Pharmacology and Clinical Use of Diuretics

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Katie Herndon is not speaking on behalf of Pfizer, but solely as a medical professional with an expertise in pharmacotherapy.

Objectives

- Review the mechanism of action, pharmacokinetics, and pharmacodynamics of diuretics
- Contrast the pharmacology of different classes of diuretic agents
- Discuss the clinical use of diuretics

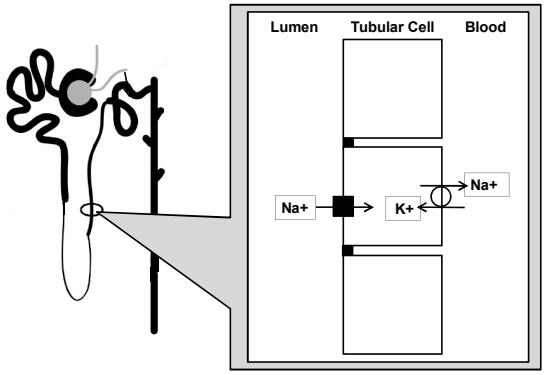
Diuretic Classes

- Thiazide Diuretics
  - Hydrochlorothiazide
  - Chlorothiazide
  - Methyclothiazide
  - Polythiazide
  - Bendroflumethiazide
- Thiazide-Like Diuretics
  - Chlorthalidone
  - Metolazone
  - Indapamide
- Loop Diuretics
  - Bumetanide
  - Ethacrynic acid
  - Furosemide
  - Torsemide

Diuretic Classes

- Potassium-Sparing Diuretics
  - Amiloride
  - Triamterene
- Aldosterone Antagonists
  - Spironolactone
  - Eplerenone
- Carbonic Anhydrase Inhibitors
  - Acetazolamide

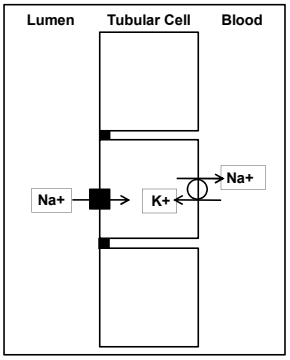
Sodium Reabsorption in the Renal Tubule



Dis Mon 1998;44:254-268

Sodium Reabsorption in the Renal Tubule

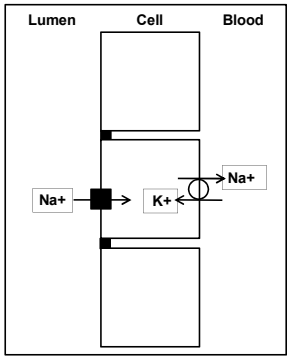
- Na^+ is reabsorbed by a two-step process:
  1. Na^+ entrance into the cell via a Na+ transporter present in the luminal cell membrane
  2. Once Na^+ enters the tubular cell, it is transferred across the basolateral membrane into the interstitium and blood by the Na^+-K^+-ATPase pump
- Cell interior is electrically negative in relation to the extracellular fluid



Dis Mon 1998;44:254-268
Expert Opin Drug Saf 2010;9:243-257

Sodium Reabsorption in the Renal Tubule

- The electrochemical gradient is the force driving positively charged Na^+ ions across the luminal membrane into the cell
- Na^+ movement is facilitated by transporters on the luminal side of the tubular epithelial cell
- Transporter pathways differ between various segments of the nephron



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Principles of Diuretic Action

- Diuretics act by inhibiting sodium reabsorption in the renal tubules, thereby increasing urinary sodium, and consequently, water loss
- Agents differ with respect to the specific tubular ion transport systems they inhibit
  - Site of action within the nephron
  - Natriuretic efficacy
  - Pharmacological effects
  - Clinical indications

Expert Opin Drug Saf 2010;9:243-257

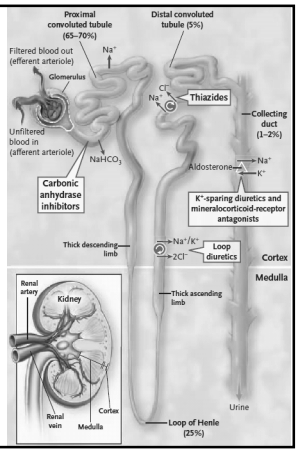
Principles of Diuretic Action

- Site of action is located on the luminal surface of the tubule
- Extensively bound to serum albumin
- Transported into the proximal tubule lumen by active secretion
  - Organic acid secretory pathway: thiazides, loop diuretics, acetazolamide
  - Organic base secretory pathway: potassium-sparing diuretics
  - Exception: spironolactone and eplerenone enter renal tubules from plasma

Expert Opin Drug Saf 2010;9:243-257

Sites of Diuretic Action in the Nephron

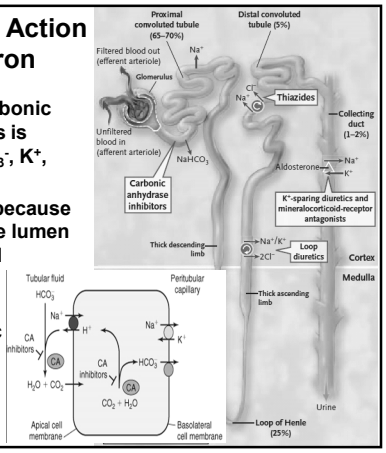
- Under physiological conditions of Na^+ intake, FE_{Na} remains under 1%
- After formation of a plasma ultrafiltrate in the glomerulus, the tubular fluid enters the proximal convoluted tubule
- 65-70% of filtered Na^+ is reabsorbed in the proximal tubule



NEJM 2009;361:2153-64
Expert Opin Drug Saf 2010;9:243-257

Sites of Diuretic Action in the Nephron

- The net effect of carbonic anhydrase inhibitors is increased Na^+, HCO_3^-, K^+, and water loss
- Diuresis is modest because Na+ remaining in the lumen is absorbed at distal segments
- Alkaline diuresis leading to metabolic acidosis



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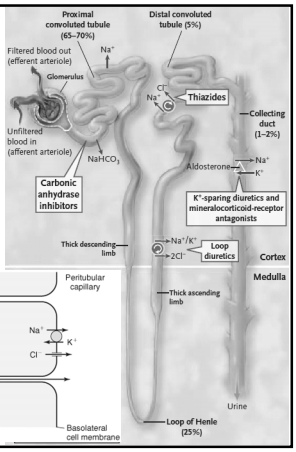
Sites of Diuretic Action in the Nephron

- Loop diuretics act at the thick ascending limb of the loop of Henle where ~ 25% of filtered Na^+ is reabsorbed
- Loop diuretics bind to the Na^+-K^+-2Cl^- co-transport protein, impairing the reabsorption of Na^+, K^+, and Cl^-



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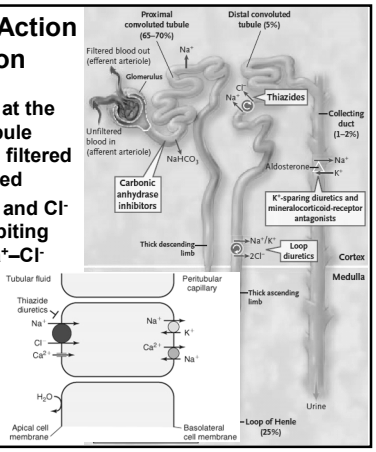
Wile D. Diuretics: a review [published online ahead of print July 10, 2012]. Ann Clin Biochem. doi: 10.1258/acb.2011.011281.

Sites of Diuretic Action in the Nephron

- Thiazides act mainly at the distal convoluted tubule where ~ 5-10% of the filtered Na+ load is reabsorbed
- Thiazides inhibit Na^+ and Cl^- reabsorption by inhibiting the electroneutral Na^+–Cl^- symport



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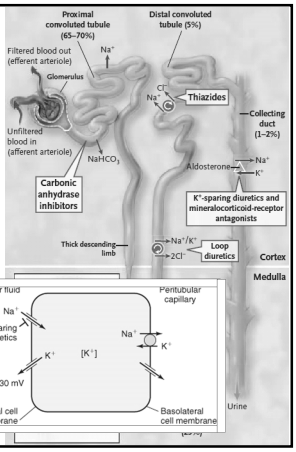
Sites of Diuretic Action in the Nephron

- K^+-sparing diuretics (amiloride and triamterene) act primarily at the cortical part of the collecting duct where only ~2% of Na^+ is reabsorbed
- Na^+ movement creates an electrical gradient that drives K^+ from the epithelial cell to the lumen
- K^+-sparing diuretics inhibit the epithelial Na^+ channel of the collecting duct



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Diuretic Tolerance

- Use of diuretics elicits both short and long-term adaptations intended to protect intravascular volume
- Short-term tolerance: Decreased response to the after the first dose of diuretic has been administered
  - Nephron is primed to avidly reabsorb sodium after drug levels decline below the diuretic threshold
  - Triggered by intravascular volume depletion
  - Renin-angiotensin system and sympathetic nervous sytem thought to contribute
  - Post-dose sodium retention significantly influenced by dietary sodium intake

NEJM 1998;339:387-395
Semin Nephrol 2011;31:483-494
NEJM 2009;361:2153-64

Diuretic Tolerance

- Long-term tolerance: Gradual return of sodium-chloride balance to an electroneutral level
  - Loop diuretics cause sodium to flood more distal nephron sites
  - Over time, increased exposure to sodium causes hypertrophy of distal nephron segments with concomitant increases in the reabsorption of sodium
  - Persistent volume removal appears to trigger long-term activation of the renin-angiotension-aldosterone system
  - Up-regulation of sodium transporters downstream from the primary site of diuretic action

NEJM 1998;339:387-395
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NEJM 2009;361:2153-64

Loop Diuretics

- Most potent diuretic class with maximally effective doses causing excretion of 20-25% of filtered Na^+
- Primary role is edematous disorders (heart failure, cirrhosis, neprotic syndrome), blood pressure and volume control in chronic kidney disease
- No evidence of a significant difference in potency if administered in equipotent doses
- Not recommended for treatment of uncomplicated hypertension due to short duration of action
- In normal patients, 40 mg IV furosemide (or equivalent dose of other loop) elicits a maximal response: 200 to 250 mEq of sodium in 3 to 4 L of urine over 3 to 4 hours

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Loop Diuretics

- Amount of loop diuretic absorbed is normal in patients with edema, although absorption is slower than normal
- Variability of absorption is likely more important than absolute bioavailability
- 40 mg IV furosemide = 20 mg torsemide = 1 mg bumetanide

Drug	Bioavailability	$t_{1/2}$	Route of Elimination	IV:PO
Furosemide	50% (Highly variable)	1.5-2 hr	Renal	1:2
Bumetanide	80-100%	1 hr	Liver	1:1
Torsemide	80-100%	3-4 hr	Liver	1:1
Ethacrynic acid	~100%	1 hr	Liver	1:1

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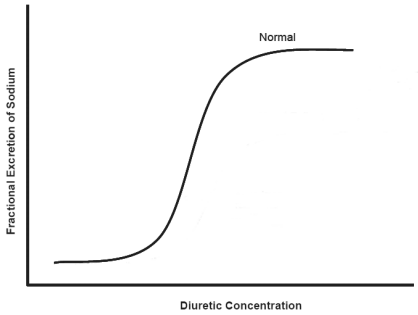
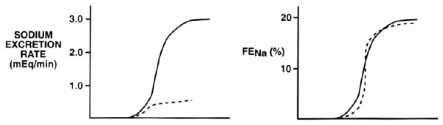
Pharmacodynamics of a Loop Diuretic



Congest Heart Fail 2010;16 (suppl 1):S68-S72

Conditions of Diminished Response to Loop Diuretics: Renal Insufficiency

- Loop diuretics are diuretics of choice
- Pharmacodynamics are not altered; residual nephrons retain their responsiveness to the diuretic
- Fe_{Na} is similar to healthy subjects, but absolute Na^+ excretion is lower due to the decrease in the filtered Na^+ load



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Conditions of Diminished Response to Loop Diuretics: Renal Insufficiency

- With a CrCl = 15 ml/min, 1/5 to 1/10 as much loop diuretic is secreted into the tubular fluid
- Bioavailability of loop diuretics is the same in patients with renal insufficiency
- Strategies:
  - Larger doses should be administered to attain effective drug amounts at the site of action
  - Administer effective doses several times per day
  - Add an oral thiazide diuretic
  - Continuous intravenous infusion of diuretic

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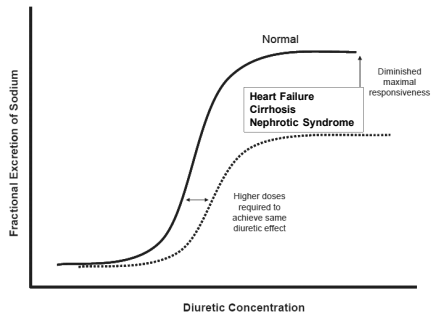
Pharmacodynamics of a Loop Diuretic



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Conditions of Diminished Response to Loop Diuretics: Heart Failure

- Access of diuretics to site of action is normal
- Slower po absorption. Use IV for immediate response
- Patients with NYHA Class II and III HF have 1/4 to 1/3 the natriuretic response to maximally effective doses of loop diuretics
- Diuretic resistance results from an interaction between the pathophysiology of Na^+ retention in HF and the renal response to diuretic therapy
- Strategies:
  - Administer effective doses several times per day
  - Add an oral thiazide diuretic
  - Addition of a K^+-sparing agent

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Conditions of Diminished Response to Loop Diuretics

- **Nephrotic Syndrome**
  - **Mechanism of diminished response to diuretics is unknown**
  - **Hypoalbuminemia and albuminuria may have a PK effect**
  - **Strategies:**
    - **2-3 times higher dose to attain normal amounts of unbound diuretic in urine**
    - **Administer effective doses several times per day**
    - **Add an oral thiazide diuretic**
- **Cirrhosis**
  - **Mainstay of diuretic therapy is spironolactone**
  - **Mechanism of diminished response to loop diuretics is unknown**
  - **Add a thiazide or loop to spironolactone if needed**

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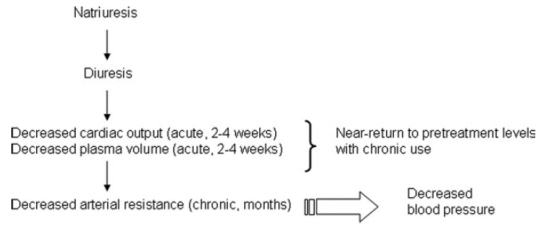
Thiazide Diuretics

- **Mainstay in the treatment of hypertension**
  - **Most have half-lives permitting once-daily dosing**
  - **Reductions in systolic and diastolic blood pressures of 10 to 15 mm Hg and 5 to 10 mm Hg, respectively**
  - **Combined effectively with most antihypertensive classes, often producing an additive decrease in blood pressure**
  - **Multiple studies demonstrating reductions in cardiovascular morbidity and mortality**
- **Generally considered ineffective with CrCl <30 ml/min (exception is metolazone)**
- **Shallow dose-response curve**
- **Lower doses typically prescribed today (12.5 to 25 mg of HCTZ)**

NEJM 2009;361:2153-64
Expert Opin Drug Saf 2010;9:243-257
Semin Nephrol 2011;31:495-502

Hemodynamic Effects of Thiazide Diuretics

- **Long-term blood pressure lowering due to a reduction in systemic vascular resistance (exact mechanism unclear)**



Semin Nephrol 2011;31:495-502

Thiazide Diuretics

Table 1. Pharmacokinetic Characteristics of the Thiazide Diuretics Approved for Use in the United States.*

Diuretic†	Relative Carbonic Anhydrase Inhibition‡	Oral Bioavailability	Volume of Distribution	Protein Binding	Route of Elimination	Elimination Half-Life
		percent	*liters per kilogram*	*percent*		*hr*
Thiazide-type						
Chlorothiazide	++	15–30	1	70	100% Renal	1.5–2.5
Hydrochlorothiazide	+	60–70	2.5	40	95% Renal	9–10
Methychlothiazide	—	—	—	—	Hepatically metabolized	—
Polythiazide	+	—	—	—	25% Renal	26
Bendroflumethiazide	0	90	1.0–1.5	94	30% Renal	9
Thiazide-like						
Chlorthalidone	+++	65	3–13	99	65% Renal	50–60
Metolazone	+	65	113 (total)§	95	80% Renal	8–14
Indapamide	++	93	25 (total)§	75	Hepatically metabolized	14

* All the diuretics listed are available in generic form in the United States as monotherapy, except polythiazide (not currently available) and bendroflumethiazide (available only in combination with nadolol). Dashes indicate an absence of data.
† The terms thiazide-type and thiazide-like are used to group thiazides on the basis of the presence of a benzothiadiazine molecular structure. Thiazide-like diuretics lack the benzothiadiazine structure but have a mechanism of action similar to that of thiazide-type diuretics, which have the benzothiadiazine structure.
‡ Plus signs indicate inhibition, with greater numbers of plus signs reflecting increased inhibition (lower inhibition constants); the zero indicates an inhibition constant of 0.
§ The volumes of distribution of metolozone and indapamide are given for the total volume, in liters; data on liters per kilogram were not available.

NEJM 2009;361:2153-64

Adverse Effects of Diuretics

- **Hypotension and Orthostasis**
- **Volume Depletion**
- **Electrolyte Disorders**
  - **Hypokalemia**
  - **Hypomagnesemia**
  - **Hyponatremia**
  - **Hypocalcemia (loop diuretics)**
  - **Hypercalcemia (thiazides)**
- **Hyperuricemia**
- **Hyperglycemia, glucose intolerance**
- **Dyslipidemia**
- **Photosensitivity and skin reactions**
- **Ototoxicity**
- **Interstitial nephritis**

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Treatment and Prevention of Diuretic-Induced Hypokalemia

Table 1. Treatment and Prevention of Diuretic-Induced Hypokalemia

Use low doses of the diuretic
Moderate Na^+ restriction (70-100 mEq/24 h)
Correct magnesium deficit if present
Oral K^+ supplements (20-40 mEq/24 h)
Combined therapy with an angiotensin-converting enzyme inhibitor, an angiotensin II–receptor antagonist, or a direct renin inhibitor
Combined therapy with a K^+-sparing diuretic

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