DIURETICS

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Introduction -

Diuretics are chemical agents which increase the excretion of urine by kidneys. They lead to the secretion of excess water and that accumulate in tissues and urine, results in decrease in body fluids especially the extracellular fluid. So, diuretics are used in management of heart failure, oedema, or hypertension.

Diuretics are drugs that promote the output of urine excreted by the kidneys. The primary action of most diuretics is the direct inhibition of Na^+ transport at one or most of the four major anatomical sites along the nephron, where Na^+ reabsorption place. The increased excretion of water and electrolytes by the kidneys is dependent in three different processes viz., glomerular filtration, tubular reabsorption active and passive and tubular secretion. The functional unit of kidney is nephron where urine is formed. Nephron consists of two anatomical parts i.e. glomerular and tubule. The glomerular part is closed, cup shaped and known as bowman's capsule.

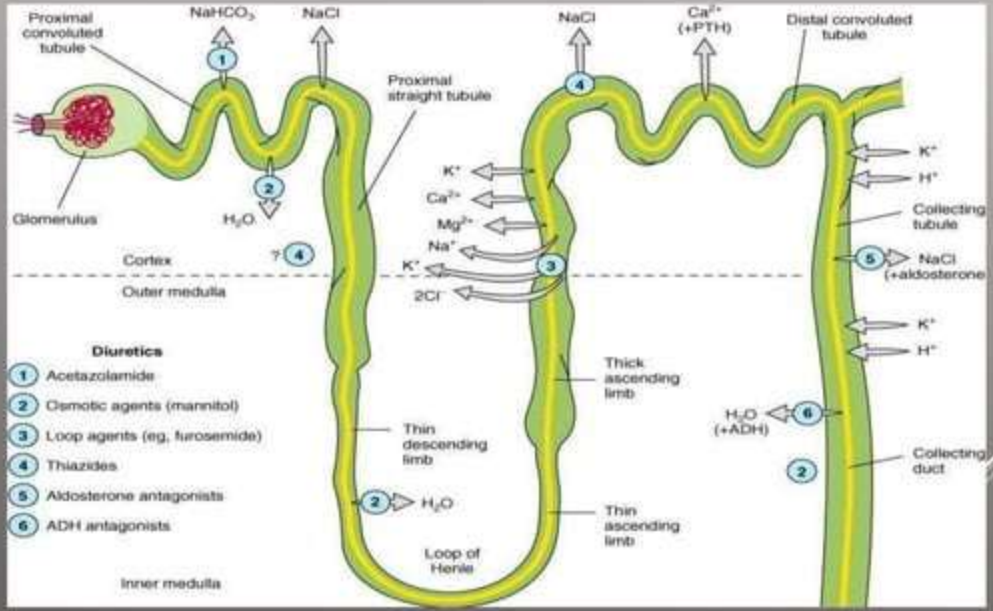
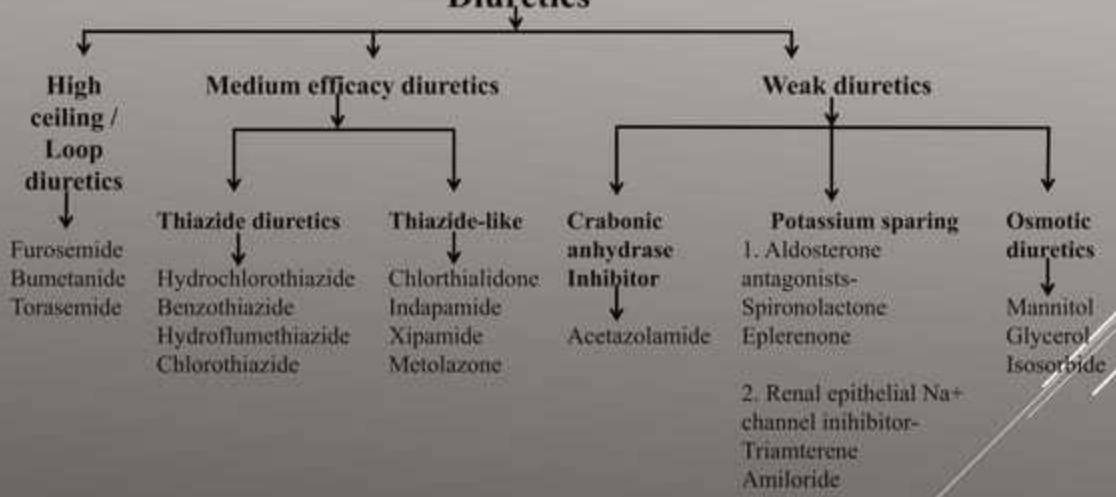


Diagram:- Nephron structure

Classification of Diuretics -



1. HIGH CEILING/LOOP DIURETICS -

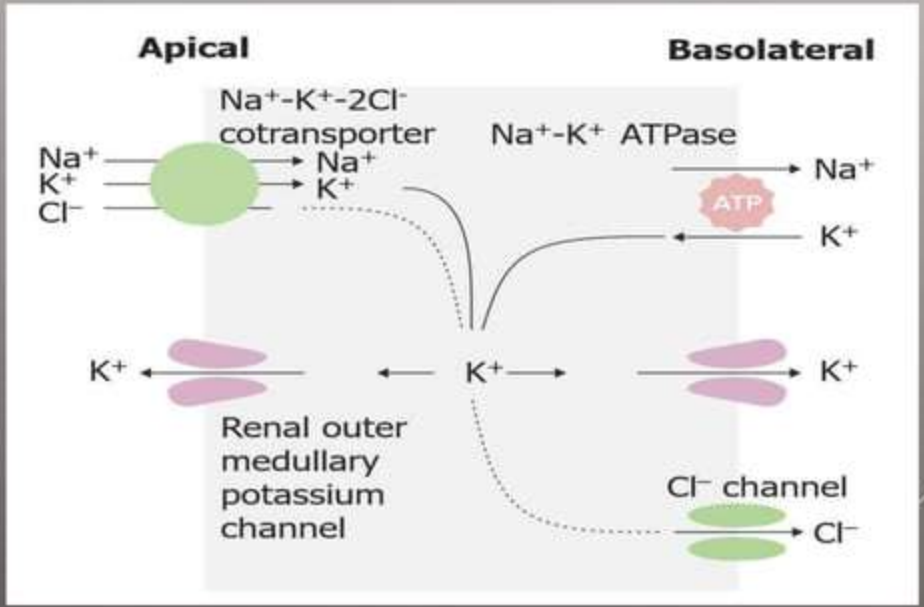
Loop diuretics acts mainly at thick ascending limb of the loop of Henle. These diuretics produce peak diuresis which is much greater than other diuretics. Loop diuretics inhibit reabsorption of Na+, Cl- and K+ ions by inhibiting Na+/K+/2Cl- symport of the thick ascending limb of loop of Henle. By inhibiting Na+/K+/2Cl- symport, these agents also inhibit reabsorption of Ca++ and Mg++.

The most effective compounds in this category are ethacrymic acid, furosemide and Bumentanide. The other loop diuretics are torasemide, azosemide, muzolimine, tripamide and piretanide.

The high ceiling diuretics are effective in the treatment of acute pulmonary odema, hypertension, hypercalcaemia, hyperkalemia, acute renal failure and in treatment of toxic ingestion of bromide, fluoride and iodide.

Examples:- Furosemide, Bumetanide, Torasemide

Mechanism of action of High ceiling/Loop diuretics -



FUROSEMIDE :-

Furosemide is a loop diuretic medication used to treat fluid build-up due t heart failure, liver scarring, or kidney disease. It may also be used for the treatment of high blood pressure. It can be taken by injection into a vein or by mouth. When taken by mouth, it typically begins working within an hour, while intravenously, it typically begins working within five minutes. Common side effects include feeling lightheaded with standing, ringing in the ears, and sensitivity to light. Potentially serious side effects include electrolyte abnormalities, low blood pressure, and hearing loss. Blood tests are recommended regularly for those on treatment. Furosemide is a type of loop diuretic that works by decreasing the reabsorption of sodium by the kidneys.

BUMETANIDE :-

Bumetanide, sold under the trade name Bumex among others, is a medication used to treat swelling and high blood pressure. This includes swelling as a result of heart failure, liver failure, or kidney problems. It may work for swelling when other medications have not. For high blood pressure it is not a preferred treatment. It is taken by mouth, or by injection into a vein or muscle.

Effects generally begin within an hour and lasts for about six hours. Common side effects include dizziness, low blood pressure, low blood potassium, muscle cramps, and kidney problems. Other serious side effects may include hearing loss and low blood platelets. Blood tests are recommended regularly for those on treatment. Safety during pregnancy and breastfeeding is unclear. Bumetanide is a loop diuretic and works by decreasing the reabsorption of sodium by the kidneys.

Uses :-

- Acute pulmonary oedema.
- Congestive cardiac failure.
- Forced diuresis in barbiturate poisoning.
- Hypercalcemia – loop diuresis with saline infusion.

ADVERSE EFFECTS OF LOOP DIURETICS -

- Hypokalemic metabolic acidosis.
- Hypocalcemia.
- Hypomagnesemia.
- Hyperglycemia.
- Hyperuricemia.
- Ototozicity.

Contraindications to loop diuretics include :-

- Anuria
- History of hypersensitivity to furosemide, bumetanide, or torsemide (or sulfonamides)
- Hepatic coma
- Severe states of electrolyte depletion

2. MEDIUM EFFICACY DIURETICS -

It is divided in mainly two parts:-

1. Thiazide diuretics
2. Thiazide-like

1. Thiazide diuretics -

Thiazide diuretics act on the early distal convoluted tubule and inhibit the sodium-chloride symporter leading to a retention of water in the urine, as water normally follows penetrating solutes. Frequent urination is due to the increased loss of water that has not been retained from the body as a result of a concomitant relationship with sodium loss from the convoluted tubule. The short-term anti-hypertensive action is based on the fact that thiazides decrease preload, decreasing blood pressure. On the other hand, the long-term effect is due to an unknown vasodilator effect that decreases blood pressure by decreasing resistance.

Example:- chlorothiazide, Hydrochlorothiazide, Benzothiazide, Hydroflumethiazide,.

CHLOROTHIAZIDE :-

It is an organic compound used as a diuretic and as an antihypertensive. It is used both within the hospital setting or for personal use to manage excess fluid associated with congestive heart failure. Most often taken in pill form, it is usually taken orally once or twice a day. In the ICU setting, chlorothiazide is given to diuresis a patient in addition to furosemide.

Side effects:-

- Nausea/Vomiting
- Headache
- Dizziness
- Excess urine production Dehydration
- Hypoelectrolytemia (hypokalemia / hypomagnesia).

HYDROCHLOROTHIAZIDE :-

Hydrochlorothiazide (HCTZ or HCT) is a diuretic medication often used to treat high blood pressure and swelling due to fluid build-up. Other uses include treating diabetes insipidus and renal tubular acidosis and to decrease the risk of kidney stones in those with a high calcium level. Hydrochlorothiazide is less effective than chlortalidone for prevention of heart attack or stroke. HCTZ is taken by mouth and may be combined with other blood pressure medications as a single pill to increase effectiveness.

Potential side effects include poor kidney function; electrolyte imbalances, including low blood potassium, and, less commonly, low blood sodium, gout, high blood sugar, and feeling lightheaded with standing

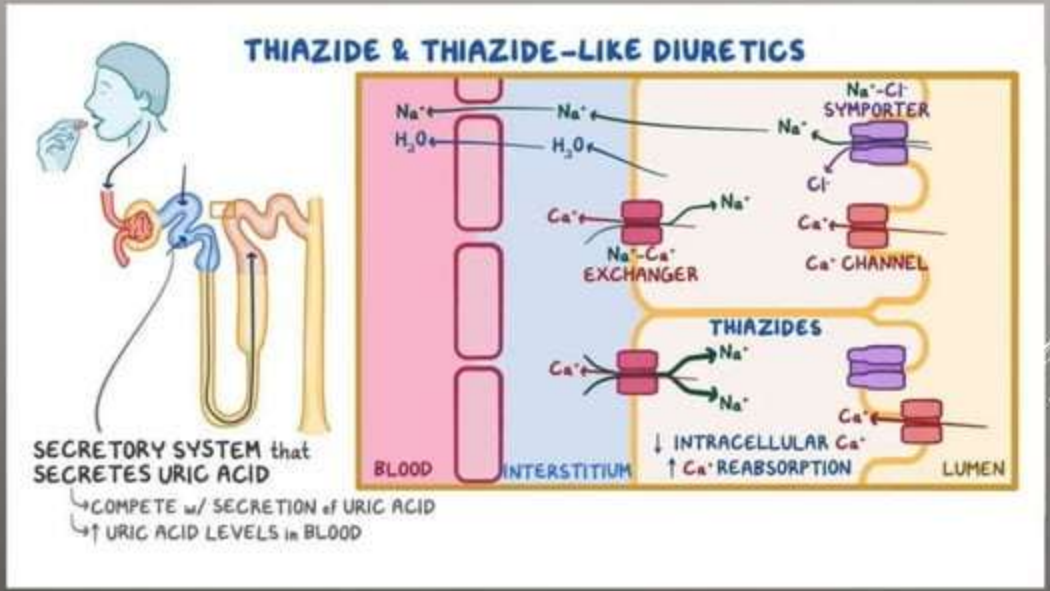
SIDE EFFECTS OF THIAZIDE :-

- Hypokalemia.
- Hyponatremia.
- Metabolic alkalosis.
- Hypercalcemia.
- Hyperglycemia.
- Hyperuricemia.
- Hyperlipidemia.
- Sulfonamide allergy.

Uses :-

- Hypertension and CCF.
- Idiopathic hypercalciuria.
- Nephrogenic diabetes incipidus.
- Diuretics of choice used as a prophylactic in patients with tendency to form calcium stones.

Mechanism of action of thiazide and thiazide like diuretics -



2.THIAZIDE-LIKE -

These diuretics are behave like thiazide diuretics.

Examples:- Chlorthialidone, Indapamide, Xipamide, Metolazone

Chlorthalidone Drug :-

Chlorthalidone is a particularly long-acting compound with a half-life 40-50 hours, used exclusively as hypertensive. chlorthalidone also found was to act as a GABAA receptor negative allosteric modulator, potently inhibiting GABAA-mediated currents. In animals it is a powerful convulsant, robustly enhancing epileptiform activity. And inducing seizures, but without producing any apparent neuronal death. Chlorthalidone has been found to act as a non-competitive antagonist of the mGluR1. It is selective for mGluR1 over other metabotropic glutamate receptors.

Indapamide Drug :-

Indapamide is a thiazide-like diuretic drug generally used in the treatment of hypertension, as well as decompensated heart failure. Combination preparations with perindopril (an ACE inhibitor antihypertensive) are also available. Thiazide-like diuretics (indapamide and chlorthalidone) results in more reduction i the risk of major cardiovascular events and heart failure in hypertensive patients when compared with thiazide-type diuretics (hydrochlorothiazide).

Xipamide :-

Xipamide is used for cardiac oedema caused by decompensation of heart failure Renal oedema, chronic renal disease (but not with anuria) Hepatic oedema caused by cirrhosis Ascites Lymphoedema hypertension in combination with chronic renal disease.

3. WEAK DIURETICS -

1. CARBONIC ANHYDRASE INHIBITOR -

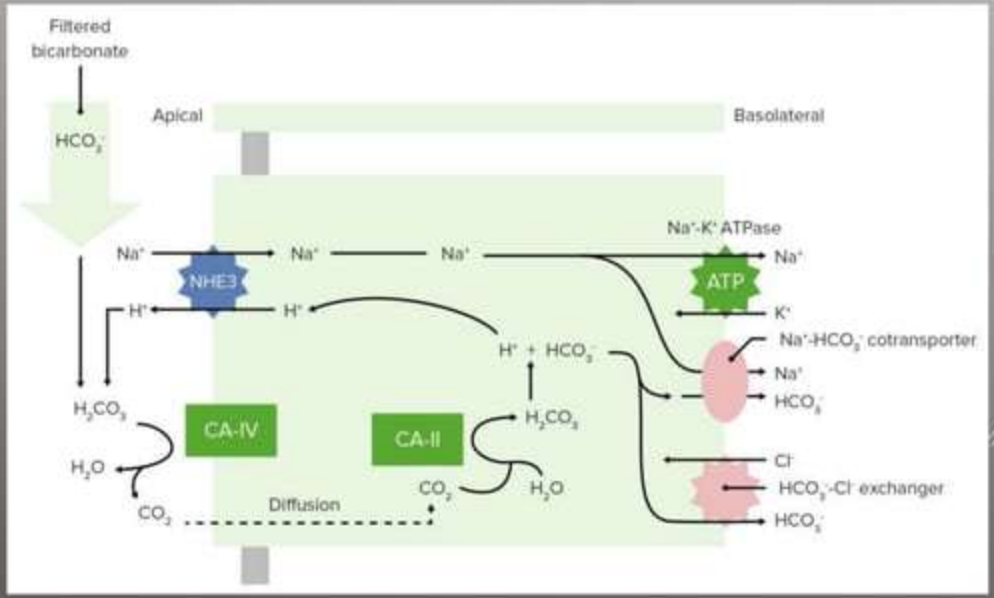
The discovery of carbonic anhydrase in the kidney was made in 1941 by Davenport and Wilhelmi, and it is now known to be a zinc metalloenzyme found in large amounts in the luminal and basolateral membranes. Carbonic anhydrase inhibitor acts on proximal convoluted tubule.

Carbonic anhydrase inhibitors are a medication used in the management and treatment of glaucoma, idiopathic intracranial hypertension, altitude sickness, congestive heart failure, and epilepsy, among other diseases.

The use of the bacteriostatic agents, sulphonamides, led to the realization that they caused an alkaline diuresis with hyperchloraemic metabolic acidaemia.

Example:- Acetazolamide

Mechanism of action of Carbonic anhydrase Inhibitor -



ACETAZOLAMIDE :-

Acetazolamide, sold under the trade name Diamox among others, is a medication used to treat glaucoma, epilepsy, altitude sickness, periodic paralysis, idiopathic intracranial hypertension (raised brain pressure of unclear cause), and heart failure. It may be used long term for the treatment of open angle glaucoma and short term for acute angle closure glaucoma until surgery can be carried out. It is taken by mouth or injection into a vein.

Common side effects include numbness, ringing in the ears, loss of appetite, vomiting, and sleepiness. It is not recommended in those with significant kidney problems, liver problems, or who are allergic to sulfonamide. Acetazolamide is in the diuretic and carbonic anhydrase inhibitor families of medication. It works by decreasing the formation of hydrogen ions and bicarbonate from carbon dioxide and water.

Uses :-

- Glaucoma.
- Urinary alkalinization.
- Acute motion sickness.
- Periodic paralysis.
- Epilepsy.

ADVERSE EFFECTS OF CARBONIC ANHYDRASE :-

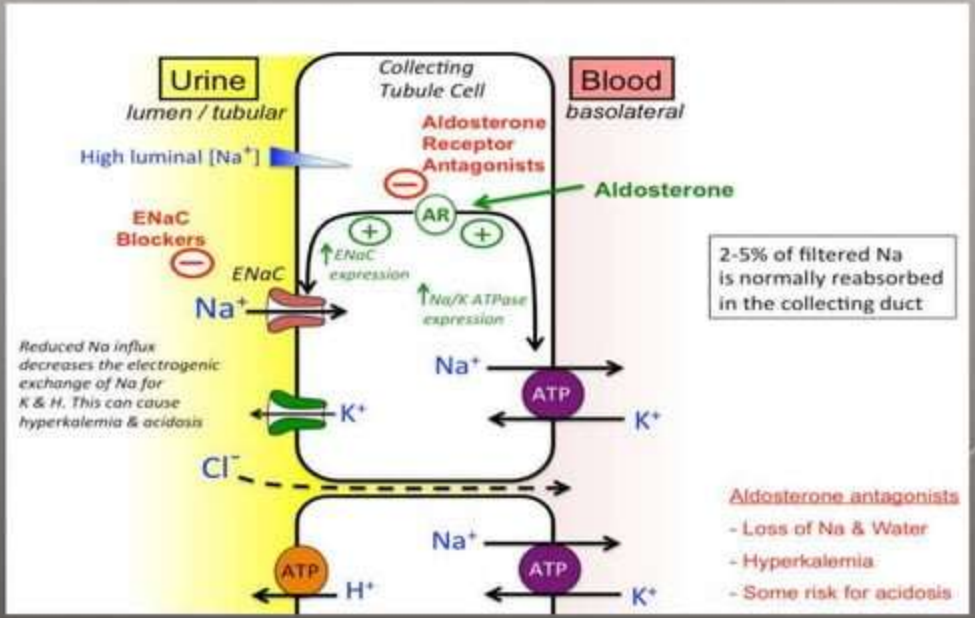
- Diarrhea.
- general feeling of discomfort or illness.
- increase in frequency of urination or amount of urine (rare with methazolamide)
- loss of appetite.
- metallic taste in mouth.
- nausea or vomiting.
- numbness, tingling, or burning in hands, fingers, feet, toes, mouth, lips, tongue, or anus.
- weight loss.
- Hypokalemia.
- Hyperchloremic metabolic acidosis.

2. POTASSIUM SPARING -

These are diuretics which do not promote the secretion of potassium into the urine; thus, potassium is retained and not lost as much as with other diuretics. Potassium sparing diuretics act on cortical collecting tubule. These type of diuretics inhibit sodium reabsorption in late distal tubule and indirectly spare potassium excretion. These are mild diuretics and tend to cause bicarbonate loss but not chloride. Potassium sparing diuretics are of two types:-

1. Aldosterone antagonists.
2. Renal epithelial Na+ channel inhibitor.

Mechanism of action of Potassium sparing -



(A). ALDOSTERONE ANTAGONISTS –

The adrenal cortex steroidal hormones (mineralocorticoids) plays an important role in the body. Some of them influence the electrolyte and water balance in body. These hormones increase the absorption of sodium ions and increase the urinary excretion of both potassium and hydrogen ions. Among all the adrenal cortex hormones, aldosterone is most potent.

Examples:- Spironolactone, Eplerenone.

Spironolactone:-

Spironolactone is a steroid. It is chemically related to mineralocorticoid aldosterone, It is sold under the brand name Aldactone among others, is a medication that is primarily used to treat fluid build-up due to heart failure, liver scarring, or kidney disease. It is also used in the treatment of high blood pressure, low blood potassium that does not improve with supplementation, early puberty in boys, acne and excessive hair growth in women, and as a part of transgender hormone therapy in transgender women. Spironolactone is taken by mouth. Common side effects include electrolyte abnormalities, particularly high blood potassium, nausea, vomiting, headache, rashes, and a decreased desire for sex.

EPLERENONE :-

Eplerenone, sold under the brand name Inspra, is an aldosterone antagonist type of potassium sparing diuretic that is used to treat chronic heart failure and high blood pressure, particularly for patients with resistant hypertension due to elevated aldosterone. It is a steroidal antiliberal corticoid of the spironolactone group and receptor antagonist (SARA).

It is never more selective aldosterone antagonist which has much lower affinity for androgen and progesterone receptors; therefore much less likely o produce hormonal disturbances like gynaecomasatia, impotence, menstrual irregularities. Eplerenone is a selective aldosterone more selective than spironolactone at the mineralocorticoid receptor relative to binding at androgen, progestogen, glucocorticoid, or oestrogen receptors.

(B). RENAL EPITHELIAL NA+ CHANNEL INHIBITOR -

Amiloride and triamterene are two drugs in this class. These drugs are the derivatives of pyrazine and pteridine respectively. Their actions are different than the spironolactone. They inhibit sodium channel of the collecting tubule which results in fall of electro-chemical gradient created by sodium pump. This gradient is one f the driving forces for secretion of potassium ions. The decrease in this gradient probably decrease the secretion of potassium ions.

Triamterene and amiloride are two nonsteroidal organic bases with identical actions. Their most important effect is to decrease K+ excretion, particularly when it is high due to large K+ intake or use of a diuretics that enhances K+ loss.

The luminal membrane of late DT and CD cells expresses a distinct ' renal epithelial' or 'amiloride sensitive' Na+ channel through which Na+ enters the cell down its electrochemical gradient which is generated by Na+K+ ATPase operating at the partially membrane.

Examples:- Triamterene, Amiloride

TRIAMTERENE :-

It is incompletely absorbed orally, partly bound to plasma proteins, largely metabolized in liver to an active metabolite and excreted in urine.

plasma half life is 4 hours and effects of a single dose lasts 6-8 hours.

Side effects are consist of nausea, dizziness, muscle cramps and rise in blood urea.

Amiloride :-

Amiloride, under trade name Midamor medications treat blood pressure or swelling heart failure cirrhosis the liver. It is 10 times potent than triamterene. At higher doses it also inhibits Na^+ reabsorption in proximal tubule but this is clinically insignificant. It decreases Ca^{++} and Mg^{++} excretion but increases urate excretion.

Amiloride is classified potassium-sparing diuretic. Amiloride is often together with another diuretic, such a thiazide diuretic. It taken by mouth. Onset of action is about two hours and it lasts for about day.

ADVERSE EFFECTS OF POTASSIUM SPARING DIURETICS :-

- Hyperkalemia (increased levels of potassium in the blood).
- Nausea and vomiting.
- Abdominal discomfort.
- Gynaecomastia.
- Drowsiness.
- Confusion.
- Ataxia (loss of control on bodily movements due to lack of coordination between muscles and brain)
- Kidney stones.

Contraindications :- Potassium sparing diuretics are contraindicated in patients with hyperkalemia or who are at risk of developing hyperkalemia.

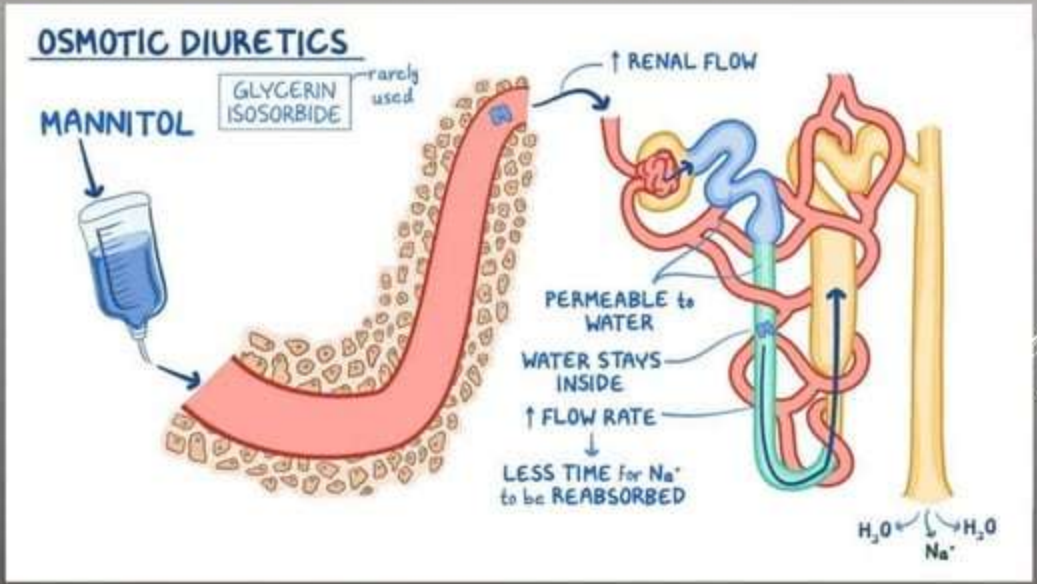
3. OSMOTIC DIURETICS -

Osmotic diuretic is a type of diuretic that inhibits reabsorption of water and sodium (Na). They are pharmacologically inert substances that are given intravenously. They increase the osmolarity of blood and renal filtrate.

In the nephron, osmotic diuretics act at the portions of the nephron that are water-permeable like proximal convoluted tubule, descending limb of loop of Henle, collecting tubuel.. Osmotic diuretics work by expanding extracellular fluid and plasma volume, therefore increasing blood flow to the kidney. This stops the loop of Henle from concentrating urine, which usually uses the high osmotic and solute gradient to transport solutes and water.

Examples:- Mannitol, Glycerol, Isosorbide

Mechanism of action of osmotic diuretics -



MANNITOL :-

Mannitol is a nonelectrolyte of low molecular weight that is pharmacologically inert – can be given in large quantities sufficient to raise osmolarity of plasma and tubular fluid.

Mannitol is never used for the treatment of chronic edema or as natriuretic. It can be used for the reduction of intracranial pressure and brain mass, to reduce intraocular pressure if this is not achievable by other means to promote diuresis for acute renal failure to prevent or treat the oliguric phase before irreversible damage, and to promote diuresis to promote excretion of toxic substances, materials, and metabolites. When using mannitol for medical purposes, it is given intravenously.

Isosorbide and Glycerol :-

These are orally active osmotic diuretics which may be used to reduce intraocular or intracranial tension. Intravenous glycerol can cause haemolysis.

ADVERSE EFFECTS OF OSMOTIC DIURETICS :-

- Chest pain.
- Congestive heart failure.
- Hypotension (low blood pressure)
- Phlebitis (inflammation of the vein)
- Convulsions.
- Chills.
- Dizziness.
- Headache.

Contraindications :- Established acute renal failure, Anuria, Acute tubular necrosis, Pulmonary edema, Cerebral haemoraahage.

USES OF DIURETICS -

- Heart failure.
- Liver failure.
- Fluid buildup in the body.
- Certain kidney disorders, such as kidney stones.
- Thiazide diuretics are recommended as one of the first medicines to treat high blood pressure.

THANK YOU