

DIURETICS.

1) Carbonic Anhydrase Inhibitors [CAIs]

~~It~~ belongs to the class of weak / osmotic

diuretics

eg: acetazolamide

Acetazolamide:

It is a sulfonamide derivative which non competitively but reversibly inhibits [CAse (type II)] in PT cells resulting in slowing of hydration of CO_2 . This decreases availability of H^+ to exchange with luminal Na^+ through the $\text{Na}^+ - \text{H}^+$ antiporter.

* Inhibition of brush border CAse (type IV) retards dehydration of H_2CO_3 in the tubular fluid so that less CO_2 diffuses back into the cells.

* The net effect is the inhibition of HCO_3^- and accompanying Na^+ reabsorption at PT.

* Secretion of H^+ by intercalated cells of DT and CD is also interfered.

* When CAse inhibitors are given, the distal $\text{Na}^+ - \text{K}^+$ exchange takes place only with K^+ which is lost in excess. For the same degree of natriuresis, CAse inhibitors cause the most marked kaliuresis compared to other diuretics. Urine produced under acetazolamide action is alkaline and rich in HCO_3^- which is matched by both Na^+ and K^+ . Continued action of this drug depletes body HCO_3^- & causes acidosis.

Extrarenal Action

* lowering of intraocular tension due to decreased formation of aqueous humor.

* Raised level of CO_2 in brain and lowering of PA, producing sedation & elevation of seizure threshold.

* Decreased gastric HCl and pancreatic NaHCO_3 secretion

Pharmacokinetics: Well absorbed orally & excreted unchanged in urine

Action of single dose lasts 8-12 hrs

Uses:
① Migraine,
② Epilepsy,
③ maintain sodium
④ water diuresis

Adverse effects;

* Acidosis, hypokalaemia, drowsiness, paraesthesia, fatigue, abdominal discomfort, Need risk of phosphate store formⁿ in kidney.

* Hypersensitivity reactions - fever, rashes.

* Contraindicated in lower doses

* Acidosis is more likely to occur in patients of UPO

* Bone marrow depression is rare but serious

2) Osmotic Diuretics

Mannitol;

Mannitol is a nonelectrolyte of low molecular

weight that is pharmacologically inert;

• can be given in large quantities sufficient to raise osmolality of plasma as well as tubular fluid

• It is minimally metabolised in body; freely filtered at glomerulus and undergoes limited absorption; essentially suited to be OSMOTIC DIURETIC.

* It appears to limit tubular H_2O and electrolyte reabsorption in a variety of ways.

→ Retains H_2O osmotically in PT and descending limb of LOH which are freely permeable to H_2O .

~~* It~~

→ Expands extracellular fluid volume - increases GFR and inhibits renin release

→ Increases Renal blood flow, especially to medulla, partially washing off medullary hypertonicity. With countercurrent osmotic

- gradient is dissipated by passive salt reabsorption is reduced.

→ Also, excretion of all cations (Na^+ , Mg^{2+} , Ca^{2+} , K^+) and anions (Cl^- , HCO_3^- , PO_4^{3-}) is also enhanced.

Administration.

• Not absorbed orally, has to be given IV as 10-20% soln

It is excreted unchanged with a $t_{1/2}$ of 0.5-1.5 hr.

Uses.

• It is never used for treatment of chronic edema or as a natriuretic.

• Its indications are;

• Increased intracranial pressure / intraocular pressure

∴ to counteract low osmolality of plasma and etc due to rapid hemodialysis or peritoneal dialysis.

Mannitol is contraindicated in renal insufficiency, acute tubular necrosis, anuria, pulmonary edema, acute left ventricular failure, CHF and cerebral hemorrhage.

Side Effects -

Headache, nausea, vomiting (common), Hypersensitivity reactions (rare)

other osmotic diuretics - sorbitide and glycerol.

3) Natriuretic Peptides (NPs)

• group of hormones primarily involved in regulating fluid balance, BP, cardiovascular homeostasis. they are secreted by heart, brain & other tissues in response to ↓ed bld vol, pressure/stress on the circ.

→ Natri tide.

∴ Recombinant BNP.

- Used by continuous IV infusion to relieve dyspnea & other symptoms in refractory CHF.
- Enhances salt and H_2O excretion and is a potent vasodilator with profile of action similar to iv glyceryl trinitrate it ↓s ventricular filling pressure.
- Added to standard therapy, additional hemodynamic or symptomatic improvement can be obtained for short periods, but no long

terms benefits are evident in CHF.

→ Carperitide.

Recombinant form of ANP

MOA. acts on NPR-A.

Action of guanylate cyclase, increases cGMP,
vasodilation → ↓ preload & afterload.

Natriuresis and diuresis by increasing GFR and

↓ Na^+ reabsorption used as IV infusion.

4) ADENOSINE RECEPTOR INHIBITORS

(i) Methoxyanthine.

Exerts diuretic effect.

MOA:

↓ Adenosine Receptor Antagonism: ↓ Na^+
reabsorption which leads to Na^+ and H_2O
excretion.

↑ GFR - by inhibiting adenosine vasoconstrictor
effect on the afferent arteriole, methyl
xanthines enhance Renal bld flow & filtration.

(ii) Phosphodiesterase inhibition.

* Inhibition leads to increased levels of
cAMP in cells promotes relaxation of vascular sm
including those in kidneys which enhances
Renal BF, contribute indirectly to diuresis by
improving perfusion of nephron

(iii) Direct effect of Renal tubules.

Enhancing H_2O & electrolyte excretion.

5) Drug Interactions of Diuretics.

① Loop Diuretics.

- NSAIDs: ↓ se diuretic efficacy by inhibiting PG_2 synthesis leading to ↓ Renal BF & Na^+ excretion
- Aminoglycosides - ↑ risk of ototoxicity & nephrotoxicity, particularly with high doses of loop diuretics.
- Digoxin - Hypokalemia caused by loop diuretics increases the risk of digoxin toxicity.
- Lithium: ↓ clearance can lead to toxicity
- Corticosteroids - ↑ risk of hypokalemia when used concurrently.
- ACE inhibitors: cause excessive hypotension, especially in volume depleted patients
- Antihyperglycemics: cause hypoglycemia, counteracting effect of these drugs.

② Thiazide Diuretics.

- NSAIDs - ↓ efficacy of thiazide diuretics.
- Digoxin - Hypokalemia & hypomagnesemia caused by thiazides ↑ risk of digoxin toxicity.
- Lithium - Thiazides reduce renal clearance & ↑ Li toxicity.
- Antiarrhythmics - ↑ risk of torsades de pointes due to thiazide induced hypokalemia &

hypomagnesaemia.

- Antidiabetic agent: Raise bld sugar levels, requiring adjustments in antidiabetic drug doses.
- Ca supplements - thiazide reduce Ca excretion, ↑ risk of hypercalcaemia
- ACE inhibitors - cause hypotension, especially in dehydrated/elderly patients.

① K^+ sparing diuretics.

- K^+ supplements - produce dangerous hyperkalaemia
- Aspirin - blocks spironolactone by inhibiting tubular secretion of its active metabolite
- ACE inhibitors - pronounced hyperkalaemia.
- Digoxin: spironolactone ↑ plasma digoxin concentration.