CARBONIC ANHYDRASE INHIBITOR

- Acetazolamide and other CA inhibi. — more often use for their other action than DU effect
- less efficacious than thiazide & loop.

ACETAZOLAMIDE MOA

⇨ Inhibit CA located intracellularly (cytop.) and on apical memb. of PT (surface of plasma membr. that faces inward of lumen)

⇨ CA — catalyse the rex of CO_2 and H_2O

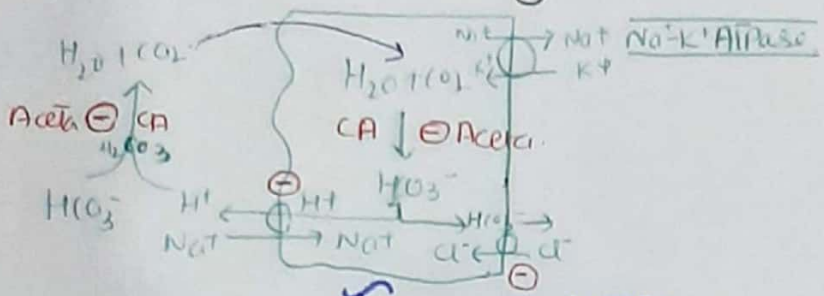
$$H_2O + CO_2 \rightleftharpoons H_2CO_3 \xrightleftharpoons[\text{Spontan.}]{\text{Oxid.}} H^+ + HCO_3^-$$

⇨ ↓se ability to exchange Na^+ for H^+ in presence of Acetazo. ⇨ Mild Diuresis

⇨ HCO_3^- retain in lumen → ↑se urinary pH

⇨ loss of HCO_3^- → Hyperchloremic metabo. acidosis & ↓se DU efficacy following several days of therapy

⇨ phosphate excretion → ↑se by unknown mechanism



Therap. USES

Glaucoma

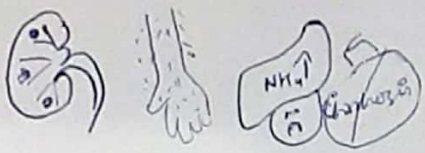
- Aceta ↓se production of aq. humor & ↓se IOP in pts ē chronic open-angle glaucoma — Blocking CA in ciliary body of eye
- Topical CA inhibitor — NOT cause systemic effects
  - Dorzolamide
  - Brinzolamide.

Motion Sickness [like Scopolamine]

- use in prophylaxis
- prevent weakness, breathlessness, Dizziness, Nausea and cerebral as well as pulmonary edema

★-KINECTICS:

✓ Adm. orally
✓ 90% PBB
✓ Elimin. by both active tubular secretion & passive reabsorp.



ADVERSE-EFFE.

- Metabolic acidosis (mild)
- K^+ depletion
- Renal stone formation
- Drowsiness & paresthesia (abnormal sens. of skin e.g tingling, pricking, chilling, burning & numbness)
- Avoid in pt ē Hepatic cirrhosis, bcoz pt could lead to ↓se excretion of NH_4^+

LOOP OR HIGH CEILING DIURETICS

- Site of action: Ascending LOH
- Furosemide – most commonly used
- Bumetanide & torsemide – are more potent (their use is increasing)
- Ethacrynic acid – infrequently used (ADR profile ↑)
- Highly efficacious in mobilizing Na^+ & Cl^- from the body.

MOA

Inhibit $Na^+/K^+/2Cl^-$ co-transport in luminal membr. in ascending limb of LOH

Ascending limb account for 25–30% of filtered NaCl – downstream sites are unable to compensate for ↑se Na^+ load

greatest DU effect of all drugs.

ACTION

Act promptly even in pt. ē poor renal function or lack of resp. to other diuretics

- ↑se Ca^{2+} content in urine
- In pt. ē normal serum Ca^{2+} hypocalcemia doesn't occur bec of Ca^{2+} reabsorb. in DCT

- ↑ RBF, possibly by ↑sing Prostagl-synthesis
- NSAIDS (thr use ↓se prosteg. sy.) ↓se DU action.

Therapeutic uses

Acute pulmonary edema (Pulmonary congestion)
+
acute/chronic periph. edema from HF or renal imp.
- (Drug of choice)
- given IV in emergency

∴ Lasix (Tab + inj) = furosemide

Hypercalcemia
(Loop DU + hydration)
trial Hypercal.

Hyperkalemia

↓T (rarely used alone)
↓ renal vascular resis.
↑ RBF

KINETICS

- Oral + IV
- DOA (2–4hrs)
- secreted in urine.

ADRs

OTOTOXICITY

- Permanent or reversible ototoxi, particularly ē ototoxic drugs (Aminoglycos. or Cisplatin)
- Ethacrynic acid is most common causative agent
- Induce vertigo

Hyperuricemia

Furosemide & E.A compete ē uric acid for renal secretory system ⇓ exacerbating Gouty attack

Acute Hypovole.

- Hypotension
- Shock
- Cardiac arrhy.

K^+ depletion

- Heavy load of Na^+ presented to CT results in ⇓
  ↑se exchange of Na^+ ē K^+ → Hypokalemia
- Loss of K^+ from cells in exchange for H^+ lead to Hypokalemic alkalosis

(K^+ sparing DU or supplementation ē K^+ can prevent this)

Hypomagnes.

Chronic + ↓ dietary Mg^{2+} use ⇓ Hypomagne. (Particular in elder)

Supplementation ē oral mag.

POTASSIUM-SPARING DIURETICS

- Site of action = collecting Tubule & late distal - Inhibit Na^+ reab & K^+ excretion
- Major use → HT (in combin ē thiazide or loop) - Avoided in pt ē renal dysfuno because of ↑se risk of Hyperkalemia
  - ↓ HF (aldosterone antag.)
- Types of class: (1) Aldo. antag. (2) Na^+ channel blocker.

★ ALDO. ANTAG: Spironolac. & eplerenone

MOA (synth steroid)

Spiro. antagonize Aldo. at intracellular cytoplasmic receptor site ⇒ Rendering spiro-recep complex inactive ⇒ prevent translocation of complex into nucleus of target cell → failure to produce mediator protein (⊖) that normally stimulate Na/K+ exchange site of CT → Thus lack of m. protein prevent Na^+ reabs.

Pharmaco-study YouTube

(⊖) Trans port Na^+ channel from cytoplasm to membra

(⊖) Activate ald inactive Na^+ channel

(⊖) Form new Na^+ channel

and K^+ and H^+ secretion.

★ eplerenone have less ↓ endocrine effect than spironolactone (comp antag at ↓ affinity for Glucocorticoid, Androgen & progest recep)

ACTION:

In edematous state = Aldoste ↑ses = Na^+ retention so spiro. uses

- NSAIDs diminish their effect.

★ THERAPEUTIC USES

Diuretic

- low Na^+ excre efficacy
- High K^+ retention so use ē other DU e.g thiazides
- Spiro. DOC in pt ē hepatic cirrhosis, as edema in these pts is caused by Secondary Hyperaldosteronism

Secondary Hyperaldos.

- Secon. Hyperaldo. such as Hepatic cirrhosis & Nephrotic Syndrome
- In pt. ē NO significant Aldo. level (e.g addison's disease), there is NO DU effect ē these drugs.

HF

- Prevent remodeling of heart due to HF
- ↓se mortality also. ē HF (esp in pt. ē reduc. ejection fraction)

Resistant HT

defined as use of 3 or more medic. without reaching the BP goal, often respond to K^+-sparing (ē or ēout incres Aldo. level) pts

ASCITES

(complication of Hepa. cirrhosis)
Spiro = effective.

PCOS

Block androgen receptor & inhibit steroid synthesis at high doses — helping to offset ↑sed androgen level. (off-label use)

★-KINETICS:

- abs. orally
- ↑ PBB
- metabo → Active metab. (DU also)
- Spiro → potent inhibi of P-glycoprotein
- eplerenon — metab by CYP450 (3A4)

★- ADRS

- Gastric upset
- Resemble sex steroids, may
  - (1) induce Gynecomastia in male
  - (2) Mens. irregu. in female
- Hyperkalemia
- Nausea
- lethargy
- mental confusion

Caution ē other K^+ drugs causing Hyperkalemia

- (1) ACE-inhibitor
- (2) K^+ supplement

TRIAMTERENE AND AMILORIDE

⇩

- Both block Na^+-channel transport - CT

↓

Use Na^+/K^+ exchange

- NOT depend on Aldosterone

⇨ Like Aldo. antag., They're not very efficacious DU

⇨ Use in comb. ē other DU

⇨ S.E: ↑se uric acid, renal stones & K^+ retention
(TZ&LOOP) (like AZM). (Aldo)

THIAZIDE — DIURETICS — most widely used

- Sulfonamide derivatives — SITE OF ACTION = DCT, ascending LOH
- All have same efficacy → differ only in potency
- Sometimes called "low ceiling diuretics" becoz — ↑dose above Normal dose ≠ ↑Diuretic response
- chlor & Hydrochlorthiazide — reprens. of Thiazide diuretic (same efficacy) (more ↓ potent)
- *-Chlorthalidone, indapamide and metolazone — Thiazide-like diuretics (Have sulfonamide residue in their chemical structure — MOA is similar)

Mechanism

- inhibit Na/Cl cotransport → ↑se conc. of Na^+ & Cl^- in tubular fluid.
- Becoz the site of action is on luminal membrane these drugs must be excreted into tubular lumen ⇒ ↓se renal = efficacy loss
- Efficacy ↓se ē co-adm. of NSAIDs — (indomethacin) which inhibit produc. of renal prostaglan. thereby ↓sing renal blood flow

ACTION

GFR < 30ml/min/m²

- ↑se Na & Cl excre → Hyperosmolar urine
  - NOT affected by Acid-base status of body
  - NOT change Acid-base status of blood
- loss of K^+ → more K+ esp. at start of therapy (Due to more absorp of Na^+ in principal cells & K+ is exchanged ē Na^+)
- Mg^{2+} loss → Mg-supplemnt use if there is chronic use of diuretics.
- ↓se Ca^{2+} excre → - promote reabsorp. of Ca^{2+} by parathyroid hormone. - preserve bone mineral density
- ↓PVR (Perip. vascular resistn) → ↓Blood vol. → ↓CO ⇒ ↓PVR; ↓BP (by relaxn of arterio smooth muscle) (unknown mechanism)

THERAPEUTIC USES

- **Hypertension** (mild–moder. essential HT) — DOC — effective in combn ē ACE, ARBs, β-block, K+-sparing. However Thiazide added if additional diuretic effect req. (Thiazide adm. 30min prior to loop diu.)
- **HF** — Loop diuretics'le (DOC in ↓sing EC-vol. in HF)
- **Hypercalciuria** — Kidney stones — effective for pt ē Ca-oxalate stones in UT. — Inhibit Ca^{2+} excretion.
- **Diabetes Insipidus** — Ability to produce Hyperosmolar urine — Urine vol. drop from 11 L/Day → 3L/day.

*-KINECTICS:

- orally effective
- Take 1–3 weeks to produce stable ↓se in BP
- Prolong $t_{1/2}$
- Secreted by organic acid secretory sys of kidney.

ADRs

(1) Hypokalemia
- ventricular arrhy. in pt. taking digoxin
- K+ supplements (citrus fruit, Bananas and prunes)
- Thiazides → ↓ intracel. vol → Activate RAAS (↑Na & H₂O reabs and K+ excrete) ← ↑K+ depletion
- spironolactone / triamterene / amiloride
- Adminis → ↓se K+ depletion

(2) HyponatremiA
- Limit water intake & lowering dose → prevent Hyponat.

(3) Hyperuricemia
- ↓se excretion by organic acid secretory system
- Being insoluble, uric acid precipitate in joints → Gouty attack

(4) Hyperglycemia
- causes
  - Glucose intolera.
  - impair insulin release & Gluc uptake

(5) Hypercalcemia

DM

Thiazid-Like Diuretics

- lack Thiazid structure
- But have unsubs sulfonamide groups
- Therap use & S.E are similar

Chlorthalidone

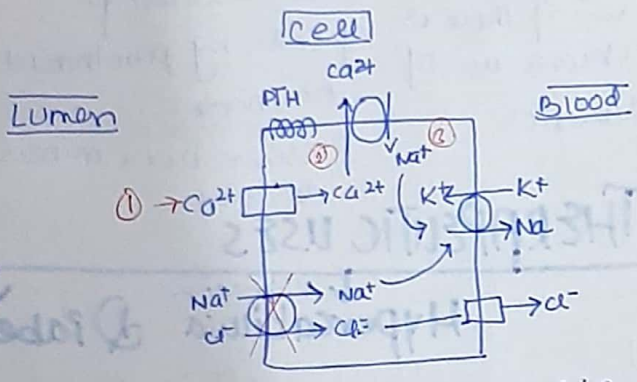
- long duration
- OD → For HT

Metolazone

- more potent
- Unlike Thiazides cause Na^+ excre even in adv. renal failure

INDAPAMIDE

- Lipid - soluble
- long duration
- At low doses → show signif. antihyp action & minimal Diuretic eff.
- metab. & excreted by GIT & Kidney Thus it less likely to accumulate in pt ē renal failure & may be useful in treatment



- When cell become deficient in Na^+, it start taking Ca^{2+} from lumen & exchange it ē Na^+ from blood. → ↑ Ca^{2+} reabsorption.

✓ Metro is dapper in RF

✗ Meto & indap → dapper - RF

✗ dapper - Metro -

OSMOTIC DIURETICS

⇨ Simple, Hydrophilic chemical sub that're filtered through glomerulus e.g MANNITOL AND UREA result in some degree of diuresis

⇨ presence of these sub. ⇨ High osmolality of tubular fluid.
⇩
prevent further water reabsorp.
⇩
osmotic Diuresis & small amount of Na^+ loss.

⇨ Mostly use for increasing Water excretion and rarely use in case of Na^+ retention

★. Use to maintain urine flow following acute toxic ingestion of sub. capable of producing acute renal failure

★. Mainstay treatment ⇨ ↓ Increased ICP or ARF due to shock, drug toxicities & trauma

⇨ Maintaining urine flow preserve long-term kidney function
⇩
Save pt. from dialysis

★. Mannitol NOT abs. orally & Given IV.

ADVERSE-EFFECTS:-
- EC water expansion ⟹ Becoz the presence of Mannitol in ECF extract water from cells & causes Hyponatremia until Diuresis occur.
- Dehydration
- Hypo or Hypernatremia