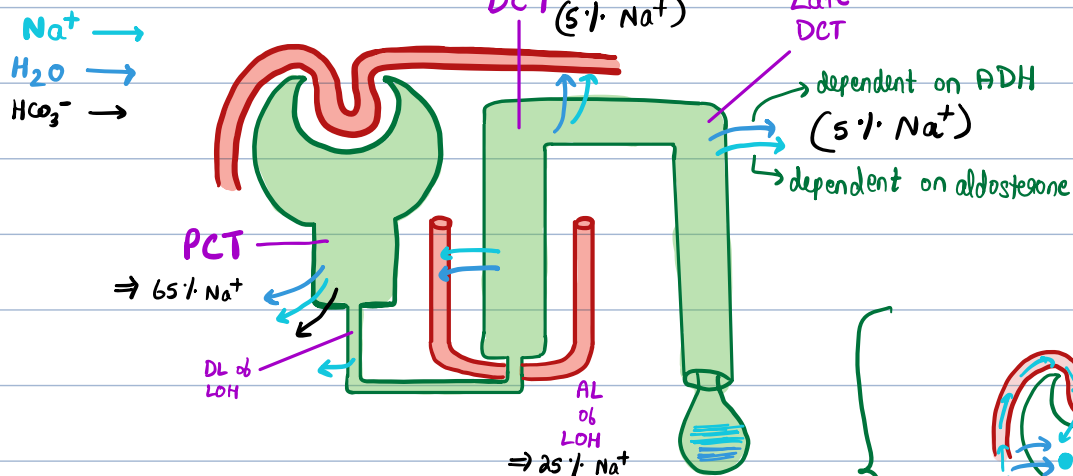


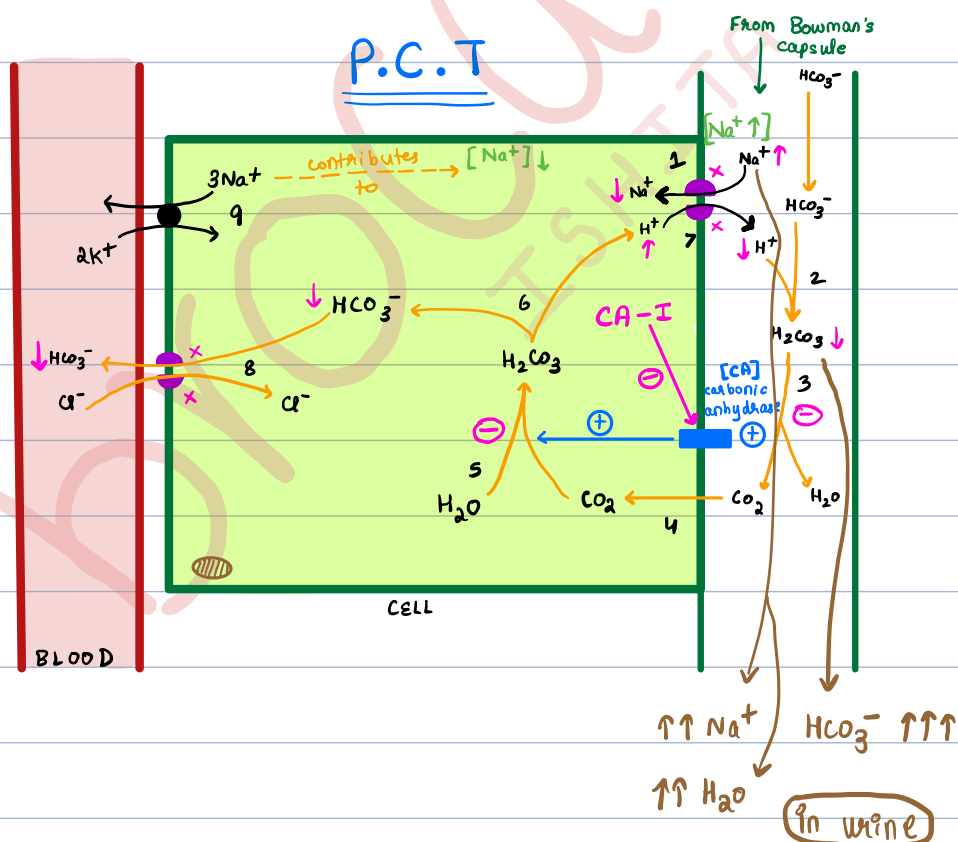
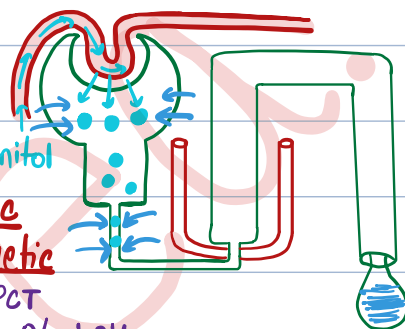


Sites of Diuretic Action:

- [I] P.C.T (eg: CA inhibitors) $\rightarrow$ CA-I
- [II] AL of LOH (eg: Loop diuretics)
- [III] Early D.C.T (thiazide diuretics)
- [IV] Late D.C.T (K^+ sparing diuretics)

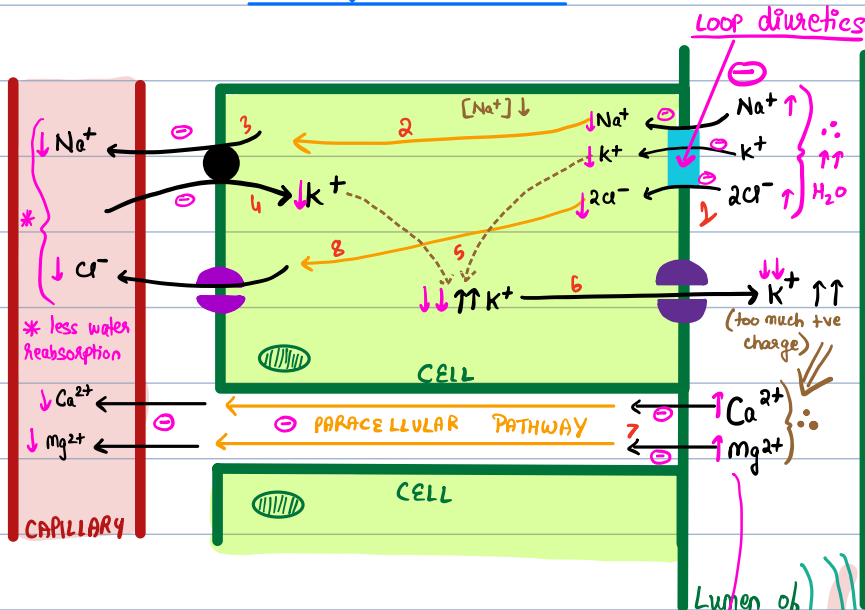
osmotic diuretic

at PCT & DL of LOH



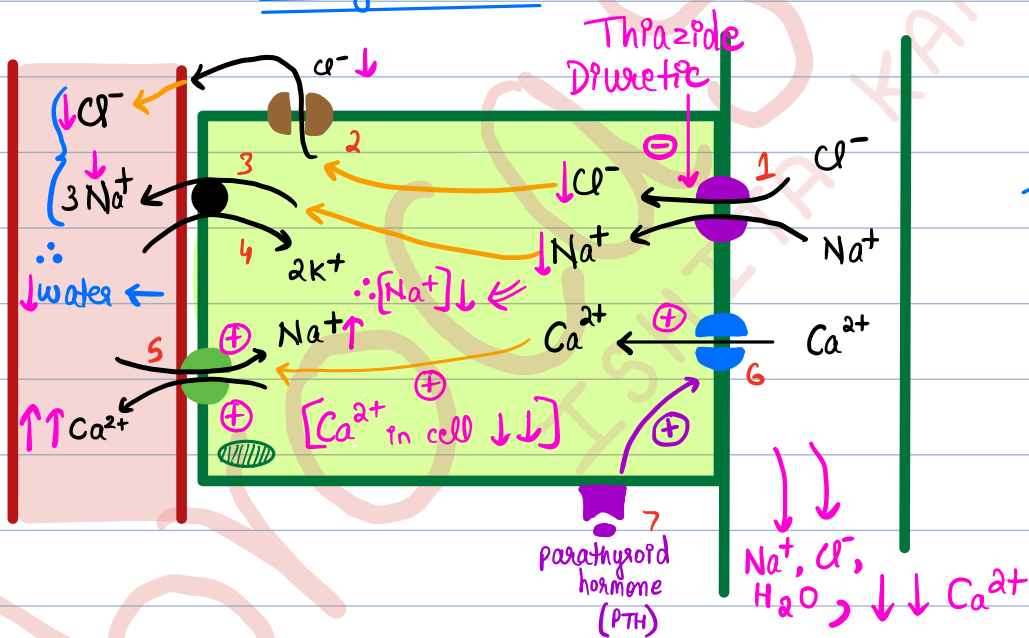
Carbonic Anhydrase Inhibitors

Ascending Limb of LOH



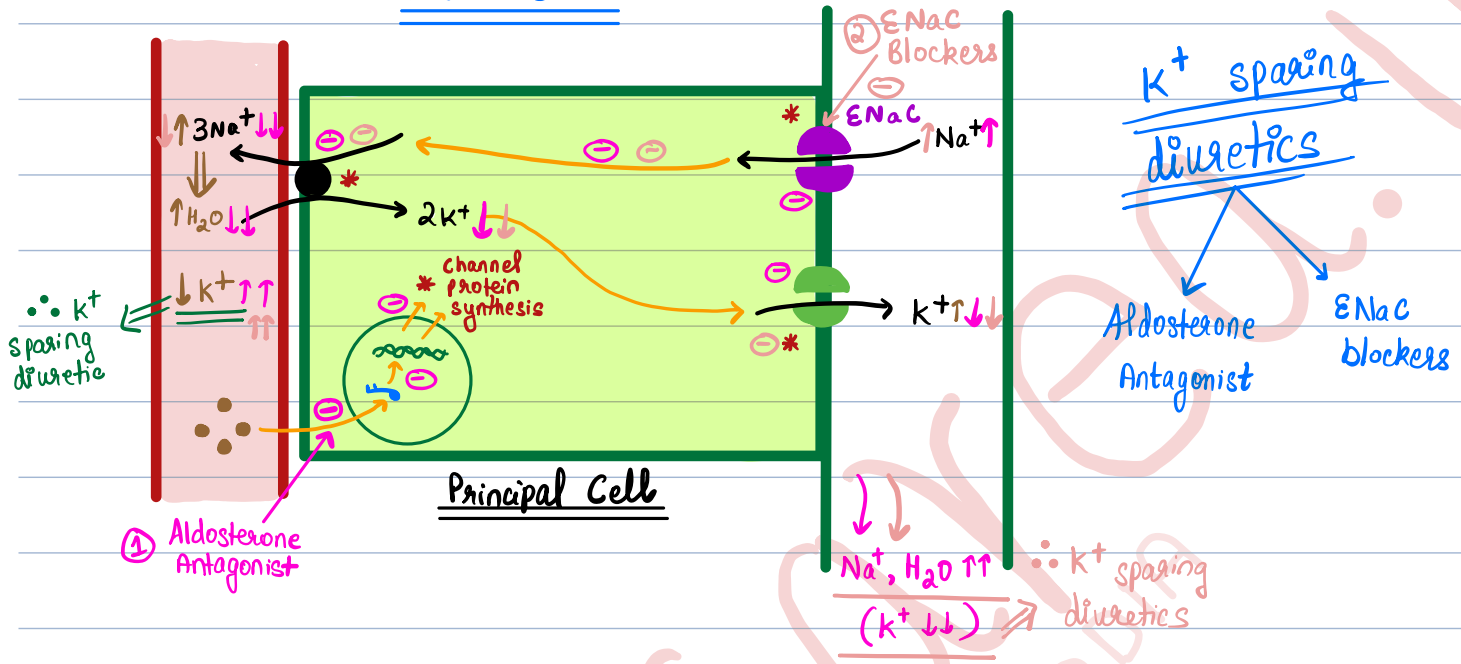
Loop Diuretics

Early DCT



Thiazide diuretic

Aldosterone •
Late DCT



Diuretics

High Ceiling (Inhibit $\text{Na}^+ - \text{K}^+ - 2\text{Cl}^-$ cotransporter)
[aka Loop Diuretics]

- Furosemide (aka Lasix)
(frusemide)

- Bumetanide

- Torasemide

- Ethacrynic acid

Medium Efficacy
(Inhibit $\text{Na}^+ - \text{Cl}^-$ symport)
[aka Thiazide Diuretic]

Benzothiadiazines

- Hydrochlorothiazide

- Hydroflumethiazide

- Benzthiazide

Thiazide-like

- Chlorthalidone

- Metozalone

- Xipamide

- Indapamide

- Clopamide

Weak / Adjunctive
Diuretics

Carbonic Anhydrase
Inhibitors

- Acetazolamide

K^+ Sparing
Diuretics

Aldosterone

Antagonists

- Spironolactone

- Eplerenone

Osmotic
Diuretics

- Mannose

- Isosorbide

- Glycerol

Renal epithelial Na^+ channel
(ENaC) Inhibitors

- Amiloride

- Triamterene

Osmotic Diuretics:

- Mannitol
- Urea

Site of action:

- PCT
- descending limb of LOH

- Indications
- cerebral edema (high ICP)
 - acute glaucoma (high IOP)
 - drug overdose

- Complications/Adverse effects:
- Hypovolemia
 - Hypotension
 - Hypernatremia in blood
- ($\because$ loss of water $\gg \gg$ Na^+)

In damaged kidneys $\Rightarrow$ all the water taken into plasma cannot be excreted out by the damaged kidneys.

$\Rightarrow$ fluid accumulation in lungs $\rightarrow$ pulmonary edema

$\Rightarrow$ hyponatremia (relatively, water $\gg \gg$ Na^+)

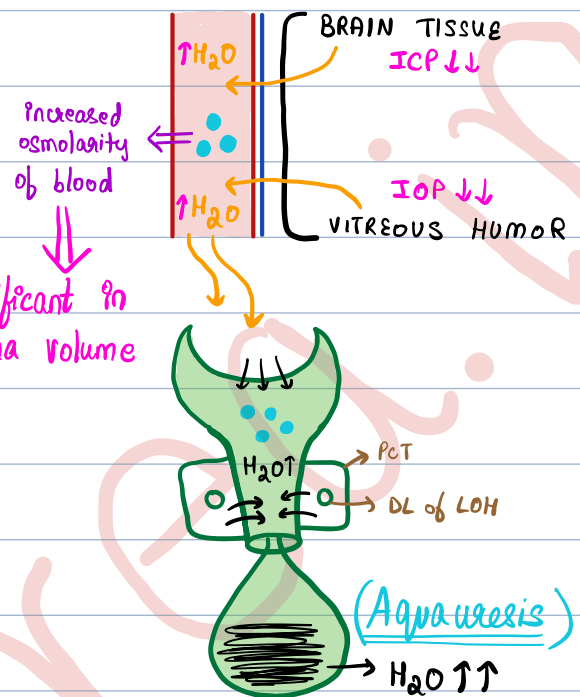
C/I: • Anuria

• Severe dehydration

• Severe pulmonary congestion/edema

• Active intracranial bleeding

• Severe renal dysfunction

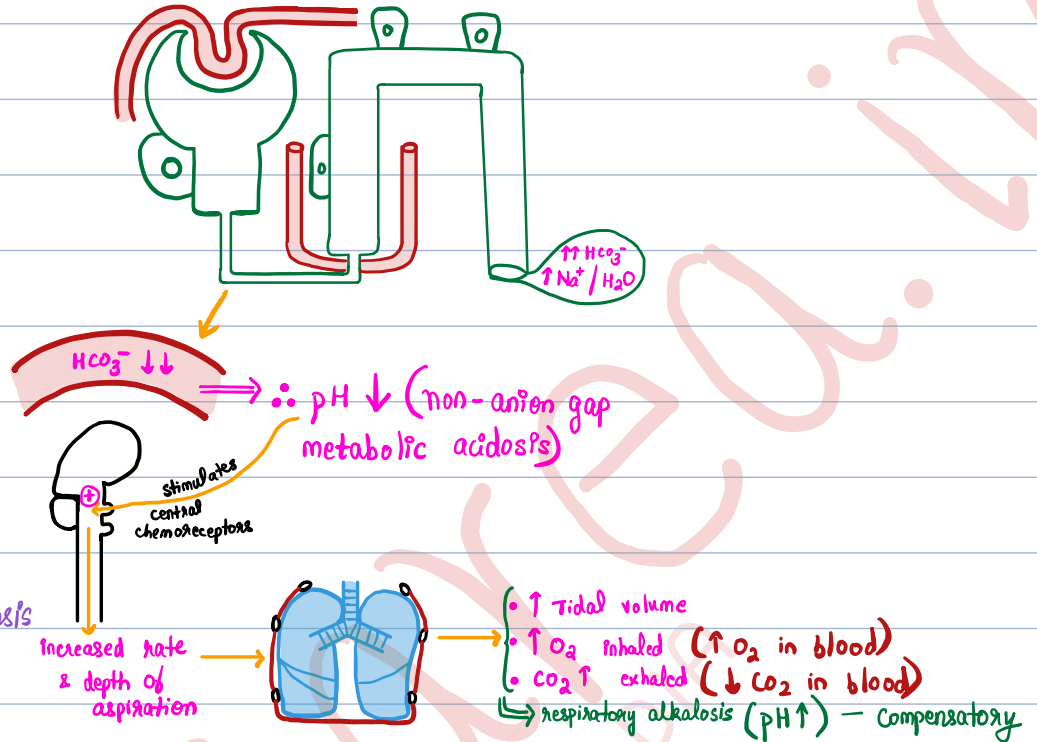


Carbonic Anhydrase Inhibitors: site of action - PCIT

- Acetazolamide

Indication:

- altitude sickness (leading to high altitude pulmonary edema)
- fluid diuresis (treatment of metabolic alkalosis)
- glaucoma - edema
- epilepsy - metabolic alkalosis
- pseudotumor cerebri



Acetazolamide also -

- decreases aqueous humor production (in eye) $\Rightarrow \downarrow$ IOP (in glaucoma)
- works on ependymal cells in the ventricles of the brain & decrease CSF production (beneficial in patients with high ICP that's idiopathic - idiopathic intracranial hypertension (IIH) or pseudotumor cerebri)

C/I: • Severe renal dysfunction

• Adrenal gland dysfunction

• Pregnancy & breastfeeding

• Cirrhosis & liver dysfunction

• Hyponatremia

• electrolyte imbalance

CHAPS

Uses: • Glaucoma • To alkalinize urine • Epilepsy • Periodic paralysis

• Mountain sickness (pulmonary & cerebral edema)

Adverse Effects: • Acidosis • Hypokalemia • Paresthesia • Fatigue

• Abdominal discomfort

• Hypersensitivity

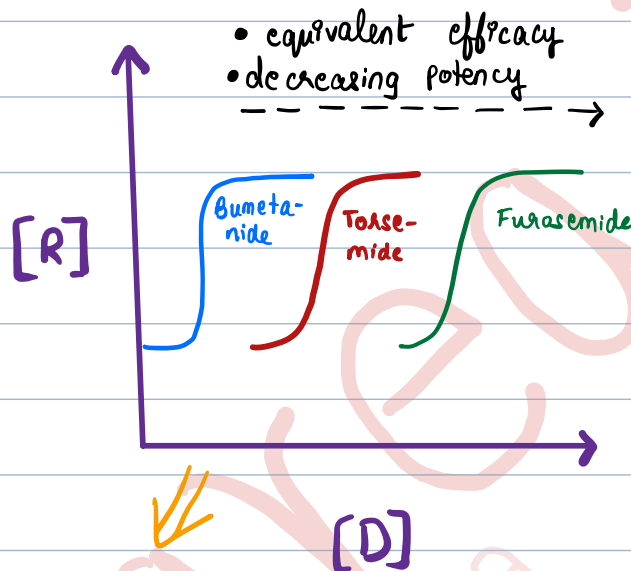
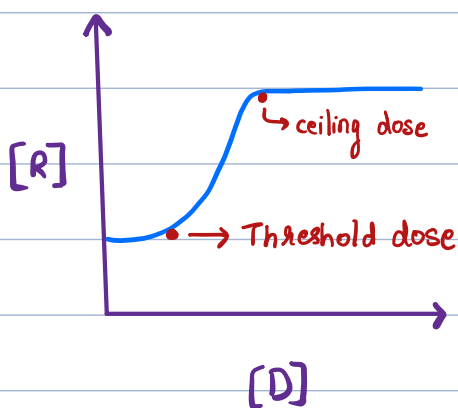
• Bone marrow depression

BPH^2
 P^2F

Loop Diuretics: site of action = ascending limb of loop of Henle (LOH)

- Furosemide (Lasix)
- Torsemide
- Bumetanide
- Ethacrynic acid

Dose-Response Curve:

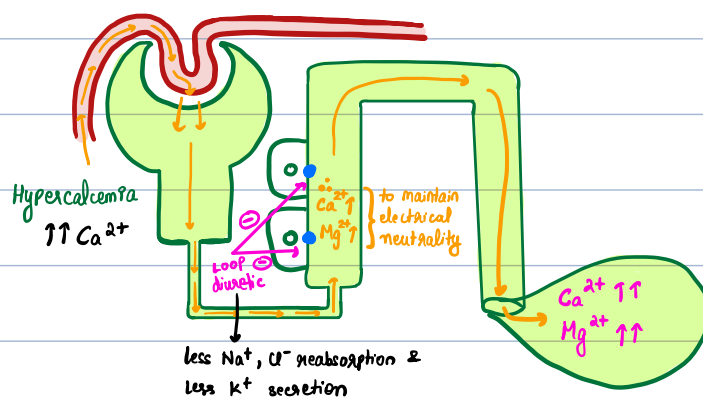
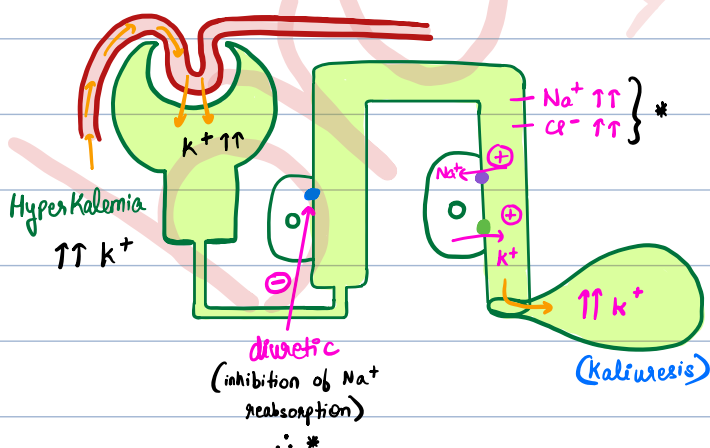


Equivalent Doses

Furosemide	Torsemide	Bumetanide
40 mg	20 mg	1 mg
$F = 50\%$	$F > 80\%$	$F > 80\%$
(oral bioavailability)	$\approx IV$	$\approx IV$
$\therefore \text{oral dose} = 2 \times IV \text{ dose}$		

Indications:

- Hyperkalemia
- fluid diuresis
- HTN
- Hypercalcemia
- nephrotic syndrome
- Refractory edema
- AKI



C/I: • Anuria

• Pre-existing hearing loss

• Severe renal failure

• Severe dehydration

$\uparrow \text{GAP}$

Furosemide:

Dose: Usually 20-80 mg OD in the morning

→ in renal insufficiency $\Rightarrow$ upto 200 mg 6 hourly i.m/i.v.

→ in pulmonary edema $\Rightarrow$ 40-80 mg i.v

LASIX 40 mg tab, 20 mg/2 ml inj; LASIX HIGH DOSE 500 mg tab, 250 mg/25 ml inj. (solution degrades spontaneously on exposure to light)

SALINEX 40 mg tab; FRUSENEX 40, 100 mg tab.

Bumetanide: Dose: 1-5 mg oral OD in the morning; 2-4 mg i.m/i.v
(max = 15 mg/day in renal failure)

BUMET 1 mg tab., 0.25 mg/ml inj.

Torsemide: Dose: 2.5-5 mg OD in hypertension; 5-20 mg/day in edema;
upto 100 mg BD in renal failure.

DIURETOR 10, 20 mg tabs; DYTOR, TIDE 5, 10, 20, 100 mg tabs,
10 mg/2 ml inj.

AMOGH³

Adverse Effects:

- Hypervolemia
- Hypokalemia
- Glucose intolerance
- Ototoxicity
- Myopathy
- Hyperuricemia (gout)
- Arrhythmia (metabolic)

Uses:

- Edema
- Acute pulmonary edema
- Acute LVF following MI
- Cerebral edema
- Hypertension
- Hypercalcemia of malignancy
- Infused along with blood transfusion to prevent volume overload in severely anemic patients

$\text{C}_6\text{H}_5\text{N}_2\text{O}_2$

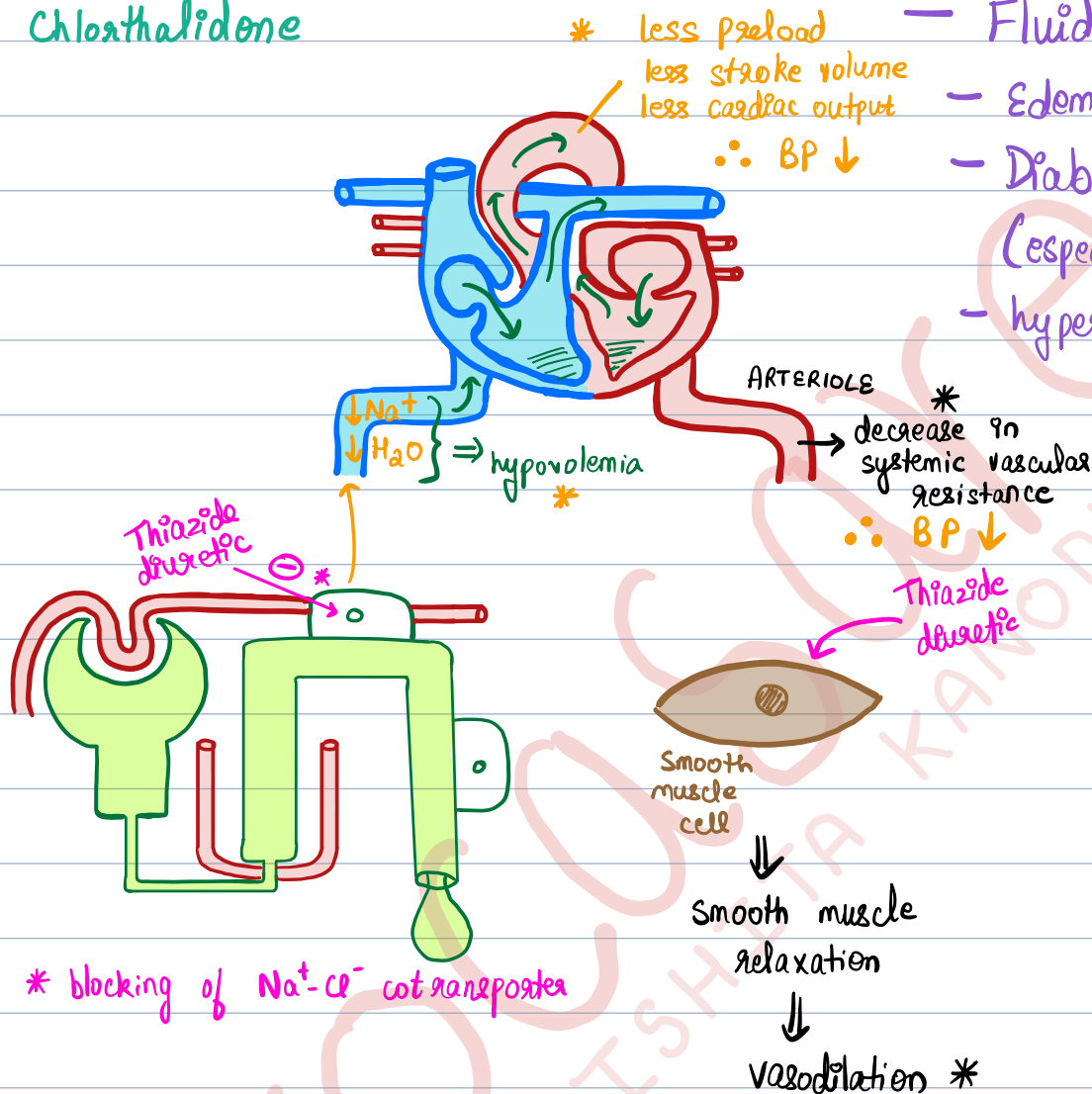
→ can cause vasodilation

Thiazide Diuretics: site of action: Early DCT

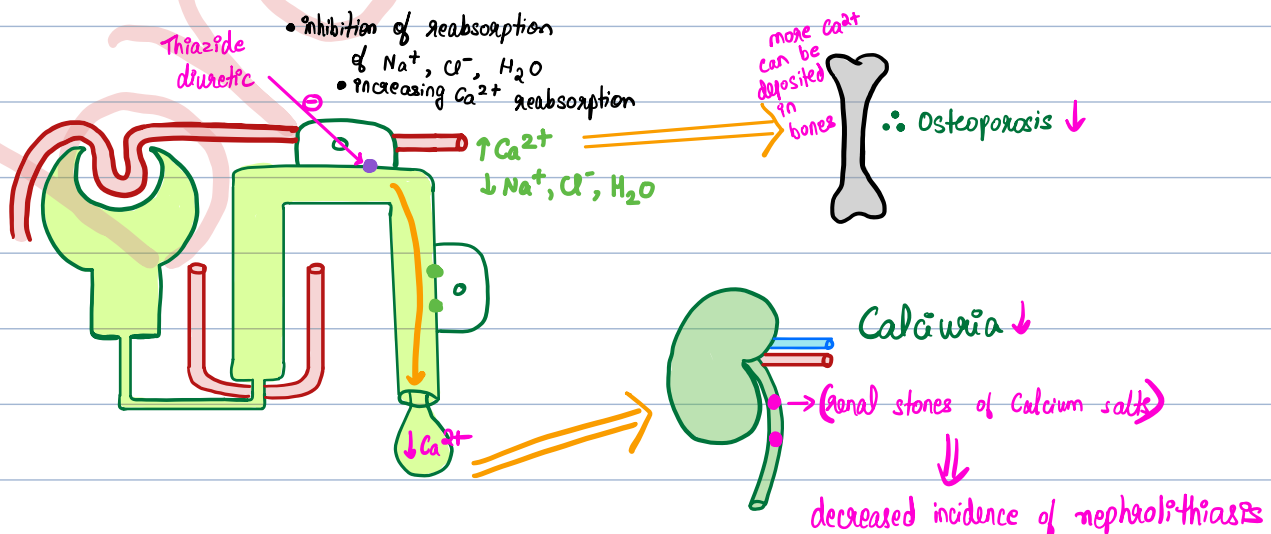
- Hydrochlorothiazide (HCTZ)
- Chlorthiazide
- Metolazone
- Chlorthalidone

Indications:

- Essential Hypertension
- Calciuria (nephrolithiasis)
- Osteoporosis
- Fluid Diuresis
- Edema
- Diabetes insipidus (especially - nephrogenic)
- hypertensive nephropathy



* blocking of Na⁺-Cl⁻ cotransporter



Uses:

- Mild to moderate edema
- Hypertension
- Diabetes insipidus (nephrogenic > pituitary)
- Hypercalcaemia
- Osteoporosis

$M-H^2O$

Adverse Effects:

- Hypokalaemia (especially if dietary intake of K^+ is low)
- Alkalosis
- Acute saline depletion — dehydration, orthostatic hypotension
- Dilutional hyponatraemia
- Nausea, vomiting, Diarrhoea
- Headache, giddiness
- Ototoxicity — hearing loss
- Hypersensitivity — rashes, photosensitivity
- Hyperuricaemia
- Hyperglycaemia
- Dyslipidaemia
- Hypocalcaemia
- Magnesium depletion
- Aggravation of renal insufficiency
- Precipitates mental disturbances & hepatic coma
- Avoided in toxemia of pregnancy (in which blood volume is low despite edema)

$H^+ A^- N O_3^-$ MOF

Drug Interactions:

- potentiates all other antihypertensives
- Enhances digoxin toxicity
- prolongs QT interval
- NSAIDs diminish the action of loop & thiazide diuretics by inhibiting PG synthesis in the kidney
- Probenecid inhibits tubular secretion of thiazide & loop diuretics & thus, decreases their diuretic action

P^3EN

C/I:

- Anuria
- Gout
- Severe renal failure
- Pregnancy & breastfeeding

$GAPS$

Drug	Available form	Daily dose (mg)
Hydrochloro - thiazide	AQUAZIDE, HYDRIDE THIAZIDE (12.5, 25, 50 mg) ESIDREX (50 mg)	12.5 - 100
Chlorthalidone	HYTHALTON (50, 100); HYDRAZIDE, THALIZIDE (12.5, 25 mg)	12.5 - 50
Metolazone	XAROXOLYN (5, 10 mg); DIUREM, METORAL (2.5, 5, 10 mg)	5 - 20
Xipamide	XIPAMID (20 mg)	20 - 40
Indapamide	LORVAS (2.5 mg)	2.5 - 5
Clopamide	BRINALDIX (20 mg)	10 - 60

Carbonic Anhydrase Inhibitors

Loop Diuretics

Thiazide diuretics

K⁺-sparing diuretics

Uses $\text{THF} - \text{L}^2\text{P}$

A/E HD - B²G²L

K⁺ Sparing Diuretics:

Conn's Syndrome

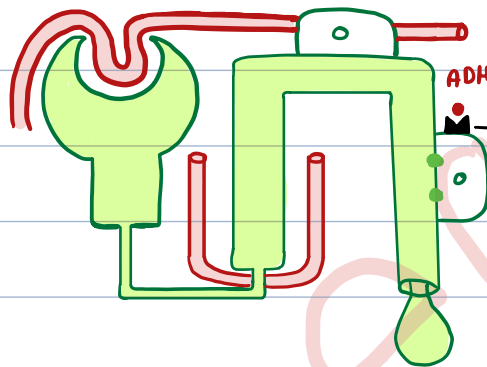


→ Hyperaldosteronism

Aldosterone Antagonist

- Hypernatremia ↓
- ↑ H₂O reabsorption ↓
(∴ hypervolemia, ↑ BP) ↓
- Hypokalemia ↓
- metabolic alkalosis ↓

Site of action: Late DCT



ENaC Blockers

ADH → V₂ receptor

[ADH is present & binds to V₂ receptor, but V₂ receptor is insensitive]

Nephrogenic Diabetes Insipidus

Indications: - CHF with chronic hypokalemia & hypertension

aldosterone blockers

- Conn's syndrome (hyperaldosteronism)

- Nephrogenic Diabetes Insipidus } ENaC Blockers

- Lithium-induced " " } Amiloride

- Hepatic edema } Spironolactone

- PCOS (spironolactone) → to reduce androgen levels

- Heart failure

TH² LP²

Uses: • To counteract K⁺ loss due to thiazide & loop diuretics

- Edema
- Hypertension
- Heart failure
- Primary hyperaldosteronism (Conn's Syndrome)

Adverse Effects: • Drowsiness • Ataxia • Epigastric distress • Loose motions

• Gynaecomastia • Erectile dysfunction/loss of libido • Breast tenderness/Menstrual irregularities

• Hypokalemia • Acidosis

C/I: Peptic ulcers

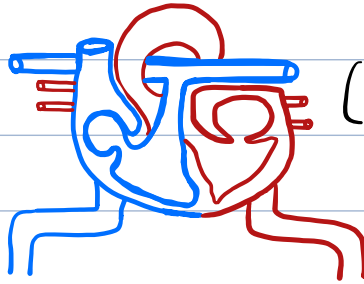
HD
BA²GE²L

Fluid Diuresis:

- Indications - pulmonary edema, pleural effusion
- generalised edema (anasarca)
 - localised edema, etc.
 - fluid overload (HF)



Peripheral
pitting edema

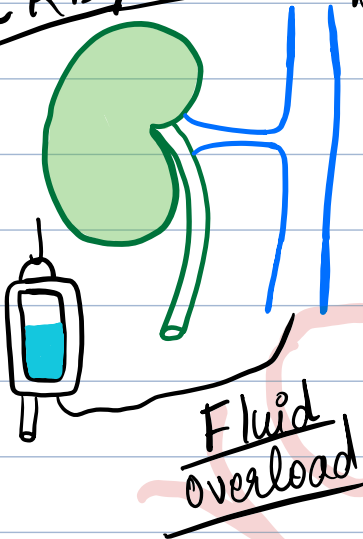


Abdominal distension
(due to fluid retention)

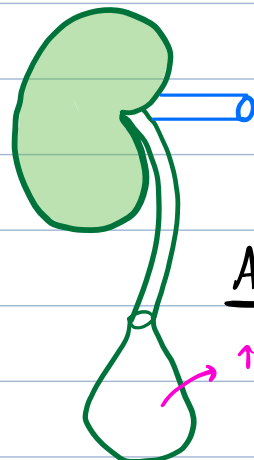
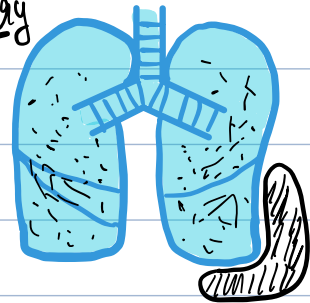
- Ascites
- Hepatomegaly

due to
heart
failure

CKD/AKI ⇒ ↓ urine output
↓
hypervolemia



Pulmonary
edema
Pleural
effusion



↓ H_2O ⇒ ↓ blood volume
↓ Na^+

↓
↓ preload ⇒ ↓ congestion

Aim of Diuretics

↑↑ Na^+ , ↑↑ H_2O , ↑↑ Cl^-

REGIMEN

→ may lead to hypernatremia

[I] Loop diuretic → blocks $\text{Na}^+ - \text{K}^+ - 2\text{Cl}^-$ cotransporter

[II] Thiazide diuretics → blocks $\text{Na}^+ - \text{Cl}^-$ cotransporter
→ ↑ diuresis

+ → cause more $\text{Na}^+ \gg \text{H}_2\text{O}$ excretion ($\therefore$ serum $\text{Na}^+ \downarrow$)

[III] Carbonic Anhydrase Inhibitors (given to combat the metabolic alkalosis created by Loop & thiazide diuretic combo)
→ ↑ HCO_3^- excretion → ↓ pH → improves diuresis by increasing efficacy of Loop & thiazide diuretics

[IV] K^+ sparing diuretics (given to combat the hypokalemia produced by Loop & thiazide diuretics & thus, prevent arrhythmias)
→ ↑ K^+ retention & also enhances diuresis

excess Na^+ in DCT

increased Na^+ reabsorption in DCT

H^+ is secreted into urine (in exchange for Na^+) to maintain electrical neutrality

K^+ is also secreted with H^+

$\text{K}^+ \uparrow \uparrow$ & $\text{H}^+ \uparrow \uparrow$ in urine.

- Hypokalemia
- Metabolic alkalosis

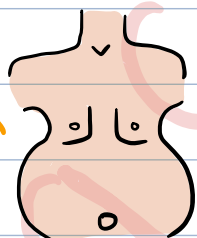
* inhibits the efficacy of Loop & thiazide diuretics

Ascites Diuresis: (Pitting edema/Ascites)

$\therefore$ the need for a drug * that blocks aldosterone

Thus, ↓ Na^+ , H_2O reabsorption

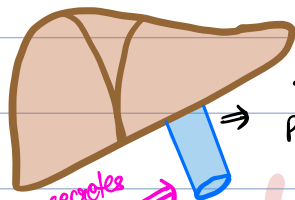
↓ ascites, pitting edema



Pitting edema/Ascites

worsening of ascites & pitting edema

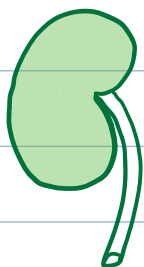
Cirrhosis



increase in portal blood pressure

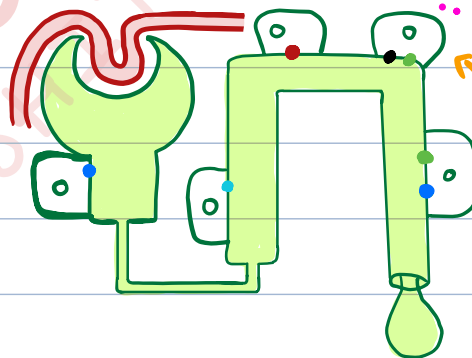
* liver secretes No to cause vasodilation of portal vein to increase blood flow

No not only vasodilates the portal vein, but also other abdominal veins & increase blood flow to the GIT



Reduced perfusion of kidneys

activates RAAS → Angiotensin II



$\therefore$ ↑ Na^+ reabsorption
↑ K^+ excretion
↑ H_2O reabsorption

acts on DCT

activates adrenal cortex to synthesize aldosterone



Aldosterone Blockers (high doses)

+ Loop diuretics (lower doses) (to enhance diuresis)

Adverse Drug Reactions:

Loop Diuretics:

- hyponatremia (H_2O loss $\gg$ Na^+ loss)
- hypovolemia
- Low Ca^{2+} & Mg^{2+} in blood
- hypokalemia & metabolic alkalosis
- hyperuricemia (& gout)
- hyperglycemia (loop diuretics either inhibit insulin release or induce insulin resistance)
- ototoxicity (more common with ethacrynic acid)

Thiazide Diuretics:

- hyponatremia (Na^+ loss $\gg$ H_2O loss)
- hypercalcemia
- hypomagnesemia
- hypokalemia & metabolic alkalosis
- hyperuricemia (& gout)
- hyperglycemia (loop diuretics either inhibit insulin release or induce insulin resistance)
- hyperlipidemia

K^+ sparing Diuretics:

- hyperkalemia
- metabolic acidosis
- Gynecomastia (with aldosterone antagonists) / Erectile dysfunction / Menstrual disturbance in females

(Aldosterone $\Rightarrow$ not only stimulates Na^+ reabsorption & K^+ excretion, but also stimulates H^+ excretion into urine)

Carbonic Anhydrase Inhibitors:

- metabolic acidosis (due to decreased HCO_3^- reabsorption into blood)
- risk of kidney stones (due to alkalization of urine by excess HCO_3^- excretion)
- hyperammonemia ($\uparrow NH_3$) (risk of encephalopathy, paresthesias, cerebral edema)
- hypokalemia