DIURETICE

FIZIOLOGIE

TABLE 15–1 Major segments of the nephron and their functions.

Segment	Functions	Water Permeability	Primary Transporters and Drug Targets at Apical Membrane	Diuretic with Major Action
Glomerulus	Formation of glomerular filtrate	Extremely high	None	None
Proximal convoluted tubule (PCT)	Reabsorption of 65% of filtered $Na^+/K^+/CA^{2+}$, and Mg^{2+}; 85% of $NaHCO_3$, and nearly 100% of glucose and amino acids. Isosmotic reabsorption of water.	Very high	Na/H^1 (NHE3), carbonic anhydrase	Carbonic anhydrase inhibitors Adenosine antagonists (under investigation)
Proximal tubule, straight segments	Secretion and reabsorption of organic acids and bases, including uric acid and most diuretics	Very high	Acid (eg, uric acid) and base transporters	None
Thin descending limb of Henle's loop	Passive reabsorption of water	High	Aquaporins	None
Thick ascending limb of Henle's loop (TAL)	Active reabsorption of 15–25% of filtered $Na^+/K^+/Cl^-$; secondary reabsorption of Ca^{2+} and Mg^{2+}	Very low	Na/K/2Cl (NKCC2)	Loop diuretics
Distal convoluted tubule (DCT)	Active reabsorption of 4–8% of filtered Na^+ and Cl^-; Ca^{2+} reabsorption under parathyroid hormone control	Very low	Na/Cl (NCC)	Thiazides
Cortical collecting tubule (CCT)	Na^+ reabsorption (2–5%) coupled to K^+ and H^+ secretion	Variable[2]	Na channels (ENaC), K channels,[1] H^+ transporter,[1] aquaporins	K^+-sparing diuretics Adenosine antagonists (under investigation)
Medullary collecting duct	Water reabsorption under vasopressin control	Variable[2]	Aquaporins	Vasopressin antagonists

[1]Not a target of currently available drugs.
[2]Controlled by vasopressin activity.

MECANISMELE DE TRANSPORT TUBULAR

- TCP: reabsorbtia $NAHCO_3$, NaCl, glucoza, amino-acizi prin intermediul transportorilor specifici
- aproximativ 66% din sodiul filtrat, 85% din $NAHCO_3$, 65% din K, 60% din apa si aproape intreaga cantitate de glucoza si amino-acizi sunt reabsorbiti in TCP
- apa-reabsorbita pasiv→ mentinerea osmolaritatii TCP

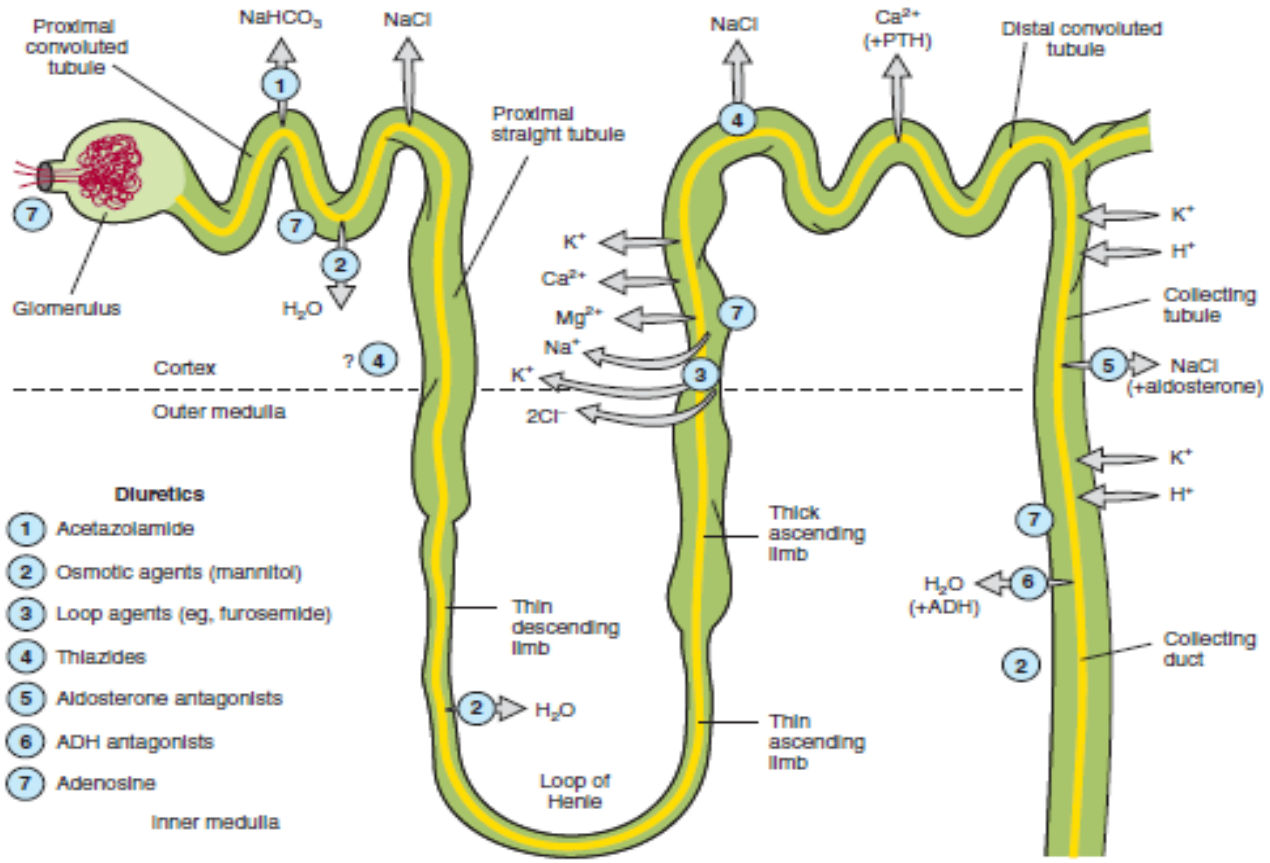


FIGURE 15–1 Tubule transport systems and sites of action of diuretics. ADH, antidiuretic hormone; PTH, parathyroid hormone.

TABLE 15–1 Major segments of the nephron and their functions.

FIZIOLOGIE

- portiunea initiala, descendenta a ansei Henle: impermeabila pentru ioni, permeabila pentru apa (reabs.10-20% din apa filtrata)
- Ramura ascendenta: reabs.Na, Cl si Mg, plus un procent important de Ca; impermeabila pentru apa
- TCD: continua reabs. Na, Cl si se completeaza reabs. Ca, sub actiunea PTH
- portiunea finala a TCD si tubul colector: sub act.aldosteronului-reabs. Na, la schimb cu K si H
- ADH completeaza reabsorbtia de apa

DIURETICE

- **STIMULAREA DIUREZEI (↑ CRESTEREA EXCRETIEI DE NA SI H2O)**

- **FOLOSITE CA ANTIHIPERTENSIVE, REDUCEREA EDEMELOR, ETC.**

DIURETICE

I. **DIURETICE DE ANSA**

-cele mai potente

-act. la nivelul portiunii ascendente a ansei Henle

-Fiziologic: reabsorbtia Na si Cl, sub actiunea ATP-azei Na+/K+ localizate la nivel membranar (introduce K, extrage Na)

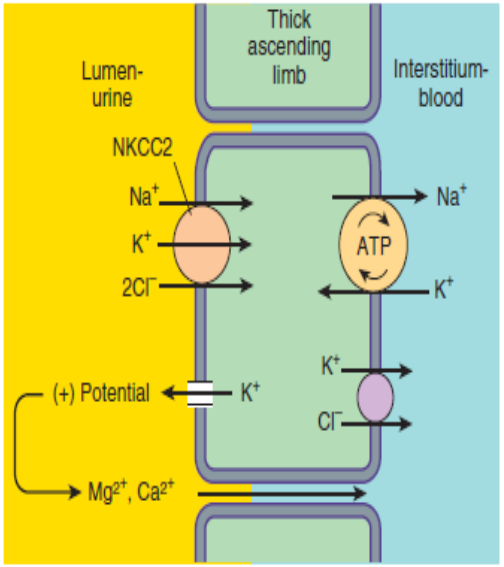
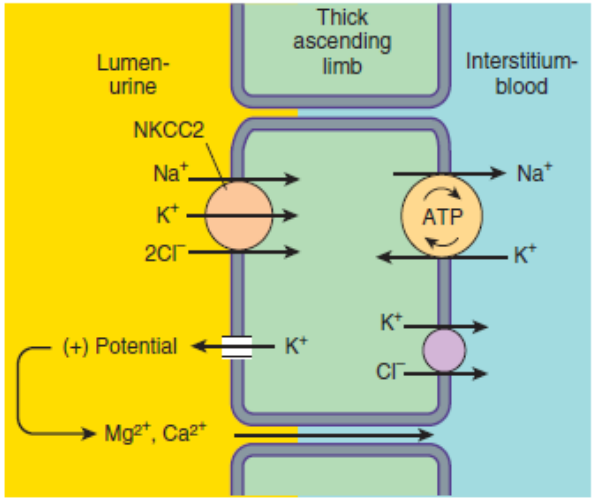


FIGURE 15–3 Ion transport pathways across the luminal and basolateral membranes of the thick ascending limb cell. The lumen positive electrical potential created by K^+ back diffusion drives divalent (and monovalent) cation reabsorption via the paracellular pathway. NKCC2 is the primary transporter in the luminal membrane.

DIURETICE DE ANSA



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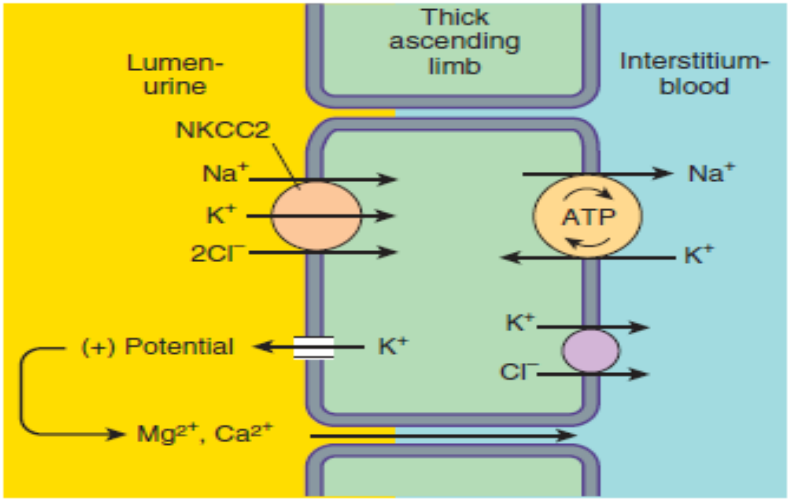
→↑Na interstitial➔initiaza reabs. acestuia din lumenul tubular

→deoarece ramura ascendenta nu este permeabila pentru apa, reabsorbtia este completata de un co-transportor, localizat la nivelul membranei apicale, impreuna cu un ion de K+ si 2 ioni de Cl (Na/K/2Cl sau NaKCC2)

DIURETICE DE ANSA



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→K reabsorbit paraseste celula prin canale specifice, localizate atat la nivelul membrane apicale, cat si la nivelul celei bazale, in sensul gradientului de concentratie

→Cl paraseste celula doar la nivelul membranei bazale

DIURETICE DE ANSA

→diureticele de ansa **blocheaza** co-transportorul

➔25% din Na filtrat glomerular ramane neabsorbit, impreuna cu un echivalent de apa =>cantitati importante de K, Mg si Ca raman neabs.➔ dezechilibre electrolitice!

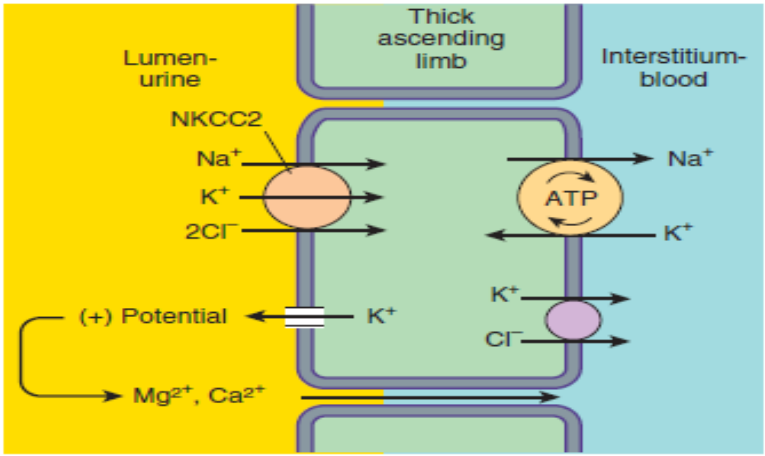


FIGURE 15–3 Ion transport pathways across the luminal and basolateral membranes of the thick ascending limb cell. The lumen positive electrical potential created by K^+ back diffusion drives divalent (and monovalent) cation reabsorption via the paracellular pathway. NKCC2 is the primary transporter in the luminal membrane.

DIURETICE DE ANSA

Indicatii:

- **Edemul pulmonar acut**
- **Insuficienta renala acuta**
- **Criza hipertensiva**
- Hipercalcemie
- Hiperkaliemie
- Edeme
- Tratmentul cronic al HTA

DIURETICE DE ANSA

Interactiuni: AINS, in special indometacin, ↓ efectul, probablil prin ↓filtratului glomerular

!!! singurele diuretice al caror efect este direct proportional cu doza!

Fc: absorbtie digestive buna, metabolizare hepatica, eliminare renala, sub forma de metaboliti inactivi

Efecte adverse:

→↓Na, K, Mg

→↓K→aritmii

→ototoxicitate, de obicei reversibila

DIURETICE DE ANSA

EFECTE ADVERSE:

→alcaloza sistemica

→hiperuricemie

→rr alergice

→deshidratare, hipovolemie, hTA ortostatica

→cresc calciuria

Precautii: ciroza hepatica avansata, insuficienta cardiaca avansata, insuficienta renala stadiile 3, 4

DIURETICE DE ANSA

Reprezentanti:

→***Furosemid:*** cpr 40mg; fiole 20mg

-efect in 3-15 minute dupa inj iv, max in 15-30 min, durata 2-5 ore

-oral: efect in 20-60 minute, max 2-3 ore, durata 4-6 ore, maximum 240mg/zi

Indicatii: ca diuretic, in toate tipurile de edeme, inclusiv in urgente-edem cerebral, edem pulmonar acut

-insuf. renala acuta cu oligurie

-ca antihipertensiv, inclusive in crize

DIURETICE DE ANSA

Reprezentanti:

→***Acid etacrinc*** 50-200mg/zi, risc> ototoxicitate; diuretic de rezerva, in edemele severe, refractare la alte diuretice.

→***Bumetanid*** 0.5-2mg/zi

→***Torasemid*** 5-20mg/zi

II.DIURETICE TIAZIDE

-blocheaza reabsorbtia de Na la nivelul TCD, prin blocarea transportorului Na/Cl

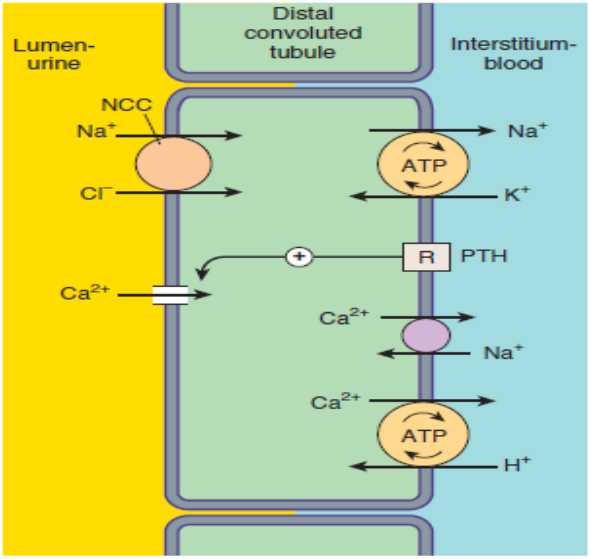


FIGURE 15–4 Ion transport pathways across the luminal and basolateral membranes of the distal convoluted tubule cell. As in all tubular cells, Na^+/K^+ ATPase is present in the basolateral membrane. NCC is the primary sodium and chloride transporter in the luminal membrane. (R, parathyroid hormone [PTH] receptor.)

-spre deosebire de diureticele de ansa, ↑ reabsorbtia de Ca: la nivelul TCP, secundar depletiei volemice, produc reabs. activa de Na si pasiva de Ca, iar la nivelul TCD➔schimb Na/Ca

➔↑calcemiei este rar semnificativa clinic, dar poate evidentia hipercalcemia secundara altor afectiuni (hiperparatiroidism, tumori maligne, sarcoidoza)

DIURETICE TIAZIDE

Reprezentanti:

→potenta mare (eficace in doza de 0.25-15mg/zi)**: indapamida,** ciclotiazida, politiazida, ciclopentiazida, meticlotazida

→potenta medie (eficace in doza de 25-50mg/zi): clopamid, clorotiazida (singurul care se poate administra si injectabil!), **hidroclorotiazida**

→potenta redusa (eficace in doze de 50-100mg/zi): clortalidona

DIURETICE TIAZIDE

-

TABLE 15–5 Thiazides and related diuretics.

Drug	Total Daily Oral Dose	Frequency of Daily Administration
Bendroflumethiazide	2.5–10 mg	Single dose
Chlorothiazide	0.5–2 g	Two divided doses
Chlorthalidone[1]	25–50 mg	Single dose
Hydrochlorothiazide	25–100 mg	Single dose
Hydroflumethiazide	12.5–50 mg	Two divided doses
Indapamide[1]	2.5–10 mg	Single dose
Methyclothiazide	2.5–10 mg	Single dose
Metolazone[1]	2.5–10 mg	Single dose
Polythiazide	1–4 mg	Single dose
Quinethazone[1]	25–100 mg	Single dose
Trichlormethiazide	1–4 mg	Single dose

[1]Not a thiazide but a sulfonamide qualitatively similar to the thiazides.

DIURETICE-TIAZIDE

HIDROCLOROTIAZIDA

-po abs.rapida si completa;

-legare 85% de prot.plasmatice

-elim. renala, nemetabolizata, prin filtrare glomerulara si secretie tubulara.

-latenta 1-1.5 ore, durata 8-12 ore

DIURETICE-TIAZIDE

HIDROCLOROTIAZIDA

Efecte adverse:

- dezechilibre hidro-electrolitice si acido-bazice (↓k, alcaloza hipercloremica),
- dezechilibre metabolice (hiperglicemie, hiperlipemie, hiperuricemie, hipocalciurie, hiperazotemie)
- leucopenie, agranulocitoza, trombocitopenie
- reactii alergice cutanate (eruptii, fotosensibilizare)

DIURETICE-TIAZIDE

HIDROCLOROTIAZIDA

Indicatii:

→toate tipurile de edeme+/alte diuretice

→HTA

→hipercalciurie idiopatica (pentru prevenirea litiazei), litiaza urinara oxalica (ca tratament adjuvant)

***Administrare*:** 50-100mg/zi initial apoi 25mgx2-3/zi

DIURETICE-TIAZIDE

INDAPAMID

-profil similar cu hidroclorotiazida, cu anumite particularitati si avantaje:

Avantaje:

- durata lunga (24-36 h),
- ! act.vasodilatatoare, cu reducerea rezistentei vasculare arteriolare si vasculare totale→potenteaza efectul antihipertensiv si grabeste aparitia aparitiei efectului maxim
- absenta reactiilor adverse asupra metabolismului glucidic si lipidic

DIURETICE-TIAZIDE

INDAPAMID

EA:hTA , hipopotasemie

CI: AVC recente (datorita actiunii vasodilatatoare), hipopotasemie refractara, sarcina, alaptare; precautie in guta.

-cpr 1.5mg, 1cpr/zi

DIURETICE-TIAZIDE

CLORTALIDONA

-profil simiar cu hidroclorotiazida

-durata lunga 24-48h

-latenta instalarii efectului aprox. 2h

Indicatii si doze:

HTA: 50-100mg/zi

Diuretic: initial 50-200mg priza unica, ulterior doze ajustabile

Diabet insipid: initial 200mgx2/zi, intretinere 50mg/zi

DIURETICE-TIAZIDE

CLORTIAZIDA

-flacon inj. 500mg

-cpr 250mg/500mg

-conc. plasmatica maxima injectabil 30min; po 4h

Indicatii: HTA, edeme-insuf. cardiaca, ciroza, insuf. renala…

DIURETICE-TIAZIDE

XIPAMIDA

-similar cu hidroclorotiazida, cu anumite particularitati

***Mecanism de actiune**:*

- *Inhiba reabsorbtia de Na si Cl la nivelul TCD-similar cu hidroclorotiazida*
- *Stimuleaza secretia de K la nivelul TCD si tubului colector→hiperK-similar cu hidroclortiazida*
- *La doze mari intervine si la nivelul TCP, prin inhibarea anhidrazei carbonice, si creste eliminarea urinara de bicarbonat de sodiu, cu alcalinizarea urinei.*

DIURETICE-TIAZIDE

XIPAMIDA

Administrare:

- *Ca diuretic, in edeme, 40-80mg/zi, cu posibilitatea reducerii dozei*
- *In HTA 20mg/zi, priza unica*

***Reactii adverse**:*

- *hipopotasemie (modif.EKG, aritmii, greata, voma),*
- *hipoNa-emie,*
- *hipoMg-emie,*
- *alcaloza hipocloremica,*
- *hTA-in special in asociere cu alte antihipertensive.*

III.DIURETICE-CARE ECONOMISESC POTASIU (ANTIALDOSTERONICE)

-actioneaza la nivelul portiunii finale a TCD si tubului colector

Clasificare:

❖**anatgonisti competitivi**

(antialdosteronice)

spironolactona

❖**pseudoantialdosteronice**

amilorid, triamteren

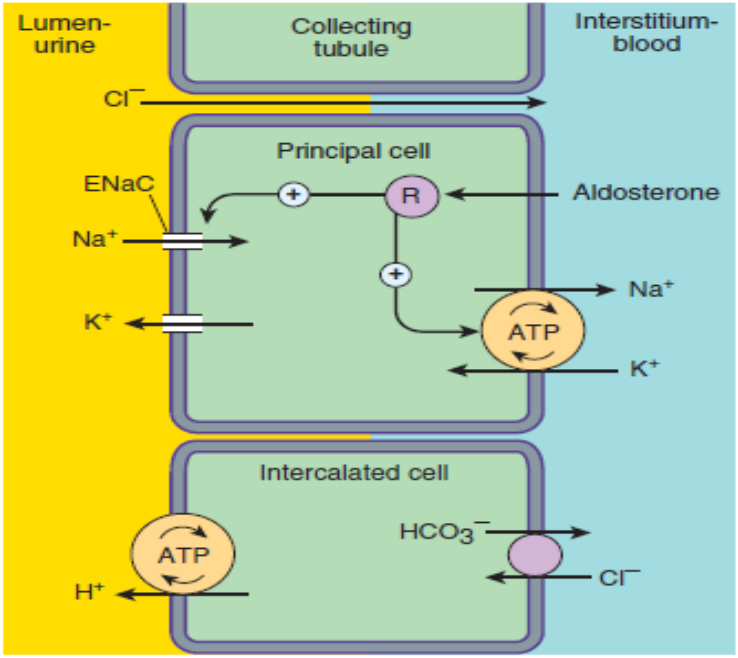


FIGURE 15–5 Ion transport pathways across the luminal and basolateral membranes of collecting tubule and collecting duct cells. Inward diffusion of Na^+ via the epithelial sodium channel (ENaC) leaves a lumen-negative potential, which drives reabsorption of Cl^- and efflux of K^+. (R, aldosterone receptor.)

III.DIURETICE-CARE ECONOMISESC POTASIU (ANTIALDOSTERONICE)

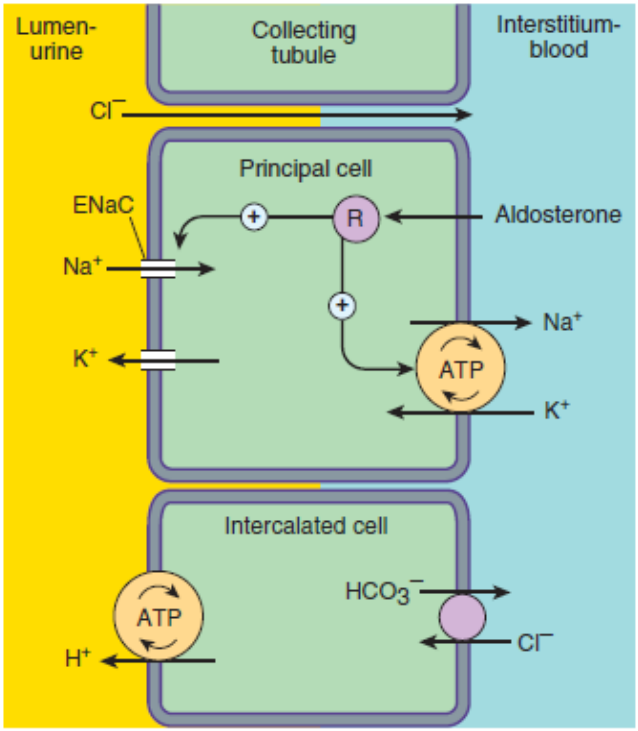
III.I ANTIALDOSTERONICE

-Aldosteronul, la nivelul TCD, stimuleaza reabsorbtia de Na si, automat, excretia de K si protoni

-stimuleaza direct pompa de protoni

→diureticele antialdosteronice→blocheaza fixarea aldosteronului pe rr→ ↓absorbtia de Na si secretia de K, H→se elimina Na, Cl si un echivalent osmotic de apa

-urina devine alcalina (se elimina bicarbonat)



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DIURETICE-CARE ECONOMISESC POTASIU (ANTIALDOSTERONICE)

I. Antialdosteronice

→Spironolactona

-absorbtie orala buna, metabolizare hepatica, eliminare renala

-T1/2 lung, aproximativ 14 ore

Farmacodinamica: latenta>24h, efect maxim 2-3 zile, durata 2-3 zile de la intreruperea tratamentului

EA:

- ↑K,
- eruptii cutanate,
- hiperandrogenism-→ hirsutism la femei, ginecomastie, uneori dureroasa, la barbati

DIURETICE-CARE ECONOMISESC POTASIU (ANTIALDOSTERONICE)

I. Antialdosteronice

→Spironolactona

Indicatii:

- edeme cu hiperaldosteronism primar sau secundar (ICC, ciroza hepatica),
- ↓k,
- insuficienta hepatica
- HTA

Administrare: ca diuretic 25-50mgx4/zi (in retentie hidrosalina cu hiperaldosteronism), HTA 50-100/zi

Contraindicatii: hiperpotasemie, IR acuta, insuficienta hepatica grava;

! Scade efectul digitalicelor prin hiperpotasemie

DIURETICE-CARE ECONOMISESC POTASIU (ANTIALDOSTERONICE)

I. Antialdosteronice

→Eplerenona (Inspra)

-mai selectiva comparativ cu Spironolactona, in ceea ce priveste actvitatea mineralcorticoida, cu risc<<<<<<< ef. hormonale

-Cpr 25/50mg

-tp. de 1/2: 3.5-6h, max. 1-2h

DIURETICE-CARE ECONOMISESC POTASIU (ANTIALDOSTERONICE)

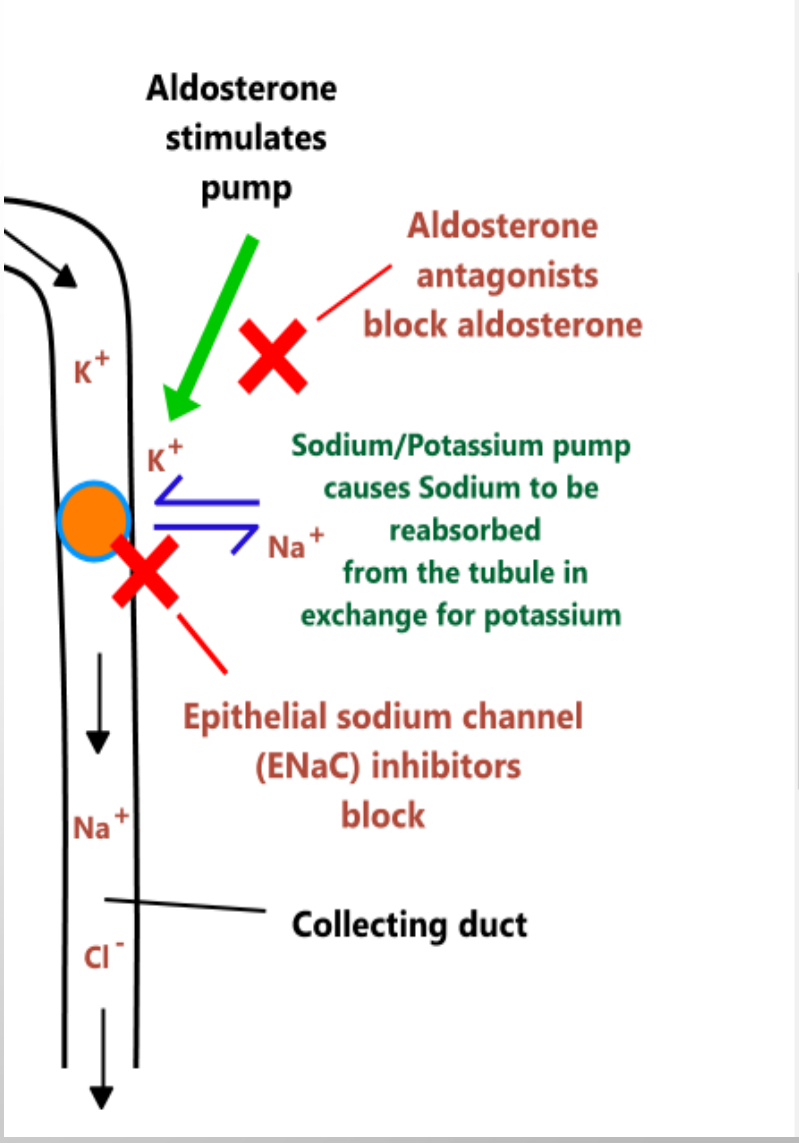
III.II.**PSEUDOANTIALDOSTERONICE**

→***Triamteren***

-antagonism de efect, avand efect contrar aldosteronului la nivelul TCD

-inhiba schimbul Na/K prin blocarea canalelor de Na la nivelul membranei apicale a portiunii finale a TCD si tubului colector→ blocheaza reasorbtia Na, K nu se mai excreta,

creste eliminarea de NAHCO3



DIURETICE-CARE ECONOMISESC POTASIU (ANTIALDOSTERONICE)

III.II.**PSEUDOANTIALDOSTERONICE**

→*Triamteren*

--durata medie de actiune (7-10h), latenta 2 ore, efect maxim la 2-3 zile de tratament

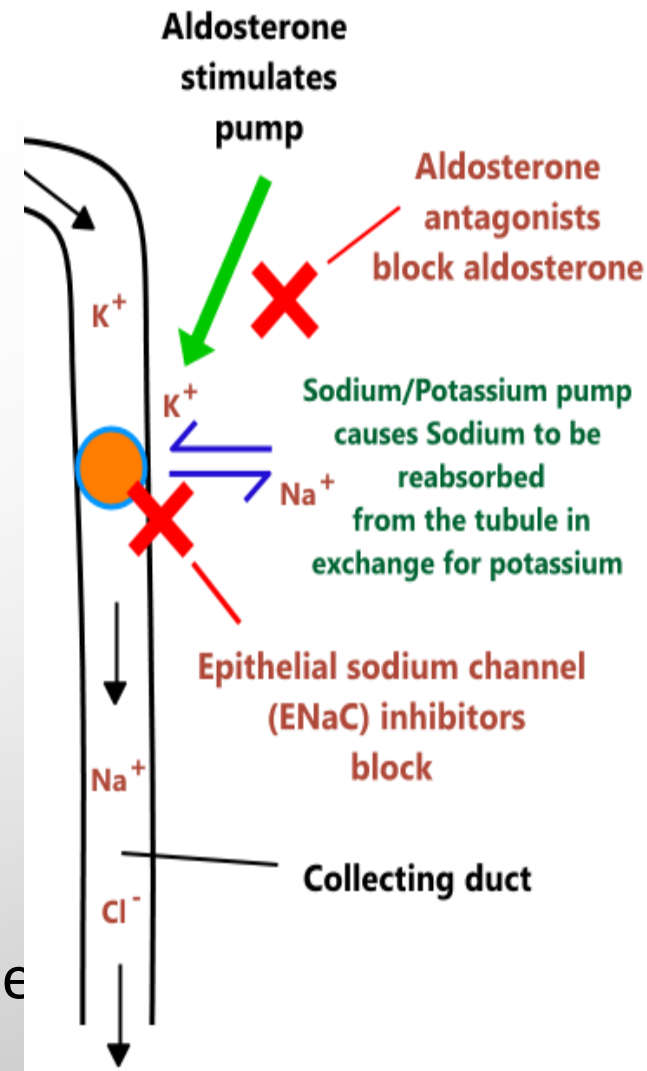
-administrare: initial 100mgx3/zi, maxim 600mg/zi; intretinere 100mgx2/zi

→*Amilorid*

-similar cu triamteren

-tp. de ½ lung, de aproximativ 21 de ore, durata de actiune lunga, de aprox.24h, late aproximativ 2 h.

-15-20mg/zi



IV.DIURETICE OSMOTICE

-TCP si ramura descendenta a ansei Henle sunt permeabile pentru apa

-orice agent osmotic care este filtrat glomerular, dar nu este absorbabil, determina cresterea presiunii osmotice a urinei tubulare, retentia unui echivalent osmotic de H_2O si eliminarea acesteia-diureza apoasa, cu o concentratie redusa de Na

-prototip: **manitol**

→adm. po→diaree

→inj.iv→nu se metabolizeaza→eliminare renala in 30-60minute

IV.DIURETICE OSMOTICE

INDICATII:

- profilaxia anuriei la pacientii cu soc, arsuri
-↓ presiunii intraoculare in glaucomul acut congestiv, ↓presiunii intracraniene la pacientii cu edem cerebral, -
- edeme
-iv lent sau perfuzabil, 1-1.5g/kgc/zi (flacon 200mg/ml, 100ml-20g)

DIURETICE OSMOTICE

REACTII ADVERSE:

-expansiunea volumului extracelular si hiponatremie de dilutie→agraveaza insuf.cardiaca si poate precipita aparitia unui edem pulmonar acut cardiogen

-cefalee, greata, varsaturi

V. DIURETICE INHIBITOARE ALE ANHIDRAZEI CARBONICE

Anhidraza carbonica =enzima ce exista in toate tesuturile, dar concentrata in hematii, tubi renali, mucoasa gastrica, pancreas, SNC, globi oculari

-catalizeaza formarea acidului carbonic (din CO2 si H2O), care disociaza in H+ si HCO3

Anhidraza carbonica intervine in:

→ secretia de H+ in tubii renali proximali, cu reabsorbtia prin schimb a Na (NaHCO3)

→ secretia de H+ de catre celulele parietale gastrice si formarea de HCl

→ scretia alcalina a pancreasului exocrin

→ secretia umorii apoase ocular

→ sedare

DIURETICE INHIBITOARE ALE ANHIDRAZEI CARBONICE

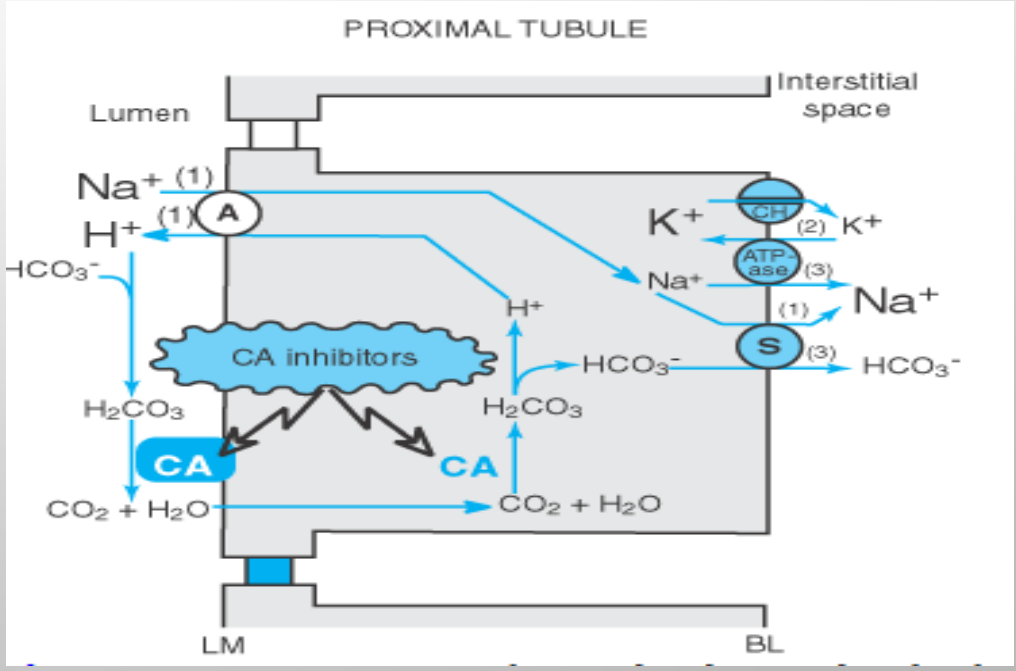
***ACETAZOLAMIDA-ACT.DIURETICA:**

-bloc.formarea de H+, cu diminuarea secretiei de H si reabsorbtiei de schimb a ionului de Na

=>excretie crescuta de Na (NaHCO3), cu un echivalent osmotic de apa (urina alcalina)

-se elimina HCO3, sub forma de KHCO3➔↓K

-acidoza hipocloremica



DIURETICE INHIBITOARE ALE ANHIDRAZEI CARBONICE

***ACETAZOLAMIDA**

EA:

-numeroase tulburari hidro-electrolitice si acio-bazice

-cristalurie, litiaza renala, hiperglicemie, hiperuricemie

-leucopenie, trombocitopenie

-greata, voma, dureri abdominale

somnolenta

DIURETICE INHIBITOARE ALE ANHIDRAZEI CARBONICE

ACETAZOLAMIDA

INDICATII:

-diuretic, in edeme

-antisecretor gastric, in ulcer gastric si duodenal

-glaucom, forme rezistente la tratamentul local si preoperator

-epilepsie, adjuvant

-comprimate 250mg, 250-1000mg/zi