



GENITOURINARY SYSTEM

SUBJECT : Pharma
LEC NO. : "2"
DONE BY : Nada Dwaikat

وَقُلْ رَبِّ زِدْنِي عِلْمًا

Genitourinary System Module

Pharmacology

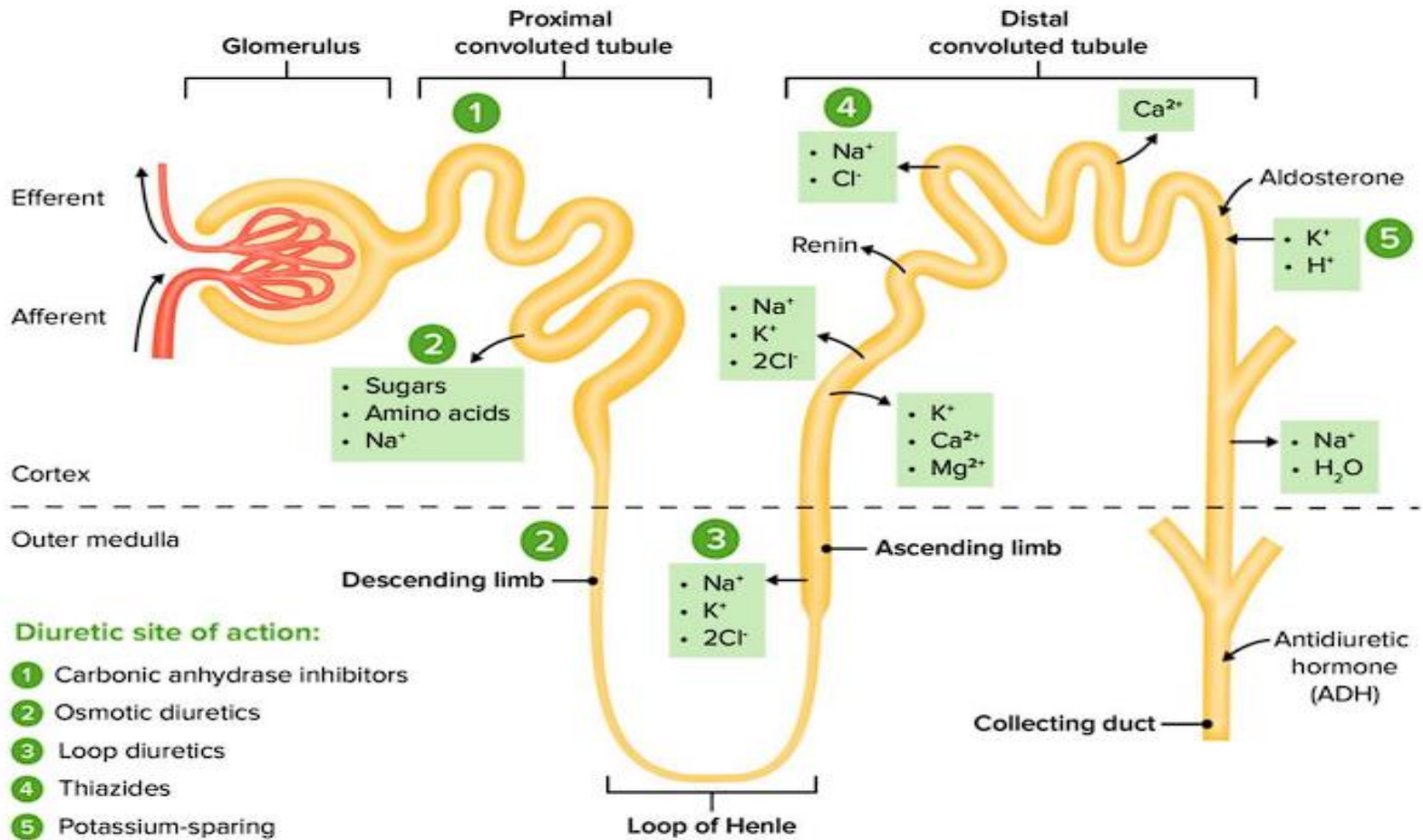
Lecture (2)

Diuretics (2)

Faculty of Medicine

The Hashemite University

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Loop Diuretics

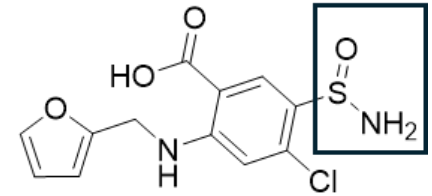
This transporter is the target

- Diuretics inhibit the cotransport of $\text{Na}^+ / \text{K}^+ / 2\text{Cl}^-$ in the luminal membrane in the thick ascending limb of the loop of Henle
- They reach their target site by active secretion from the blood into the urine by the organic acid transporters present in the proximal tubules.

* مثل thiazide و مشابيح الدواء يوصلون إلى Target ناهه لدرنا يسير (Secretion) ويقوم ذلك مع خلال acid Transporters

• Drugs:

- Furosemide (Lasix): most commonly used
- Bumetanide
- Torsemide
- Ethacrynic acid: used infrequently due to its adverse effect profile.



Furosemide

لا يتوجب على Sulfonamide Group

All, but ethacrynic acid contain sulfonamide group, but generally don't cause allergic rxn in patients who are allergic to sulfonamide antibiotics.

Actions

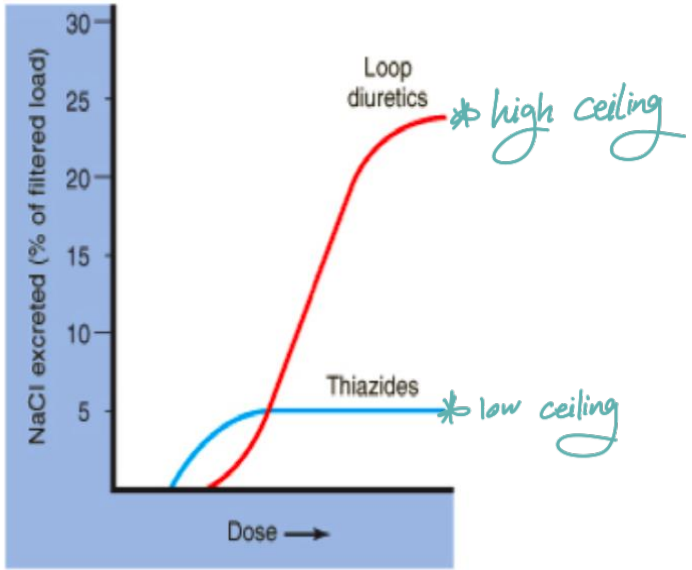
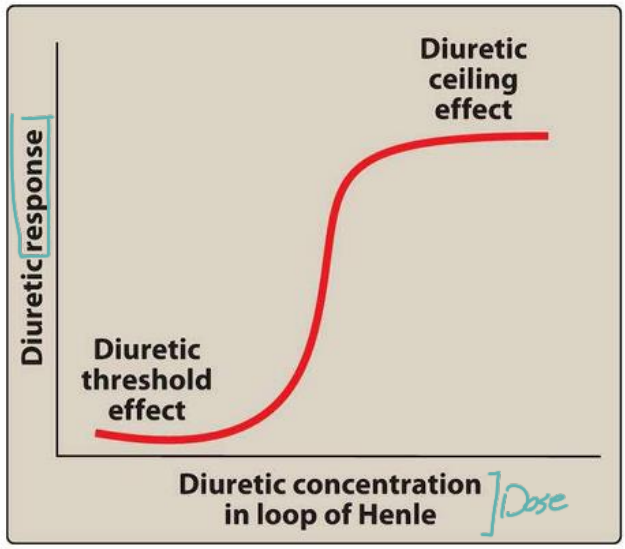
1. **Diuresis:** inhibition of Na/K/2Cl cotransporter results in reduced reabsorption of these ions into the renal medulla, creating a lower osmotic pressure in the medulla, which then reduces water reabsorption in water permeable segments.

- 25% to 30% of filtered NaCl is filtered in the ascending loop therefore loop diuretics have the greatest diuretic effect.
- They show 'high ceiling effect' with great diuretic response to a small change in the dose.

↳ loop of Henle is thin, rigid & so the second segment can't compensate for the loss of water and electrolytes
∴ Stronger action by diuretic

loop diuretics ^{أما} loop ^{أما} thiazide ^{أما} low
 High ↑

High Vs low ceiling diuretics



* Dose - Response graph

no Threshold : النقطة التي لا يلاحظ فيها استجابة
 response

no Ceiling : النقطة التي لا يمكن زيادتها
 response ^{أما} response ^{أما} response
 ثابت وما يتغير .

Actions

2. Increased urinary calcium excretion: Unlike thiazides, loop diuretics increase the Ca^{2+} content of urine. They are used in hypercalcemia treatment
3. Venodilatation : loop diuretics cause acute venodilatation and reduce left ventricular filling pressures via enhanced prostaglandin synthesis.



loop diuretics
Venodilatation
بشكل سريع جداً

Furosemide فاصلة

فبتكون ال effect ناغ venodilatation
فترجع من Diuresis

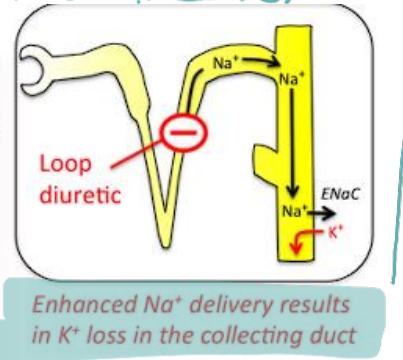
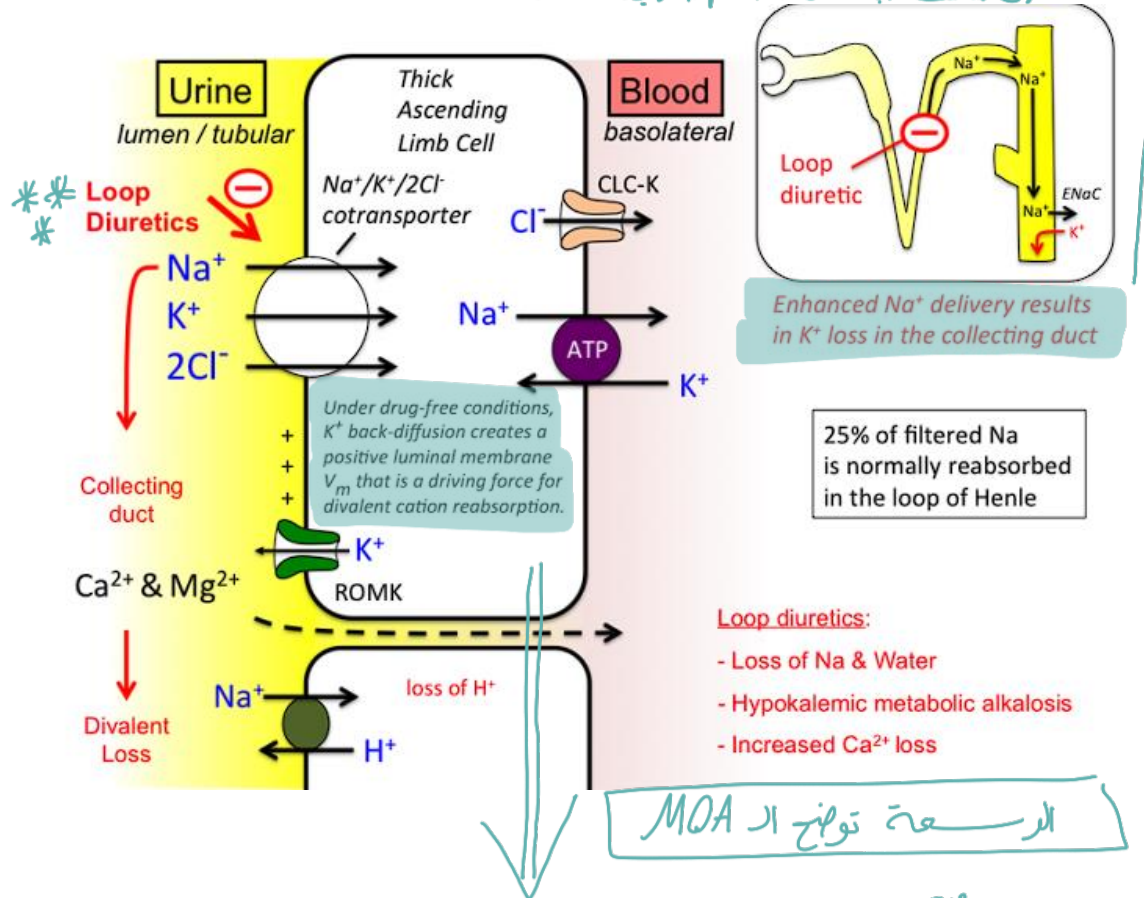
وهذا شيء كويس فاصلة في مريض
Heart failure

Effects of loop diuretics on ion composition of urine and blood

مثل Thiazide
سبب أن تركيز Na^+ في الـ urine عالي، فلما يوصل إلى منافذ أهد خلال Loop of Henle، يحدث تبادل بين Na^+ مع K^+ ، وهذا يجعل كمية K^+ في urine عالية.

Urine	Blood
↑ Na^+	Hyponatremia
↑ Cl^-	Hypochloremia
↑ H_2O	Hypovolemia
↑ K^+	Hypokalemia
↑ H^+	Alkalosis
↑ Mg^{++}	Hypomagnesemia
↑ Ca^{++}	Hypocalcemia

هذا الجدول يوضح أثر الـ loop diuretics على electrolytes في الدم والـ urine



25% of filtered Na is normally reabsorbed in the loop of Henle

* ليس بزياد Ca^{2+} في urine عند استخدام loop diuretics

← في الموضع الطبيعي دور Diuretic، K^+ ينتقل إلى lumen وخاصة أن له Permeability عالية،

وانتقاله هذا يسبب فرق في الشحنة بين lumen (+) ، و inner surface of the cells

← ولأنه لدرنا تغير Net charge ← صفر، تنتقل Ca^{2+} و Mg^{2+} إلى الدم من خلال Transporter في intercellular gaps

صحيح أما كنت تأثير Loop Diuretic، يكون الفرق في الشحنة المتكون قليل وعليه كمية Ca^{2+} و Mg^{2+} الناقصة إلى الدم تصبح قليلة كذلك

Loop diuretics: Pharmacokinetics

- Loop diuretics are administered orally or ^{IV} parenterally.
- Furosemide has unpredictable bioavailability of 10% to 90% after oral administration.
*من ذلك لما تطبخ المريض tablet منه
لذا تشبه على effect تارة*
- Bumetanide and torsemide have reliable bioavailability of 80% to 100%, which makes these agents preferred for oral therapy.
- Furosemide and bumetanide DoA is ~ 6h, and moderately longer for torsemide.
**** loop Diuretics have shorter duration of action
مقارنة مع thiazide
وهذا يعني لذا تطبخ المريض doses أكثر*

Therapeutic uses

are the main and the first line drugs for edema → *Peripheral or pulmonary*

1. Edema: loop diuretics are used more for the therapy of edema than long term therapy of hypertension. They are the drugs of choice for treatment of pulmonary edema and acute/chronic peripheral edema caused from heart failure or renal impairment. Because of their rapid onset of action, the drugs are useful in emergency situations such as acute pulmonary edema.
2. Hypercalcemia
3. Hyperkalemia

Furosemide *أفيس*
IV preferred

Adverse effects

لأنهم كثير efficient, Potent خاصة إذا أعطوا بشكل Fusion وكان سريع

1. **Acute hypovolemia**: Loop diuretics can cause a severe and rapid reduction in blood volume, with the possibility of **hypotension**, **shock**, and **cardiac arrhythmias**.
2. **Hypokalemia**: **the most common** adverse effect of the loop diuretics. The loss of K^+ from cells in exchange for H^+ leads to hypokalemic alkalosis. **Use of potassium-sparing diuretics or supplementation with K^+ can prevent the development of hypokalemia.**
3. **Hypomagnesemia**
4. **Ototoxicity**: **Reversible or permanent hearing loss may occur with loop diuretics, particularly when at fast rates, at high doses, or when used in conjunction with other ototoxic drugs (for example, aminoglycoside antibiotics). Ethacrynic acid has been known to have a more ototoxic potential than the other members**
5. **Hyperuricemia**: **may cause or exacerbate gouty attacks.**

Diuretic ينطهون

Rare

بقل في Blood بنفس طريقة Ca^{2+}

عشان يكون هو the least to be used Diuretics بين

Be cautious لذلك وقت تعطي ال loop Diuretic أو thiazide إلى مريض gout

وهنا لأن loop Diuretics و thiazide ممانع يغير لهم Filter ، يتج من خلال acid transporter وبالتالي بنافسوا ال uric acid .

Drug-drug interactions

- **Aminoglycosides** and **cephalosporins**: Risk of ototoxicity
- **Digoxin**: combination with **loop diuretics** (also with **thiazide** and **potassium-sparing diuretics**) increases the risk of digoxin toxicity (**anorexia, nausea, neurological symptoms, fatal arrhythmias**).
- NSAIDs reduces efficacy of diuretics.
- **Lithium**: can cause lithium retention.

Digoxin* هو عبارة عن Glycoside يتسبب في
atrial arrhythmias مع

وهو نظير لانه
its therapeutic dose and toxicity dose
could overlap
∴ it needs to be monitored
when given to the patient.

لأنه آثر على
renal filtration
تقلل من efficacy

lithium
is a mood stabilizer
ويقلل الجسم من خلال
renal clearance
loop diuretic
فهو يؤثر على
clearance
تأثير lithium الذي يسبب
retention of lithium
inside the body
which could cause
toxicity.

loop Diuretics
تقلل من renal filtration
وإن NSAIDs تقلل من renal filtration

* نختار ال Thiazide مع heart failure ، First choice ،
 نستخدم وقت بدنه resistance ل loop diuretics

Causes & management of loop diuretics Resistance

Diuretics resistance: can be defined as an unsatisfactory rate of diuresis/natriuresis despite an adequate diuretic regimen

A. Pharmacokinetic Causes:

« أثر الجسم على الدواء »
 absorption و secretion ...

I. Defective intestinal absorption in decompensated HF (of oral furosemide)

لما نطلبه orally
 يكون absorption قليل
 وبالتالي Bioavailability قليلة
 وعليه efficacy قليلة

Give the diuretic IV.

II. Defective plasma protein binding in hypoalbuminemic states (liver cirrhosis & nephrotic syndrome) → extravascular diffusion of diuretic → ↓ renal excretion

Mix the diuretic with albumin prior to infusion.

III. Defective excretion of diuretics by the acid secretory system in renal impairment due to accumulation of acids.

⇐ لدرج loop diuretics تتنافس acids
 فلما يزيد ال acids يزيد ال Competition

↑ **Dose of diuretics**

* لما يوصل ال Loop Diuretic إلى الدم
 مشان يدمت ال transport لدرج يرتبط
 مع albumin ، حتى يصل إلى kidney
 ليحدث ال excretion ال خلال acid transporter
 وهذا Protein Binding ال مشان يمنع ال diffusion لدرج الدواء
 ويكون ال diffusion تاحة فقط Selective إلى kidney

⇐ أما في حال
 قسا وجود ال
 Protein binding
 مع ال Diffusion لدرج
 ال loop diuretic
 ويقادر ال Circulation إلى
 Tissues
 ثانية غير kidney

Causes & management of loop diuretics resistance

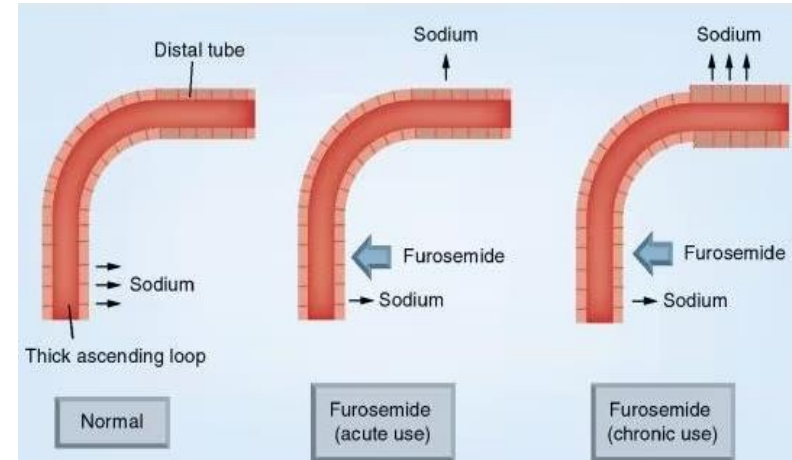
B. Pharmacodynamic Causes

- I. Hypertrophy of distal tubular cells (on chronic use \rightarrow \uparrow Na^+ reabsorption \rightarrow blunts the action of the diuretic)

Add thiazides

- II. activation Na retaining mechanism such as aldosterone. Na^+ lost by loop diuretics reabsorbed in exchange with K^+ in distal tubules (under the effect of aldosterone):

Add the aldosterone antagonist spironolactone.



* Diuresis يحدثها
وزيد لا excretion ناعى و Na⁺
loop Diuretics و thiazide
تلك على عكس
يقلوا retention د K⁺ فلا ينتج hypokalemia

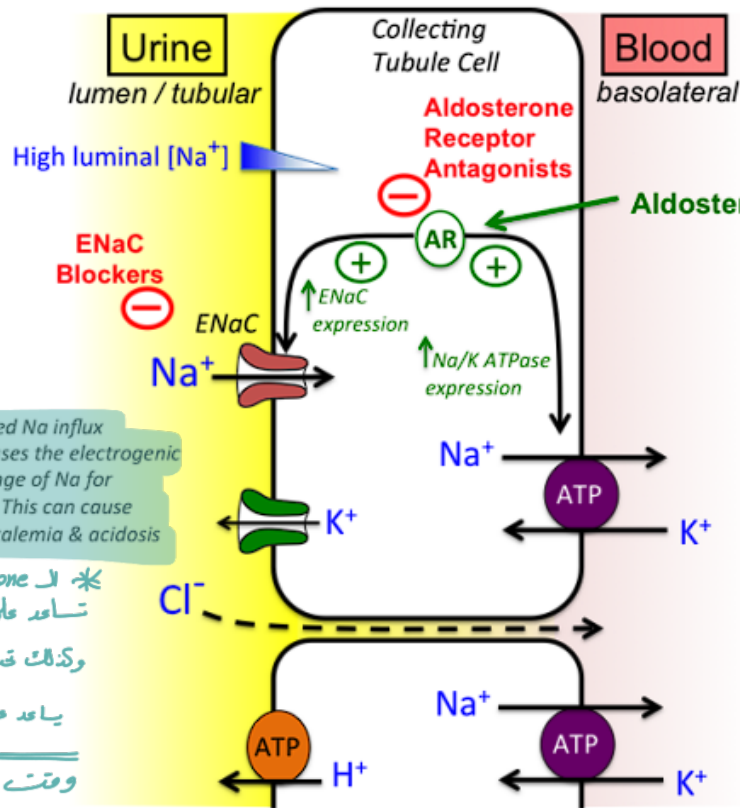
Potassium-Sparing Diuretics

- Potassium-sparing diuretics act in the collecting tubule to inhibit Na⁺ reabsorption and K⁺ excretion
- Potassium levels must be monitored in patients treated with potassium-sparing diuretics.
- These drugs should be avoided in patients with severe renal dysfunction because of the increased risk of hyperkalemia
- They include: aldosterone antagonists and epithelial sodium channel blockers.

* K⁺ sparing diuretics effect
كل العائلة راجع يعلوا
وذلك يختلف في MOA

Aldosterone antagonists: spironolactone and eplerenone

- Both synthetic antagonists of aldosterone.
- Aldosterone promotes expression and translocation of ENac (epithelium sodium channel) and expression of Na/K ATPase.
- Aldosterone antagonists prevent Na⁺ reabsorption and K⁺ and H⁺ secretion.
- Eplerenone is more selective and causes less endocrine effects (gynecomastia) than spironolactone, which also binds to progesterone and androgen receptors.



2-5% of filtered Na is normally reabsorbed in the collecting duct

Reduced Na influx decreases the electrogenic exchange of Na for K & H. This can cause hyperkalemia & acidosis

* لا الaldosterone قوت قوت Na^+ تساعد على reabsorption ناي Na^+ وكذلك قوت Na^+/K^+ pump يساعد على secretion ناي K^+ في urine

وقت رايبر inhibition من خلال aldosterone antagonist
 ← رح يقل الreabsorption Na^+ وكذلك رح يقل secretion K^+

- Aldosterone antagonists**
- Loss of Na & Water
 - Hyperkalemia
 - Some risk for acidosis

Therapeutic uses

1. **Edema:** Given in high doses for trx of edema associated with secondary hyperaldosteronism, such as *hepatic cirrhosis and *nephrotic syndrome. Spironolactone is the diuretic of choice in patients with hepatic cirrhosis with fluid in the peritoneal cavity (ascites).
2. **Hypokalemia:** given in conjunction with thiazide or loop diuretics to prevent K⁺ excretion that occurs with those diuretics.

Therapeutic uses

myocardial remodeling ^{التغيير} وانا Diuresis ^{في لثاية} من الدواء ^{من} heart failure ^{مرضى} لما ^{نغلي}

3. **Heart failure:** given at lower doses to prevent myocardial remodeling mediated by aldosterone. Decrease mortality in patients with reduced ejection fraction.
4. **Resistant hypertension:** this effect can be seen in those with or without elevated aldosterone levels.
5. **Polycystic ovary syndrome** Spironolactone is often used off-label for the treatment of polycystic ovary syndrome, it blocks androgen receptors and inhibiting steroid synthesis

→ Females ^{فيمال}
وقت يكون كذا ^{من} ال
male sex hormones
شوي ^{أعلى} من الطبيعي

Adverse effects

hyperkalemia) risk = dose ↙

1. **Hyperkalemia**: The most common side effect. Dose-dependent and increases with renal dysfunction or use of other potassium-sparing agents such as angiotensin-converting enzyme inhibitors and potassium supplements.
2. **Gynecomastia in male patients and menstrual irregularation in female** only associated with Spironolactone use.

∴ You need to be careful
وقت نكلمهم
في هاي الحالات

enlargement of Breast tissue in men. →
less selective
وليس قدي
antagonisation
to other receptors of other tissues.

Triamterene and amiloride

- Block epithelial sodium channels, resulting in a decrease in Na^+/K^+ exchange.
- Commonly used in combination with other diuretics, for their potassium-sparing properties.

. loop diuretics, thiazide مع Na^+/K^+ ←

Carbonic Anhydrase Inhibitor

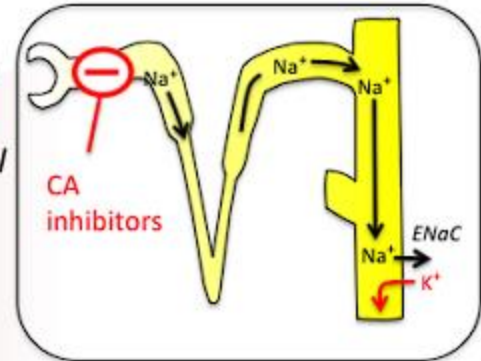
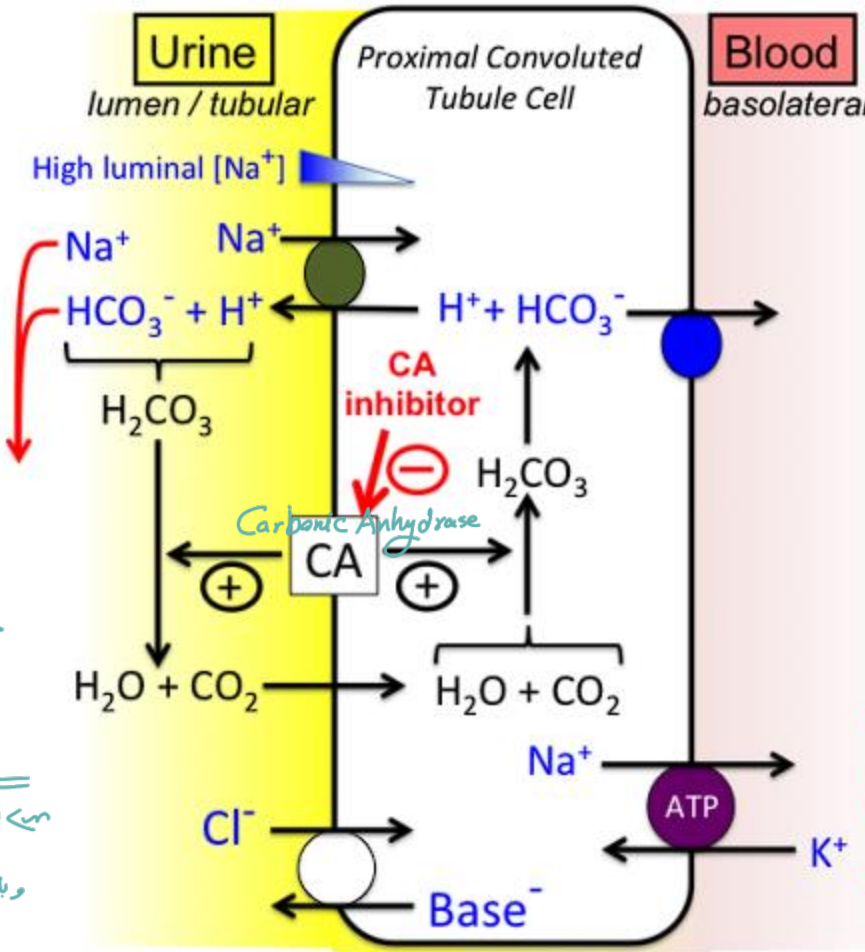
- Acetazolamide inhibits carbonic anhydrase located intracellularly (cytoplasm) and on the apical membrane of the proximal tubular epithelium.
- There is decreased ability to exchange Na^+ for H^+
- HCO_3^- (bicarbonate) is retained in the lumen, with marked elevation in urinary pH.
- The loss of HCO_3^- causes a hyperchloremic metabolic acidosis.
- Less efficacious than the thiazide or loop diuretics. Most of the fluid loss is reclaimed in loop of Henle.

* عننا إنزيم اسمه CA
 Carbonic Anhydrase
 مسؤول عن
 $CO_2 + H_2O \rightleftharpoons H_2CO_3$
 * حيث في Urine يتفكك H_2CO_3
 إلى CO_2 و H_2O

* صلا CO_2 تدخل الخلية
 وترتبط في الخلية مع H_2O
 فيتكون H_2CO_3
 * الذي يتفكك إلى
 $HCO_3^- + H^+$
 * H^+ يحدث له exchange
 مع Na^+ وهنا
 reabsorption
 Na^+

من حصول الأدوية جعلوا inhibition
 على CA
 وبالتالي يقل تكون H^+ داخل الخلية
 وعليه يقل التبادل بين
 Na^+ و H^+

← وهذا ال inhibition سبب
 زيادة في أيونات Na^+ و HCO_3^-
 في urine



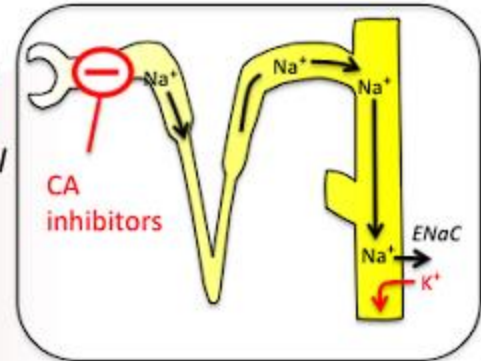
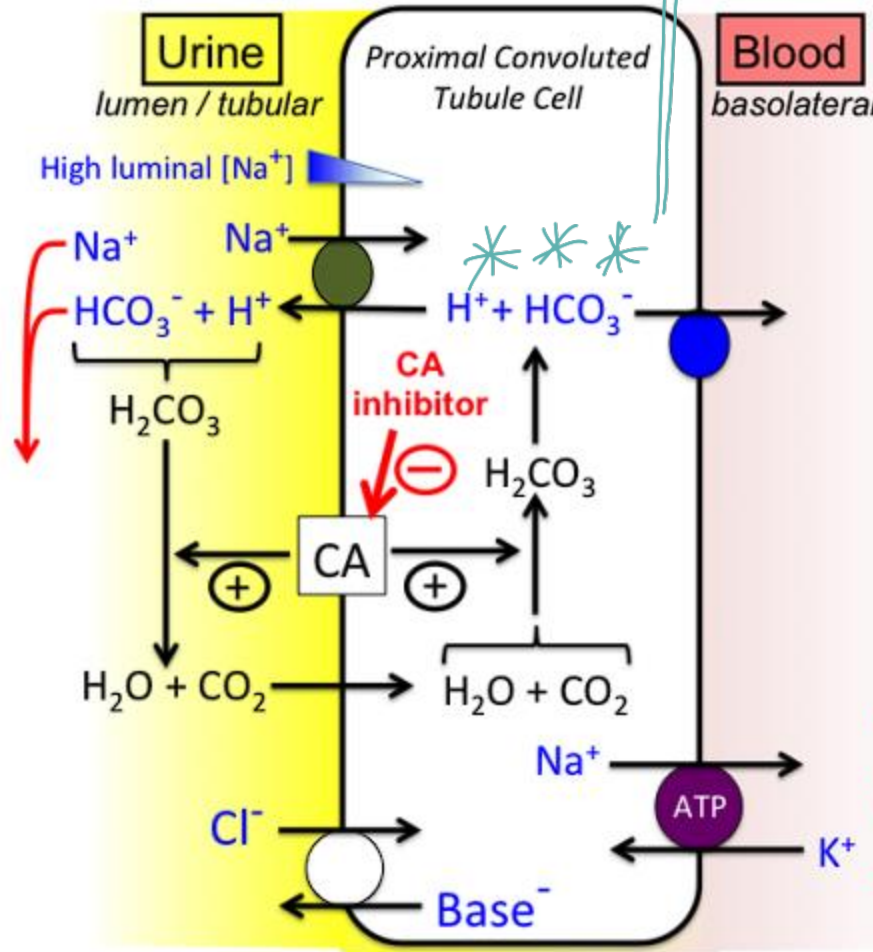
Enhanced Na^+ delivery results
 in K^+ loss in the collecting duct

~66% of filtered Na &
 85% of $NaHCO_3$
 is normally reabsorbed
 in the proximal tubule

Carbonic Anhydrase Inhibitors:

- Loss of $NaHCO_3$
- Hypokalemic metabolic acidosis
- Tolerance develops after 2-3 days

* نسبة صوديوم HCO_3^- لارتفاع يروج على الدم
 بسبب inhibition of CA ، لأن يتكون HCO_3^-
 وبالتالي كمية HCO_3^- في الدم تقل ولهذا يحدث acidosis



Enhanced Na^+ delivery results in K^+ loss in the collecting duct

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Carbonic Anhydrase Inhibitors:

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Therapeutic uses

من الادوية التي نأخذها من غير ان تكون renal
منها ما يستخدم في renal issues

1. **Glaucoma:** Oral acetazolamide decreases the production of aqueous humor and reduces intraocular pressure in patients with chronic open-angle glaucoma. Dorzolamide & Brinzolamide are given by topical application to minimize systemic and renal side effects
2. **Altitude sickness** used in the prophylaxis of symptoms of altitude sickness.



من خلال أنهم جيبوا
decrease of cerebrospinal fluid

O₂ intake وبالتالي لها CSF يقل ، يزيد

Adverse effects

1. Metabolic acidosis (mild)
2. Potassium depletion
3. Renal stone formation
4. Drowsiness
5. Paresthesia (tingling sensation)

The drug should be avoided in patients with hepatic cirrhosis, because it could lead to a decreased excretion of NH_4^+ .

← لأن في hepatic cirrhosis
أصلًا liver tissue يكون ضعيف
وغير قادر تحول ammonia إلى Uric acid
وبالتالي يحدث increase of ammonia in blood
وهذه الأدوية تسبب زيادة ammonia في الدم.

Osmotic Diuretics: Mannitol

* نسبة زيادة في
excretion of water ONLY

- Hydrophilic Sugar alcohol filtered through the glomerulus
- Filtered substances that undergo little or no reabsorption result in a higher osmolarity of the tubular fluid. This prevents further water reabsorption at the descending loop of Henle and proximal convoluted tubule.
- It produces a greater loss of water compared to sodium and potassium.
- These agents are not useful for treating conditions in which Na⁺ retention occurs.

* لذلك ماء ينزلهم للمرضى مع Hypernatremia

Osmotic Diuretics: Mannitol

Uses:

1. Maintenance of urine flow following acute toxic ingestion of substances capable of producing acute renal failure.
2. Mainstay of treatment for patients with increased intracranial pressure.

سبب بحدوث تقليل أو Toxicity
وهذا في حال كانت المادة
Soluble in water.

Mannitol is not absorbed when given orally and should be given intravenously

لأن Mannitol
هو سبب زيادة osmolarity
فلا يكون في الدم بحسب الماء
من tissues و من حاي tissues
فيقللوا Pressure فيها .
intracranium

Adverse effects:

Dehydration and extracellular water expansion from the osmotic effects in the systemic circulation. This causes hyponatremia until diuresis occurs.

أي في Blood

Mannitol is not commonly used in patients with edema, because the initially it induces further volume expansion, which can precipitate the development of pulmonary edema in patients with heart failure.

* لا يتغلوا على ions

* ولكن فقط بزيادة Osmolarity فزيادة سب الماء

