

CARBONIC ANHYDRASE INHIBITORS: ACETAZOLAMIDE

- They mainly catalyze the Reversible Reaction $H_2O + CO_2 \rightleftharpoons H_2CO_3$.
- Action PCT cell $\downarrow$ the Availability of H^+ to exchange with Na^+ through $Na^+ H^+$ Antiporter.

The net effect is inhibition of HCO_3^- reabsorption in PCT.

→ Acetazolamide

When this drug is used urine produced will be Rich in HCO_3^- which is matched by both Na^+ & K^+ . continued Action causes excess depletion body's HCO_3^-
 $\downarrow$ cause
Acidosis.

Other Action → Lower $\downarrow$ IOP; $\downarrow$ Aqueous humor production
→ $\uparrow$ CO_2 level $\downarrow$ pH level
→ $\downarrow$ gastric HCl.

PK → well Absorbed orally
single doses

Uses → It is not used as diuretic because of Acidosis, hypokalemic others:

→ Glaucoma

→ Mountain sickness: occur due to pulmonary edema (compression)
 $\downarrow$ pH. ~~For~~ transport is by pH Alkalosis

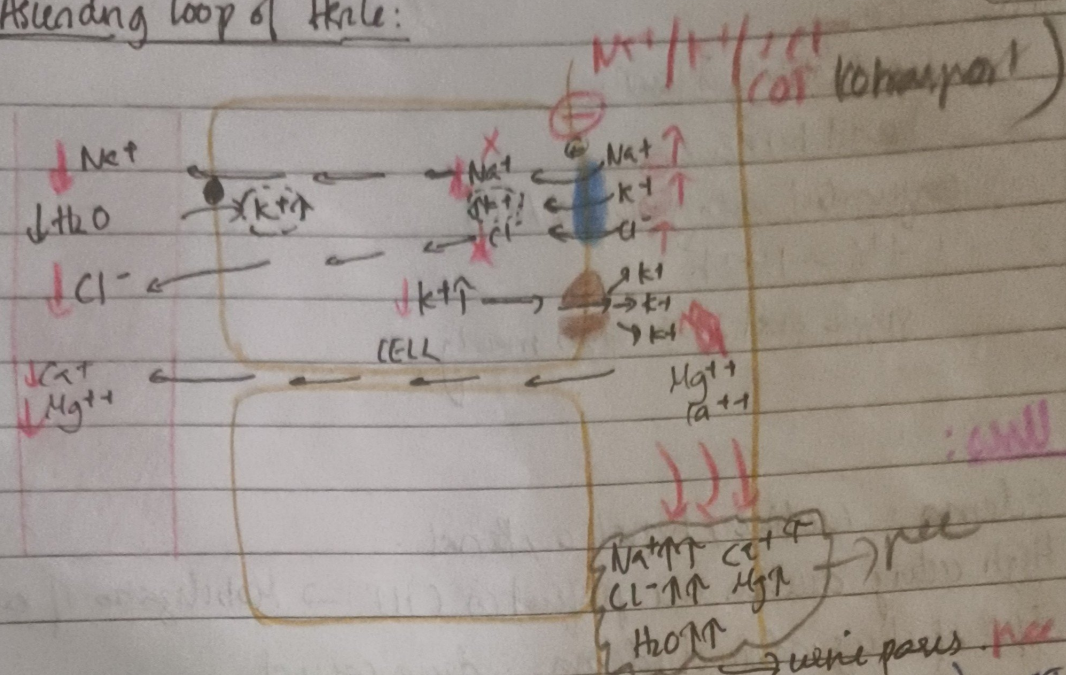
→ Epilepsy → Adjuvant in seizure.

→ To Alkalize urine → As promote excretion of Acidic drug.

→ more common (OPD)

ADR → Acidosis, hypokalemia, drowsiness, Abdominal discomfort, fatigue,
Hypertension, kidney stone,
C/D in liver disease.

Ascending loop of Henle:



HIGH CEILING (LOOP) DIURETICS

- Furosemide
- Torsemide (more potent than Furosemide) longer Action.
- Bumetanide ~ 40 times more potent (very effective in Pul edema)
- Rapidly Acting highly efficacious oral diuretic
- site of Action is Thick Ascending limb of loop of Henle (TAL)
- Hence called loop Diuretics
- Inhibit $\text{Na}^+ - \text{K}^+ - \text{2Cl}^-$ COT.
- Act on luminal side of membrane
- diuretic Action is independent of Acid-Balance Balance (doesn't affect HCO_3^-)
- ↑ Local PG synthesis.
- Responsible for quick relief in LHF, pulmonary edema
- Ca^{2+} & Mg^{2+} excretion.
- ↑ Uric Acid level ↓ ECF volume

⇒ A glycoprotein with 12 membrane spanning domain has been found to function as the $\text{Na}^+/\text{K}^+/\text{2Cl}^-$ cotransporter in many epithelial performing function including TAL. (Furosemide attaches to Cl^- binding site of this binding site of this protein to inhibit its transport function)

PK

- orally

Lipid solubility is low.

bind to PPB.

conjugated with glucuronic Acid

$t_{1/2}$ - 1-2 h

single oral dose given many.

Uses:

Edema: cardiac, hepatic, Renal.

High ceiling diuretics are preferred in CHF. $\rightarrow$ Mobilization of edema fluid.

$\rightarrow$ $t_{1/2}$ of drug induced edema drug caused

$\rightarrow$ $\downarrow$ the need of dialysis.

2) Acute pulmonary edema: (HT, LHF)

- IV Furosemide provides relief.

$\downarrow$ B.V & Venous Return.

- $\rightarrow$ clonidine
- $\rightarrow$ Methyldopa
- $\rightarrow$ Growth hormone
- $\rightarrow$ Glucocorticoids
- $\rightarrow$ Prazosin
- $\rightarrow$ NSAIDs.

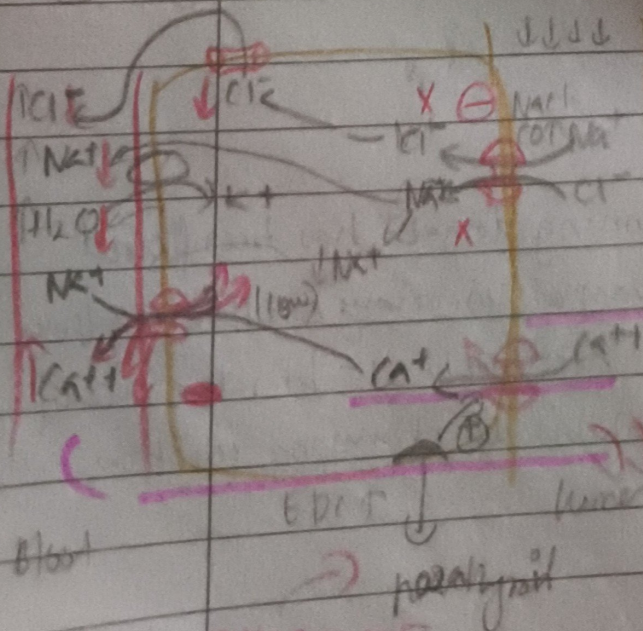
3) cerebral edema:

4) Hypertension $\rightarrow$ only in the presence of renal insufficiency

5) Hypocalcemia $\rightarrow$ excrete Ca^{2+} in large volume of urine

EARLY DISTAL CONVOLUTED TUBULE

LATE DISTAL CT.



when thiazide drug are given

Inhibit Na^+

$\downarrow Na^+ \downarrow Cl^-$

$\downarrow$ low Na^+

$\downarrow$ effect of water reabsorption

$\uparrow \uparrow Ca^{2+}$ in blood

THIAZIDE (Inhibitor of $\text{Na}^+ - \text{Cl}^-$ symport)

Thiazides

- Hydrochlorothiazide
- Hydroflumethiazide
- Benzthiazide

Thiazide-like

- Metolazone $\rightarrow$ useful in edema of CHF
- Xipamide $\rightarrow$ $\downarrow$ $\text{K}^+ \text{ loss}$ + edema
- clopamide
- Chlorthalidone $\rightarrow$ Anti hypertensive
- Indapamide

$\Rightarrow$ primary site = early DT

$\Rightarrow$ Inhibit $\text{Na}^+ - \text{Cl}^-$ symport at the luminal membrane.

$\hookrightarrow$ 12 membrane spanning glycoprotein.

$\rightarrow$ don't alter Acid-Base balance.

$\rightarrow$ $\downarrow$ Blood volume & external haemodynamics, so $\downarrow$ G.F.R.

$\rightarrow$ $\downarrow$ Ca^{2+} excretion & $\uparrow$ Mg excretion by DCT Aches.

PK $\rightarrow$ orally, no im, iv, sc.
large volume of distribution.
excreted unchanged
Prolonged duration of Action.

Uses:

1) Edema $\rightarrow$ h/ cardiac edema

2) Hypertension $\rightarrow$ HCTZ, Indapamide 1st line drug

3) Diabetes Insipidus $\rightarrow$ $\downarrow$ proximal free water clearance.

Reduce urine output

$\downarrow$ RBS $\uparrow$ Na^+ reabsorption

4) Hypocalcaemia: $\downarrow$ Ca^{2+} excretion.

COMPLICATION OF High ceiling of thiazide type D Therapy.

$\rightarrow$ Hypokalaemia $\rightarrow$ occurs due to prolonged intake of diuretic.
weakness, fatigue, muscle cramps, cardiac Arrhythmias.

normal
25 to 5 mEq/L.

Htby High dietary K^+ intake
supplement of K^+

Alkalosis may develop.

2013 AUG

- 2) Acute saline depletion: may cause dehydration & fall in B.P.
↑ Risk of peripheral venous thrombosis
- 3) hyponatremia: unable to retain ^{salt} due to salt diuresis.
feeling mushy.
- 4) GIT & CNS disturbances:
- 5) Hearing loss → ↓ salt in R and lymph & direct toxic action of diuretic on hair cell in ear.
- 6) Allergic manifestation:
- 7) Hyperuricemia → ↑ blood urate level
- 8) Hypoglycemia - of dyslipidemia.
→ Metabolic change
- 9) Hypocalcemia.
- 10) Magnesium depletion → paronychia.
- 11) ppt Mental disturbance.

Resistance occurs due to
→ Renal insufficiency
→ CHF
→ unavailability of liver
→ Nephrotic syndrome.

OSMOTIC DIURETICS

Mannitol

→ ↑ osmolality of Blood

↓

Retain water from PP, ATIA, DCT
draws water from the intracellular compartment

↓

↑ RBF.

↓

↑ urinary volume & excretion of
anions (Na⁺, K⁺, Ca²⁺, Mg²⁺)
Anion (Cl⁻, HCO₃⁻, PO₄³⁻)

diuretic
used to ↓ albumin
edema

↓ ↓ ↓

↑/↓ of glucose.

↓ ↓ is Renal
insufficiency
CHF, liver

POTASSIUM SAVING DRUGS:

Aldosterone

Antagonists

Spironolactone

Eplerenone

Renal epithelial Na^+ channel inhibitor

Amiloride

Triamterene

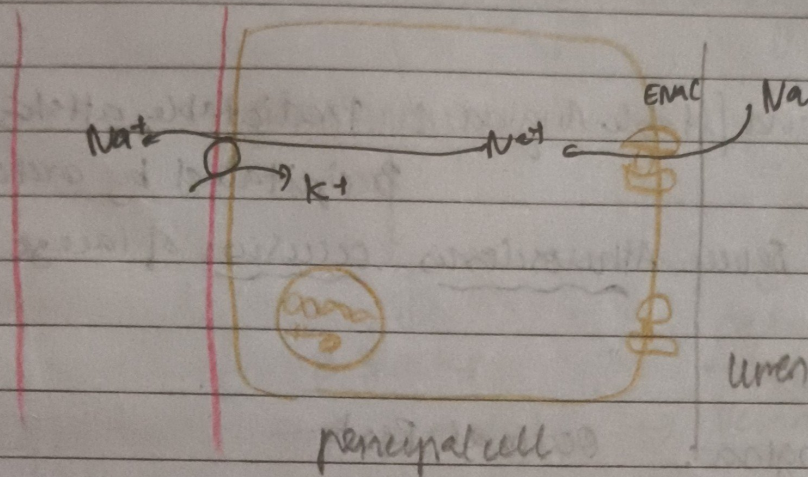
Urea

→ a diuretic

→ Hyponatremia

→ heart failure

→ Primary hyperaldosteronism



Aldosterone from Adrenal cortex

bind with mineralocorticoid Receptor in this cell

Form Aldosterone-receptor complex

Induce transcription leading to synthesis of some mRNAs.

mRNA translate to protein (Aldosterone-induced protein)

- ↳ ENAC
- ↳ ~~Na+~~ channel
- ↳ $Na^+ / K^+ ATPase$

Spironolactone binds with

Mineralocorticoid Receptor. Prevents synthesis of mRNA so APP is not produced

↓
↓ Reabsorption of sodium
↓ Na^+ excretion

Urea → same

However it Antagonize K^+ loss induced by other diuretics

Done
not left