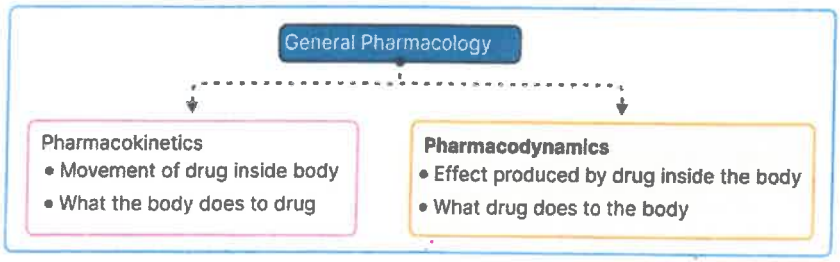
PHARMACOLOGY

1 GENERAL PHARMACOLOGY

Pharmacokinetics

- Absorption
- Distribution
- Metabolism
- Excretion
- Pharmacokinetics - k/s ADME study
- Primary pharmacokinetic parameters:
  - In absorption - BA (bioavailability)
  - In distribution - Vd (volume of distribution)
  - In elimination (metabolism + excretion) - Cl (clearance)
  - With help of BA, Vd, Cl other pharmacokinetic parameters are calculated
    - → Loading dose
    - → Maintenance dose
    - → Half life



Absorption

Pathways of Absorption

1. **Simple/passive diffusion**
   - Most common pathway of drugs - to cross cell membrane - enter into blood
   - Cell membrane is made up of phospholipids
     - Only lipid soluble drugs cross cell membrane
     - By simple/passive diffusion

Non-ionized / lipid soluble / non-polar drugs	Strong ions/water soluble/polar drugs	Weak ionic drugs
• Cross cell membrane • Enters the cell by simple/passive diffusion	• Cannot cross cell membrane • Not absorbed into blood • Not given orally o Aminoglycosides o Heparin	• Weak acidic or weak basic drugs • Depending on pK value o These drugs cross the cell membrane

pK value

- If drug kept in a media - with certain pH
- pH at which a drug is 50% ionised and 50% non-ionized
- That pH is pK value of drug
- Measured by Henderson - Hasselbalch equation

Henderson-Hasselbalch equation

$pH = pKa + Log_{10}([A^-]/[HA])$

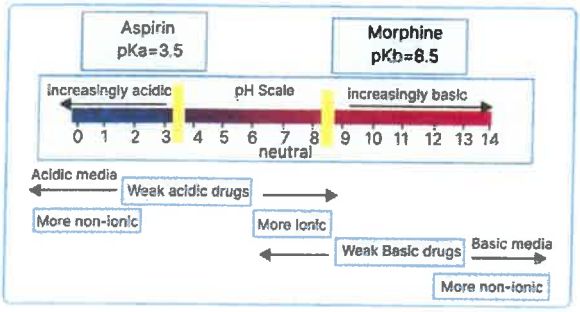
- A^- – ionic concentration of drug
- HA – non ionic concentration of the drug
- If A^- and HA become 50%
  - $Log_{10}(1) = 0$
  - Then pH = pKa

PYQ

Q1. If pH of media is changed to 1, by how much ionisation changes?

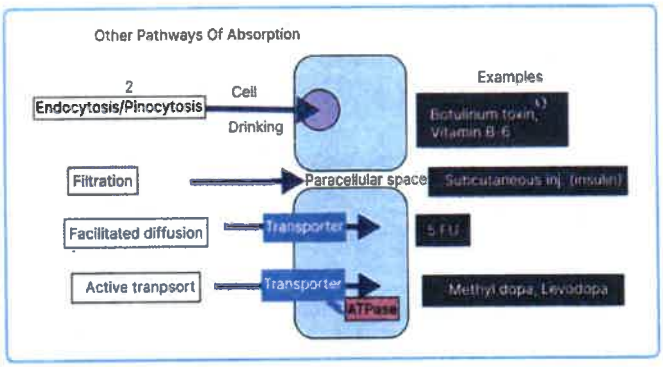
Ans. If the pH of the media is changed to 1, the ionisation changes by 10%

- If weak acidic drug and weak basic drug are kept in different media:
  - Weak acidic drug in a more acidic media OR Weak basic drug in a more basic media
    - → Drug becomes more non-ionic
    - → Lipid soluble



- Weak acidic drug in more basic media OR Weak basic drug in a more acidic media
  - → More ionic forms
  - → Water soluble
- For example, Aspirin has a pKa 3.5

Oral aspirin - enter stomach (pH 0-1)	Inside stomach cell (pH - 7.4)
• Becomes non ionized • Crosses cell membrane of the stomach • Enters into the stomach cell	• Ionized Aspirin shows ion trapping inside the stomach cell so that it can enter into the blood. • S/E: Gastric ulcers



P-glycoprotein

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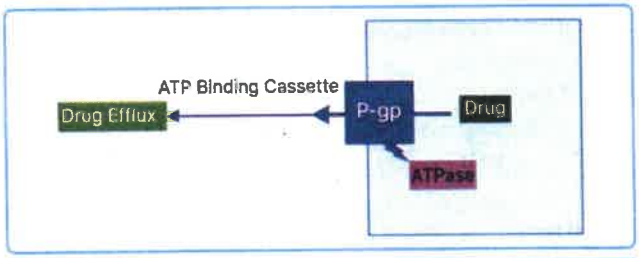
- Active transporter
- **Also known as** efflux transporter
- Requires ATP **and thus is known as** ABC protein (ATP binding cassette)
- Also known as MRP-2 protein (Multi-drug resistant protein)
  - If p-gp identifies a drug in;
    - → GIT – reduce absorption/bioavailability
    - → Kidney – increase excretion of the drug
    - → Liver – increases bile excretion
    - → BBB, placenta – reduce the entry
- Substrate of p-gp: Digoxin
- P-gp inducers vs P-gp inhibtors:
- Immunosuppressive drug - given in organ transplant - Cyclosporine
  - Inhibits p-gp
  - P-gp responsible for excretion of bile
  - Reduces the excretion of bile
  - Cyclosporine causes cholestatic jaundice
    - → By inhibiting p-gp



P-gp inducers	P-gp inhibitors

• Drugs increase the activity of p-gp
• Example: Rifampicin
• If Rifampicin combined with digoxin
  ○ Increase urinary excretion of digoxin
  ○ Reduce plasma concentration
  ○ Loss of effect of digoxin
	• Reduce the activity of p-gp
	• Drugs - mnemonic: **QVACK**
	  ○ Quinidine
	  ○ Verapamil
	  ○ Amiodarone
	  ○ Clarithromycin/erythromycin
	  ○ Ketoconazole
	• When these drugs combined with digoxin
	  ○ Reduce the urinary excretion of digoxin
	  ○ Increases plasma concentration
	  ○ Leads to toxicity

Q2. Digoxin is excreted in urine by which transporter?
Ans. P-glycoprotein

Routes of administration of drug

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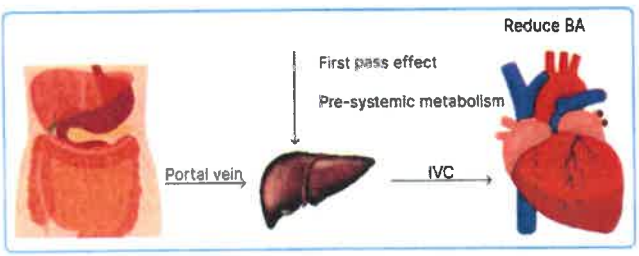
Oral route

- Most common route of administration
- Oral drug - enter stomach - to the intestine
- All drugs absorbed through small intestine (duodenum) >> stomach
  - Due to its greater surface area
- From intestine - drug enter portal circulation (portal vein) – reaches liver
- Drugs undergo first pass metabolism (degradation) in liver
  - First pass effect



- Also k/s: Pre-systemic metabolism
- Reduces bioavailability

- Less amount of drug reaches heart through IVC

Oral Drugs having high First pass metabolism effect

- Not given orally
- If given then taken in high oral dose

Drugs not given orally	Drugs given in high oral dose
• Lignocaine • Fentanyl • Natural steroids o Hydrocortisone o Aldosterone o Oestrogen → Hencé synthetic oestrogen is given orally in OCP o Testosterone	• Propranolol • Morphine • Nitrates

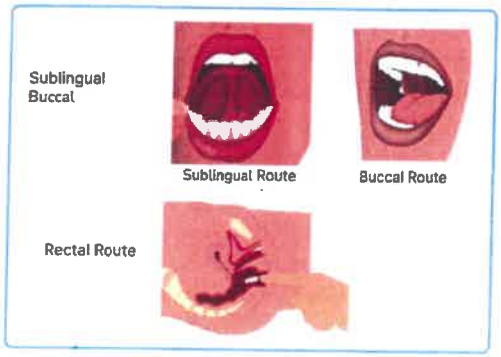
Q3. How to bypass the FPM of the liver?

Ans. By giving the drug by all other systemic routes except the oral route

- Because then the drug directly reaches the heart.

Sublingual/buccal route

- The drug enters superior vena cava > Reaches heart > Bypass the first-pass metabolism
- Example
  - Sublingual nitrates
    → **DOC** in Acute Angina



Rectal route

- Drug enters external hemorrhoidal vein
- Enters inferior vena cava
- Bypass the first-pass metabolism
- Example
  - Rectal diazepam- **DOC in** febrile seizures in children

Intramuscular route

- Drug given intramuscularly enters muscle, then can leak back from muscle and can stain subcutaneous tissue
- To avoid this staining of subcutaneous tissue or leaking back
  - Z technique is used, in which:
- Drugs given by Z technique
  - Anti-psychotics
  - Iron dextran

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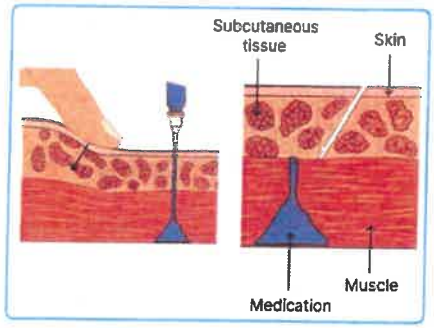
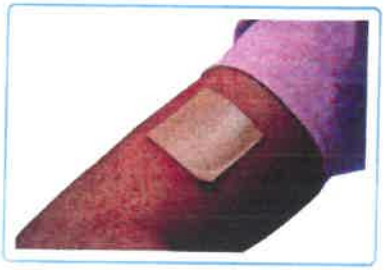


Transdermal/topical route

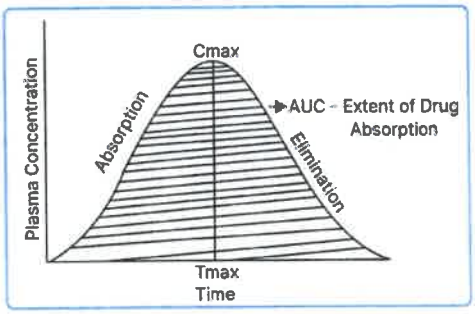
- Transdermal patches
- Long-acting route
  - Drug absorbed continuously and Sustained plasma levels achieved
- Usually given for long-term chronic diseases
- Site of maximum absorption:
  - Post auricular area > Scrotum > face and neck
- Site of least absorption: Where the skin is thick - due to heavy keratinization
  - Palms
  - Soles



Patch	Indication
Nicotine patch	Smoking cessation
Hyoscine (scopolamine), Diphenhydramine	Motion sickness
Nitrates	Chronic Angina
Clonidine	Hypertension
Selegiline	Depression
Rivastigmine	Alzheimer's
Rotigotine	Parkinson's disease
Oestrogen, progesterone	HRT (Hormone Replacement Therapy)

Bioavailability 00:20:49

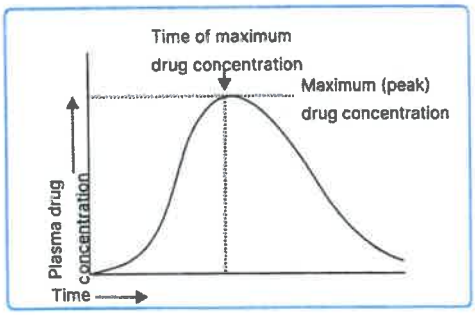
- Fraction of drug that reaches systemic circulation in unchanged form with time and is not degraded by liver PYQ: NICET 2022
- BA of IV drugs: 100%
  - Drug directly administered into the systemic circulation
  - No cellular barriers or absorption involved
- Rest of all other routes: BA < 100%
- BA calculation
  - Then bioavailability is calculated from the AUC of oral drug and AUC of the IV drug.
  - **Bioavailability (F) = AUC_{po}/AUC_{iv}**
- BA has no units
  - It's a fraction
  - Symbol: F



PYQ: NICET 2022

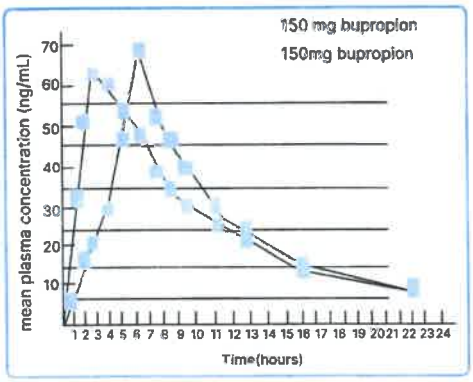
Area under the curve (AUC)

- Calculated by Trapezoidal rule
- The maximum (peak) drug concentration corresponds to C_{max}
- Time at which C_{max} achieved – T_{max}
  - Defines rate of absorption
    → How fast the drug is getting absorbed
- If Tmax;
  - Small - Drug get rapidly absorbed
  - Large - Drug get slowly absorbed into blood
- C_{max} - Maximum plasma concentration achieved in the blood
- AUC - Total extent of absorption of a drug



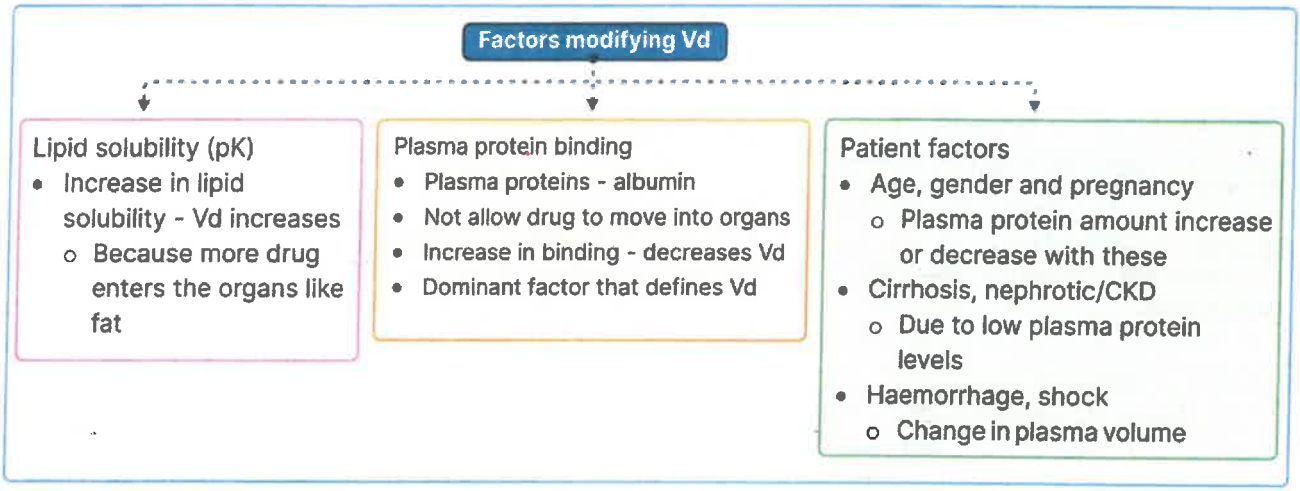
Bioequivalence

- Compare the bioavailability of different brands of same drug (generic drugs)
- Acceptable variation in BA: 80% - 125%
  - Drugs having equal variation are known as bioequivalent drugs.
  - Can interchange the brands
- Exception;
  - Phenytoin
    → Even 80-125% variation is harmful
    → No two brands of Phenytoin are never equal to each other
    → Bio-inequivalent



Volume of distribution 00:26:43

- Extra vascular movement of the drug (into organs)
- It's false or apparent volume of plasma PYQ: INICET 2022
  - Not true volume of plasma
- **Definition:** Volume of plasma (liters) required to contain a drug in equal concentration as that of plasma
  - More amount of drug enters the organ - more Vd



Warfarin is highly lipid soluble and 99% albumin-bound.

- Warfarin has low Vd due to high protein bound (Predominant factor)

Q5. Do all epileptics increase each other's toxicity?

Ans. Displace each other from albumin

Increase free fraction → Free drug enters organs → Increase Vd → Toxicity

Q6. Why is Sulfonamide (cotrimoxazole) avoided in neonates and 3rd trimester of pregnancy?

Ans. Sulfonamides cause the displacement of bilirubin (endogenous toxin) from albumin

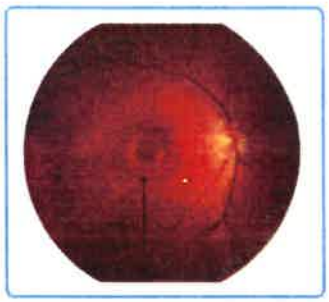
- This makes Bilirubin free
- This can enter the brain of the neonates
  - As BBB is not fully developed in neonates
- Damages organs - **causes kernicterus**(encephalopathy)

Hemodialysis 00:31:25

- Drug with high Vd - not present in blood
  - Deposited in organ
  - Poisoning of that drug - hemodialysis is not effective

Do hemodialysis Mnemonic: **BLAST**	**No role** Mnemonic: **AVOID ABC**
• **Barbiturates** • **Lithium** • **Alcohols** • **Aspirin** • **Salicylates** • **Theophylline**	• **Amphetamin** • **Verapamil/warfarin** • **Organophosphate** • **Imipramine** • **Digoxin (Vd- 450 litres)** • **Amiodarone** • **Benzodiazepines** • **Chloroquine**

- Chloroquine has highest volume of distribution - around 15000 litres
  - Deposits in all organs
  - It get deposited in retina
    → Cause Bull's eye maculopathy - permanent blindness



Redistribution

Seen with highly lipid-soluble drugs like:

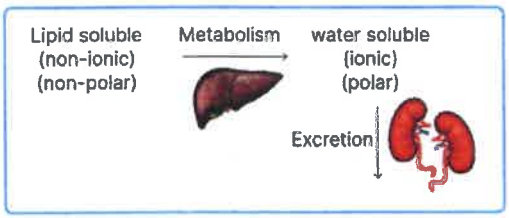
1. Thiopentone
2. Fentanyl

Q7. Action of thiopentone terminated by?

Ans. Redistribution into fats not by elimination in urine

Metabolism and Excretion (Elimination) 00:35:03

- Metabolism
  - Converting lipid soluble/non-ionic/non-polar drug into water-soluble/ionic/polar form
  - Liver is the most common organ of metabolism
- Water soluble forms are easily excreted out of the body
  - Through saliva/urine/sweat
- Most common route of Excretion - Urine by kidneys



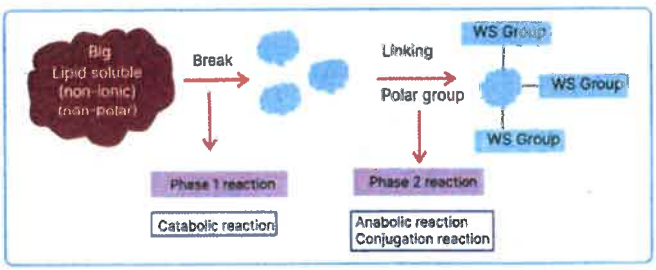
Activity of drug after metabolism

Active drug to active form	Active drug to inactive metabolite	Inactive forms (prodrug) to active metabolite
• Most drugs converted to inactive forms after metabolism • Example; mnemonic - **FADS CP** o **Fluoxetine** o **Allopurinol** o **Diazepam** o **Spironolactone** o **Codeine** o **Primidone**	• Most drugs undergo this process	• Examples of prodrugs; mnemonic - **PLASMA CCD** o **Prednisone** o **Levodopa** o **ACE inhibitors (pril)** o **Sulfasalazine** o **Mycophenolate mofetil** o **Acyclovir/ganciclovir** o **Carbimazole** o **Clopidogrel/prasugrel** o **Dipivefrin**

Q8. What are ACE inhibitors that are not prodrugs?

Ans. Captopril and lisinopril

Hepatic metabolism 00:39:34



- 2 chemical reactions carried out

Phase 1 reaction	Phase 2 reaction
• Catabolic reaction	• Anabolic reaction/conjugation reaction • Linking or conjugation of polar group to each small fragment • Drug become water soluble
• Drug becomes active or inactive • Prodrug converted to active form	• Drug becomes inactive only • Except for morphine and minoxidil – they become active
Reactions • Oxidation o Carried out by CYP450 enzymes in liver • Reduction o Carried out by CYP450 enzymes in liver • Dehydrogenation • Deamination • Cyclization • Decyclization	Reactions PYQ: FMGE 2021 • Glucuronide conjugation (Most common) o Carried out by UDP-GT enzyme in liver • Glycination • Sulfation • Methylation • Acetylation • Glutathione conjugation
• All phase 1 reactions – Microsomal reaction (inside smooth endoplasmic reticulum)	• All phase 2 reactions – Non Microsomal reaction o Occur outside smooth endoplasmic reticulum o Except glucuronide conjugation → Microsomal reaction

CYP450 Enzymes

- Cytochrome P450 enzymes
  - Contains heme pigment
  - Show genetic variation/polymorphism in high/ low amount
- **CYP enzyme inducers**
  - Drugs that increase the activity of CYP
  - Mnemonic: **GRASS**
    - → **G**riseofulvin
    - → **R**ifampicin
    - → **A**lcohol (chronic)
    - → **A**ll antiepileptics (Except valproate)
      - – Phenobarbitone
      - – Phenytoin
      - – Carbamazepine
    - → **S**moking
    - → **S**t. John Wort
      - – Plant product
- **CYP Enzyme Inhibitors**
  - Drugs that inhibit CYP action
  - Mnemonic: **COKE IVC GAR**
    - → **C**imetidine
    - → **O**meprazole
    - → **K**etoconazole
    - → **E**rythromycin
    - → **I**soniazid

CYP type PYQ: NEET 2023	Substrate (drugs that gets metabolised)
• CYP1A2	• Theophylline, clozapine
• CYP2C9 (least quantity)	• Phenytoin, warfarin
• CYP2C19	• Clopidogrel, Azoles, PPI
• CYP2D6	• Mnemonic: **PATTSON** • Propranolol, Antiarrhythmics (quinidine), TCA (tricyclic antidepressants), Tamoxifen, Codeine, Antipsychotic, SSRI
• CYP2E1	• Paracetamol
• CYP3A4 (maximum quantity)	• >50% drugs are metabolised

Important Information

- All antiepileptics are CYP inducers except Valproate
- Valproate is a CYP inhibitor
- Chronic alcohoism will act as CYP inducer
  - Increase metabolism of other drugs
- Acute alcoholism acts as a CYP inhibitor

→ Valproate
→ Ciprofloxacin
→ Grape-fruit juice
→ Alcohol (acute)
→ Ritonavir (HIV)

- Isoniazid inhibits all CYP types, Except CYP2E1 which it induces.
- Grape-fruit juice contains furanocoumarins which act as CYP inhibitor.

Drug interactions

- **CYP inducers or inhibitors** when combined with a substrate of CYP, it may increase or reduce plasma levels of substrate.
  - Shows drug interactions.
- **They are:**

I. Oestrogen (oral contraceptive pill) - Metabolised by CYP3A4 - If given with Rifampicin → CYP inducer - Oestrogen gets rapidly metabolized - Causing Contraceptive failure	II. Cisapride (for constipation), Astemizole and Terfenadine (antihistaminic) - Metabolised by CYP3A4 - When combined with Erythromycin/ketoconazole → CYP inhibitors - Plasma levels of substrates increase - Lead to toxicity – Torsades de pointes → QTc increases - Hence these are banned	III. Clopidogrel (prodrug) - Converted to active form – by CYP2C19 - Antiplatelet drugs can cause stomach bleeding - Omeprazole is given (CYP inhibitor) - Clopidogrel not converted to active form - Leads to increased risk of MI/Stroke

Drugs metabolised by Acetylation

- Mnemonic: **SHIP-DP**
  - Sulfonamide
  - Hydralazine
  - Isoniazid
  - Procainamide
  - Dapsone → First drug for leprosy → Sulphonamide
  - PAS → First drug for TB
- Enzyme cause acetylation - NAT
  - N acetyl Transferase enzyme

Fast acetylators	Slow acetylators
• Individuals with high NAT level	• Individuals with poor NAT level • SHIP drugs accumulate in the plasma leading to toxicity • Causes DLE (drug induced lupus erythematosus)

Elimination

- Drug moving out of body with time
- Rate of removal of drug (mg/min)
- Elimination - metabolism + excretion
  - Most common site of metabolism - liver
  - Most common route of Excretion - urine (kidney)
- Excretion - route of elimination
  - Drug move out of body through body secretions

→ Urine	→ Saliva
→ Bile	→ Tears
→ Sweat	→ Milk

- **Bile**
  - Oral contraceptive pills (OCP) excreted in bile
  - Undergo enterohepatic reabsorption through intestinal bacteria and again enter liver
  - Antibiotics (doxycycline and ampicillin) – kill intestinal bacteria
    → Reduce enterohepatic reabsorption of OCPs
    → OCPs plasma levels fall
    → Cause contraceptive failure
- **Milk**
  - Drugs avoided in breastfeeding
  - Mnemonic: **SMALL**

→ Sulfonamides – Cause kernicterus → Methotrexate – Hepatotoxic → Aspirin – Reye's syndrome (liver disease)	→ Lithium – Seizures – Metabolic abnormalities → Levetiracetam – Anti-epileptic drug to be secreted maximum in the breast milk.

Urinary excretion

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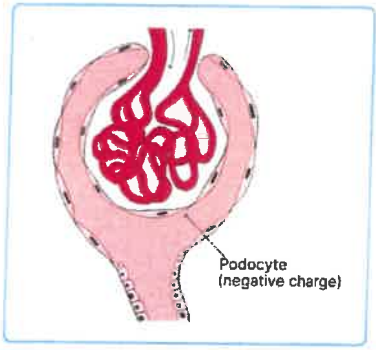
- 2 methods
  - Glomerular filtration
  - Active tubular secretion



Glomerular filtration	Active tubular secretion
• Passive process • Occurs through Paracellular spaces o Spaces between podocytes • Protein binding reduces GFR • Podocytes contain negative charge o Repels negative charge of basic drug o Basic drugs filtered less than acidic drugs	• Active process o Require ATP • Drug excreted into urine - by transporters through pumps • Protein binding increases secretion rate • OATP transporter o Organic anion transport protein o Excretes acidic drugs: Penicillins o Probenecid inhibits OATP • OCTP transporter o Organic cation transport protein o Excretes basic drugs: Tubocurare • P-gp o P-glycoprotein o Excretes neutral drugs: Digoxin

Important Information
- Probenecid inhibits the OATP transporter
- Probenecid + penicillins -- inhibit urinary excretion of penicillins
- Makes penicillins longer acting

- Passive tubular reabsorption
  - Lipid soluble drugs get reabsorbed