Ch.1:

Pharmacokinetics:

Kidney Excretion:

A. Acidic drug. Pyrimethamine

→ Make urine basic

→ Use $NaHCO_3$. Orally or IV

B. Basic drug. Phenobarbital

→ Make urine acidic

→ Use Ascorbic acid / Vit. C OR NH_4Cl

↳ Without citrate!

ATP-binding cassette family:

→ Efflux of drug outside cell. Less bioavalibility

→ Less selective

A. P-Glycoprotein (MDR1 transporter):

* Brain
* Testes
* Intestines
* neoplastic cells (abnormal cell growth.. benign or malignant) (Metastatis= spread of cancer to other tissues)

B. MRP transporters:

* Excretion (Efflux) into urine & bile
* Used by some cancer cells to be resistant to chemotherapeutic agents

SLC families:

→ Active transport via ion gradients, don't bind ATP.

→ Secondary active transport

→ Re-uptake of neurotransmitters

→ Used by drugs

Endocytosis:

→ Vitamin B12 - Intrinsic factor complex into blood stream in gut

↓
Cbl large

→ Iron - transferrin complex in RBCs.

Liver chirrosis:

→ Less oral drug lost via first pass effect.. blood bypass liver

→ Drug toxicity

Solubility & low F:

Atenolol → too polar

Acyclovir → too non-polar

Grapefruit juice:

→ Inhibits P-glycoprotein, MDR... MRP transporters. Less drug efflux

→ Inhibit first pass affect

→ ∴ more drug bioavailability

→ CYP450 inhibitor. More active drug. (Less if prodrug)

F:

IV = 1 or 100 %

A. Oral + complete absorption + first pass effect

$$F = 1 - ER$$

ER: drug lost in first pass effect

B. Oral + incomplete absorption + first pass effect

$$F = f(1 - ER)$$

f: fraction absorbed

Vd =

Morphine:

→ ER = 0.67. Oral + complete absorption

→ F = 1 - 0.67. **F = 0.33**

Charcoal:

→ Used in drug overdose

→ Absorb drug & stops it from entering enterohepatic cycle.

→ More drug excretion. Reduce half-life

Vd:

$$Vd = \frac{\text{Drug in body}}{\text{Drug plasma conc.}}$$

$$\frac{m}{\frac{m}{v}} = \frac{mv}{m} = v \qquad V = \frac{n}{c}$$

Drug binding proteins:

Albumin

α_1-acid-glycoprotein – binds to basic drugs

Clearance:

$$Cl = \frac{\text{rate of elimination}}{\text{Drug plasma conc.}}$$

$Cl \downarrow V/t$

note: See how factors affect Cl & know if x or ÷.

Cl should always be V/t

$$k = \frac{0.693}{t_{1/2}} \qquad Cl = k \times Vd \Rightarrow Cl = \frac{0.693}{t_{1/2}} \times Vd$$

$t_{1/2} \downarrow$ Cl ↑

Vd ↑ Cl ↑

$\Rightarrow Cl = \frac{0.693}{t_{1/2}} \times Vd \rightarrow \frac{L}{t}$

$$Cl_R = \frac{\text{Drug conc. in urine} \times \text{Urine flow rate}}{\text{Drug plasm conc.}}$$

$$Cl_H = Q \cdot ER$$

Q = blood flow

ER = extraction ratio $= \frac{C_i - C_o}{C_i}$

C_i = Drug conc. entering liver

C_o = Drug conc. exiting liver

ER < 1

First Order $\quad V_0 = \frac{[S] \times V_{max}}{[S] + km}$

$$L_D = Vd \times Css_{desired}$$

Emergencies. When $t_{1/2}$ too long. L_D used

$$M_D = Cl \times Css_{desired}$$

First order elimination drugs:

- Most

Zero order / saturable elimination drugs:

→ A. P. E

* Aspirin
* Phenytoin
* Ethanol

High hepatic extraction ratio drug:

* Metabolized by liver fast, most in first pass effect.
* MLPV → Metabolism Liver Pass Very "fast"
* Morphine

MLPV

* Lidocaine
* Propranolol
* Verapamil

Ch.2

Routes

Angina pectoris:

→ Use sublingual route. Rapid onset

Lipid-soluble drugs:

→ CANT use IV. As precipitates in blood

Oily / Ethylene glycol:

→ Reservior at site of administration in IM. Slower release

Asmtha drug & Anesthetics:

→ Inhalational / Respiratory route

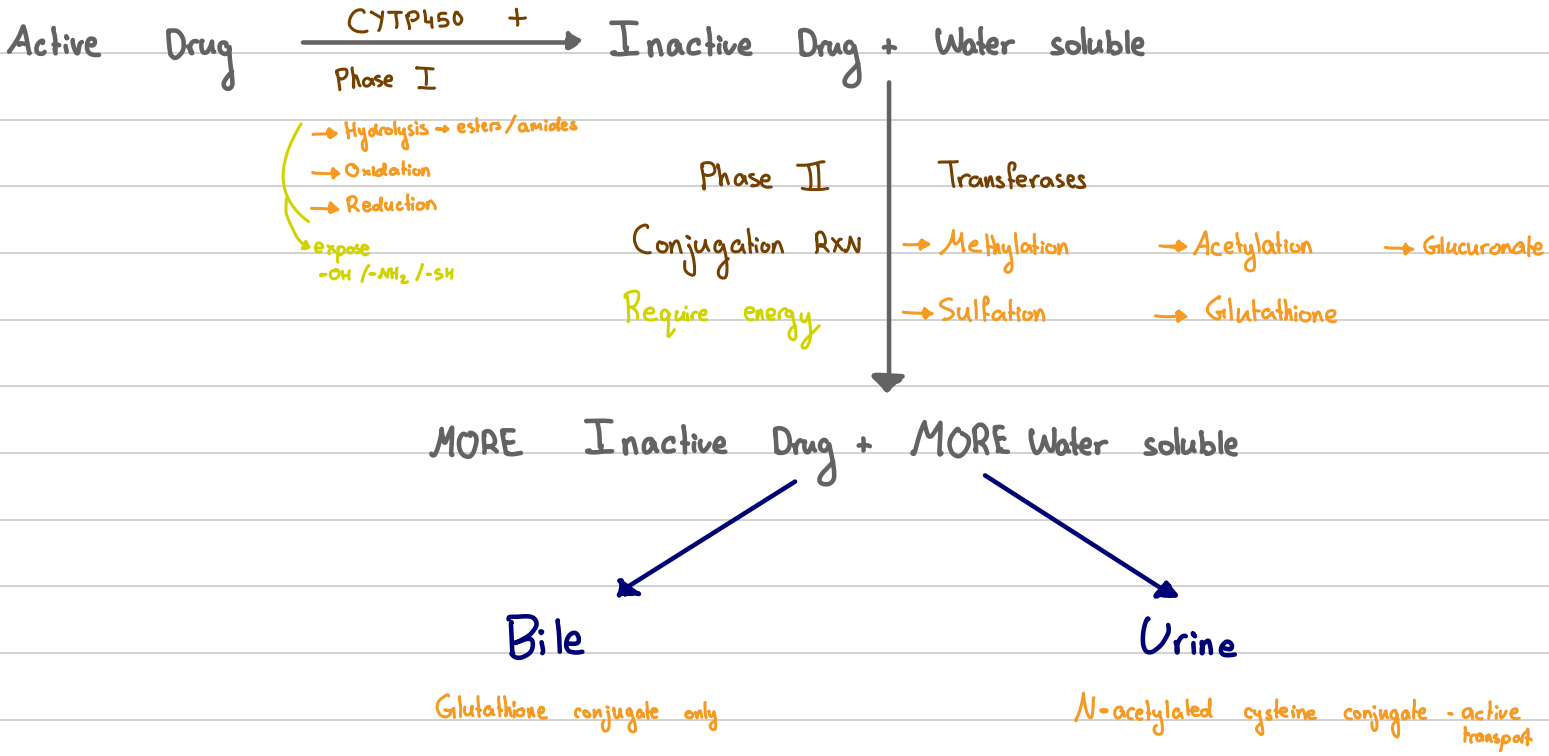
Angina:

→ Transdermal route. On skin for systemic effect.

Ch. 3

Drug Biotransformation (metabolism):

No order.



Prodrugs: (inactive to active, CYP450)

* Codeine (codeine → morphine)
* Levadopa (levadopa → dopamine)
* Minoxidil (activated by phase II sulfation)

Drug to toxin: (CYP450)

* Paracetemol / Acetaminophen ⟶ N-acetyl-p-benzaquinoneimine (hepatoxin)
  - NAPQI
  - ↳ give patient N-acetyl Cysteine
* Halothane ⟶ Free Radicals (hepatoxin)

Important CYP450 enzyme:

> 50% of prescribed drugs

* CYP3A4

CYP450 inducers:

* Carbamazepine - autoinduction → Drug tolerance
* Barbiturates
* Phenytoin
* Rifampin
* St Johns wort
* Cruciferous vegetables
* Tobacco smoke + charcoal meat

CYP450 inhibitors:

* Erythromycin - Antibiotic. Inhibits CYP3A4
* Grapefruit furanocoumarins - Suicide inhibitor + P-glycoprotein inhibitor. Inhibit CYP3A4

Phase II points:

Type of Conjugation	Endogenous Reactant (Reactant w/ Drug)	Transferase (Location) (Enzyme)	
Glucuronidation (Adults more; Most common)	UDP glucuronic acid	UDP glucuronosyltransferase (microsomes) UGT's	-OH -NH -SH -COOH -NHOH
Acetylation	Acetyl-CoA cofactor	N-Acetyltransferase (cytosol) NATs	
Glutathione conjugation	Glutathione (GSH) Nucleophile	GSH-S-transferase GSTs (cytosol, microsomes)	-epoxides -halogen replacement
Sulfation (Infants more)	Phosphoadenosyl phosphosulfate PAPS	Sulfotransferase (cytosol) SULT's	-OH -NH -SH -COOH -NHOH
Methylation	S-Adenosylmethionine SAMs	Transmethylases (cytosol) MTs	-N -O -S

Glucuronidation and Sulfation: together

Glutathione conjugated drug excretion:

Drug — Glutathione conjugate → Cysteine conjugates → N-acetylated cysteine conjugates Mercapturic Acid conjugates

Bile excretion only

Urine excretion - active transport

Drugs that get more active / more toxic with phase II metabolism:

A. Morphine —glucuronidation→ Morphine-6-glucuronide (more potent.)

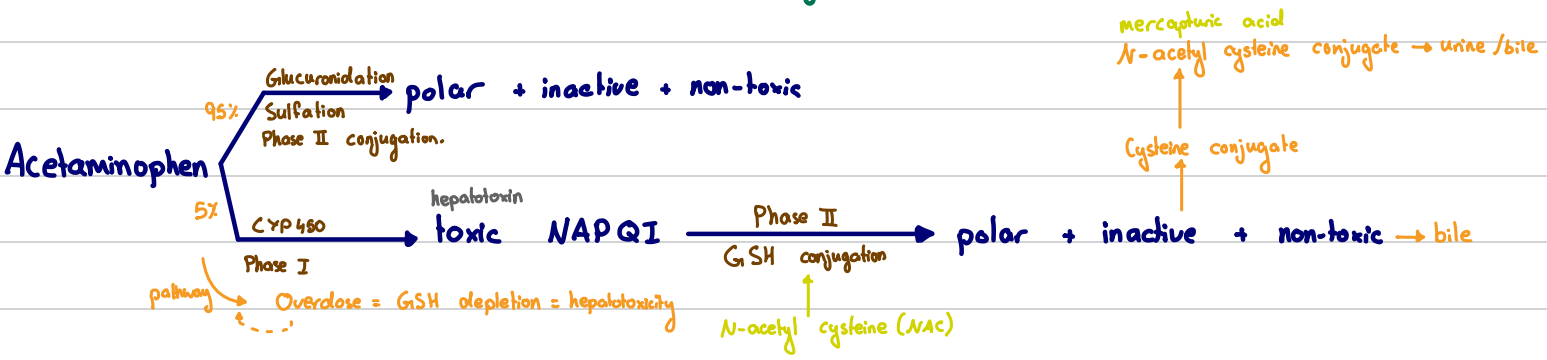
B. Non-steroidal anti-inflammatory drug Acyl glucuronidation. UGTs & UDP-glucuronic acid

C. Isoniazid N-acetylation. NATs & acetyl CoA.

D. N-hydroxyacetylaminoflourine O-sulfation. SULTs & PAPs
don't be fooled.

E. Inactive prodrug minoxidil Sulfation. SULTs & PAPs

Acetaminophen / Paracetemol metabolism & toxicity:



Overdose: Within 8-16 hrs. Administer N-acetyl cysteine to replenish GSH & drive GSH conjugation → eleminate toxic NAPQI

(not GSH cuz can't cross membrane)

Pharmacodynamics 1:

Receptors:

* GABA - ion channel receptor new
* nicotinic - ion channel receptor
* Muscarinic - G-protein coupled receptor
* adrenergic - G-protein coupled receptor α_1 α_2 β_1 β_2 β_3
* Opioid - G-protein coupled receptor new
* Insulin - Enzyme linked, RTK
* Steroid - Intracellular receptor

Therapeutic Index: Toxic Dose : Therapeutic Dose

antibiotic

Penicillin: Safe drug. Wide TI. Big gap between toxic & safe dose

Warfarin: Narrow safety margin. Narrow TI. Small gap between toxic & safe dose

anti-coagulant

Beta blockers:

* Beta adrenergic antagonist
* Beta receptors on heart less activated. Slower heart rate.
* Antihypertensive. Decrease blood pressure

Warfarin:

* Anticoagulant
* Vit.K helps in blood clotting. Warfarin inhibits Vit. k
* Vit. K antagonist

Insulin:

* Muscle & Liver cells increased glucose uptake

Pharmacodynamics 2:

Agonists:

A. Adrenaline / Epinephrine:

* Adrenergic receptor agonist

B. Morphine:

* Opioid GPCR agonist
* CNS depressant
* Risk of respiratory depression. Increased risk if coupled with antihistamines

Partial Agonist:

A. Buprenorphine:

* Opioid GPCR partial agonist.
* Weaker submaximal response ∴ Less risk of respiratory depression
* No full agonist - Buprenorphine acts as agonist
* Full agonist present - Buprenorphine acts as a (competitive) antagonist

Antagonists:

A. Naloxone:

* Opioid GPCR antagonist
* Blocks morphine analgesic (↗ pain relief) & respiratory (↗ Depressant) effects
* Reverses opioid overdose
* Given to rehab patients ~ heroin

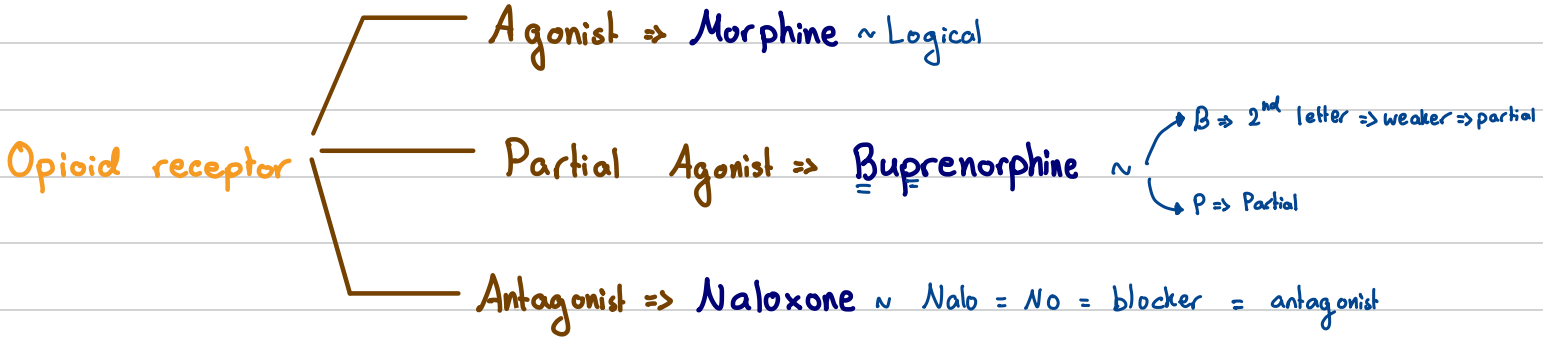
B. Beta blocker:

* Adrenergic β antagonist of heart
* Antihypertensive
* End with -lol

C. Warfarin:

* Vit.K antagonist. Anticoagulant.

Opioid Receptor memo tips:



Grapefruit Juice:

* Inhibit P-glycoprotein - less drug efflux
* Inhibit first pass effect - less metabolism. More bioavailability
* Inhibit (suicide) CYP3A4 - less metabolism. More bioavailability

Additive 1 + 1 = 2 Aspirin & Warfarin

Synergic 1 + 1 >> > 2

Potentiation Increase effect of other without having effect

Antagonistic 1 + 1 < 2 Naloxone & Morphine

Warfarin + Aspirin:

Warfarin - * Vit.K antagonist. Anticoagulant.

Aspirin - Blocks COX, less thromboxane A2. NSAID. Less blood coagulation. More A.A directed towards PGI_2 / Prostacyclins, blood coagulation inhibited

Additive effects. 1 + 1 = 2

Alcohol + Benzodiazpines / Diazepam

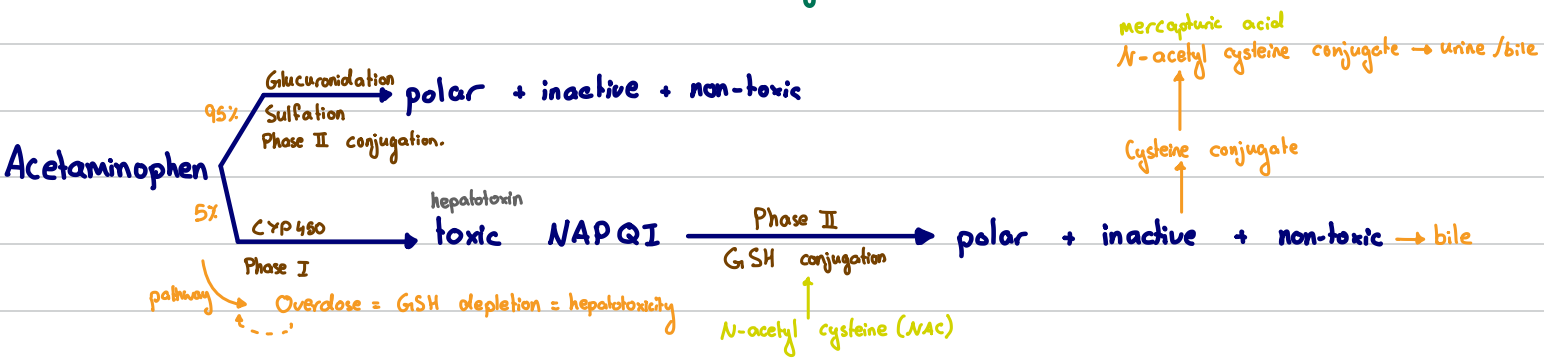
Both are CNS depressantss.

Sedative effects (GABA)

Respiratory Depression !!

Synergic effects. 1 + 1 > 2

Acetaminophen / Paracetemol metabolism & toxicity:



Overdose: Within 8-16 hrs. Administer N-acetyl cysteine to replenish GSH & drive GSH conjugation

(not cont GSH cuz cross membrane)

↓

eleminate toxic NAPQI

Acute Liver Failure