Renal Pharmacology

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Introduction

- ***Pharmacokinetics***: Effects of body on drugs

1. Absorption
2. Distribution
3. Metabolism
4. Elimination

Pharmacodynamics: Effects of drug on body

MOA, Clinical uses & SEs

ADME

- Are important for:

1. Onset of drug action
2. Effect intensity
3. Drug action duration

Target Concentration:

Conc. of a drug that produces the desired therapeutic effect (Determined by ADME)

Therapeutic Index

- Calculates the safety margin of drugs.
- TI in human= 3 or more.

** Drugs tend to pass through membrane if ***UNCHARGED***

** At PH of 7.35 drugs can be:

- Neutral = 7
- Weak acidic = < 7
- Weak basic = > 7

Absorption

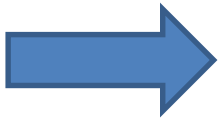
- Drugs have to be ***uncharged*** to be absorbed.
- Non Ionized or Lipid soluble.
- ***Pka of drug***: PH at which the drug molecules are half ionized & half unionized.
- Alkalinazation & Acidification are important in drug poisoning.
- **Bioavailability**: fraction of the unchanged drug that reaches the sys. circulation. ***Affected by 1st pass metabolism.***

Distribution

- From blood stream to tissues or organs.

- Conditions affecting distribution:

**Protein binding capacity:

Drug + protein  Drug protein complex

(Active, Free) (Inactive, bound)

Special barriers to distribution

Placenta

- Small molecular weight.
- Lipid soluble drugs
- Fetal blood levels are usually lower than maternal
- ***C.V*** Safer in pregnancy:

  -Water soluble

  -Large

  -Protein bound

PTU vs. Methimazole.

BBB

- Very small molecular weight
- Lipid soluble drugs
- Li^+ & Ethanol:

Li^+ is the smallest drug

Ethanol is very small

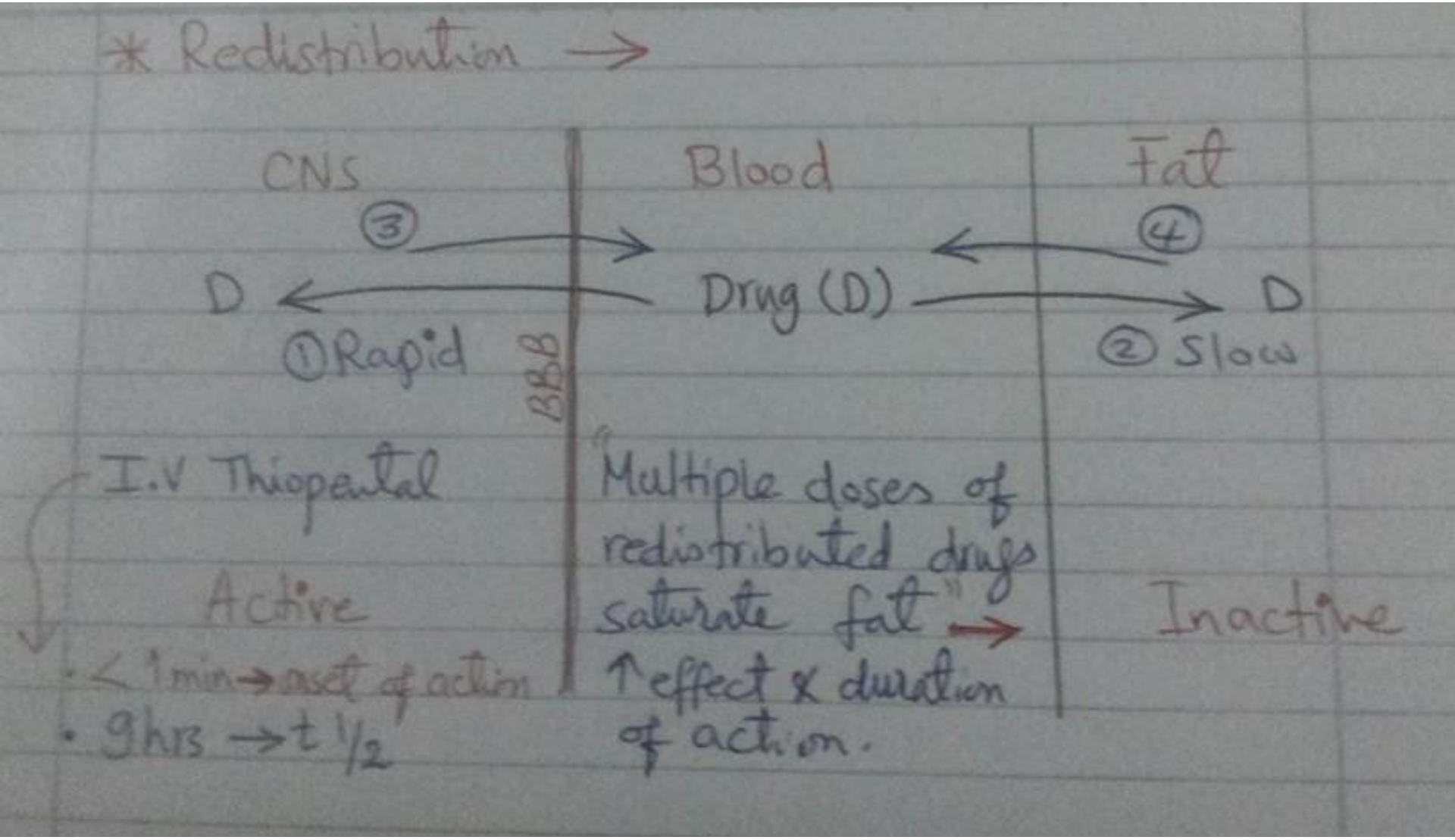
C.V : If drug crosses BBB, it will easy cross the placenta

Apparent Volume of Distribution

- Is a hypothetical volume
- Vd = Dose/Conc. at zero time
- ↑ Vd →→
  - dec. Plasma protein binding
  - Inc. Accumulation of drug in tissue
  - Dialysis is not useful.

Where is the Drug? If most in plasma, Vd is low. If outside plasma, Vd is high (> 42L).

Redistribution



Biotransformation of Drug

- Many drugs are unionized & lipid soluble by metabolism are converted into ionized & water soluble.
- Sites of Metabolism:

GIT, Blood, Lungs, Skin, Kidney & ***LIVER***

Prodrug → Drug

Drug → inactive (most) or Another active drug

Metabolism Phases

- ***Phase I:***

  1. Microsomal Enzymes:

Cytochrome P450 in SER*. Many families & enzymes (2D6/3A4)

Inducers: Phenobarbital, Phenytoin, Carbamezepine, Rifampin, Chronic alcohol.

Inhibitors: Cimitidine, Macrolides, Ketoconazole, avirs, acute alcohol & grapefruit juice (Statins).

2. Non Microsomal: Oxidation, Reduction & Hydrolysis.

Metabolism Phases

- **Phase II:**

Conjugation with endogenous compounds via **Transferase** Enzyme.

1. **Glucorunidation:**

** Most common

** Glucoronosyl transferase

** Dec. Activity in neonates (Chloramphenicol toxicity).

** Inducible & undergo enterohepatic cycling.

Metabolism Phases

2. Acetylation:

** **Genotypic** variation → Fast & slow metabolizer.

** Drug induced ***SLE*** by slow acetylators with →

Hydralazine, sulphonamides, Procainamide & isoniazid.

3. Glutathione (GSH) conjugation:

Depletion in Acetaminophen hepatotoxicity

Factors affecting drug Metabolism

1. Genetic factors
2. Age: Paediatrics & geriatrics
3. Hepatic blood flow & disease
4. Diet & Environmental factors:

   Alcohol & Cigarette → Enz. Inducers

   Starvation & Ozone → Enz. Inhibitors

C.V: Some drugs work as enzyme inhibitors → Aspirin vs. COX

Drug Elimination

- Ending of drug action.
- Steps of elimination are:

a. Metabolism to inactive metabolites

b. Renal excretion (Most drugs)

c. Other sites like: Bile, Lung, Sweats, Tears, Saliva, vagina, Milk.

Elimination half life

- Time to eliminate 50% of a given amount of drug.
- ***t ½*** is important for:

a. Frequency of drug administration.

b. Time required to reach Css

c. Time required for clearance

t ½ = Vd/Cl * 0.693

Types of Elimination kinetics

Zero order kinetics

- Constant **Amount** of drug is eliminated per unit time.
- Rate of elim. is **independent** of plasma conc.
- No fixed t ½ (**variable**).
- Enzyme capacity is **Limited.**
- Few drugs: Zero PEAs

  Phenytoin, Ethanol, Salicylates (Aspirin)

80mg—70mg—60mg—50mg

1st order elimination rate

- Constant **fraction** of drug is eliminated per unit time.
- Rate of elim. is **dependent** on plasma conc.
- Fixed t ½ (**constant**).
- Enzyme capacity is **Unlimited.**
- Most drugs
- 80mg—40mg—20mg—10

Renal Elimination

- Rate of elimination= ***GFR*** (active & inactive metabolites) + ***Active tubular secretion*** (cation & anion systems) – ***Tubular Reabsorption*** (Unionized & lipid soluble)
- ***Filtration*** is a non- saturable linear function.
- ***Ionized & Unionized*** drugs are filtered, but protein bound drugs are not.

Clearance

- Volume of blood cleared of drug per time unit.
- Cl is constant in 1st order kinetic
- Cl = GFR when there is no:

a. Reabsorption
b. Secretion
c. PP binding

**Protein bound drug is not cleared:

Cl = Free fraction% X GFR

**To estimate GFR:

Inulin clearance is used b/c ***inulin*** is neither reabsorbed nor secreted

Normal GFR= ???

Clearance

- Clearance < GFR → reabsorbed drug
- Clearance > GFR → secreted drug
- Water soluble drugs are easily excreted except from **LUNG.**
- **Factors affecting renal excretion:**

a. PH of urine.

b. Renal Disease.

c. Other drug excreted by the same route: (Penicillin vs. Probenicid)

Antimicrobials & PH of Urine

- Drugs that are more active in ***alkaline*** urine:

1. Macrolides.
2. Sulphonamides.
3. Aminoglycosides.

* Drugs that are ***not affected*** by PH of urine:
  Flouroquinolones (Ciprofloxacin).
* Drugs that are more active in ***acidic*** urine:
  The rest of antimicrobials.

Tubular Secretion

- Drugs compete for ***active*** tubular secretion:

1. Penecillins.
2. Cephalosporins (ceftriaxone .....)
3. **Probenecid.**
4. Uric Acid.
5. Loop diuretics.
6. Thiazide Diuretics.
7. Carbonic anhydrase inhibitors.
8. NSAIDs.

All the previous drugs (except diuretics) *.....

Diuretics Excretion

- **Loop, Thiazides & CAIs** →→ Acid Carriers.
- **Triamterene & Amiloride** →→ Basic Carriers.
- **Spironolactone** →→ No need for intra-tubular action b/c aldosterone receptors located on wall surface.
- **Osmotic Diuretics** →→ The only diuretic that it is excreted through **GF**.

Steady state (Css)

- Is reached when rate in = rate out of the drug
- Constant concentration.
- The time to reach **Css** is dependent only on t ½ of a drug
- Clinical **Css** needs 4-5 t ½

Drug disposition in Renal disease

- ***Bioavailability*** is generally not affected by renal impairment.
- ***Water soluble*** drugs mainly distribute into extracellular fluid & their volumes will be affected by fluid retention & dehydration.
- **Digoxin** is an exception that renal impairment per se does not influence distribution. Digoxin volume is lower in patients with renal disease.

Protein Binding

- PB of drugs that are highly bound to ***albumin*** is reduced in renal failure.
- Binding to Alpha 1 Acid glycoprotein ***AAG*** may be increased, decreased or unchanged.
- Acidic drugs bind to albumin while basic drugs bind to AAG.
- Changes in PB do not normally alter drug dose requirements.

Drug elimination in renal diseases

- Some compounds are metabolized in kidney & elimination is impaired with renal failure.
- Renal impairment may alter the hepatic metabolism of some drugs.
- Accumulation of renally excreted active metabolites may make a drug unsuitable for use in renal impairment.
- In general, both GFR & tubular secretion are reduced in renal impairment.

Dose adjustment in renal impairment

- **Loading dose:** very important b/c the prolonged t ½ means that it takes longer to reach Css if no loading dose is given.
- **Maintenance dose:** reduce doses of wide therapeutic ranges drugs if renal function is below 50mlmin. For drugs with narrow therapeutic range, target conc.-time profile is important.

Dose Adjustments Examples

Captopril, Enalapril, lisinopril & Ramipril:

25 – 50%

Fosinopril & Quinapril:

75- 100%.

Atenolol: 25-50% whereas

Bisoprolol: 50-75%

Diuretics Dosage Adjustments

- If GFR is less than 10, AVOID: Amiloride, Spironolactone, Thiazides & Triamterene.
- Furosemide & Bumetanide need NO Adjustments.
- Spironolactone needs frequency adjustments.

Dosage Adjustment

Drugs need NO adjustments

1. Glipizide.
2. Atorvastatin
3. Omeprazole
4. Ketoconazole
5. Ceftriaxone
6. Cefuroxime
7. Azithromycin
8. Erythromycin
9. Doxycycline
10. Penicillin VK.

Avoided Drugs if GFR < 10

1. Acarbose.
2. Metformin.
3. Norfloxacin.
4. Nitrofurantoin.
5. Spironolactone.
6. Thiazides.
7. Triamterene.

Nephrotoxic Drugs

- ***CV →→***

Risk factors include:

1. Older than 60y.
2. **GFR < 50.**
3. Multiple exposure to nephrotoxins.
4. DM, HF & sepsis.

Nephrotoxic Drugs

- NSAIDs
- Acetaminophen
- Antidepressants:
- Antihistamines:
- Loop, thiazide & triamterene.
- Omeprazole & Lansoprazole.
- Allopurinol.
- Phenytoin.
- Ranitidine.

Nephrotoxic Drugs

- Acyclovir
- Aminoglycosides:
- Beta lactams:
- Quinolones:
- Sulphonamides:
- Vancomycin
- Cisplatin
- Interferon-alpha
- Methotrexate

Haemodialysis

- Endogenous waste products, drugs & metabolites are mainly removed by diffusion through the semi-permeable membrane down a conc. gradient.

Haemodialysis

- ***Factors*** influencing haemodialysis drug removal:

1. Molecular weight: < 500 Daltons.
2. BFR, dialysate FR, membrane surface area, membrane porosity & support
3. Water solubility.
4. Vd.
5. PB.

Total Drug Clearance

- **Total clearance** = **endogenous** clearance + **Haemodialysis** clearance.

Common Dialyzable Drugs

- Barbiturates.
- Lithium.
- Isoniazide.
- Salicylate.
- Theophylline/Caffeine.
- Methanol.
- Depakine
- Carbamezepine.

CV: Acidification & Alkalinazation facilitate dialysis.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