical consequences are anticipated in this population, whether or not Claritin Rapid Dissolve Tongue Tablets are administered with or without food.

Indications: Tablets and Rapid Dissolve Tongue Tablets: For the relief of symptoms associated with seasonal and perennial allergic rhinitis, such as sneezing, nasal discharge and itching, and ocular itching and burning, and for the relief of symptoms and signs of chronic urticaria and other allergic dermatologic disorders. Clinical studies to date support treatment for up to 6 months, thus medical recommendation is advised for longer-term use. The Rapid Dissolve Tongue Tablets should be taken on an empty stomach.
Syrup: For the relief of symptoms associated with seasonal allergic rhinitis, such as sneezing, nasal discharge and itching, and ocular itching and burning, and for the relief of symptoms and signs of chronic urticaria and other allergic dermatologic disorders. In children, it is intended for short-term use only unless taken under medical supervision.

Contraindications: In patients who have shown hypersensitivity or idiosyncrasy to the drug or its components.

Precautions: Patients with severe liver impairment should be administered a lower initial dose because they may have reduced clearance of loratadine; an initial dose of 5 mg once daily or 10 mg every other day is recommended.

Pregnancy and *Lactation:* The safe use of loratadine during pregnancy or lactation has not been established and therefore the compound should be used only if the potential benefit justifies the potential risk to fetus or infant.
Children: The safety and efficacy of loratadine in children younger than 2 years of age have not been established. Long-term safety and efficacy of loratadine in children between the ages of 2 and 12 have not been demonstrated. Therefore, it is desirable that loratadine not be administered to children between the ages of 2 and 12 for longer than 14 days, unless recommended by a physician.

Table V—Claritin

Adverse Experiences Reported in Adult Patients

Claritin Rapid Dissolve Tongue Tablets vs Claritin Conventional Tablets vs Placebo

Number (%) of Patients Reporting Frequently Occurring (≥ 2% of Rapid Dissolve Tongue Tablet-treated patients) Adverse Experiences Possibly or Probably Related to Treatment in Seasonal Allergic Rhinitis Studies

	Number (%) of Patients		
Adverse Experience	Loratadine 10 mg Rapid Dissolve Tongue Tablet (N=495)	Loratadine 10 mg Tablet (N=328)	Placebo (N=497)
Dry Mouth	8 (2)	8 (2)	5 (1)
Fatigue	13 (3)	12 (4)	16 (3)
Headache	40 (8)	23 (7)	55 (11)
Somnolence	22 (4)	13 (4)	3 (3)

Henderson Hasselbach Calculation - Solution #1

- Weak acid dissociation eqn: $HA \rightleftharpoons H^+ + A^-$
- Want to solve for the HA form → unionized ∴ absorbable

$$pH = pKa + \log \frac{A^-}{HA}$$

$$1.0 = 1.8 + \log \frac{A^-}{HA}$$

$$-0.8 = \log \frac{A^-}{HA}$$

$$\text{antilog}(-0.8) = 10^{(-0.8)} = 0.158 = \frac{A^-}{HA}$$

- which is the same as $\frac{0.158}{1} = \frac{A^-}{HA}$

$$\% HA = \frac{HA}{A^- + HA} \times 100 = \frac{1}{(0.158 + 1)} \times 100 = 86\%$$

Henderson Hasselbach Calculation - Solution #2