Pharmacology - Diuretics (Saluretics)

Diuretics introduction

-Diuretics increase urine excretion mainly by ↓ reabsorption of salts and water from kidney tubules.

-These agents are ion transporter inhibitors that decrease the reabsorption of Na+ at different sites of the nephron, thus **increasing the volume of the urine** and often **change its pH** as well as **the ionic composition of the urine and blood**.

-Water, digitalis, caffeine and theophylline have diuretic activity or increase urine output, **but are not considered diuretics.**

Clinical uses of diuretics

- Hypertension
- Edema of heart, renal or liver failure
- Pulmonary edema
- ↑ intracranial pressure (Mannitol)
- ↑ intraocular pressure=glaucoma (CA inhibitors) (acetazolamide)
- Hypercalcemia (Furosemide=Frusemide)
- Idiopathic hypercalciuria (Thiazides)
- Inappropriate ADH secretion (Furosmide)
- Nephrogenic diabetes insipidus (Thiazides)

-They're used in the **management of any condition associated with salt and water retention**, by acting at different sites of the nephron (The basic unit of the kidney). They're **highly effective**, **relatively safe, and cheap**.

-Diuretics are the first-line therapy for most hypertensive patients. And without any compelling indications, the JNC reports say:

-JNC 6th report recommends **Diuretics or a beta-blocker.**
-JNC 7th report recommends **Thiazide-type diuretics.**

-(Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure**)**

-Accumulating evidence proves that in hypertensive patients diuretics, **particularly thiazides** decrease the risk of cardiovascular disease, fatal and nonfatal MI and stroke. This is according to the ***ALLHAT*** *study. (**A**ntihypertensive and **L**ipid **L**owering treatment to prevent **H**eart **A**ttack **T**rial) which involved 40,000 hypertensive pts for 8 years, (1994)*

-Many other antihypertensive agents are combined with diuretics in the same tablet these days.

Diuretics MOA

-Simply by increasing urine output → ↓ plasma and stroke volume → ↓ CO → ↓ BP

-The initial ↓ in CO leads to ↑ peripheral resistance, but with chronic use extracellular fluid and plasma volume return to normal and peripheral resistance ↓ to values lower than those observed before diuretic therapy.

- Thiazides are also believed to have direct vasodilating effect

Diuretics therapy cautions

-Excessive diuretic usage may lead to a **compromise of the effective arterial blood volume** with reduction in perfusion of vital organs. (**This can lead to hypotension and collapse!**) Therefore, the use of diuretics to mobilize edema requires careful monitoring of the patient's hemodynamic status and an understanding of the pathophysiology of the underlying condition.

- Blood viscosity rises due to an increase in erythro- and thrombocyte concentration, which could lead to an increased risk of intravascular coagulation or thrombosis.

Classification of diuretics

-Diuretics are usually categorized by their site of action in the kidney, their MOA and to a lesser extent by their potency.

- Many diuretics (loop diuretics, thiazides, amiloride, and triamterene) exert their effects on specific membrane transport proteins in renal tubular epithelial cells.

- Other diuretics **exert osmotic effects** that prevent water reabsorption (mannitol)

- Others **inhibit enzymes** (acetazolamide)

- Some others interfere with **hormone receptors** in renal epithelial cells (spironolactone)

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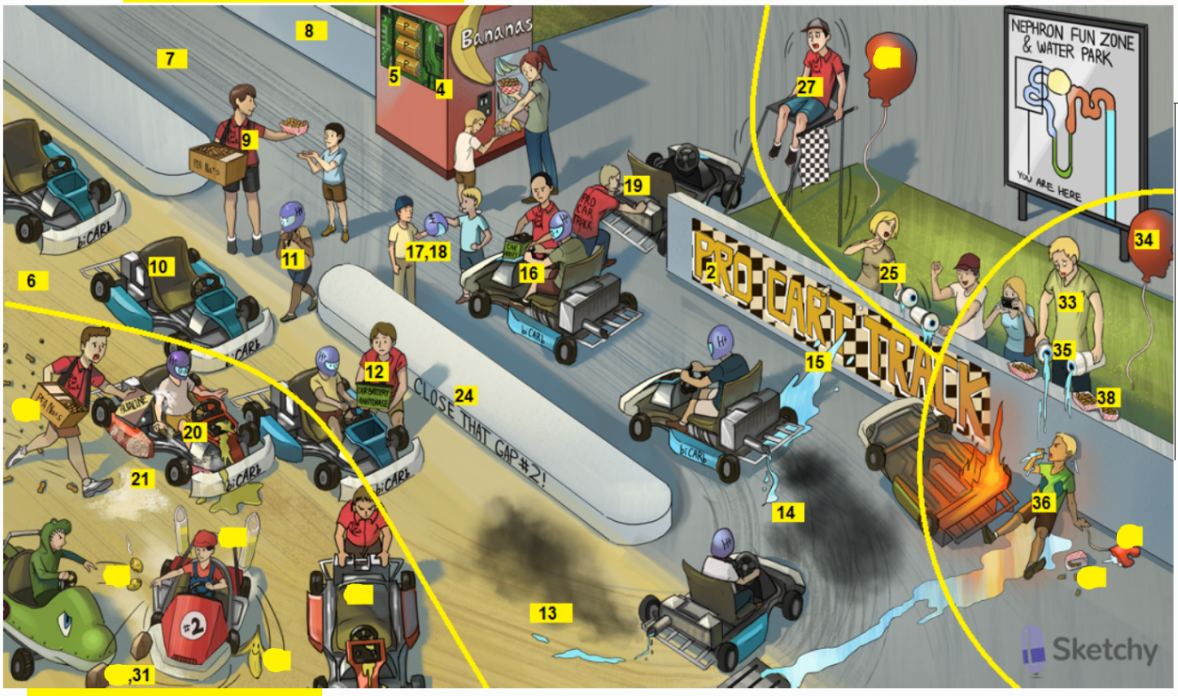
Acetazolamide, Mannitol



Sketchy

1. WHERE EVER SODIUM GOES, WATER WILL FOLLOW
2. Pro cart track: proximal convoluted tubule
3. Proximal convoluted tubule: site of action of acetazolamide and mannitol; sodium, Cl-, K+, glucose and amino acids will be absorbed here. Bicarb 85% is reabsorbed here
4. Banana vending machines: Na+/K+ ATPase on the basolateral membrane
5. Three P batteries: ATPase
6. Yellow track: lumen of tubule
7. Grey track: intracellular compartment
8. Wall is the basolateral membrane
9. Track worker distributing peanuts inside and letting H+ helmets out. Na+/H+ exchanger located on the apical membrane
10. biCARb race car: Bicarb in the lumen in the PCT
11. Rider with H+ helmet sitting in biCARb secreted H+ combines with the bicarb in the tubular lumen to form carbonic acid H2CO3
12. Car battery anhydrase on the inside track: lumen carbonic anhydrase (CA)
13. Battery powered car producing H2O and CO2 exhaust: Luminal CA converts carbonic acid to H2O and CO2
14. H2O and CO2 exhaust on the outside track: H2O and CO2 enters the intracellular space via diffusion
15. Water is sprayed over the wall: water is reabsorbed with solutes at the PCT (High Permeability)
16. Car battery anhydrase on the outside track: intracellular CA converts H2O and CO2 back into carbonic acid (H2CO3)
17. H+ helmet leaving the biCARb: intracellular carbonic acid disassociated back into H+ and Bicarb
18. Recycled H+ helmet: H+ transported back into the lumen by the Na+/H+ exchanger
19. biCARb taken away: intracellular bicarb is absorbed vis basolateral transporter

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*Carbonic anhydrase enzyme is important enzyme responsible for reabsorption of Na+HCO3 from proximal convoluted tubules and for formation of aqueous humor (fluid of the eye), inhibition of carbonic anhydrase increases urine outflow and decreases formation of aqueous humor.

Acetazolamide

2. Pro cart track: proximal convoluted tubule
20. Batery acid breaking car batery: Acetazolamide inhibits carbonic anhydrase (preventing reabsorption of bicarb)
21. Spilled alkaline substance on inside track: CA inhibitors (acetazolamide) cause bicarb to stay in the tubular lumen leading to urine alkalization to excrete weak acids (excretion of weak acids is enhanced by increasing urinary pH)
24. Close the gap #2!: CA inhibitors cause a normal anion gap metabolic acidosis leading to a hyperchloremic state which results from chronic reduction of body bicarbonate stores
25. Spilled eyeball cups: CA inhibitors (acetazolamide) decreased production of aqueous humor (useful in the management of glaucoma) *Major clinical use*
27. High elevation: CA inhibitors are useful in the treatment and prevention of mountain sickness
(Absence seizures and myoclonic seizures)
31. Rocks on the inside track: CA inhibitors promote the formation for calcium phosphate stones (insoluble at high pH)

Addition:
1-Acetazolamide is effective orally and as an ophthalmic drops
2-Dorzolamide & Brinzolamide are other available topically (ophthalmic drops) active carbonic anhydrase inhibitors

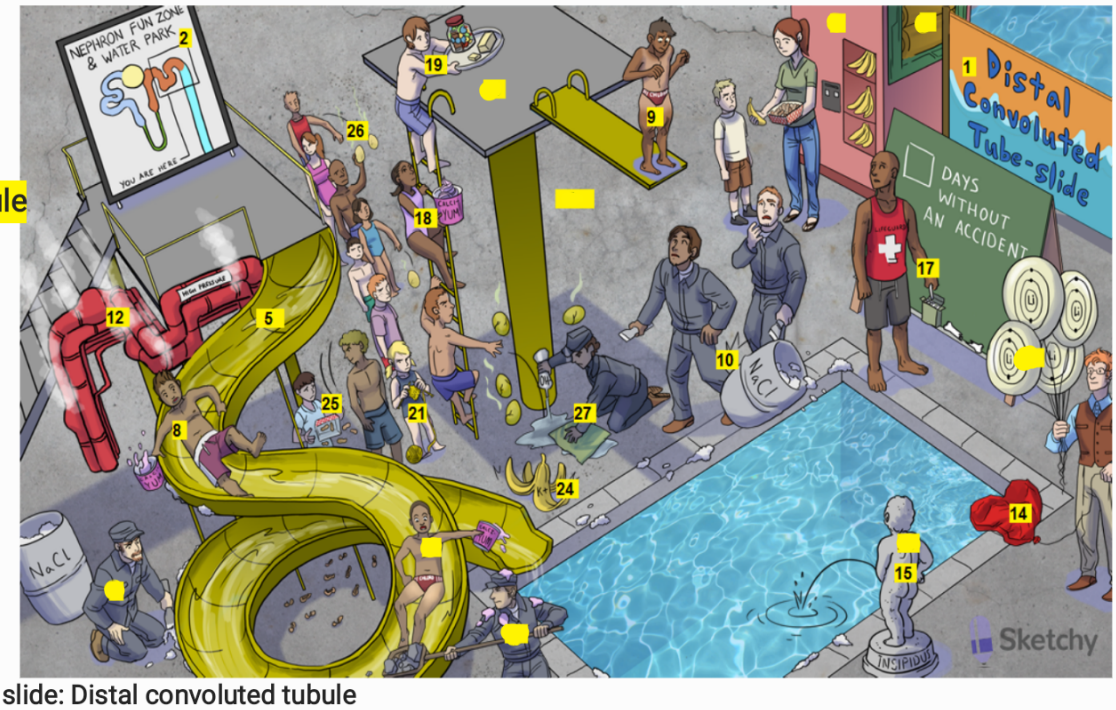
Mannitol

33. Tall Man: mannitol (osmotic diuretic) acts at the PCT
34. High pressure head balloon: mannitol draws free water out of the CNS (useful in the treatment of elevated intracranial pressure)Major clinical use
35. Spilled eyeball cups: Draws free water out of the eye, (decreases intraocular pressure)
36. Tall man causing wet lungs:clearance of mucus in patients with bronchiectasis.
38. Elevated salty peanuts: mannitol induced water depletion can cause hypernatremia & hyperkalemia

Addition:

1*It is a sugar, not absorbed by kidney tubules, has no systemic effects and not metabolized.
2*MAO: ↑ osmotic pressure in kidney tubules → withdraw H2O → ↑ urine excretion by ↓ H2O reabsorption with little ↑ in NaCl excretion.((Maintain urine volume and prevent anuria.))
3*Promotes removal of renal toxins

Thiazides
- Distal Convoluted Tubule



1. Distal convoluted tube slide: Distal convoluted tubule
2. Distal convoluted tubule: site of action for thiazide diuretics
5. Yellow tube slide: tubular lumen
8. Active slider dropping the calci-yum ice cream: calcium is actively reabsorbed at the DCT (regulated by PTH) (that's why it is used in idiopathic hypercalciuria) and used for Hypercalciuria
9. Chloro-thighs, thiodore Roosevelt on high dive:Hydrochloriathiazide and chlorothalidone (thiazide diuretics) /Indapamide
10. Sodium chloride dumping into pool: thiazides inhibit NaCl reabsorption by blocking the NaCl cotransporter
12. High pressure pipes: thiazide diuretics are one of the first linetreatments for mild or moderate HTN
14. Floppy failing heart balloon: use of thiazides can be useful in the symptomatic treatment of heart faulure & Used for Edema of HF; liver cirrhosis...etc
15. Insipidus fountain: thiazide diuretics treat nephrogenic diabetes insipidus
17 .The most frequent and dangerous: muscle weakness and serious cardiac arrhythmias (High risk in LVH, previous MI, cardiac arrythmia, on digoxin therapy pts)لمدرب بنقذ الناس الي صابهم ضعف بعضلاتهم
18. Elevated calci-yum ice cream: thiazide diuretics can cause hypercalcemia
19. Elevated Candy jar and stick of butter: Thiazide diuretics can promote Hyperglycemia and also hyperlipidemia.(↑ LDL, ↑TG's)
21. Yellow kniting needles: thiazide diuretic can cause hyperuricemia (can precipitate gout)
- The effect of thiazides on uric acid is dose dependent:
Low doses → hyperuricemia
Large doses → ↓ uric acid reabsorption
24. Potassium depleted banana peel: Thiazide diuretics block the Na+/Cl+ cotransporter in the distal convoluted tubule, increasing sodium delivery to the collecting duct. This leads to increasing potassium secretion by the collecting duct in exchange for Na+ reabsorption leading to hypokalemia +hypomagnesemia

Adition

1-they are the most frequently used, least expensive, has low to moderate efficacy
2- usually given orally (Chlorthiazide may be given I.V), strongly bind plasma albumin, reach kidney tubules via a specific secretory mechanism (not filtered) and eliminated mostly unchanged by the kidney (small fraction biliary excretion)
3-MAO: by Inhibition of thiazide-sensitive Na+/Cl- transporter in distal convoluted tubule, inhibiting Na+ reabsorption → ↑ Na+,K+, Cl-, HCO3 and H2O excretion (5-10% loss of filtered Na+)
4-Their early hypotensive effect is related to a reduction in blood volume
5-Their long-term effect is related to a reduction in peripheral vascular resistance
6-↑ in dose will not lead to further increase in their diuretic effect (low ceiling)
7-They are ineffective in pts with impaired renal function or pts with GFR< 20 ml/min
8-They have synergistic effect with other lowering BP drug
9-can cause Pancreatitis and Erectile dysfunction

Loop Diuretics

1Furosemide(Frusemide),
2 Bumetanide,
3 Ethacrynic acid (prodrug)
,4 Torsemide (active metabolites)all can be given orally and IV

MAO: Inhibition of Na+/K+/2Cl- (transporter leading to 10-25% loss of filtered Na+)

1. Loop de Loop of Henle: Loop of Henle
2. Thick ascending Limb of the loop of Henle: site of action of most loop diuretics. Most relevant is sodium chloride blocks
5. Yellow track: lumen of the renal tubule
6. Platform: intracellular compartment
7. Background wall is the interstitium
8. Track worker taking peanuts, bananas, and 2 chloride packets:Na+/K+/2Cl cotransporter (NKCC) reabsorbs these ions at the luminal membrane of the TAL thick ascending limb *Loop diuretics ↑ excretion of Na+, Cl-, K+, H+,H2O and HCO3- *
9. Water secured in car: the TAL is impermeable to water (diluting segment)
10. Furious kid: furosemide (loop diuretics)
11. Furious kid clinging to food: furosemide selectively blocks the NKCC transporter on the luminal membrane of the TAL, keeping sodium in the lumen in the tubule representing furosemides ability to reduce reabsorption of NaCL

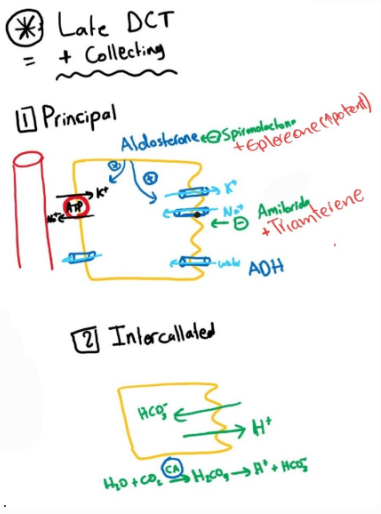
12. Loop diuretics are the most efficacious currently *The strongest diuretics, have rapid OOA and short DOA*
A-* High ceiling effect unlike thiazide, so ↑ dose → ↑ diuretic effect; over-treatment → dehydration
B-* Effective even at GFR below 10 ml/min (they are most effective in patients with renal insufficiency = creatinine level > 2.5 mg/dl) or resistant cases to other diuretics (unlike thiazides)
C-*They are effective orally (OOA 30-60 min ; DOA ≈ 6 hrs) and parenterally (OOA 5 min; DOA ≈ 2 hrs)
D-*They are albumin bound, eliminated in urine by filtration and tubular secretion and 1/3rd of oral dose is excreted in bile

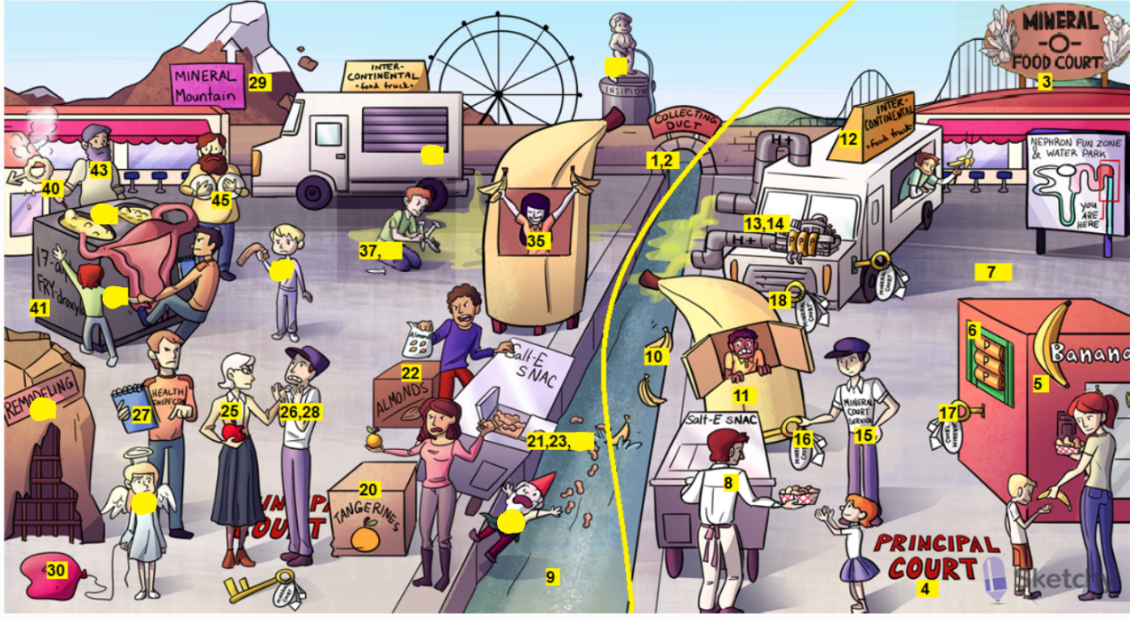
13. Ethics: ethacrynic acid (loop diuretic)
14. Furious kid clinging to magnets and calci-yum ice cream:promoting the excretion of Mg2+ and Ca2+ + K+
15. Falling magnets: prolonged use of loop diuretics can cause hypomagenesmia
16. Falling calci-yum ice cream: Loop diuretics can cause hypocalcemia
21. Failing heart balloon: loop diuretics are 1st line for the symptomatic treatment of acute decompensated heart failure
22. Wet lungs: reduction for peripheral or pulmonary edema
23. Yellow inner tube: loop diuretics treat ascites in liver failure (juadince)
24. High pressure pipes: loop diuretics can be useful in the treatment of HTN
26. Banana peel: hypokalemia
27. Loud gong: loop diuretics can cause hearing loss (dose related and more common with I.V administration)
31. Kniting needles: loop diuretics can cause hyperuricemia + hyperglycemia
32. Park employee cleaning the floor with contracted bleach bottle: contraction alkalosis

Addition

1-Can used for Edematous states (ascitis; CHF; renalfailure...etc) + Syndrome of Inappropriate ADH secretion
2- it may cause Allergic reactions

K+ sparing Diuretics





General (لا تركز كثير حطيته للفهم بس و ما تعمق فيه الدكتور اهتم للأدوية تحت)

1. Central gutter: work in the collecting duct
2. Collecting duct (site of action of the K+ sparing diuretics)
3. Mineral-O-Food court: mineralocorticoids site of action (aldosterone) in the collecting duct
4. Principal court: principle cell of the collecting duct (major site of Na+/K+/H2O transport
7. Food court ground: intracellular compartment
8. Salt-E sNaC cart: epithelial Na+ channels (ENaC) reabsorb Na+
9. Water in gutter: tubular lumen
10. Banana stand dumping bananas: K+ channels allow the excretionof K+
12. Alpha intercontinental food truck: alpha intercalated cell of the collecting duct (major site of H+ excretion)
15. Mineral court services: intracellular mineralcorticoids (aldosterone) receptor
16. Mineral key: aldosterone binds to the salt-E sNaCk upregulating ENaCs on the apical membrane, increasing Na+ reabsorption
17. Mineral Key activaing the banana vending machine: aldosterone upregulates Na+/K+ ATPse on the basolateral membrane
18. Mineral key activating the banana stand: aldosterone upregulates K+ channels on the apical membrane, ↑K+ excretion

Amiloride; Triamterene (None steroidal potassium sparing diuretics)

20. Tangerines: triamterene (K+ sparing diuretic)
21. Tangerines blocking the salt-E sNaCk cart: triamterene inhibits Na+ reabsorption through ENAC
22. Almonds: amiloride (K+ sparing diuretic)
23. Almonds blocking the Salt-E sNaC cart: amiloride inhibits Na+ reabsorption through ENaC
37. Worker holding 4 acid tubes: K+ sparing diuretics causing a type 4 renal tubular acidosis * Renal tubular damage especially reported following the use of Triamterene + Hydrochlorothiazide*

Addition:

1-Orally effective and available alone or combined with thiazides
2- MOA: Blockade of epithelial Na+ channels → ↓ Na+ reabsorption, ↓ K+ excretion
3-Use for Hypertension & Hypokalemia
4-Side effects Hyperkalemia & Renal tubular damage

Spironolactone, Eplerenone (more potent form) ((Aldosterone competitive antagonists))

25. Apple with the teacher: eplerenone (K+ sparing diuretic)
26. Teacher with apple antagonizing the mineral court services man: eplerenone antagonizes the mineralocorticoid receptor
27. Health inspector with Spiral bound notebook: spironolactone (a K+ sparing diuretic)
28. Health inspector antagonizing the mineral court services man: spironolactone antagonizes the mineral corticoid receptor
29. Crumbling mineral mountain:treatment of 1 and 2 hyperaldosteronism
30. Failing heart balloon: K+ diuretics (spironolactone, eplerenone) are useful in the treatment of heart failure
35. Elevated banana's: K+ sparing diuretics can cause mild or even dangerous(hyperkalemia)→ cardiac arrhythmias (More common in diabetes, chronic renal disease pts or patients on ACE inhibitors) (More severe with eplerenone)
40. Fried male symbol: testosterone produced from cholesterol
41. Health inspector inhibiting 17 aplha "fry"droxylase: spironolactone inhibits 17alpha-hydroxylas Important in testosterone synthisis (inhibit testosterone syntisis) 17الفا فقط اعرف انو بمنع التستوستيرون انساك من ال
43. Bushy beard: symptoms of androgen excess trear (hirsutism)(antiandrogenic effect)
45. Lids on chest: Gynecomasta in men & Breast tenderness in woman (rare with Eplerenone)

Addition

1-*Given orally; have delayed OOA
2-*Weak diuretics, usually combined with other antihypertensives or thiazides
3-treat Hypertension Hypokalemia and others

Diuretic-induced hypokalemia is a serious problem among most of pts on loop diuretics or thiazides . However, we can solve it by:

- Combining thiazide or loop diuretic + oral K+ supplement

- Combine thiazide or loop diuretic with a K+ sparing diuretic

** Unlike thiazide diuretics….. loop and K+ sparing diuretics have no effects on blood lipids

Reasons for diuretic resistance or refractoriness (Therapeutic Failure):

- Continued ingestion of salt

- Impairment of organic acid secretion mechanisms in the proximal tubules due to diseases or drugs

- Secondary hyperaldosteronism

- Lowered renal blood flow $\rightarrow\uparrow$ Na+ reabsorption (post diuretic salt retention)

- Lowered bioavailability of the drug

Management of diuretic resistance

By restriction of sodium intake, changes in dose, changes in timing, and combination of diuretic therapy

Abdulla halawa