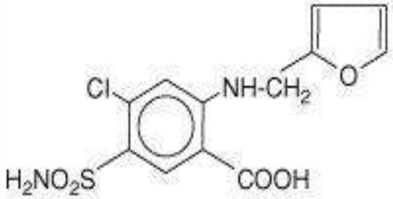
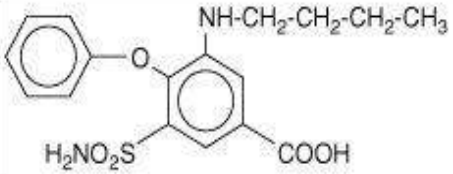
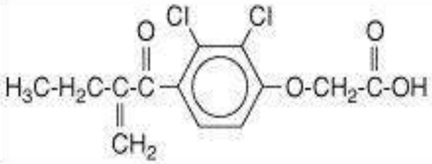
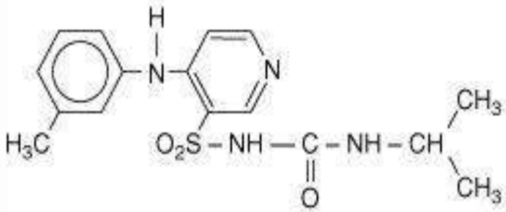
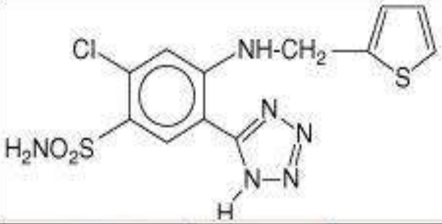
Loop Diuretics (High Ceiling)

- works at the thick ascending limb of the loop of Henle
- are highly efficacious, and for this reason, they sometimes are called *high-ceiling diuretics.*
- Furosemide and bumetanide contain a sulfonamide moiety.
- Ethacrynic acid is a phenoxyacetic acid derivative and torsemide is a sulfonylurea
- loop diuretics increase in the urinary excretion of Na^+ and Cl^- profoundly, also K_+
- also results in marked increases in the excretion of Ca^{2+} and Mg^{2+}.

Table 28-4. Inhibitors of Na^{+}-K^{+}-$2Cl^{-}$ Symport (Loop Diuretics, High-Ceiling Diuretics)

DRUG	STRUCTURE	RELATIVE POTENCY	ORAL AVAILABILITY	T 1/2 (HOURS)	ROUTE OF ELIMINATION
Furosemide (LASIX)		1	~60%	~1.5	~65% R, ~ 35% M*
Bumetanide (BUMEX)		40	~80%	~0.8	~62% R, ~38% M
Ethacrynic acid (EDECRIN)		0.7	~100%	~1	~67% R, ~33% M
Torsemide (DEMADEX)		3	~80%	~3.5	~20% R, ~80% M
Axosemide*		1	~12%	~2.5	~27% R, 63% M

sulfonamides

يجني المرضى اللي عندهم حساسية منهم

مادة أعطيهم إياهم + أي دواء كثيري الـ Sulfonamides moiety فرع يتفاعلوا مع بعض ويعطي الـ allergic reaction

→ Contraindicated: لأنه ممنوعة من antibiotics اسمها الـ aminoglycosides؛ ممنوعة من أدوية السكري اسمها Sulfonylurea

مشابهة بالتركيب

Side effects

- **Adverse Effects :**

1. abnormalities of fluid and electrolyte balance
2. Hyponatremia
3. Hypotension
4. thromboembolic episodes — Coagulation تزيد من عملية الـ
5. circulatory collapse ← (نتيجة) تقلص حجم الدم الكلي
6. increased urinary excretion of K^+ and H^+, causing a hypochloremic alkalosis → ارتفاع الـ pH داخل الجسم.
7. Hypokalemia
8. Hypomagnesemia
9. Hypocalcemia
10. Ototoxicity → مشاكل بالأذن الوسطى وممكن تفقد منهم كلية السمع

- Contraindications to the use of loop diuretics :

❖ hypersensitivity to sulfonamides

❖ Anuria ⇒ diuretics لكل أنواع ال diuretics خاصةً ال Loop diuretics → الأشخاص اللي بشتكوا من سوء ال urination فإذا أعطيتهم هذه الأدوية رح تزيد المشكلة.

- Drug interactions :

➢ Aminoglycosides antibiotics حيوية

➢ Anticoagulants

➢ digitalis glycosides (increased digitalis-induced arrhythmias), ← القلب (دواء الديجوكسين) يزيد ال contractility. ↑ لتقليل ال K

➢ propranolol (increased plasma levels of propranolol)

➢ Sulfonylureas

➢ NSAIDs

Therapeutic Uses

- Acute pulmonary edema → تراكم السوائل داخل الرئتين → diuretics نحتاج له قوي
- chronic congestive heart failure → لأنه صار احتباس لسوائل بالجسم
- edema and ascites of liver cirrhosis → تليف الكبد ↓ edema (ascites) خصوصًا في البطن
- HTN (not first choice) however in ER

↓ First Line ك

* أول شي نلجأ له هو ال ACE وال ARBs

ال diuretics نخفض فيهم الضغط.

Combination.

نستخدمها لها في حالات ال emergency

في حالة الطوارئ وارتفاع ضغط الدم القوي → نستخدم ال loop diuretics → لحتى المراقبة

وحتى لا ... اعطاها بدرة

ليش؟ ⟶ مش عالي reabsorption لأنه الـ

moderate effect.

DCT لل water retention أقل

THIAZIDE AND THIAZIDELIKE DIURETICS

(الأكثر استخدامًا)

لأنه الشخص بيقدر يكمل life style تبعه طبيعي

- Sulfonamides, derivatives of benzothiadiazine
- Drugs that are pharmacologically similar to thiazide diuretics but are not thiazides were developed and are called *thiazidelike diuretics.*
- inhibit NaCl transport in the **DCT**
- the proximal tubule may represent a secondary site of action
- increase Na^+ and Cl^- excretion

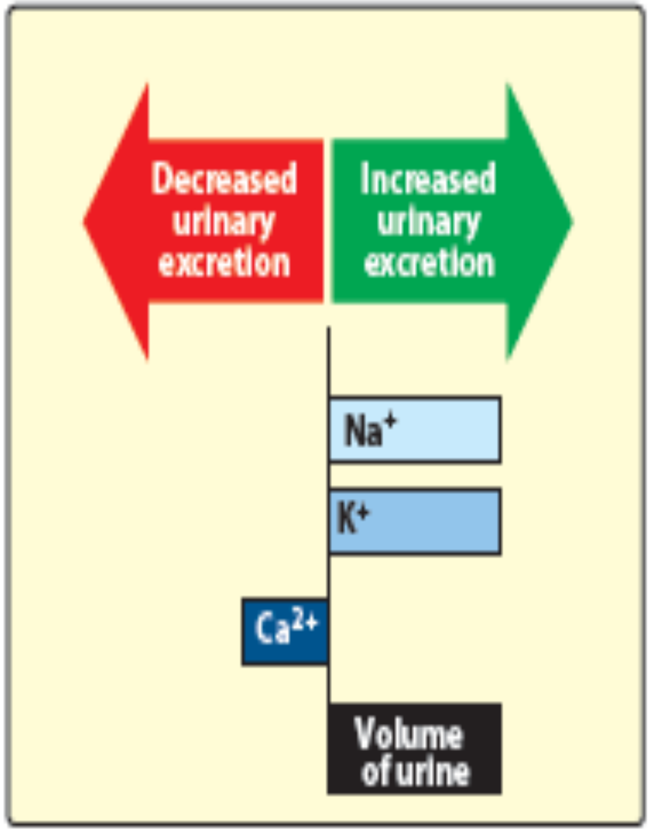


Figure 22.4
Relative changes in the composition of urine induced by thiazide diuretics.

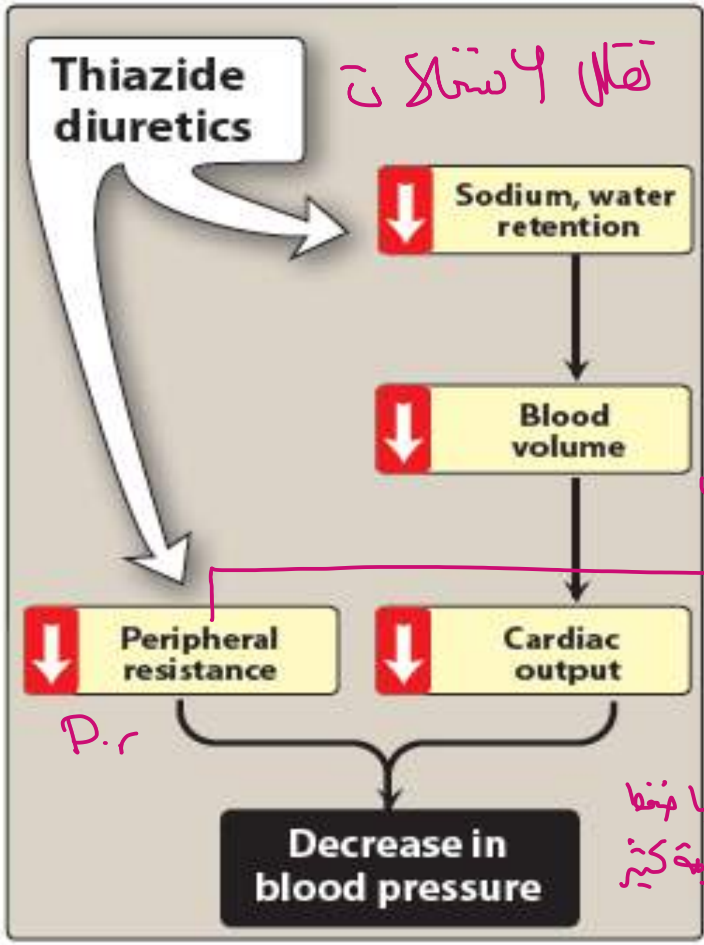
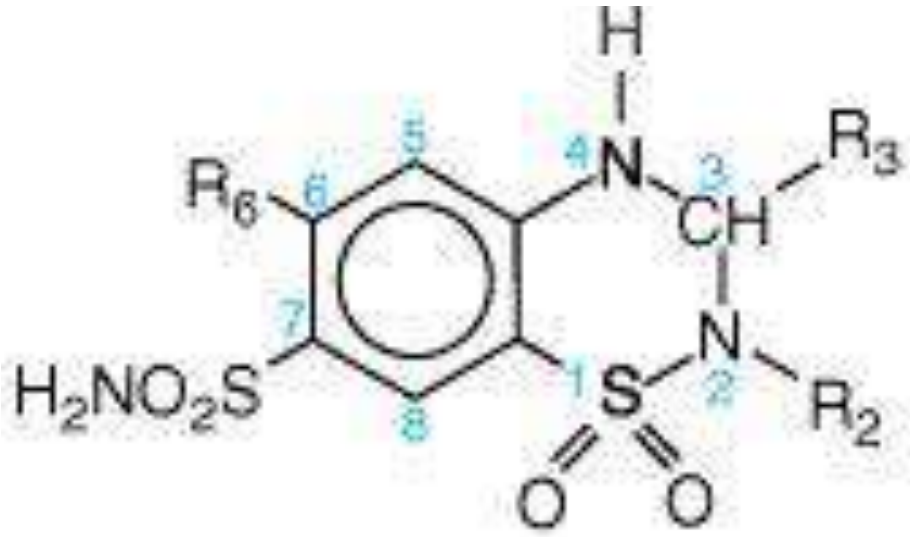


Figure 19.8
Actions of thiazide diuretics.

الدم المار بالـ Blood Vessel
بواجه مقاومة من جدار الـ
Blood Vessel نفسها ... فهاي
المقاومة تزيد إذا صار
عنا Vaso Constriction وتقل إذا
صار عنا Vasodilation ...
هاي المقاومة هي اللي تحدد
ضغط الدم .. اذا زادت معناها ضغط
الدم عالي HTN وإذا كانت قليلة كثير
معناها فيه انخفاض Hypotension
وبالتالي نريدها بالـ peripheral resistance
بكمية معينة -- في حالة الـ HTN
تقلل الـ P.r فيقل ضغط الدم.

- thiazides are only moderately efficacious , because approximately 90% of the filtered Na^+ load is reabsorbed before reaching the DCT
- increase the excretion of K^+

Thiazide core structure



↑ Loop diuretics معشا بيوتحد

Adverse effects :

- extracellular volume depletion
- Hypotension
- hypokalemia
- hyponatremia
- hypochloremia
- metabolic alkalosis
- Hypomagnesemia
- hypercalcemia Loop ال مزعدن
- hyperuricemia diuretics

الاستعمالات

Therapeutic Uses

متوسطة

- Edema : (CHF, RF, Liver cirrhosis)
- Moderate HTN either alone or in combination with other antihypertensive drugs
- A common dose for hypertension is 25 mg/day of hydrochlorothiazide or the dose equivalent of another thiazide.
- The ALLHAT study (ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group, 2002) provides strong evidence that thiazide diuretics are the best initial therapy for uncomplicated hypertension, a conclusion endorsed by the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (Chobanian *et al.2003)*

هاي الدراسة تحكي انه أفضل First Line لمريض الـ HTN هم الـ Thizides

(يعني أول دواء اعطيه هو الـ Thiazides) ولكن (لمشاكلها وخطورتها) ما كان ينزل الضغط بالشكل المطلوب لحاله فـ **adjuvant therapy** دواء مساعد.

aldosteron antagonist أو

K+-SPARING DIURETICS

K ← Na →
تطلع صوديوم وتدخل بوتاسيوم

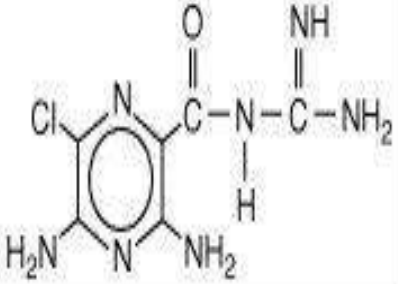
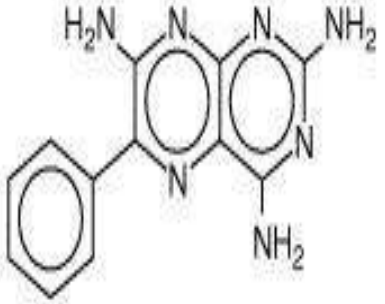
- **Inhibitors of renal epithelial Na^+ channels**
- ***Triamterene*** and ***Amiloride*** are the only two drugs of this class in clinical use
- Both drugs cause small increases in NaCl excretion and usually are employed for their antikaliuretic actions to offset the effects of other diuretics that increase K^+ excretion
- 1. **Triamterene** and 2. **Amiloride,** along with 3. Spironolactone (*see* next section), often are classified as *potassium* (K^+)*-sparing diuretics.*

* ملاحظات مهمة *

* They are weak diuretics بالعموم ال effect تاعها قليل diuretics.
بيستخدموا بـ combination مع other diuretics. ←

* hyperkalemia بيعملوا

Table 28-6. Inhibitors of Renal Epithelial Na^+ Channels (K^+-Sparing Diuretics)

DRUG	STRUCTURE	RELATIVE POTENCY	ORAL AVAILABILITY	$t_{1/2}$ (HOURS)	ROUTE OF ELIMINATION
Amiloride (DYRENIUM)		1	15-25%	~21	R
Triamterene (MIDAMOR)		0.1	~50%	~4.2	M

Abbreviations: R, renal excretion of intact drug; M, metabolism; however, triamterene is transformed into an active metabolite that is excreted in the urine

Adverse Effects

1. • The most dangerous adverse effect of Na^+-channel inhibitors is hyperkalemia, therefore contraindicated:
   - ❖ with NSAIDs
   - ❖ With K supplement, or ACEIs,
2. • nausea, vomiting, diarrhea, and headache
3. • CNS, gastrointestinal, musculoskeletal, dermatological

Therapeutic Uses

- seldom are used as sole agents (نادراً ما تستخدم كالها) // (غالبا)
- major utility is in *combination* with other diuretics
- augments the diuretic and antihypertensive response to thiazide and loop diuretics (also decreases incidence of hypokalemia associated with loop andthiazide)

* بعطو hyperkalemia (Side effect خطير تد يودي بحياة المريض)
* هم ال diuretics مخاف (نعطيهم Combination مع أدوية أخرى) يعني ممكن نعطيه مع Loop diuretics عشان نعمل Balance بال K

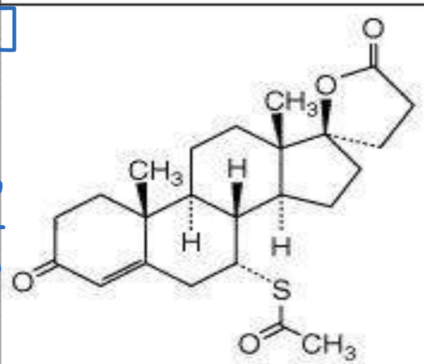
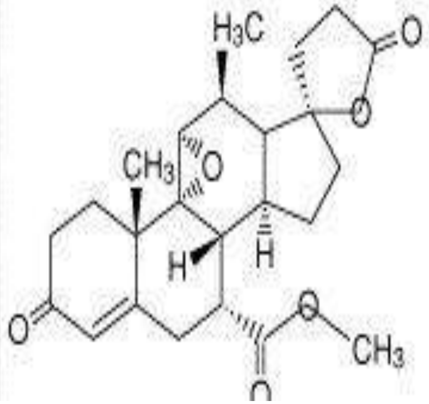
eplerenone & spironolactone

ALDOSTERONE ANTAGONISTS, K^+-SPARING DIURETICS

- **antagonists of mineralocorticoid receptors**
- Mineralocorticoids cause retention of salt and water and increase the excretion of K^+ and H^+ by binding to specific mineralocorticoid receptors
- spirolactones block the effects of mineralocorticoids; this finding led to the synthesis of specific antagonists for the mineralocorticoid receptor (MR).
- two MR antagonists are available :
- *spironolactone* (a 17-spirolactone) and *eplerenone*

- Spironalactone acts on the distal convuluted tubules and the collecting duct
- Drugs such as spironolactone and eplerenone competitively inhibit the binding of aldosterone to the MR
- They increase excretion of Na and water, also enhance K and H retention.

Since spironolactone and eplerenone block the biological effects of aldosterone, these agents also are referred to as *aldosterone antagonists*

DRUG	STRUCTURE	ORAL AVAILABILITY	$t_{1/2}$ (HOURS)	ROUTE OF ELIMINATION
Spironolactone (ALDACTONE)		~65%	~1.6	M
Eplerenone (INSPRA)		ID	~5	M

progesterone

epoxide group

- Spironolactone has some affinity toward progesterone and androgen receptors and thereby induces side effects: as gynecomastia, impotence, and menstrual irregularities.
- An active metabolite of spironolactone, canrenone, has a half-life of approximately 16.5 hours, which prolongs the biological effects of spironolactone
- Owing to the 9,11-epoxide group, eplerenone has very low affinity for progesterone and androgen receptors (<1% and <0.1%, respectively) compared with spironolactone.

في الإناث
↓
بـ بيتنافسوا على نفس الـ receptor
وبعدين قالي تأثير الـ progesterone
فاحنا بنستغل عشانها
التستوستيرون أكتر وبعدين تظهر
عشانها صفات ذكورية زي:-
① ظهور الشعر على أماكن ما كانوا
يظهر فيها وتسمى هذه
الحالة (hirsutism)
زي الشعر على الوجه .
② deep voice +
خشونة في الصوت .
③ menstrual irregularities
خربطة في الدورة الشهرية .

في الذكور ← بـ بيعطوه صفات انثوية

١. gynecomastia
+
٢. impotence

(هاي الأعراض ترجع حادي لما يوقف المريض عنا آخذ الدواء)

Adverse Effects

(خطير جدًا)

لازم المريض يراجع الدكتور خلال فترات العلاج

- may cause life-threatening hyperkalemia
- Salicylates may reduce the tubular secretion of canrenone and decrease the diuretic efficacy of spironolactone
- spironolactone may alter the clearance of digitalis glycosides
- gynecomastia, impotence, decreased libido, hirsutism, deepening of the voice

Therapeutic Uses

- spironolactone often is coadministered with thiazide or loop diuretics in the treatment of edema and hypertension
- treatment of primary hyperaldosteronism
- hepatic cirrhosis
- heart failure

(كانت هاي أول مجموعة علومها)

تعمل ال HCO_3^- للـ reabsorption فانزيد ال excretion

لـ HCO_3^- في تتعاكس ع بعير excretion of water

INHIBITORS OF CARBONIC ANHYDRASE

- *Acetazolamide* is the prototype of a class of agents
- Proximal tubular epithelial cells are richly endowed with carbonic anhydrase
- Carbonic anhydrase plays a key role in $NaHCO_3$ reabsorption and acid secretion.
- In the lumen, H^+ reacts with filtered HCO_3^- to form H_2CO_3, which decomposes rapidly to CO_2 and water in the presence of carbonic anhydrase (thousands of times)

ال HCO_3^- هو Base

فلما بزيد الـ excretion

لاه في ال urine

ع بعير alkalosis

في ال urine حتى ال pH

لل urine بعير عالي

reabsorption ال على Ions يأثر

لحتى الأدوية كان ممكن تعمل

Chemicals لبعض ال disturbance

اللي بيتاجها الجسم (اضطرابات)

في أشياء أنا احتاجها ممكن

تتأثر وتطلع برا الجسم

+

Weak diuretics هم

(Thiazides + Loop diuretics) باستثناء ال diuretics كل أنواع ال

- Carbonic anhydrase inhibitors potently inhibit both the membrane-bound and cytoplasmic forms of carbonic anhydrase, resulting in nearly complete abolition of $NaHCO_3$ reabsorption in the proximal tubule.

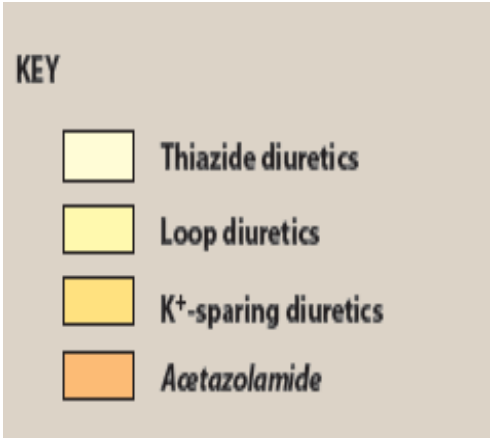
- Inhibition of carbonic anhydrase results in more alkaline urine (more HCO3 in urine)

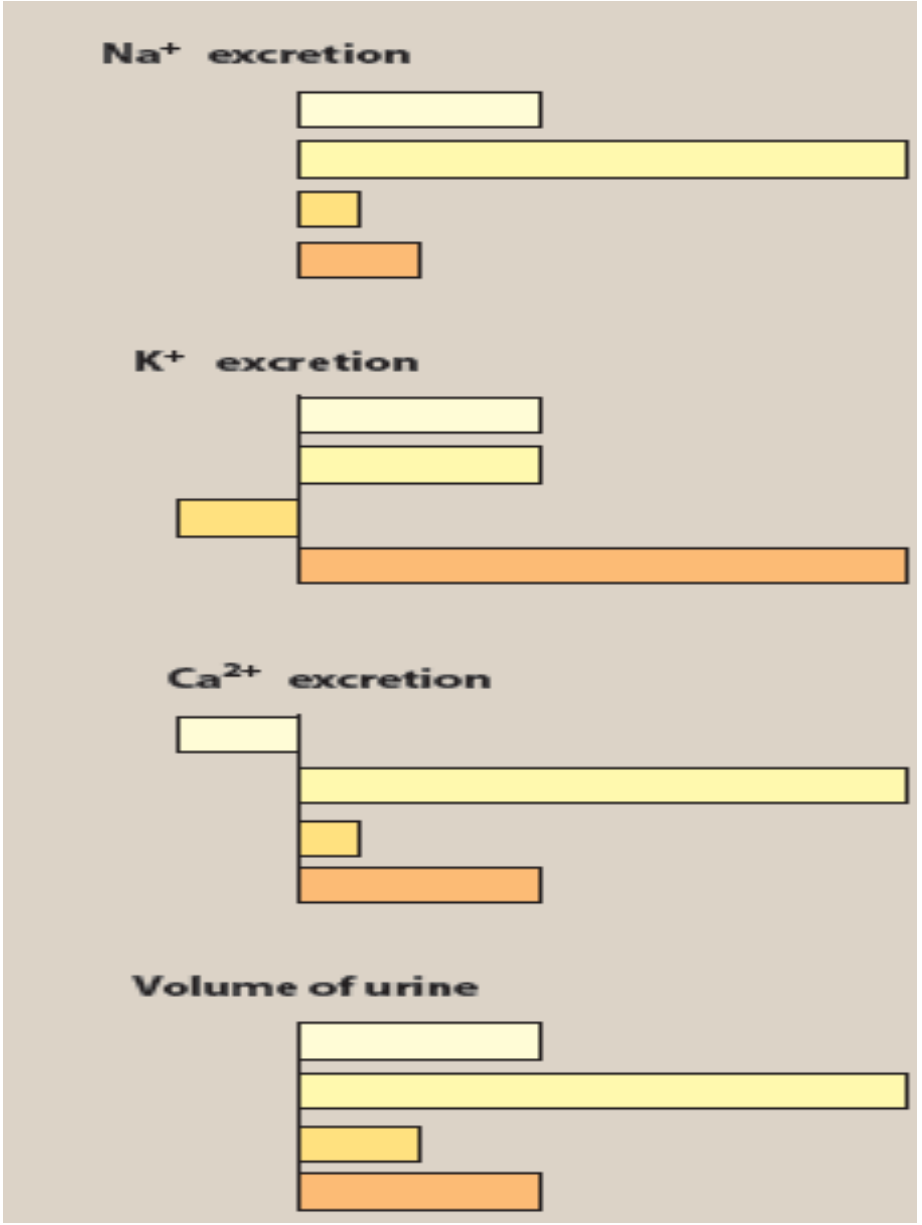
Adverse Effects

- Mainly well tolerated
- may cause bone marrow depression, skin toxicity,
- metabolic or respiratory acidosis

Therapeutic Uses

- Seldom used in clinical practice for HTN
- open-angle glaucoma (major indication) topically as eye drops


KEY
Thiazide diuretics
Loop diuretics
K+-sparing diuretics
Acetazolamide


Na+ excretion
K+ excretion
Ca2+ excretion
Volume of urine

«هيعمل حالة خاصة»

OSMOTIC DIURETICS → osmosis

(تقل الماء من تركيز الملح أقل إلى التركيز الملح الأعلى)

- relatively inert pharmacologically
- administered in large enough doses to increase significantly the osmolality of plasma and tubular fluid
- four currently available osmotic diuretics :

➢ *Glycerin*

➢ *isosorbide*

➢ *mannitol*

➢ *urea*

(لما نطعم بأي مكان يصير يسحب الماء باتجاههم)

Mechanism and Site of Action

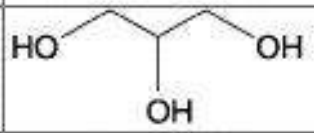
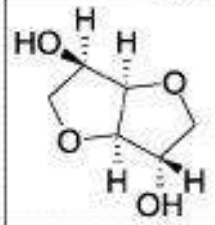
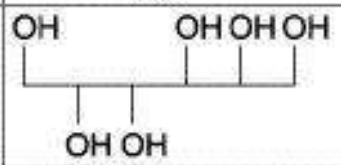
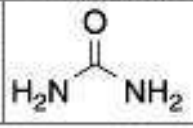
- Major site of action of osmotic diuretics is the loop of Henle.

1. ✓ extracting water from intracellular compartments
2. ✓ expand the extracellular fluid volume
3. ✓ decrease blood viscosity
4. ✓ inhibit renin release
5. ✓ These effects increase RBF
6. ✓ increase in renal medullary blood flow
7. ✓ removes NaCl and urea from the renal medulla

كل هاي الأشياء ح تزيد ← Renal blood flow ح تزيد كمية العوامل اللي
فبالتالي ح يزيد الـ Water excretion من الجسم ..

- Osmotic diuretics increase the urinary excretion of nearly all electrolytes, including Na^+, K^+, Ca^{2+}, Mg^{2+}, Cl^-, HCO_3^-, and phosphate.

Table 28–3. Osmotic Diuretics

DRUG	STRUCTURE	ORAL AVAILABILITY	$T_{1/2}$ (HOURS)	ROUTE OF ELIMINATION
Glycerin (OSMOGLYN)		Orally active	0.5–0.75	~80% M ~20% U
Isosorbide (ISMOTIC)		Orally active	5–9.5	R
Mannitol (OSMITROL)		Negligible	0.25–1.7*	~80% R ~20% M + B
Urea (UREAPHIL)		Negligible	ID	R

Adverse Effects

- In patients with heart failure or pulmonary congestion, they may cause frank pulmonary edema (since there is expantion in extracellular fluid volume)
- Hyponatremia
- Dehydration
- elevation of blood ammonia levels

(ما نستخدمهم كثير لدته تأثيرهم حتى)

Therapeutic Uses

فقط في حالات:-

- osmotic diuretics extract water from the 1. eye and 2. brain 3. spinal cord
- reduce cerebral edema
- In glucoma → (إذا كانت كثير بسيطة) نستخدمهم مع أدوية ال glucoma نفسهم.

edema

(هاي الأماكن هي كثير تطلع الماء منها فنستخدمهم لسبب اخي منهم)

ما بنتحمل الأدوية اللي قبل (محمودة كلها).

OTHER VASODILATORS ⟹

* بنزل فيها ضغط الدم عن طريق عمل Vasodilation يعني .. ما عندهم mechanism ثانية بيشتغلوا فيها.

α-ADRENOCEPTOR ANTAGONISTS

α-Blockers

There are two main types of α-adrenoceptor, α1- and α2. α1-Adrenoceptor antagonists lower blood pressure

Phenoxybenzamine irreversibly alkylates α-receptors. It is uniquely valuable in preparing patients with phaeochromocytoma for surgery, but has no place in the management of essential hypertension. **Prazosin is a selective α1-blocker, but** its use is limited by severe postural hypotension, especially following the first dose. It has a short elimination half-life.

→ Block of α1 receptors
↓
Vasodilation

Prazosin + Doxazosin
mechanism of action
الاثنين نفس الـ

Long duration of action

الـ Doxazosin و

prazosin الـ
has shot duration of action

Doxazosin is closely related to prazosin, but is longer lasting, permitting once daily use and causing fewer problems with first-dose hypotension. It did not compare well with diuretic, Ca2 antagonist or ACEI as first-line agent in ALLHAT, but is useful as add-on treatment in patients with resistant hypertension. It is given last thing at night.

Doxazosin improves symptoms of bladder outflow tract obstruction, and is useful in men with mild symptoms from benign prostatic hypertrophy

Mechanism of action

Noradrenaline activates α1-receptors on vascular smooth muscle, causing tonic vasoconstriction. α1-Antagonists cause vasodilatation by blocking this tonic action of **noradrenaline**

Adverse effects

• First-dose hypotension and postural hypotension are adverse effects.

+ flushing

+ peripheral edema

+ reflex tachycardia

• Nasal stuffiness, headache, dry mouth and pruritus have been reported, but are relatively infrequent.

• α-Blockers can cause urinary incontinence, especially in women with pre-existing pelvic pathology.

Doxazosin has an elimination half-life of approximately 10–12 hours and provides acceptably smooth 24-hour control if used once daily

هنا هي أدوية من ضمن ال antihypertensive agents
لكن استخداماتهم محددة جدًا وفي شي أصلا لا يُستخدم لل HTN

Table 28.3: Additional antihypertensive drugs used in special situations

Drug	Mechanism of action	Uses	Side-effects/limitations
Minoxidil	Minoxidil sulphate (active metabolite) is a K^+-channel activator	Very severe hypertension that is resistant to other drugs	Fluid retention; reflex tachycardia; hirsutism; coarsening of facial appearance. Must be used in combination with other drugs (usually a loop diuretic and β-antagonist)
Nitroprusside	Breaks down chemically to NO, which activates guanylyl cyclase in vascular smooth muscle	Given by intravenous infusion in intensive care unit for control of malignant hypertension	Short term IV use only: prolonged use causes cyanide toxicity (monitor plasma thiocyanate); sensitive to light; close monitoring to avoid hypotension is essential
Hydralazine	Direct action on vascular smooth muscle; biochemical mechanism not understood	Previously used in 'stepped-care' approach to severe hypertension: β-antagonist in combination with diuretic. Retains a place in severe hypertension during pregnancy	Headache; flushing; tachycardia; fluid retention. Long-term high-dose use causes systemic lupus-like syndrome in susceptible individuals
α-Methyldopa	Taken up by noradrenergic nerve terminals and converted to α-methylnoradrenaline, which is released as a false transmitter. This acts centrally as an α_2-agonist and reduces sympathetic outflow	Hypertension during pregnancy. Occasionally useful in patients who cannot tolerate other drugs	Drowsiness (common); depression; hepatitis; immune haemolytic anaemia; drug fever

Minoxidil: يتم استخدامه بسبب Side effect معين الي هو انه بزيد نمو الشعر (الاستخدام الأساسي له)

Nitroprusside, Hydralazine: they are Vasodilators يشتغلوا على زيادة ال NO فيصير Vaso dilation

α-Methyldopa: (Central acting antihypertensive agent)
α2 agonist ⇒ يعمل excitation of α2 receptors ⇓ يمنع ال (noradrenaline secretion) ⟶ يقلل ال Blood pressure

أدوية ال HTN التي يتم استخدامها أثناء الحمل هم 2 فقط ← α Methyldopa
وأحد من ال β-Blockers ← Labetalol

HTN لا يزال يتم استخدامه لدواء ⇒ during pregnancy ⟶ غالبًا يكون HTN قبل الحمل ويصير بعد ⟶ (غالبًا يصير ال HTN مع 20 في ال3 أشهر الأخيرة من الحمل) ⟶ يفترض بعد الولادة يرجع ولكن في ناس يضل معها الأشياء

وإن شاءالله أكون كتبت كل شيخ حكاه الدكتور ، ربي يكتب
في ميزان حسناتي وميزان حسنات موتى المسلمين ، اللهم كن في عون أهلنا في
غزة والسودان واليمن والصومال وسوريا وجميع بلاد المسلمين صاعقناصتها وما لم نتكلم
سامحونا على أي تقصير..

done by: ph. Greyhammer

دعواتكم..