DIURETICS

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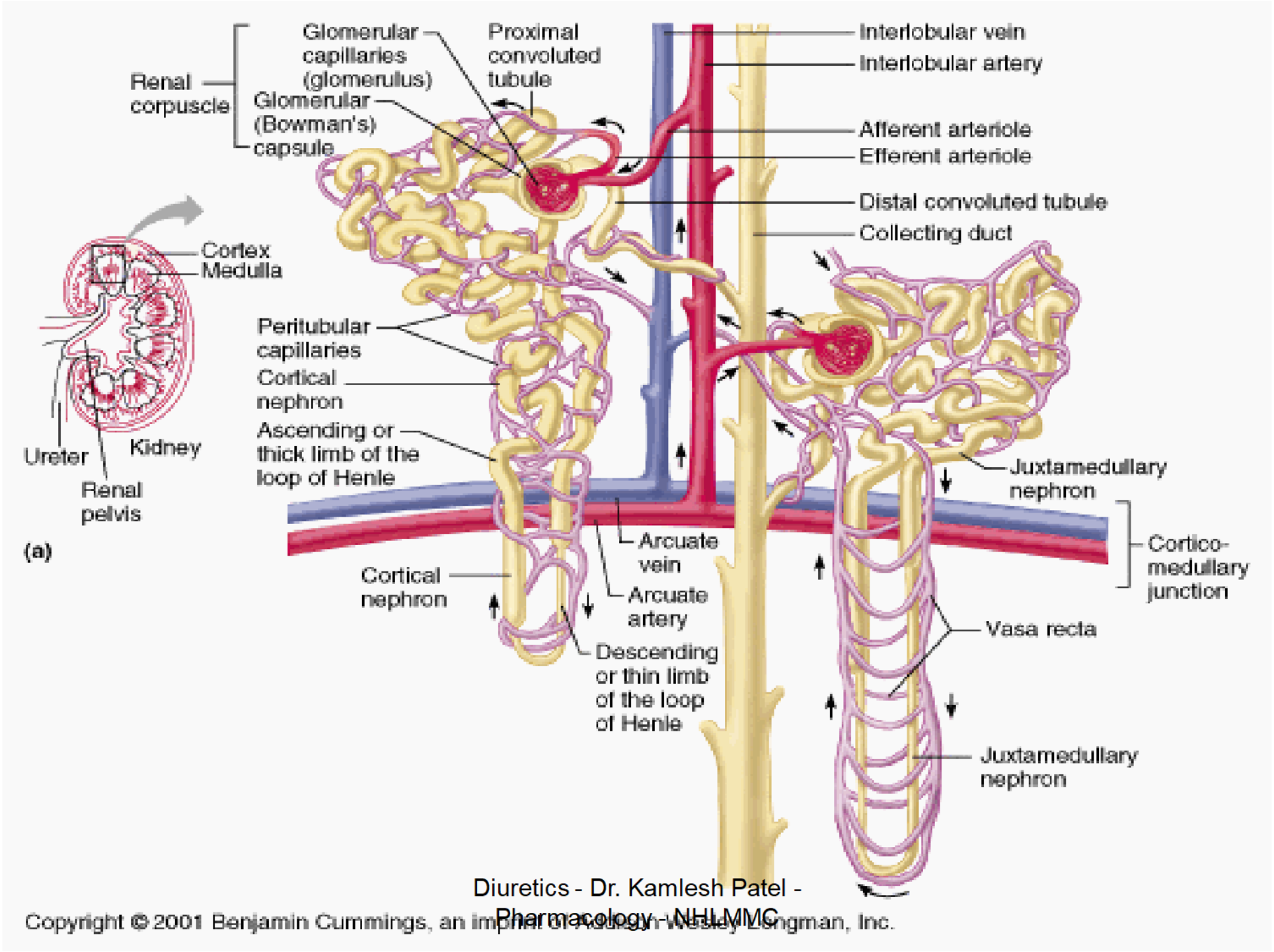

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DIURETICS

Drugs which cause a net loss of Na^+ & water in urine

CLASSIFICATION

I. ***High efficacy diuretics*** :

1. Sulphamoyl derivative.: Frusemide, Torsemide, Bumetamide,
2. Phenoxy acetic acid derivative: Ethacrynic acid
3. Organo-mercurials: Mersalyl

II. *Medium efficacy diuretics:*

1. **Benzothiadiazenes(thiazides):-**

   Chlorothiazide, Hydrochlorthiazide (HCTZ)

2. **Thiazide like :-**

   Chlorthalidone, Indapamide, Metalazone.

III. *Low efficacy Diuretics*

1. Potassium sparing Diuretics:

Steroidal : Spironolactone

Nonsteroidal: Amiloride, Triamterine

2. Carbonic anhydrase inhibitors:

Acetazolamide, Torzolamide

3. ***Osmotic diuretics:***

Mannitol, Glycerol

4. Others:

Ammonium chloride, Pot. citrate, Pot.acetate

CLASSIFICATION ACCORDING TO SITE OF ACTION

1) **Drugs acting at PCT (Site 1) :-**

Carbonic Anhydrase Inhibitor : Acetazolamide, Dorzolamide

2) ***Drugs acting at Thick Ascending Limb of Loop of Henle (Site 2):***

Loop Diuretics : Furosemide, Bumetanide, Ethacrynic acid

3) ***Drugs acting at Cortical Diluting segment (Site 3) :***

Thiazides : Chlorthiazide, Hydrochlorthiazide

Thiazide like Diuretics : Chlorthalidone, Indapamide

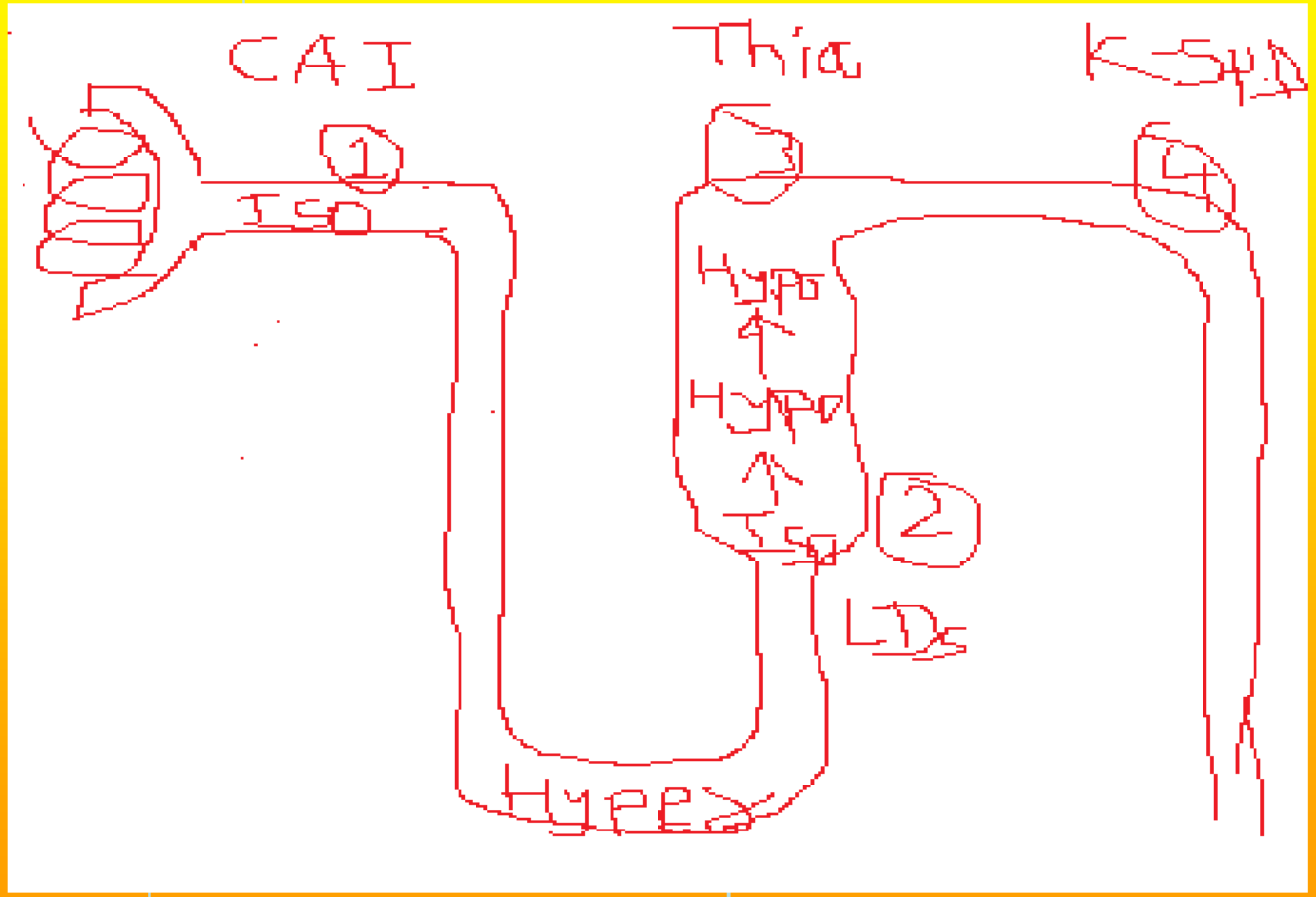
4) ***Drugs acting at Distal Convulated Tubule ; (DCT, site 4):***

Aldosterone antagonist : Spironolactone

Directly acting : Amiloride, Triamterene

5) ***Drug acting on Entire nephron :***

Osmotic diuretics : Mannitol, Glycerol, Urea.


CAI
Thia
K-Sp
1
Iso
3
4
Hypo
Hypo
2
Iso
LDs
Hypo

Proximal Convulated Tubules (Site 1)

- Filtered Sodium (Na++) actively reabsorbed
- Chloride (Cl-) passively reabsorbed
- CA plays imp. Role in Na+-H- exchange (Na+-H+- Antiporter) → helps HCO3- reabsorption.
- Potassium, glucose, AAs reabsorbed in PCT
- H2O also reabsorbed → fluid is Isotonic

Loop of Henle (Site 2)

1) Descending Loop of Henle is impermeable to Na+, cl-.

But, Permeable to H2O→ Hypertonic

2) Thick Ascending Loop of Henle (site 2):

Impermeable to H2O , but permeable to Na+, Cl-.

Active reabsorption of Na+, Cl- occurs by Na+-K+-2Cl- co-transportor.

Mg++ & Ca++ are also reabsorbed here

Blocked by Loop Diuretics

Early Distal Tubules (site 3) :

- **Impermeable to H2O, But permeable to Na+, Cl- & are reabsorbed by Na+-Cl- symporter. Blocked by Thiazides.**

- **Late Distal Tubule and Collecting Duct (Site 4) :-**

- **Na + actively reabsorbed**
- **Cl- , H2O diffuses passively**
- **Na+,K+,H+ ions are exchanged**
- **Na+/K+ exchange is under influence of Aldosterone**
- **(Aldosterone promotes Na+ absorption and K+ depletion)**
- **Absorption of fluid in CD is under ADH**
- **Absence of ADH, CD is impermeable to H2O.Hence, dilute urine is excreted**
- **H+ in urine convert NH3 to NH4 which is excreted.**

Loop Diuretics

MOA

Site: Thick ascending Loop of Henle

Inhibits Na/K/2Cl co - transport

Minor site: Proximal Tubules (Site 2)

Mechanism of Actions

Loop Diuretics (Furosemide)

↓

Binds to Luminal side of Na+-K+-2Cl- co-transporter & blocks its function

↓

Increased excretion of Na+ & Cl- in urine

↓

Tubular fluid contains large amount of Na+

↓

More sodium exchanges with K+→ K+ loss

↓

Has weak carbonic anhydrase inhibiting activity

↓

Increases excretion of HCO_3^- & PO_4^{3-}

↓

Also increases excretion of Ca^{2+} & Mg^{2+}.

Loop Diuretics

- Are called ***'High – Ceiling'*** Diuretics → Because..***They are highly efficacious – Have Maximal Na+ excreting capacity when compared to Thiazides & K-sparing diuretics.***
- **Furosemide :** oral, i.v,i.m.
- **OAA:** oral : 40 min; i.m. 20 min; i.v. 5 min
- **DOA** : 2-4 hrs

Therapeutic Uses

1. **Oedema:** Cardiac (CHF); Hepatic (Cirrhosis of Liver) ; Renal disease(Nephrotic syndrome)
2. **Acute LVF:→** Relieves Pulmonary oedema

I.V. Furosemide

↓

↑ PG synthesis & release

↓

↑ Renal blood Flow

↓

↑ Systemic venous capacitance

↓

Shifts blood from central pulmonary circulation to peripheral systemic circulation

↓

↓Left ventricular filling pressure

↓

Produces quick relief from pulmonary oedema

Therapeutic Uses of Loop Diuretics (Furosemide)

3. Hypertension: in renal insufficiency, CHF, in resistant cases, hypertensive emergencies.
4. Increase rate of urine flow & enhance K+ 3excretion in acute renal failure. Convert oliguric renal failure to non-oliguric failure → helps in renal failure management.
5. Used to treat ingestion of toxic anions like… BR, I or F.
6. Forced diuresis in barbiturate drug poisoning.
7. Cerebral oedema, But I.V. Mannitol is preferred
8. Hypertension due to renal failure, CCF, Hypertensive crisis. Not for essential hypertension.
9. In mild hyperkalaemia & mild Hypercalaemia, due to rapid excretion of K+ & Ca++ . Response enhanced by Nacl & H2O coadministration.

ADRs – Furosemide (Loop Diuretics)

A) Electrolye Disturbances :-

1. **Hypokalaemia: with hypokalaemic metabolic alkalosis → due to excess renal excretion of K+ and H+.**

   . **Charecterizised by weakness, fatigue, muscle cramps, cardiac arrhythmias**

   . **Less common than with thiazides**

   . **Treated by high dietary potassium, Kcl solution, concurrent use of potassium sparing diuretics**

   . **Alkalosis may occur- hydrogen exchanges with sodium in DT when pot. Is not available.**

ADRs – Furosemide (Loop Diuretics)

2) **Hyponatraemia :-** Overuse of Furosemide can cause severe dehydration and hypotension due to depletion of sodium from the body

3) **Hypocalaemia & Hypomagnesaemia :** due to increased urinary excretion of Ca^{++} and MG^{++}.

B) Metabolic Disturbances :-

i) **Hyperglycaemia :** due to decrease insulin secretion

ii) **Hyperuricaemia :** Decrease renal excretion of uric acid → precipitates acute attack of Gout.

iii) **Hyperlipidaemia :** Increases plasma TGs & LDL cholesterol levels.

ADRS of Furosemide (Loop Diuretics)

- **C) Ototoxicity :** manifested as deafness, vertigo, tinnitus. Reversible on stoppage of drug.

- **D) Hypersensitivity :** Skin rashes, eosinophilia, photosensitivity

Drug Interactions of Furosemide (Loop Diuretic)

1) **Furosemide X Digitalis :** ***Diuretics causes hypokalaemia → increase binding of digitalis to Na+- K+- ATPase pump → increasing digitalis toxicity.***

2) ***Furtosemide X Aminoglycoside Antibiotic :*** *Both are ototoxic → cause enhanced ototoxicity.*

3) **Furosemide X NSAIDs :** ***NSAIDs inhibit PGs synthesis → blocks PGs mediated hemodynaemic changes. Causes Na+ & H2o retention → looses antihypertensive effects of Loop diuretics.***

2. Ototoxicity more with Ethacrynic acid → disturb the electrolyte composition of endolymph due to extrusion of Na+ from endolymph to perilymph of the inner ear. Damages hair cells. Risk is more in patient with impaired renal failure, those receiving ototoxic drugs –aminoglycosides antibiotics.

THIAZIDES

- Inhibit Na^+-Cl^- co-transport
- Act at cortical segment of distal tubule (site 3) & cortical segment of ALH .
- **Act only when the GFR is > 20ml/min**
- Medium efficacy as a diuretics.

Actions- Thiazides

Inhibits Na+ - Cl- symport in early distal tubule

↓

↑ sodium & chloride excretion

↓

↑ Delivery of Na+ to Late distal tubule

↓

↑ Exchange of Na+- K+ → K+ loss

↓

Mild carbonic anhydrase inhibitory action

↓

↑ HCO3- Loss

↓

↑ Na+,↑K+, ↑ Cl-,↑ Mg++, ↑ Uric acid ↓ renal calcium excretion

- **Slowly developing relaxant action on arterioles**

ADRs – Thiazides (>25mg/Day)

1. Hypokalaemia

** In Normal person :- weakness, muscle cramps, fatigue, paraesthesia.

** In Liver Disease :- Hepatic encephalopathy & coma (Give along with K-sparing diuretics)

2. Hyponatraema, Hypomagnesaemia
3. Hypochloraemic alkalosis with urine rich in chloride
4. Hyperglycaemia (stimulates glycogenolysis & inhibit insulin secretion)
5. Hypercalcaemia (Inhibits Ca2+ secretion ..Caution in hyperparathyroidism)
6. Hyperlipidaemia
7. Hyperuricaemia (aggravate Gout attack)
8. Impotence – not preferred in young antihypertensives

USES of Thiazides

1. Oedema:

** To relieve Pulmonary oedema due to CCF, Nephrotic syndrome & Pregnancy.

(Avoided in Oedema due to Liver Cirrhosis, because Hypokalaemia & Hypochloraemic alkolosis may precipitate hepatic encephalopathy & coma).

* **Thiazides→ ↑ Protein catabolism→ ↑Amino acid levels in Blood → Cirrhotic liver cannot metabolize→ Tryptophan levels increases → crosses BBB→ accumulate in Brain → Causes Encephalopathy.**

Hypokalaemia → aggravates alkalosis → generates more NH3→ cirrhotic liver cannot convert it into urea → Coma ensues.

Uses of Thiazides

2) **In Essential Hypertension :**

** **Initial → Fall in BP because of decrease in blood volume due to diuresis..**

** **Later → Fall in BP is due to its direct vasodilating effect.**

Can be given along woth K+ supplements, B-blockers etc for long time.

3) Idiopathic Hypercalciuria → Because inhibit urinary calcium excretion → useful in patients with renal calcium oxalate stones.

Uses of Thiazides

- 4) Nerogenic Diabetes Insipidus :
- Has paradoxical effect → reduces urine volume.

- 5) In Heart Failure

Potassium Sparing Diuretics

- Spiranolactone (Aldosterone antagonist) → competes for aldosterone receptor in DT & CT → Prevents aldosterone secretion → Inhibits Na+ reasbsorption & Decrease K+ excretion.

- Amiloride, Triamterone (Inhibitors of Na++ channels at Collecting Ducts) → Inhibits Na++ reabsorption & K+ excretion.

SPIRONOLACTONE

- Synthetic steroid
- Chemically related to aldosterone
- Potent aldosterone antagonist
- Promotes Na+. H_2O excretion & K+ retention
- More effect when circulating aldosterone levels are high.
- Metabolises → Active Metabolite CANRENONE –with longer PI t1/2 (16-24hrs)

Spironolactone - Mechanism of Actions

Aldosterone combines with intracellular (Specific Mineralocorticoid) → forms Hormone – Receptor (MR-AL) complex in DT & CT

↓

Induces formation of an Aldosterone – induced proteins (AIPs)

↓

Promotes sodium reabsorption & potassiun secretion

↓

Spironolactone combines with the aldosterone receptor (Specific Mineralocorticoid Receptor in DT & CT –Site 4)

↓

inhibits Aldosterone action

Spironolactone - Actions

- ↑ Sodium excretion
- Retains potassium (Prevents K+ - Loss)
- ↑ Calcium excretion
- At high doses inhibits aldosterone synthesis

Spironolactone-ADRs

- Hyperkalaemia
- Gynaecomastia
- Hirsutism
- Impotence
- Menstrual irregularities
- Drowsiness
- Confusion
- Abd. upset

Preparations

- **Tab: 25mg, 100mg**
- **Dose: 25-50mg b.i.d-q.i.d**
- **Combination: 50mg+ 20mg Frusemide**

USES of Potassium Sparing Diuretics

1. **Edema: More useful in cirrhotic & nephrotic edema → as Hyperkalaemia produced by them is advantageous.**
2. **Specially in refractory edema, to treat Hypertension (With Thiazide / loop diuretics diuretics) → check Hypokalaemia.**
3. **To counteract potassium loss due to thiazide & loop diuretics**
4. **Amiloride :-**

i) **To reduce Lithium induced polyuria → By blocking Li + reabsorption through Na+ channels in CD.**

ii) **To treat cystic fibrosis as aerosol→ increases fluidity of respiratory secretion.**

iii) **In situation of potassium loss.**

CARBONIC ANHYDRASE INHIBITORS

- **Acetazolamide**
- **Dorzolamide**
- **Brinzolamide**

Carbonic Anhydrase Inhibitors (Acetazolamide)

Co2 & H2O diffuses into tubular cells

↓

H2O is formed under influence of CA

↓

Carbonic acid (H2Co3) dissociates into H+ + HCo3-

↓

Na+-H+ ions exchange with luminal Na+ (Na+-H+ antiporter)

↓

In Lumen, H + ions combines with HCO3-

↓

Forms H2Co3

↓

CA in brush border dissociate it into Co2 + H2O

Acetazolamide

- **Inhibition of CAH in PT cells (Site 1)**

↓

- **↓Slowing of hydration of CO2**

↓

- **↓ Availability of hydrogen to exchange with luminal sodium through Na^+-H+ antiporter**

↓

- **Excretes Na + and HCO3- in urine**

Carbonic Anhydrase Inhibitors - Actions (Acetazolamide)

- ↑ Sodium excretion
- ↑ Bicarbonate excretion
- ↑ Potassium excretion
- Urine produced is alkaline & rich in bicarbonate
- Self limiting diuretic

CA-Inhibitors - Extra renal actions

- ↓ IOT- decrease formation of aqueous formation
- ↓ Gastric HCL & pancreatic bicarbonate secretion
- ↑ Level of CO_2 in brain &↓ PH
- Alteration of CO_2 transport in lungs & tissues

CA-Inhibitors - ADRs

- Acidosis
- Hypokalaemia
- Drowsiness, paresthesia, fatigue, abd. Discomfort
- Allergic reactions: fever, rashes
- Bone marrow depression

- Acetazolamide :-
- Preparation: Tab- 250mg
- Dose : 250mg o.d/ b.i.d

CA- Inhibitors - USES

1. As diuretic rarely
2. Glaucoma- Reduces Aqueous Humour formation
3. For alkalinization of urine in drug poisoning
4. Epilepsy as an adjuvant
5. Acute mountain sickness
6. Periodic paralysis

Osmotic Diuretic - MANNITOL

- Non electrolyte of LMW
- Inert, easily filtrable, limited reabsorption
- Expands ECF volume - ↑ GFR & inhibit renin release
- ↑ RBF, specially to the medulla
- Retains water iso-osmotically in PT
- Inhibits transport processes in the thick ALH

- **Primarily increases urine volume**
- **Excretion of all cations & anions are also increased**
- **Not absorbed orally**
- **Preparation: 10%, 20%- 100,350,500ml solution**

Mechanism of Action- Mannitol

20% Mannitol I.V.↓

↓

↑Osmolality of Plasma

↓

Shift of fluid (Osmotic effect) from intracellular compartment (ICC) to Extracellular Fluid (ECF)

↓

Expansion of ECF volume

↓

↑ GFR, Mannitol freely filtered at glomerulus

↓

↑ Osmolality of tubular fluid

↓

Inhibits reabsorption of H2O

↓

Net effect → ↑ Urine volume, Urinary excretion of Na,K,Cl,Mg,HCo3, P_{04}

ADRs - Mannitol

- Headache
- N, V
- Hypersensitive reactions
- Pulmonary oedema on too rapid admission
- Glycerol → Hyperglycaemia

USES - Mannitol

1. **Cerebral Oedema : To reduce ↑ ICP following head injury, brain tumour → draws fluid from brain into circulation by osmotic effect.**
2. **To reduce IOP in Acute (Narrow) angle Glaucoma.**
3. **To maintain GFR & urine flow in impending ARF- shock, severe trauma, CV surgery, haemolytic tranfusion reactions etc**
4. **Forced diuresis in drug poisoning**
5. **To counteract low osmolality of plasma/ECF due to rapid haemodialysis or peritonial dialysis**

Contraindications

1. Acute tubular necrosis
2. Pulmonary edema
3. CHF
4. Cerebral haemorrhage