Diuretics

Diuretics drugs which increase urine (diuresis) and sodium excretion (natriuresis).

Classification:
1-**High-efficacy** (Potassium-depleting) (loop) diuretics ex .furosemide, bumetanide ,torasemide .

2-**Moderate- efficacy** (Potassium-depleting) diuretics
a-thiazides ex. Hydrochlorothiazide, bendroflumethiazide
b- thiazides- related diuretics ex. metolazone, chlorthalidone, Indapamide

3-**Low efficacy diuretics**
a-potassium- sparing diuretic:
1- aldosterone antagonists ex. Spironolactone, eplerenone,
2- inhibitors of renal sodium channel ex. triamterene, amiloride.
b -osmotic diuretics ex. Mannitol
C-carbonic anhydrase inhibitors ex. Acetazolamide, dorzolamide

Thiazides and thiazide- related diuretics:

Mechanism of action and Site of action: Inhibit sodium reabsorption by inhibiting the Na^+/Cl^- transpoter in cortical diluting segment (the early portion of distal convoluted tubule); between ascending loop of Henle and late distal tubule.

Efficacy is moderate; they cause 5- 10% of filtered sodium to be excreted, because nearly 90% of filtered sodium has already been reabsorbed before it reaches their site of action.

Hypokalaemia occur because more amount of sodium is delivered to the distal nephrones, where it exchanges with potassium.

'Ceiling' of effect is low -the dose response curve is flat; increasing the dose beyond a small range produces no additional diuresis.

Onset of action:slow - 2h (orally); so they are not suitable for clinical situations that require rapid diuresis i.e. acute pulmonary oedema or sever hypertension.

Duration of action: long e.g. (hydrochlorothiazide and bendroflumethiazide-12h, chlorthalidone-48 h) .The long duration of action allows once daily administration and they are preferably given early in the morning so that diuresis does not disturb patients' sleep).

They are ineffective in sever renal impairment and when **GFR** has fallen **below 20 ml**/min (except **metolazone**).

Chronic use reduce blood pressure in hypertensives due to thiazides-induced diuresis in addition to vasodilatation which reduces the peripheral resistance,through increasing vasodilating PGS and because reduction of Na^+ leads to reduction in intracellular Ca^{+2} which relaxes vascular smooth muscle.
Renal calcium excretion is decreased. They are preferred on loop diuretics in calcium-deficient, elderly and osteoporotic individuals who are at risk of fractures. The hypocalcuric effect of thiazides has also been used for prevention of hypercalciuria and renal calcium stones.

Renal Mg^{+2}excretion is increased.

Serum uric acid level is **increased** because diuretics are organic acids and compete with uric acid for proximal tubular secretion .

USES:
1-hypertension
2- oedema due to heart failure, renal and hepatic diseases. 3-diabetes insipidus. 4-hypercalciuria with recurrent renal calcium stones

Loop diuretics

Furosemide is prototype
Mechanism and Site of action: inhibit sodium reabsorption by inhibiting $Na^+/K^+/2Cl^-$ transporter in the medullary thick ascending loop of Henle.

Efficacy is high; cause up to 25% of filtered Na^+ to be excreted.
'Ceiling' of effect is high (diuresis goes on increasing with increasing dose) .Over-treatment can cause dehydration.

Onset of action rapid -furosemide (i.v. 30 min), (oral 1 h); therefore it is suitable for emergency situations as acute pulmonary oedema and hypertensive crisis.
Duration of action: Short- (6h), so if given late during a day it does not disturb sleep.
Hypokalaemia occur by same mechanism as thiazides.

Loop diuretics **remain effective i**n severe renal impairment and at **GFR below 10ml/min.**

Renal Ca^{+2} excretion is increased. This is utilized in treatment of hypercalcaemia. On other hand they are not preferred in elderly, osteoporotic and calcium deficient, for loop diuretics use is associated with an increased risk of fractures.
Renal Mg^{+} excretion is increased.
Serum uric acid is increased (by same mechanism as thiazides).

USES:
1-acute pulmonary oedema and acute left ventricular failure
2-oedema due to renal or hepatic diseases
3-hypertensive emergencies, hypertension associated with renal failure or congestive heart failure
4- hypercalcemia 5-cerebral oedema 6- renal failure

SIDE EFFECTS of diuretics:
A) Metabolic:
1-Hypokalaemia: risk is more with low dietary K^{+} intake, concurrent use of other drugs that cause hypokalaemia as β2-adrenoceptor agonists, theophylline and corticosteroids, g.i.t. diseases that cause electrolyte loss as vomiting or diarrhea.
Hypokalaemia causes arrhythmias.
It can be prevented or treated by high dietary potassium intake, supplement of KCl tablets or combining potassium- depleting with potassium- sparing diuretics
2- hyponatraemia and hypovolaemia 3- hypotension
4- hypomagnaesemia
5- hypercalcaemia due to thiazides and hypocalcaemia due to loop diuretics 6- hyperuricaemia ;gout may occur

7- Hyperglycemia 8- hyperlipidaemia

B) Other side effects: Thiazides: thrombocytopenia, agranulocytosis , photosensitivity, dermatitis.
Furosemide and loop diuretics: hearing loss

Drug interactions of loop and thiazides diuretics:
1 hypokalaemia induced by these drugs enhances digoxine toxicity.
2- NSAIDs reduce effect of diuretics by inhibiting synthesis of renal vasodilator PGs.
3-Diuretics precipitate lithium toxicity by inhibiting its excretion.
4-Loop diuretics potentiate aminoglycosides-induced ototoxicity.

Potassium-sparing diuretics:

Efficacy: is low; cause 5% of filtered sodium to be excreted, so they are are usually given with other more efficacious diuretics.

1-Spironolactone:

Mechanism of action: is a steroid, structurally similar to aldosterone and acts as a competitive antagonist on aldosterone receptors in the late distal tubule cells, increasing Na^+ and decreasing K^+ excretion.
It is a mild diuretic because majority of Na^+ has already been reabsorbed proximal to its site of action.

PKs:
Metabolized in liver to active metabolite (canrenone), which prolongs the diuretic effect to 48h.
Onset of action is slow (about 4 days).
Uses:
1- Hypertension with other diuretics 2-oedema and ascites due to congestive heart failure, liver cirrhosis and nephrotic syndrome
3-primary hyperaldosteronism
4- Secondary hyperaldosteronism due to hepatic cirrhosis.
5- To counteract potassium loss due to thiazides and loop diuretisc.
6-hirsutism in female due to its antiandrogen effect

Side effects:
1) Hyperkalemia 2- hormonal imbalance, Gynaecomastia, impotence, menstrual disturbance
3- Gastric upset; increased risk of gastric ulcer

Drug interactions potentiate hyperkalaemia if given with angiotensine receptor blockers or angiotensine converting enzyme inhibitors.

2-Eplerenone: aldosterone antagonisthas similar action but more selective and less hormonal imbalance side effects than aldosterne.

3-Amiloride and triamterene

Inhibit Na^+ reabsorption by blocking renal epithelial Na^+ channels in late distal tubule and collecting duct.

Uses: with loop or thiazide diuretics to counteract hypokalaemia .

Side effects: 1)hyperkalaemia 2) GIT upset

Osmotic diuretics ex. Mannitol

Is a low molecular weight substance that is filtered by the glomerulus but not reabsorbed by the renal tubule, and thus increase the osmolarity of the tubular fluid. Thus they prevent passive reabsorption of water in the proximal tubule and loop of Henle which cause an increase in urine volume.

It is not absorbed orally and given IV.

Because they increase water rather than sodium excretion , osmotic diuretics are not useful for treating oedema and other conditions caused due to sodium retention.

USES: 1- for rapid reduction of intracranial pressure

2- to maintain urine flow in acute renal failure

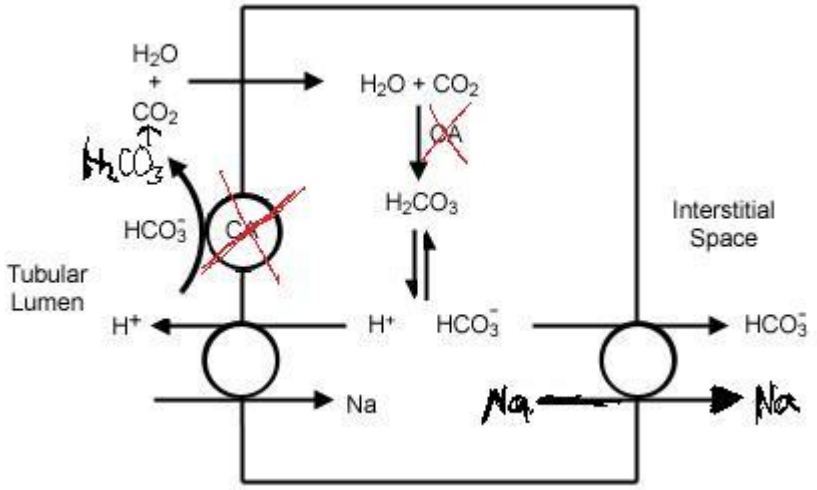
Side effects: dehydration, expansion of volume extracellular fluid

Contraindications: congestive heart failure, pulmonary oedema because it increases extra cellular fluid volume by encouraging water movement from inside cells to the extracellular fluid.

CARBONIC ANHYDRASE INHIBITORs (CAI) ex. acetazolamide

Mechanism of action: inhibit Carbonic anhydrase enzyme in cells of renal proximal tubule). Thus inhibiting the formation of hydrogen and bicarbonate ions from CO2 and water, so reduces the availability of H ions for exchange with sodium and increasing excretion of bicarbonate, sodium and water. This results in alkaline diuresis.

Diuretic effect is lost following several days, because of depletion of the body $HCO3^-$ therefore they are not used as diuretics.



USES: orally

1) treatment of chronic glaucoma(inhibition of carbonic anhydrase in ciliary body reduces formation of aqueous humor)
2) tonic-clonic, absence and partial epilepsy 3)prevention of mountain sickness 4)familial periodic paralysis

Side effects:

1) parasthesia and numbiness in toes and fingers 2) drowsiness 3)metabolic acidosis 4) Ca^{+2} renal stones, because Ca^{+2} is insoluble in alkaline urine

Dorzolamide: topical (eye drops) CAI, used chronic glaucoma has less systemic side effects.