Review of Diuretics

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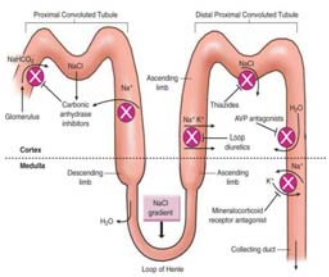
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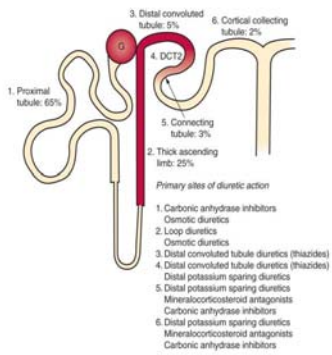
- Classification
- Mechanisms of action
- Physiologic adaptation
- Adverse effects
- Clinical uses of diuretics

Classification

- Carbonic anhydrase inhibitors
- Osmotic diuretics
- Loop diuretics
- Thiazides and thiazide-like diuetics (distal convoluted diuretics)
- Distal potassium-sparing diuretics
- Miscellaneous agents :
  dopaminergic agonist
  adenosine type 1 receptor antagonists
  vasopressin antagonist

Sites of action of diuretics in the kidney.





Carbonic anhydrase inhibitors(CAI)

CAI

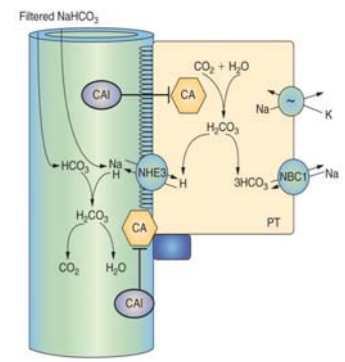
Site and mechanism of action

- Act primarily on proximal tubule cell to inhibit bicarbonate absorption
- CA important in sodium bicarbonate reabsorption and hydrogen ion secretion by renal epithelial cell
- CAI :

1) block catalytic dehydration of luminal carbonic acid at brush border of proximal tubule

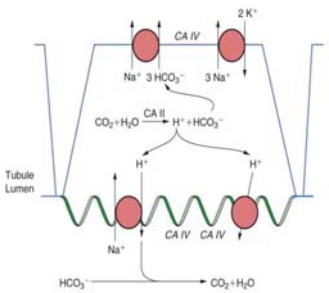
2) decrease intracellular generation of H^+(for counter transport with Na^+)

3) decrease peritubular capillary fluid uptake



Mechanisms of diuretic action in the proximal tubule

HCO3⁻ reabsorption in the proximal tubule



CAI

Pharmacokinetic

- Acetazolamide(Diamox) :
  - half-life :13 hr
- Methazolamide(Neptazane) :
  - less plasma protein binding, longer half-life, greater lipid solubility
  - favor penetration into aqueous humor and CSF : glaucoma treatment

CAI

Clinical use

- As diuretics : limited by transient action
- For alkaline diuresis
- COPD : CAI vs loop diuretics or thiazide
- Treat glaucoma : diminish transport of $HCO3^-$ and Na^+ by ciliary process – reduceing ocular pressure
- Limit formation of CSF and endolymph
- Mountain sickness : stimulating respiration, diminishing CBF and CSF formation
- Central sleep apnea : stimulate ventilation
- Prophylaxis of hypokalemic periodic paralysis : diminish influx of K^+ into cell

CAI

Adverse effects

- Diminished by NaHCO3 : weakness, lethargy, abnormal taste, paresthesis, GI distress, malaise, decreased livido
- Increases risk of nephrocalcinosis and nephrolithiasis : 10 fold
- Symptomatic metabolic acidosis in half of glaucoma patients
- Severe metabolic acidosis in elderly, elderly DM, CKD
- Allergic reaction, hepatitis, blood dyscrasias

Osmotic diuretics

Osmotic diuretics : mannitol

Site and mechanism of action

- Fluid reabsorption in water-permeable nephron segment (proximal nephron and thin limb of loop of Henle)- concentrates filtered mannitol sufficiently to diminished tubular fluid reabsorption
- Ongoing Na^+ reabsorption lower tubular fluid Na^+ - Back-flux of reabsorbed Na^+ into tubule
- Abstract water from cells : increase total RBF
- Increase medullary blood flow
- Increase GFR : increase renal plasma flow
  fall in plasma colloid osmotic pressure

Osmotic diuretics : mannitol

Pharmacokinetics and dosage

- distributed in extracellular fluid (ECF)
- filtered freely at the glomerulus
- t1/2 for plasma clearance depends on the GFR
- prolonged from 1 to 36 hours in advanced kidney failure
- infused i.v in daily doses of 50 to 200 g as a 15% or 20% solution or 1.5 to 2.0 g/kg of 20% mannitol over 30 to 60 minutes to treat raised intraocular or intracranial pressure

Osmotic diuretics : mannitol

Clinical indications

- evaluated for the prophylaxis of AKF :not been positive
- rationale : expand the ECV
  block TGF
  maintain GFR
  increase RBF and tubule fluid flow
  prevent tubule obstruction
  reduce renal edema
  scavenge oxygen radicals
- protect against AKF in cadaveric kidney transplant recipients
- convert oliguric to nonoliguric AKF
- for cerebral edema complicating hepatic failure
- for management of severe head injury
- reverse the dialysis disequilibrium syndrome

Osmotic diuretics : mannitol

Adverse effects

- Osmotic abstraction of cell water initially causes hyponatremia and hypochloremia
- Later, when the excess ECF is excreted, the decrease in cell water concentrates K^+ and H^+ within cells, which increases the gradient for their diffusion into the ECF, leading to hyperkalemic acidosis
- Electrolyte changes :normally rapidly corrected by the kidney
- Later, hypernatremic dehydration may develop if free water is not provided
- Expansion of ECV, hemodilution, and hyperkalemic metabolic acidosis occur in patients with renal failure who cannot eliminate the drug
- Circulatory overload, pulmonary edema, central nervous system depression, and severe hyponatremia require urgent hemodialysis

Loop diuretics

Loop diuretics

Site and mechanism of action

- Prime action of loop diuretics occurs from the luminal aspect of the TAL
- Primary energy for transport across TAL cells is provided via the basolateral Na^+,K^+–ATPase, which maintains a low intracellular [Na^+].
- Loop diuretics are organic anions that bind to the $Na^+/K^+/2Cl^-$ cotransporter (NKCC2) from the luminal surface
- NKCC2 is expressed on the apical membranes of medullary and cortical TALs and macula densa segments

Loop diuretics

Site and mechanism of action

- Loop diuretics increase the fractional excretion of Ca^{2+} by up to 30%. The predominant mechanism is by decreasing the magnitude of the lumen-positive transepithelial potential
- Loop diuretics can increase fractional Mg^{2+} excretion by more than 60% by diminishing voltage-dependent paracellular transport
- Initially increase urate excretion by inhibiting proximal urate transport. However, a succeeding reduction in urate clearance is largely secondary to volume depletion, which enhances proximal fluid and urate reabsorption

Loop diuretics

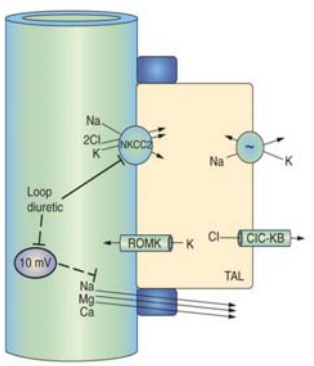
Site and mechanism of action

- Loop diuretics affect both TGF and renin secretion
- Loop diuretics, by blocking NaCl entry into macula densa cells, block the TGF completely : stimulate renin secretion, both acutely and chronically – this effect results in part from ECV depletion, a major component results from direct effects of loop diuretics on the macula densa : tend to preserve GFR, despite ECV depletion

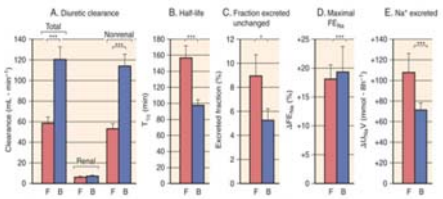
Loop diuretics

Pharmacoinetics & differences between drugs

- Absorbed promptly after ingestion, largely bound to albumin
- Loop diuretics, thiazides, and CAIs : all secreted avidly by a probenecid-sensitive organic anion transporter in proximal tubule cells
- Approximately 50% of furosemide is eliminated by renal metabolism to the inactive glucuronide. Only the unmetabolized and secreted fraction is available to inhibit NaCl reabsorption
- bumetanide and torsemide : metabolized in the liver
- Unlike bumetanide or torsemide, the elimination of furosemide, in patients with CKD is greatly reduced because its metabolism to the inactive glucuronide occurs in the kidney.
- fraction of a dose excreted unchanged in patients with CKD is greater for furosemide, leading to an enhanced natriuretic response



Mechanisms of diuretic action along the loop of Henle



Comparison of the pharmacokinetics and dynamics of furosemide (F, 160 mg; metabolically inactivated in the kidney) and bumetanide (B, 4 mg; metabolically inactivated in the liver) in 10 subjects with chronic renal insufficiency

Thiazides and thiazide-like diuretics (distal convoluted tubule diuretics)

Thiazides

Sites and mechanism of action

- Increase excretion of sodium, chloride, and potassium while reducing calcium excretion
- Major site of action of thiazide and thiazide-like diuretics is the distal convoluted tubule (DCT), where they block coupled reabsorption of Na^+ and Cl^-
- Inhibit the thiazide-sensitive Na-Cl cotransporter

Thiazides

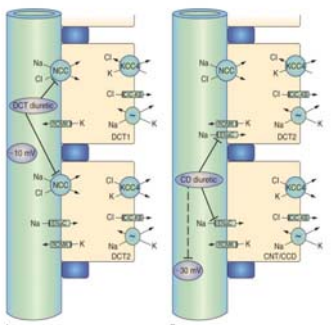
Sites and mechanism of action

- Increase potassium excretion, but they do not augment K^+ secretion by DCTs directly
  - result from their tendency :
    - to stimulate aldosterone secretion
    - to increase distal flow
    - to increase calcium reabsorption
- Reduce Ca^{2+} excretion.
- Mg^{2+} excretion is enhanced by
- reduce urate clearance secondary to ECV depletion and competition for tubular uptake

Thiazides

Pharmacokinetics

- Extensively bound to plasma protein
- Eliminated by secretion by S2 segment of proximal tubule via OAT
- t1/2 is prolonged in renal failure and in the elderly



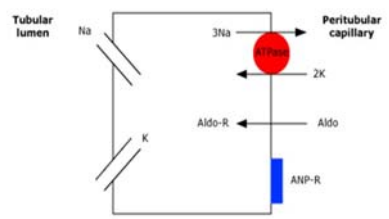
Mechanisms of distal convoluted tublue (DCT) and collecting duct (CD) diuretics.

Distal potassium-sparing diuretics

Distal K^+-sparing diuretics

Sites and mechanism of action

- Distal K^+-sparing diuretics comprise those that directly block the epithelial Na^+ channel (ENaC; amiloride and triamterene) and antagonists of aldosterone (spironolactone and eplerenone)



The potassium-sparing diuretics act by closing Na channels, amiloride and triamterene directly and spironolactone by competing with aldosterone.

Distal K^+-sparing diuretics

Pharmacokinetics

- Triamterene : well absorbed
  - rapidly hydroxylated to active metabolites
  - drug and its metabolites are secreted by the organic cation pathway in the proximal tubule
  - half-lives of 3 to 5 hour
  - triamterene and its active metabolites accumulate in : cirrhosis, elderly, CKD
- Amiloride : incompletely absorbed
  - duration of action : approximately 18 hours
  - secreted into the tubular fluid by the organic cation transport pathway

Distal K^+-sparing diuretics

Pharmacokinetics

- Spironolactone :
  - readily absorbed and circulates bound to plasma proteins
  - intrinsic half-life is short, but it is metabolized to active compounds with considerably prolonged actions
  - metabolized to canrenones (t1/2=16 hr) and to sulpher-containing metabolites, predominantly 7 alpha-thiomethylspirolactone (t1/2=13 hr)
  - spironolactone has a t1/2 of approximately 20 hours
  - lipid soluble and enters distal renal tubules from the plasma
- Eplerenone : fewer antiandrogenic and proestrogenic effects
  - half-life : 3 hr

Distal K^+-sparing diuretics

Clinical indications

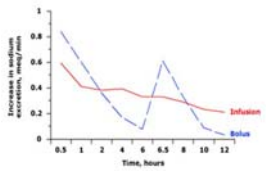
- Used to prevent or treat hypokalemic alkalosis
- Amiloride can prevent amphotericin-induced hypokalemia and hypomagnesemia
- Spironolactone :
  - first-line therapy for ECV expansion in cirrhotic ascites
  - for heart failure associated with systolic dysfunction
  - used to treat hypertension associated with hyperaldosteronism and for resistant hypertension
  - reduce proteinuria in CKD
- Eplerenone : indicated for systolic dysfunction is the setting of recent myocardial infarction (MI)

Distal K^+-sparing diuretics

Adverse effects and drug interaction

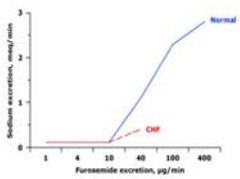
- Hyperkalemia : most common complication
- Risk is dose-dependent
- Increases in patients with CKD or in those receiving K^+ supplements, ACEIs, ARBs, NSAIDs, β-blockers, heparin, or ketoconazole
- Men : gynecomastia, decreased libido and impotence
- Women : menstrual irregularities, hirsutism, or swelling and tenderness of the breast
- Impaired net acid excretion : metabolic acidosis
- Amiloride and triamterene accumulate in renal failure
- Triamterene accumulates in cirrhosis

Peak diuresis after first dose of loop diuretic



Increase in urinary sodium excretion (UNa) after intravenous bumetanide, given as a continuous infusion (solid line) or as a bolus (dashed line), in patients with stable chronic renal failure.

Dose-response relationship between furosemide and sodium excretion



Miscellaneous agents

Dopaminergic agonists

- Normal subjects in low doses (1–3 mg/kg/min) ⇒ dopamine causes a modest increase in the GFR, reduces proximal reabsorption via a cAMP-induced inhibition of the Na^+/H^+ antiporter and increases Na^+ excretion
- Fenoldopam is a selective dopamine type 1 (DA1) receptor agonist with little cardiac stimulation
- Beneficial effects are reduced in patients who are critically ill and/or receiving vasopressors

Miscellaneous agents

Adenosine Type 1 receptor antagonists

- Aminophylline is an adenosine receptor antagonist that inhibits NaCl reabsorption in the proximal tubule and diluting segments and causes a modest increase in GFR
- Highly selective adenosine 1 (A1) receptor antagonists are natriuretic and antihypertensive and potentiate furosemide-induced natriuresis in normal humans and in patients with diuretic-resistant CHF
- A1 antagonists disrupt glomerulotubular balance and TGF, thereby decreasing proximal reabsorption and increasing GFR

Miscellaneous agents

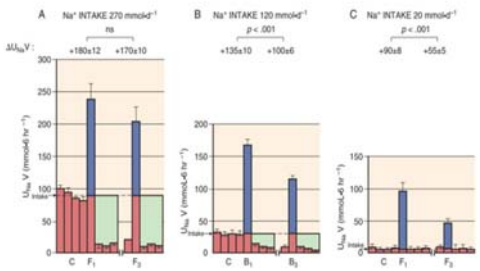
Vasopressin antagonists

- Nonpeptide, orally active vasopressin V2 receptor antagonists cause free water diuresis without appreciable natriuresis in water-deprived human subjects
- Increase urine volume, free water clearance, and serum sodium concentration in hyponatremic patients with SIADH
- Lixivaptan : oral V2 antagonist that increases SNa in patients with SIADH, CHF, or cirrhosis
- Tolvaptan :increased the urine volume, corrected hyponatremia
- Conivaptan : combined V2 and V1α antagonist
  patients with CHF : increased urine volume and reduced PCWP
  effective to treat acute or chronic conditions associated with dilutional hyponatremia.

Adaptation to diuretic therapy

Time course of diuretics

- Furosemide
- Short-acting loop diuretics
- Significant natriuresis during 6 hour
- Remaining 18 hour : very low sodium excretion : associated volume depletion ⇒ activation of sodium-retaining mechanism
- Initial fluid loss : RAA and sympathetic nervous system activation ⇒ AT II, aldosterone, norepinephrine : promote tubular sodium reabsorption

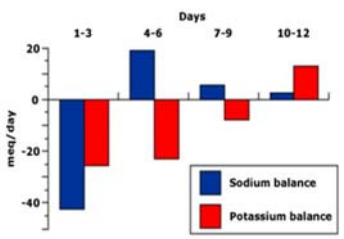


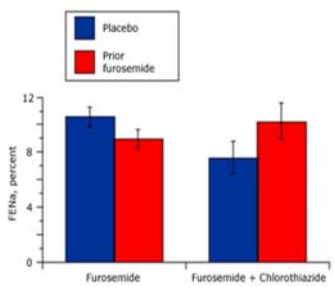
Effects of dietary salt intake on diuretic braking phenomenon

Reestablishment of steady state

- Short-lived net diuresis
- Rapidly established new steady state
  sodium intake = output
- Fall extracellular volume due to initial period of negative sodium balance
- Counterbalanced diuretic-induced sodium loss by :
  - Neurohumoral-mediated increased in tubular reabsorption at non-diuretic sensitive site
  - Flow-mediated increases in tubular reabsorption distal to site of action of diuretic : enhanced distal sodium delivery
  - Diminished diuretic entry into urine in CRF

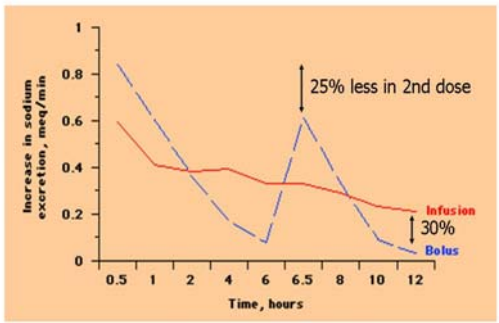
Steady state after thiazide therapy





Diuretic reponsiveness in patients previously Treated placebo or furosemide

Infusion vs bolus treatment of loop diuretics, bumetanide



Diuretic resistance

Common Causes of Diuretic Resistance

Cause	Example
Incorrect diagnosis	Venous or lymphatic edema
Inappropriate NaCl intake	Na+ intake > 120 mmol · d-1
Inadequate drug reaching tubule lumen in active form:	
Noncompliance	
Dose inadequate or too infrequent	
Poor absorption	Uncompensated CHF
Decreased renal blood flow	CHF, cirrhosis of liver, elderly
Decreased functional renal mass	AKF, CKD, elderly
Proteinuria	Nephrotic syndrome
Inadequate renal response:	
Low GFR	AKI, CKD
Decreased effective ECV	Edematous conditions
Activation of RAA axis	Edematous conditions
Nephron adaptation	Prolonged diuretic therapy
NSAIDs Indomethacin, aspirin	

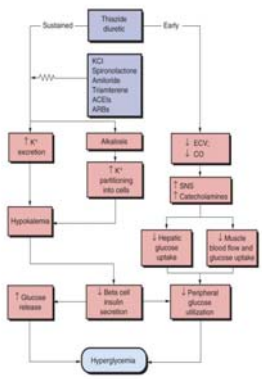
Adverse effects of diuretics

Fluid and electrolyte abnormalities

- Extracellular volume depletion and azotemia
- Hyponatremia : thiazide
- Hypokalemia : furosemide and thiazide
- Hyperkalemia
- Hypomagnesemia : furosemide and thiazide
- Hypercalcemia : thiazide
- Acid-base changes ;
  metabolic alkalosis : furosemide
  metabolic acidosis : CAI and K^+-sparing diuretics

Metabolic abnormalities

- Hyperglysemia : thiazide
- Hyperlipidemia : furosemide and thiazide
- Hyperuricemia : thiazide



Hypothesis for the hyperglycemic actions of thiazide diuretics

Other adverse effects

- Impotence : thiazide
- Ototoxicity : furosemide
- Harzard in pregnancy and newborns
- B vitamine deficiency
- Drug allergy
- Malignancy