DIURETICS

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Diuretic Action

- Diuretics are drugs that increase the rate of urine flow; however, clinically useful diuretics also increase the rate of excretion of Na^+ (natriuresis) and of an accompanying anion, usually Cl^-.
- NaCl is the major determinant of extracellular fluid volume.

Na^+ Balance

- A sustained imbalance between dietary Na^+ intake and Na^+ loss is incompatible with life.
- Although continued administration of a diuretic causes a sustained net deficit in total-body Na^+, the time course of natriuresis is finite as renal compensatory mechanisms bring Na^+ excretion in line with Na^+ intake (“diuretic braking”).
- These compensatory mechanisms include sympathetic activation, renin-angiotensin-aldosterone axis activation, decreased arterial blood pressure, hypertrophy of renal epithelial cells, increased expression of transporters, etc.

Major Indications for Use

- Systemic edematous diseases
  - Congestive heart failure
  - Liver cirrhosis
  - Nephrotic syndrome
- Hypertension
- Electrolyte disturbances: hyperkalemia, hyponatremia.
- Etc…

Strategies For Correcting Edema

- Correct the underlying disease
  - This is the most desirable course of action; however, this is often impossible.
- Restrict Na^+ intake
  - This is a favored nonpharmacological approach for the treatment of edema and hypertension; however, compliance is a major obstacle.
- Diuretics
  - The cornerstone for the treatment of edema or volume overload.

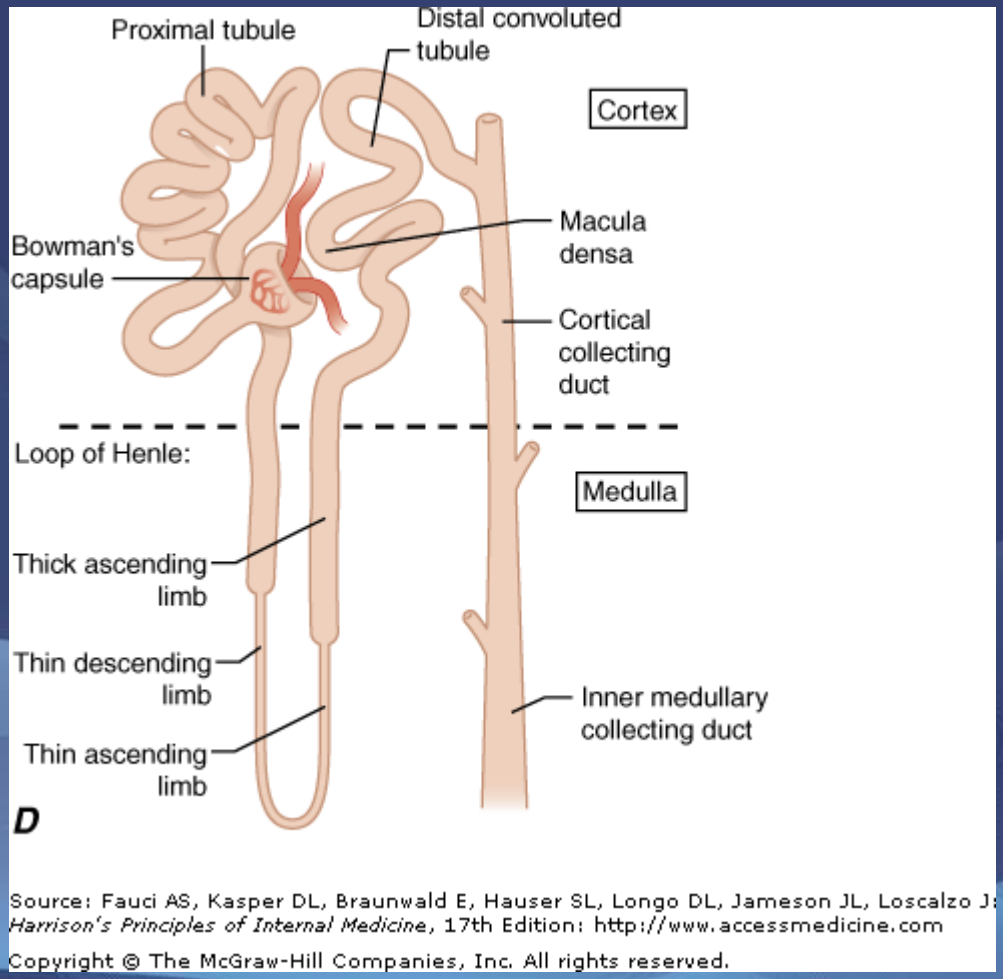
Therapeutic Regimens

- Intravenous
  - e.g. rapid IV administration of a loop diuretic for massive pulmonary edema in CHF patients.
- Oral
  - e.g. mild pulmonary and venous congestion associated with CHF.
  - Edema is not an immediate health risk.
  - Dosage should be titrated carefully to maximize benefit-to-risk ratio.

Classifications

- Site of action (e.g. *loop* diuretics)
- Efficacy (e.g. *high-ceiling* diuretics)
- Chemical structure
- Similarity of action (e.g. *thiazide-like* diuretics)
- Effects on potassium excretion (e.g. potassium-sparing diuretics)
- etc…

Parts of The Nephron

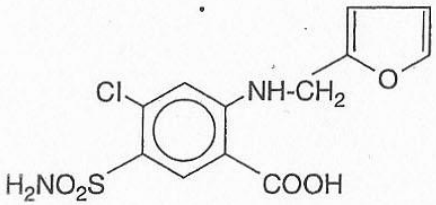
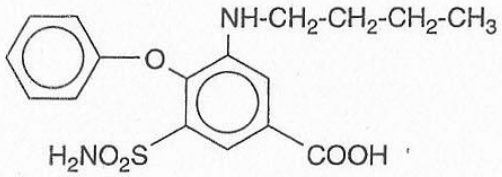
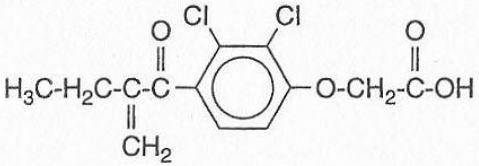
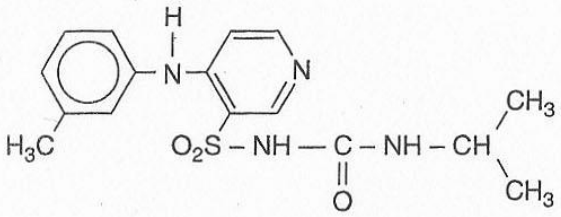


Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine*, 17th Edition: http://www.accessmedicine.com

Loop Diuretics

Loop Diuretics

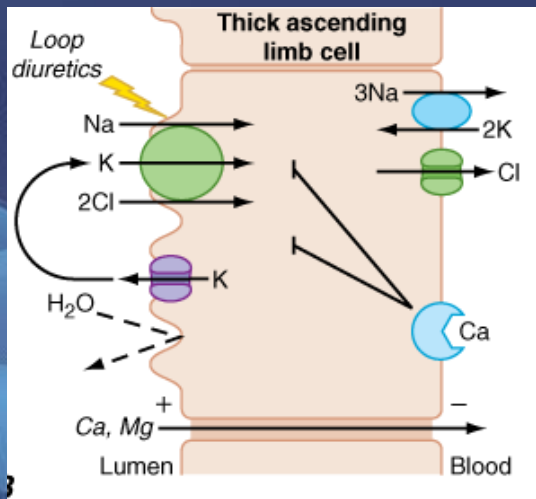
Table 29–4
Inhibitors of Na^+–K^+–$2Cl^-$ Symport (Loop Diuretics; High-Ceiling Diuretics)

DRUG	STRUCTURE	RELATIVE POTENCY	ORAL AVAILABILITY	$t_{1/2}$ (HOURS)	ROUTE OF ELIMINATION
Furosemide		1	~60%	~1.5	~65% R, ~35% M
Bumetanide		40	~80%	~0.8	~62% R, ~38% M
Ethacrynic acid		0.7	~100%	~1	~67% R, ~33% M
Torsemide		3	~80%	~3.5	~20% R, ~80% M

R= Renal excretion of intact drug, M= Metabolism

Loop Diuretics - Mechanism

- Inhibitors of Na-K-2Cl symporter in the thick ascending limb of the loop of Henle.
- Also known as “high-ceiling diuretics” for their high efficacy.
- Although the proximal tubule reabsorbs approx. 65% of filtered Na^+, diuretics acting only in the proximal tubule have limited efficacy because the thick ascending limb has a great reabsorptive capacity.
- Most loop diuretics are extensively bound to plasma proteins, so delivery of these drugs to the tubules by filtration is limited. However, they are efficiently secreted by the organic acid transport system in the proximal tubule, thereby gaining access to their binding site in TAL.



Effects on Urinary Excretion

- Due to the blockade of the Na-K-2Cl symporter, loop diuretics cause a **profound increase in the urinary excretion of NaCl.**
- All loop diuretics **increase the urinary excretion of K^+.**
- Abolition of the transepithelial potential difference also results in **marked increases in the excretion of Ca^{2+} and Mg^{2+}.**
- Some sulfonamide based loop diuretics (e.g. furosemide) have weak carbonic-anhydrase inihibiting activity, thus **increasing the urinary excretion of HCO_3^- and phosphate**.
- Inhibitors of Na-K-2Cl interfere with a critical step in the mechanism that produces a hypertonic medullary interstitium, thereby **blocking the ability to concentrate urine**. Also, since the TAL is part of the diluting segment, loop diuretics **impair the kidney's ability to excrete a dilute urine during water diuresis.**

Effects on Renal Hemodynamics

- Inhibitors of Na-K-2Cl symport generally increase total RBF. Mechanism is unknown, but prostaglandins have been implicated.
- NSAIDs attenuate the diuretic response to loop diuretics, most likely by preventing prostaglandin mediated increases in RBF.
- Loop diuretics are powerful stimulators of renin release. This effect is due to interference with NaCl transport by the macula densa.

Other Actions

- Loop diuretics, particularly furosemide, may cause *direct vascular effects*: an increase in systemic venous capacitance, thereby decreasing left ventricular filling pressure.
- This effect, which may be mediated by prostaglandins, requires intact kidneys.
- Benefits patients with pulmonary edema even before diuresis ensues.

Therapeutic Uses

- **Pulmonary edema**. A rapid increase in venous capacitance in conjunction with a brisk natriuresis reduces LV filling pressure.
- **Congestive heart failure.** When diminution of extracellular fluid volume is desirable.
- **Hypertension**. Clinical trials demonstrating reduced morbidity and mortality have been conducted with thiazides but not loop diuretics. Nonetheless, loop diuretics appear to lower blood pressure as effectively as thiazides while causing smaller perturbations in the lipid profile (van der Heijden et al., 1998).
- **Edema of nephrotic symdrome**. This kind of edema is often refractory to other classes of diuretics.
- **Edema and ascites of liver cirrhosis**. Care must be taken not to induce encephalopathy or hepatorenal syndrome.
- **Forced diuresis** combined with isotonic saline administration to facilitate renal elimination of drug overdose or to treat hypercalcemia.
- **Treatment of hyponatremia**. Loop diuretics interfere with the kidney's ability to produce a concentrated urine.

Adverse Effects

- Most adverse effects are related to abnormalities of fluid and electrolyte balance caused by the diuretic effect.
- Overuse can cause serious **depletion of total body Na^+.** This may manifest as hyponatremia and/or extracellular fluid volume depletion (hypotension, reduced GFR, thromboembolic episodes, hepatic encephalopathy).
- Increased delivery of Na^+ to the distal tubule, particularly when combined with activation of the renin-angiotensin system, leads to **increased urinary excretion of K^+ and H^+**, causing hypochloremic alkalosis. Hypokalemia may develop, as well as hypocalcemia and hypomagnesemia (a risk factor for cardiac arrhythmias).
- Loop diuretics can cause **ototoxicity** that manifests as tinnitus, hearing impairment or deafness (usually reversible), vertigo and a sense of fullness in the ears.
- Loop diuretics also can cause **hyperuricemia**, **hyperglycemia**, and can **increase LDL cholesterol**.
- Other: skin rash, photosensitivity, paresthesias, bone marrow depression, GI disturbances.

Diuretic Resistance

- Refers to edema that is or has become refractory to a given diuretic.
- If diuretic resistance develops against a less efficacious diuretic, a more efficacious diuretic should be substituted.
- Resistance to loop diuretics is not uncommon and can be due to several causes:
  - NSAIDs usage: blocks prostaglandin mediated increases in RBF.
  - Chronic renal failure: a reduction of RBF decreases the delivery of diuretics to the kidney, also competition with endogenous organic acids transport in proximal tubule.
  - Nephrotic syndrome: urinary protein binds diuretics.
  - CHF or cirrhosis: increased proximal tubule Na^+ reabsorption, leading to diminished delivery of Na^+ to the distal nephron.

Dealing with Resistance to Loop Diuretics

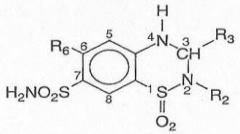
- Bed rest may improve renal circulation.
- An increase in the dose of loop diuretic may restore responsiveness.
- Administration of smaller doses more frequently or a continuous IV infusion of a loop diuretic.
- Use of combination therapy to sequentially block more than one site in the nephron may result in a synergistic interaction.
- Scheduling of diuretic administration shortly before food intake (when salt load is highest).

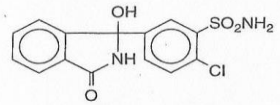
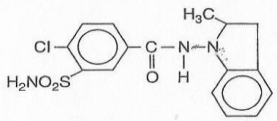
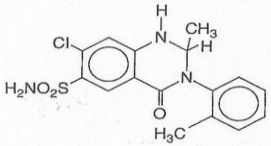
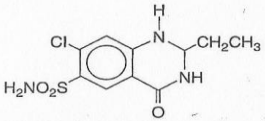
Inhibitors of Na-Cl Symport

(Thiazide and thiazide-like diuretics)

Thiazide Diuretics

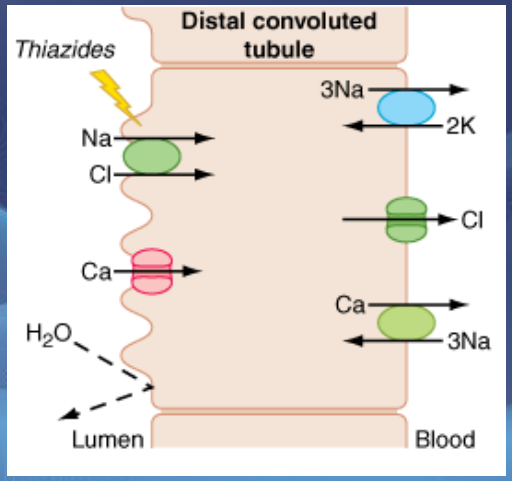
Table 29–5
Inhibitors of Na^+–K^+Symport (Thiazide and Thiazide-like Diuretics)



DRUG	STRUCTURE	RELATIVE POTENCY	ORAL AVAILABILITY	$t_{1/2}$ (HOURS)	ROUTE OF ELIMINATION
Bendroflumethiazide (NATURETIN)	R_2 = H, R_3 = CH_2–  , R_6 = CF_3	10	~100%	3–3.9	~30% R, ~70% M
Chlorothiazide (DIURIL)	R_2 = H, R_3 = H, R_6 = Cl (Unsaturated between C3 and N4)	0.1	9–56% (dose-dependent)	~1.5	R
Hydrochlorothiazide (HYDRODIURIL)	R_2 = H, R_3 = H, R_6 = Cl	1	~70%	~2.5	R
Hydroflumethiazide (SALURON)	R_2 = H, R_3 = H, R_6 = CF_3	1	~50%	~17	40–80% R, 20–60% M
Methyclothiazide (ENDURON)	R_2 = CH_3, R_3 = CH_2Cl, R_6 = Cl	10	ID	ID	M
Polythiazide (RENESE)	R_2 = CH_3, R_3 = $CH_2SCH_2CF_3$, R_6 = Cl	25	~100%	~25	~25% R, ~75% U
Trichlormethiazide	R_2 = H, R_3 = $CHCl_2$, R_6 = Cl	25	ID	2.3–7.3	R
Chlorthalidone (HYGROTON)		1	~65%	~47	~65% R, ~10% B, ~25% U
Indapamide (LOZOL)		20	~93%	~14	M
Metolazone (MYKROX, ZAROXOLYN)		10	~65%	ID	~80% R, ~10% B, ~10% M
Quinethazone (HYDROMOX)		1	ID	ID	ID

Thiazide Diuretics - Mechanism

- Thiazides inhibit the Na-Cl symporter in distal convoluted tubule (DCT).
- This class of drugs has a wide range of half-lives.
- Plasma protein binding varies considerably among thiazide diuretics. This parameter determines the contribution that filtration makes to tubular delivery of the drug.
- Thiazides are organic acids and are secreted into the proximal tubule by the organic acid secretory pathway.



Effects on Urinary Excretion

- Thiazides **increase Na^+ and Cl^- excretion**. However, they are **only moderately efficacious** (max excretion of filtered load of Na^+ is only 5%) since 90% of the filtered Na^+ load is reabsorbed before reaching the DCT.
- Like loop diuretics, thiazides **increase the excretion of K^+** due to increased delivery of Na^+ to the distal tubule.
- Some thiazide diuretics also are weak inhibitors of carbonic-anhydrase, an effect that **increases HCO_3^- and phosphate excretion**.
- The acute effects of thiazides on Ca^{2+} excretion are variable; **when administered chronically, thiazide diuretics decrease Ca^{2+} excretion**. Mechanism is unknown but may involve increased proximal reabsorption due to volume depletion as well as direct effects on DCT.

Therapeutic Uses

- **Hypertension**. Thiazides are often used as first-line agents, alone or in combination with other antihypertensive drugs. They are inexpensive, as efficacious as other classes of antihypertensive agents, and well tolerated. In addition, they have synergistic effects when combined with other antihypertensive agents.
- **Edema associated with CHF, cirrhosis, and renal disease** (nephrotic syndrome, CRF, acute glomerulonephritis). With the exception of metolazone and indapamide, most thiazide diuretics are ineffective when GFR is <30 to 40 ml/min.
- Thiazides reduce urinary excretion of Ca^{2+},and are sometimes employed to treat **calcium nephrolithiasis** and may be useful for osteoporosis.
- Thiazides are also used for treatment of **nephrogenic diabetes insipidus**, reducing urine output by inducing a state of mild volume contraction, thereby promoting increased PT reabsorption.

Adverse Effects

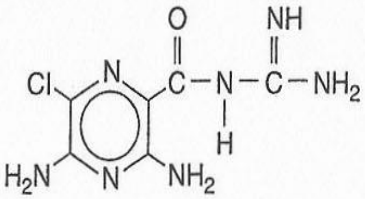
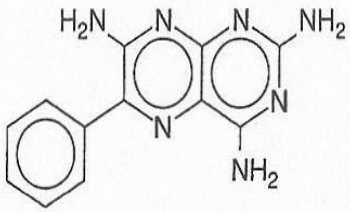
- Like loop diuretics, most adverse effects are related to **abnormalities of fluid and electrolyte balance** (volume depletion, hypotension, hypokalemia, hyponatremia, metabolic alkalosis, hypercalcemia).
- **Decreased glucose tolerance**. Latent diabetes mellitus may be unmasked during thiazide therapy.
- **Sexual dysfunction**.
- Thiazide diuretics may also **increase plasma levels of LDL cholesterol and triglycerides**.
- Rare: CNS, GI, hematological, and dermatological disorders.

Inhibitors of Renal Epithelial Na^+ Channels

(K^+-sparing diuretics)

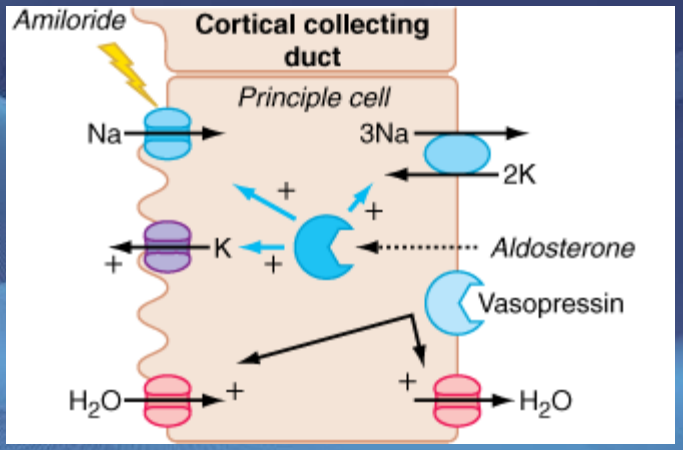
Inhibitors of Renal Epithelial Na^+ Channels

Table 29–6
Inhibitors of Renal Epithelial Na^+ Channels (K^+-Sparing Diuretics)

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

Mechanism - Amiloride

- Amiloride inhibits Na^+ channel in principle cells of cortical collecting duct (CCD), causing a small increase in NaCl excretion. This channel also provides a transmembrane potential for the secretion of K^+ ions into the lumen, thereby in the presence of amiloride K^+ secretion is decreased.
- Amiloride is eliminated predominantly by urinary excretion of intact drug.



Effects on Urinary Excretion

- Since the late distal tubule and CCD have a limited capacity to reabsorb solutes, blockade of Na^+ channels in this part of the nephron results in only a mild increase in NaCl excretion (~2% of filtered load).
- Attenuation of the lumen-negative voltage decreases the excretion rates of K^+, H^+, Ca^{2+}, and Mg^{2+}.

Therapeutic Uses

- Because of the mild natriuresis effect, these drugs are seldom used as sole agents in the treatment of edema or hypertension.
- Coadministration of Na^+-channel inhibitor augments the diuretic and antihypertensive response to thiazide or loop diuretics.
- Can be used to **reduce K+ excretion to offset the kaliuretic effects of thiazide and loop diuretics**.

Adverse Effects

- **Hyperkalemia**. Can be life-threatening. Contraindicated in patients with renal failure, patients taking ACEI, or K^+ supplements.
- Amiloride can cause nausea, vomiting, diarrhea, and headache.

Aldosterone Receptor Blockers

Spironolactone

Spironolactone

- Aldosterone causes retention of salt and water and increases the excretion of K^+ and H^+.
- Effect of spironolactone is similar to Na^+-channel inhibitors (amiloride); however, the clinical efficacy is a function of endogenous levels of aldosterone (the higher the levels of aldosterone → the greater the effects of spironolactone).
- Major side effect is hyperkalemia. Spironolactone can also induce metabolic acidosis in cirrhotic patients.
- Due to its steroid structure, spironolactone may cause gynecomastia, impotence, decreased libido, hirsutism, deepening of the voice, and menstrual irregularities.

Therapeutic Uses - Spironolactone

- Coadministered with thiazide or loop diuretics in the treatment of edema and hypertension. Such combinations result in increased mobilization of edema fluid while causing lesser perturbations of K^+ homeostasis.
- Spironolactone is particularly useful in the treatment of primary hyperaldosteronism and of refractory edema associated with secondary aldosteronism (CHF, hepatic cirrhosis, nephrotic syndrome, severe ascites, etc.).
- Diuretic of choice in patients with hepatic cirrhosis.