Pharmacology - GUS

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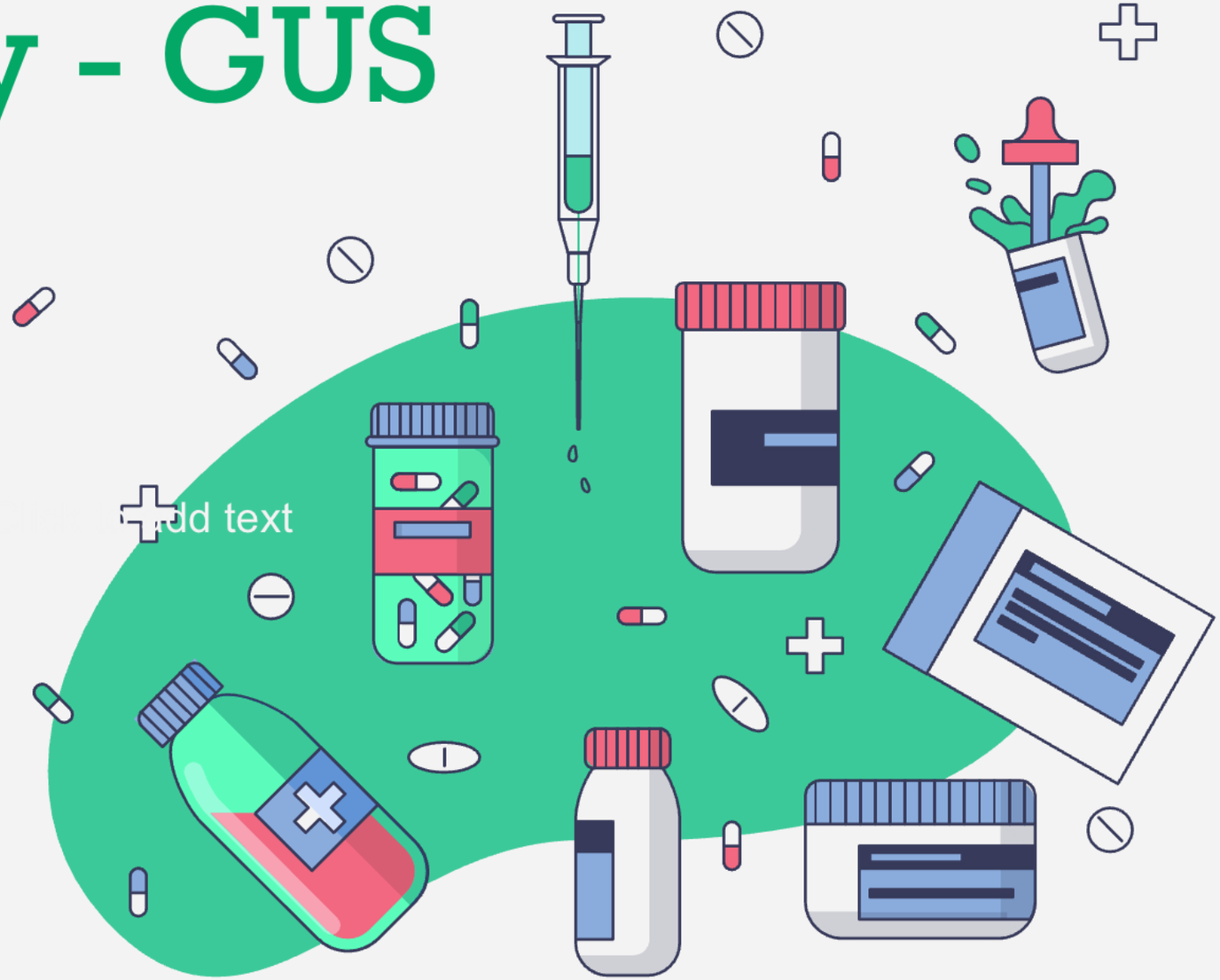

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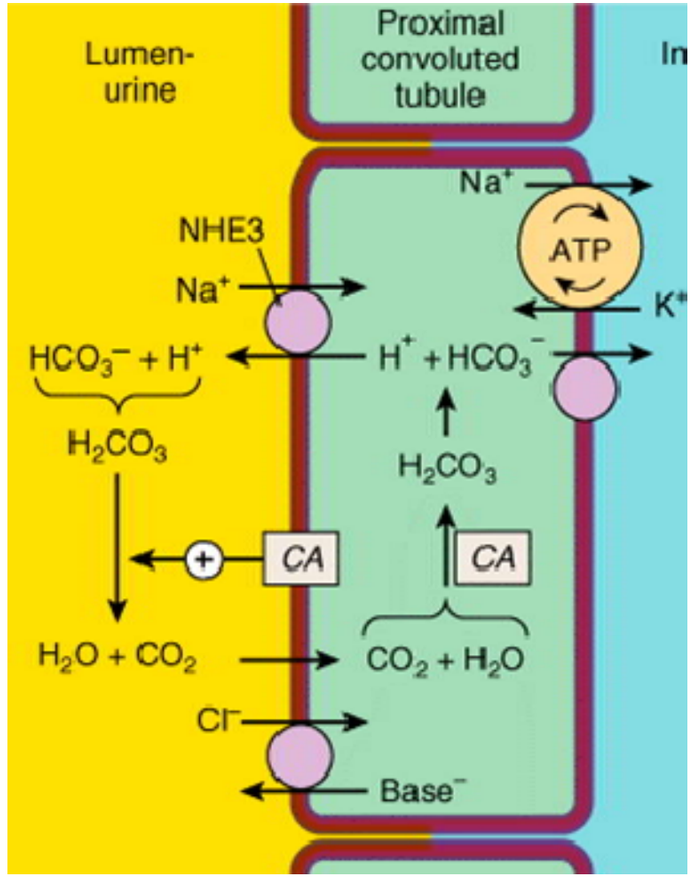
Diuretic Agents

2020

Carbonic Anhydrase Inhibitors

- Carbonic anhydrase is responsible for reabsorption of Na^+HCO_3 from proximal convoluted tubules and for formation of aqueous humor (fluid of the eye)
- Carbonic anhydrase (CA) predominant location is the luminal membrane of the PCT where it catalyzes the dehydration of H2CO3.
- CA inhibitors block NaHCO3 reabsorption & decrease Na+ /H+transporter activity
- Only mild natriuresis (1-3%)
- Increased bicarbonate in urine

Other locations are the brain , the eye and the stomach where produces H+



- **CA** inhibitors are now rarely used as diuretics, their major clinical use: treatment of glaucoma

And to reduce the intraocular pressure before ophthalmic surgery

Acetazolamide(prototype**)**

Pharmacokinetics:

- Well absorbed after oral administration.
- An increase in urine pH from the HCO_3^- diuresis is apparent within 30 minutes, is maximal at 2 hours, and persists for 12 hours after a single dose.
- Excretion of the drug is by secretion in the proximal tubule.

Pharmacodynamics

- 85% of the HCO_3^- reabsorption in the PCT is inhibited.
- Some HCO_3^- can still be absorbed at other nephron sites by CA–independent mechanisms, so the overall effect is only about 45% inhibition
- CA inhibition causes significant HCO_3^- losses & hyperchloremic metabolic acidosis.
- HCO_3^- depletion leads to enhanced NaCl reabsorption, so, the diuretic efficacy of acetazolamide decreases significantly with use over 2 or 3 days.
- The ciliary body of the eye secretes HCO_3^- from the blood into the aqueous humor.
- Formation of cerebrospinal fluid by the choroid plexus involves HCO_3^- secretion.

Clinical Indications

Glaucoma: used to control intraocular pressure during **acute attacks of glaucoma** and for **short-term reductions in intraocular pressure** both preoperatively and postoperatively in patients who require ocular surgery,

Acetazolamide is effective orally & topically.

- Topically, **dorzolamide**, **brinzolamide** reduce intraocular pressure without systemic effects.
- **Urinary alkalinization** : to increase renal excretion of weak acids e.g. cystin and uric acid.

Metabolic Alkalosis, acetazolamide produces metabolic acidosis so it is useful in correcting the alkalosis.

Acute Mountain Sickness

- Weakness, dizziness, insomnia, headache, and nausea can occur in mountain travelers who rapidly ascend above 3000 m.
- By decreasing cerebrospinal fluid formation and by decreasing the pH of the cerebrospinal fluid and brain, acetazolamide can increase ventilation and diminish symptoms of mountain sickness.

Epilepsy : because acidosis results in ↓seizures.

To increase urinary phosphate excretion during severe hyperphosphatemia.

Toxicity

- **Hyperchloremic metabolic acidosis**

  Acidosis results from chronic reduction of body bicarbonate stores.

  This limits the diuretic efficacy of these drugs to 2 or 3 days but acidosis persists as long as the drug is continued.

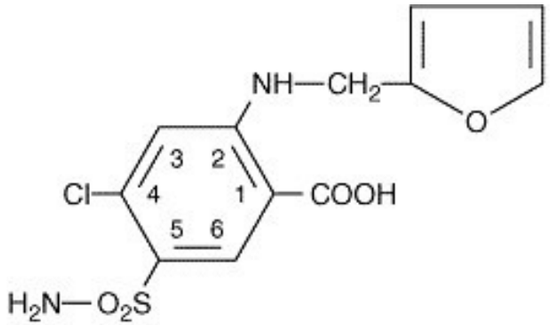
- **Renal Stones** Calcium salts & phosphate salts are relatively insoluble at alkaline pH, thus, renal stone formation from these salts is enhanced.

- **Renal Potassium Wasting Other Toxicities**

- Drowsiness and paresthesias (an abnormal sensation, typically tingling or pricking).

- Hypersensitivity reactions may also occur.

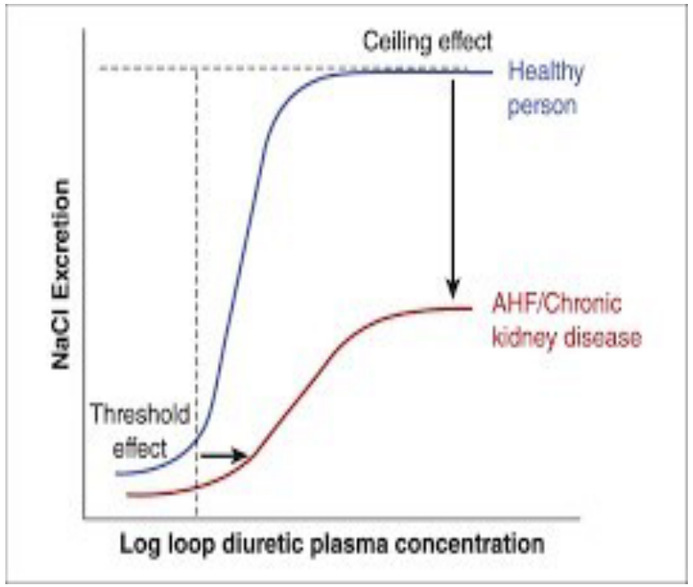
Loop Diuretics



Furosemide

- Loop diuretics selectively inhibit NaCl reabsorption in the **TAL**.
- Because of the large NaCl absorptive capacity of **TAL**, loop diuretics are the most efficacious diuretic agents currently available.
- They are high ceiling diuretics.

•**Furosemide (Frusemide)**, **Bumetanide** and **Torsemide** are sulfonamide loop diuretics but **Ethacrynic acid i**s not a sulfonamide.



Pharmacokinetics

Absorption of oral **torsemide** in1 hour, duration 4–6 hours,
furosemide 2–3 hours, duration 2–3 hours .

Elimination by the glomerular filtration and tubular secretion.

They cause 10-25% loss of filtered Na^+

↑ dose → ↑ diuretic effect; over-treatment causes dehydration.

Increasing the dose not necessarily means increase in effect

Effective even at GFR below 10 ml/min (loop diuretics are most effective in patients with renal insufficiency.

Pharmacodynamics

- Loop diuretics inhibit **NKCC2**, the luminal Na+/K+/2Cl– transporter in the **TAL** of Henle's loop.
- Loop diuretics reduce the reabsorption of NaCl and also diminish the lumen-positive potential which drives divalent cation reabsorption

causing an increase in Mg2+

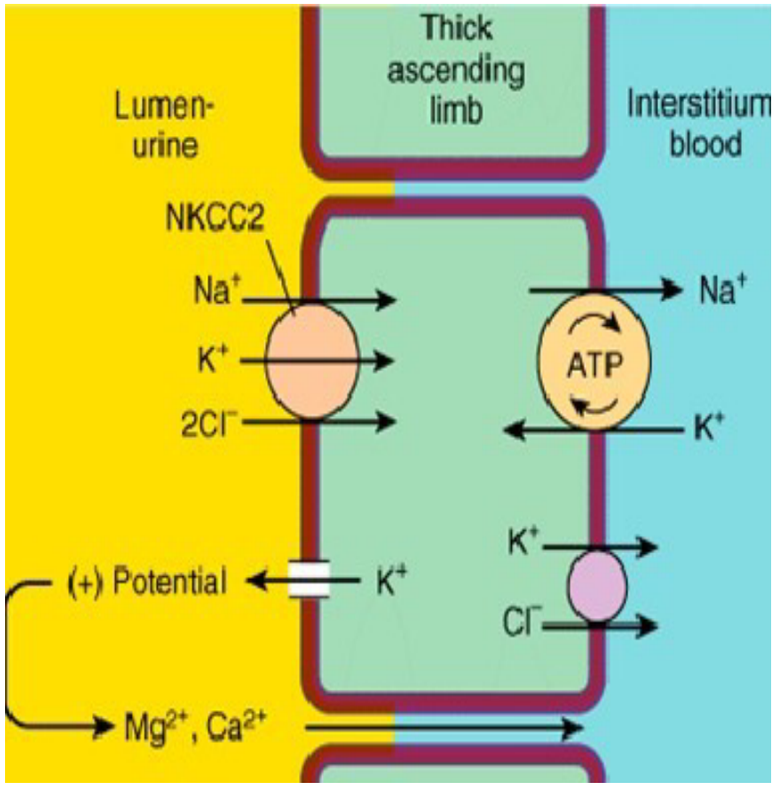
and Ca2+ excretion.

- Since Ca2+ is actively

reabsorbed in the DCT, loop

diuretics do not generally

cause hypocalcemia.



- Loop diuretics induce expression cyclooxygenase 2 (COX-2), which synthesizes prostaglandins from arachidonic acid.
- PGE2 , inhibits salt transport in the TAL and thus participates in the renal actions of loop diuretics.
- **NSAIDs** interfere with the actions of loop diuretics by reducing prostaglandin synthesis in the kidney and by reducing the secretion of loop diuretics due to competition for secretion in the proximal tubule.
- Loop agents increases renal blood flow.
- Both furosemide and ethacrynic reduce pulmonary congestion and left ventricular filling pressures in heart failure before a measurable increase in urinary output occurs. These effects on peripheral vascular tone may be due to release of prostaglandins.

Clinical Indications

Acute pulmonary edema

Decreasing blood volume reduces left ventricular filling pressures and rapidly relieves pulmonary edema.

Other edematous conditions.

Hyperkalemia

loop diuretics enhance urinary excretion of K+.

Acute Renal Failure

Loop agents can increase the rate of urine flow and enhance K+ excretion in acute renal failure.

They don't stop renal failure

Anion Overdose

Loop diuretics are useful in treating toxic ingestions of bromide, fluoride, and iodide, which are reabsorbed in the TAL

Toxicity

Hypokalemic Metabolic Alkalosis: due to increased K+ and H+ secretion

Ototoxicity: Dose-related hearing loss, usually reversible.

Hyperuricemia: common, but painful episodes of gout are rarely reported.

Unless the patient is already has gout

Hypomagnesemia: Occurs in patients with dietary magnesium deficiency.

Allergic Reactions: less common with ethacrynic acid.

Because they are derivatives of sulfonamides

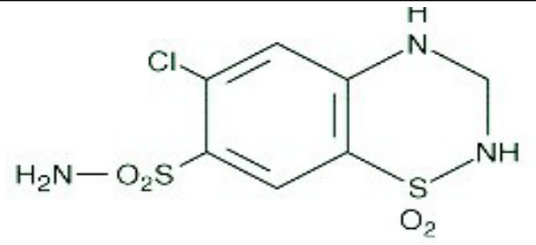
severe dehydration.

Hyponatremia is less common than with the thiazides

hypercalcemia can occur in volume-depleted patients

The increase of Ca+2 concentration is not because of increased reabsorption but because decreased blood volume

Thiazides



Hydrochlorothiazide

The thiazide diuretics emerged from efforts to synthesize more potent carbonic anhydrase inhibitors.

Some members of this group retain significant carbonic anhydrates inhibitory activity.

The prototypical is **hydrochlorothiazide.**

Pharmacokinetics

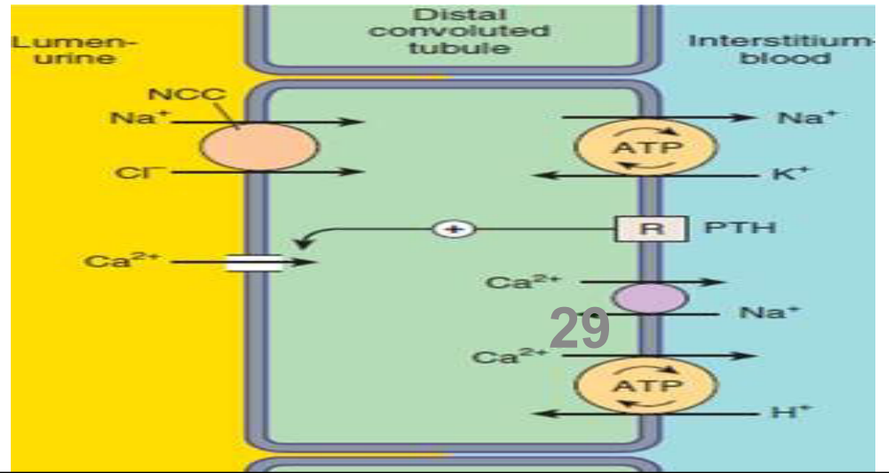
- All thiazides can be administered orally, but there are differences in their metabolism.
- **Chlorothiazide**, the parent of the group, is not very lipid- soluble and must be given in relatively large doses. It is the only thiazide available for parenteral administration.
- **Chlorthalidone** is slowly absorbed and has a longer duration of action.
- **Indapamide** is excreted primarily by the billiary system, but enough of the active form is cleared by the kidney to exert its diuretic effect in the DCT.
- All thiazides are secreted by the organic acid secretory system in the proximal tubule and compete with the secretion of uric acid by that system.
- As a result, thiazide use may blunt uric acid secretion and elevate serum uric acid level.

Pharmacodynamics

- Thiazides inhibit NaCl reabsorption in the **DCT** by blocking the Na+/Cl– transporter (**NCC**).
- Inhibition of Na^+ reabsorption →↑Na^+, K^+, Cl^-, HCO_3^- and H_2O excretion
- Thiazides enhance Ca2+ reabsorption but rarely cause hypercalcemia

Have Little carbonic anhydrase inhibitory effect.

They are number one drugs in treating hypertension. Their early hypotensive effect is related to a reduction in blood volume, their long-term effect is related to a reduction in peripheral vascular resist effect,(direct vasodilation effect **Indapamide**)



Thiazides are the most frequently used diuretics and the least expensive.

The action of thiazides depends in part on renal prostaglandin & can also be inhibited by NSAIDs under certain conditions.

Thiazides lead to ≈ 5-10% loss of filtered Na^+

High doses will not lead to further increase in their diuretic effect (low ceiling)

They are ineffective in pts with impaired renal function or pts with GFR< 20 ml/min

They are highly effective in lowering BP when combined with other antihypertensive drugs (synergistic effect)

Clinical Indications

(1) hypertension.

Also if the patient is on calcium Chanel antagonist or beta blockers

(2) Edema of heart failure ; liver cirrhosis…etc

Better to use loop diuretics

(3)Nephrolithiasis (renal stones) due to idiopathic hypercalciuria.

Because it inhances calcium reabsorption

(4)Nephrogenic diabetes insipidus (inability to concentrate urine due to impaired renal tubule response to vasopressin which leads to excretion of large amounts of dilute urine.)

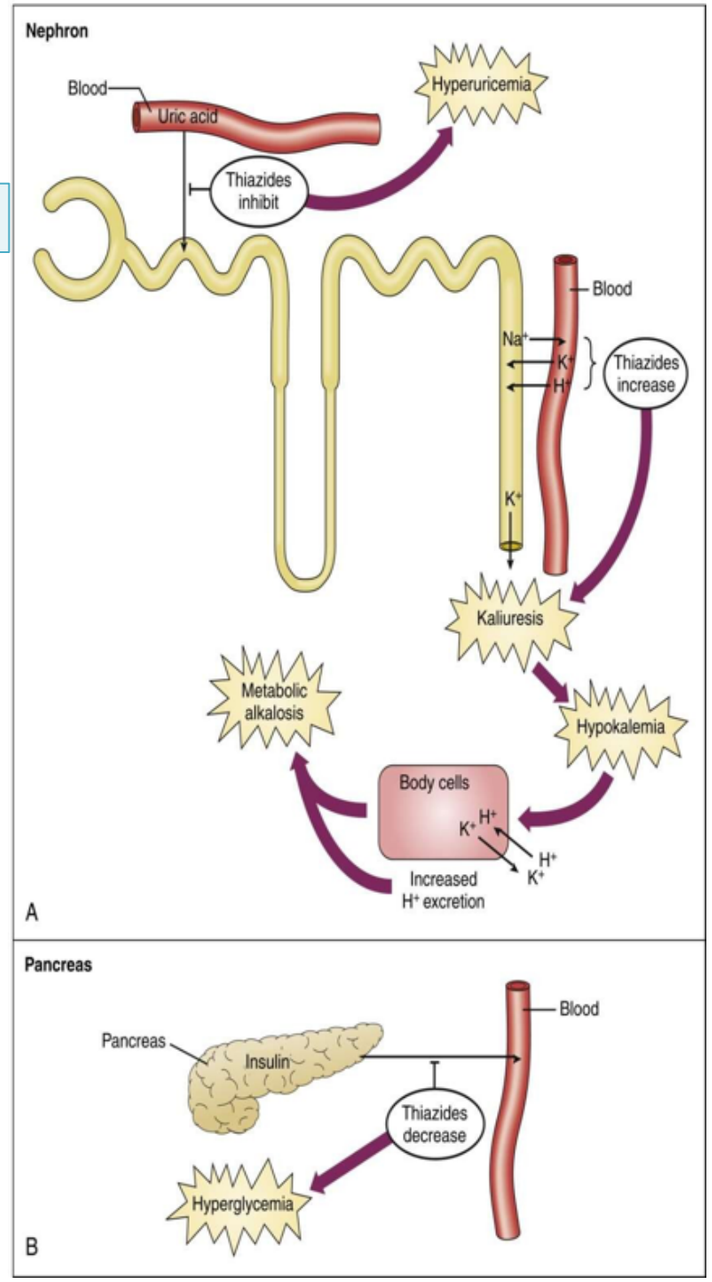
Thiazide diuretics allow increased excretion of Na+ and water, thereby reducing the serum osmolarity and eliminating volume excess. Thiazides allow increased solute excretion in the urine, breaking the polydipsia- polyuria cycle (polydipsia: thirst).

Toxicity

- **Hypokalemic Metabolic Alkalosis** Because excessive excretion of K+
- **Hyperuricemia** could precipitate gout
- **Hyperglycemia** due to both impaired release of insulin and decrease tissue utilization of glucose. Hyperglycemia is partially reversible with correction of hypokalemia.
- **Hyperlipidemia**

5–15% increase in total serum cholesterol and low-density lipoproteins (LDL). These levels may return to baseline after prolonged use.

- **Hyponatremia**



- **Allergic Reactions**

  The thiazides are sulfonamides and share cross-reactivity with other members of this chemical group.
  Photosensitivity or generalized dermatitis occurs rarely.
- **Other Toxicities**
- Weakness, fatigability, and paresthesias may occur.
- Impotence
- **Contraindications**
- Excessive use of any diuretic is dangerous in patients with hepatic cirrhosis, borderline renal failure, or heart failure.