DIURETICS

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Definition

- Diuretics are drugs that act on kidney to increase urine flow.

- Most work by decreasing reabsorption of Na+ at different sites in nephron.

- Na^+ and other ions, such as Cl^-, enter the urine in greater than normal amounts along with water, which is carried passively to maintain osmotic equilibrium.

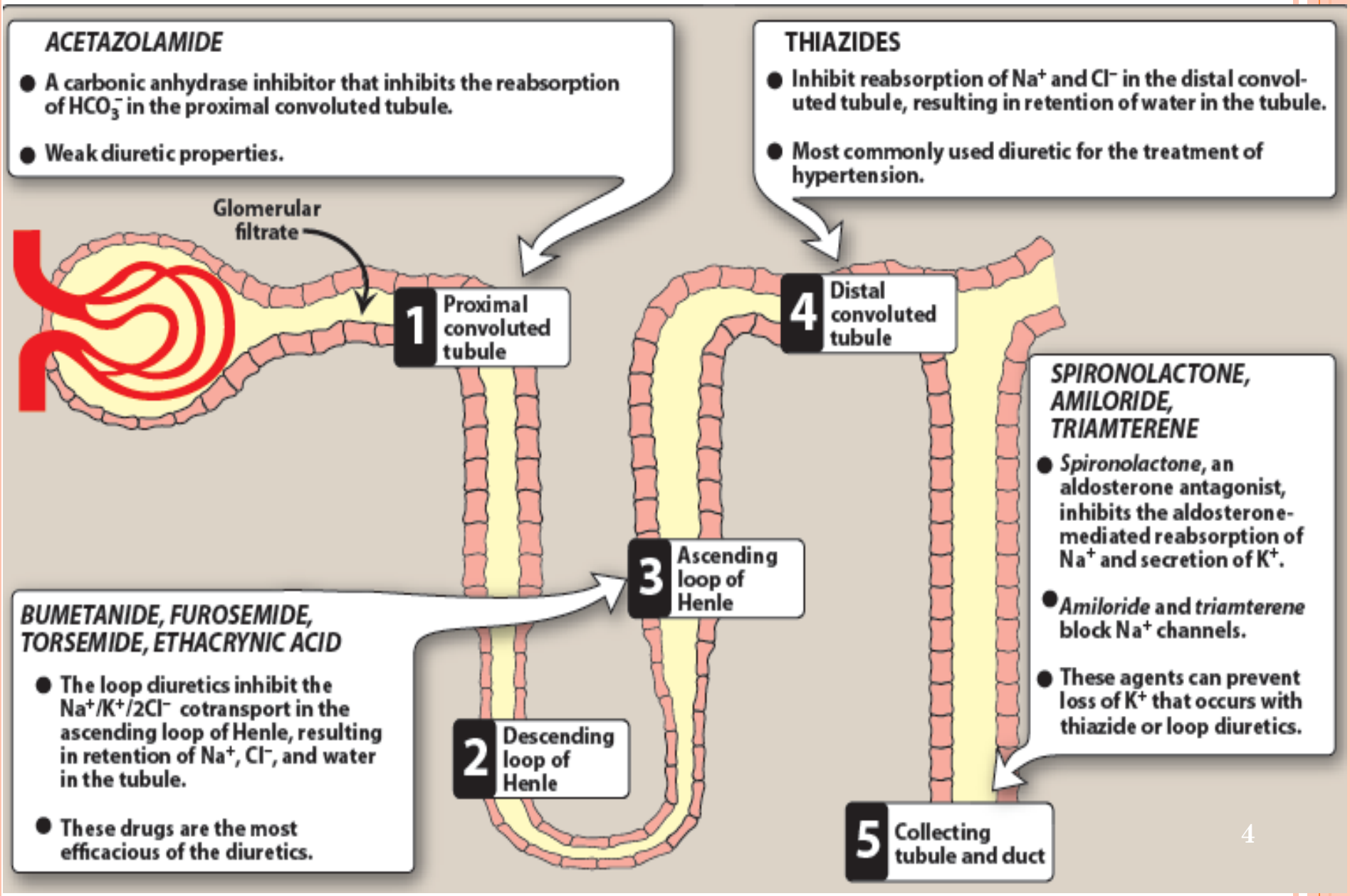
- Diuretics result in:

1. Increase volume of urine
2. Change urine pH
3. Change ionic composition of the urine and blood

Classification

Drug	Brand
THIAZIDE DIURETICS	
Chlorothiazide	DIURIL, SODIUM DIURIL
Chlorthalidone	HYGROTON
Hydrochlorothiazide (HCTZ)	MICROZIDE
Indapamide	LOZOL
Metolazone	ZAROXOLYN
LOOP DIURETICS	
Bumetanide	BUMEX
Ethacrynic acid	EDECRIN
Furosemide	LASIX
Torsemide	DEMADEX
POTASSIUM-SPARING DIURETICS	
Amiloride	AMILORIDE HCL
Eplerenone	INSPRA
Spironolactone	ALDACTONE
Triamterene	DYRENIUM
CARBONIC ANHYDRASE INHIBITORS	
Acetazolamide	DIAMOX
OSMOTIC DIURETICS	
Mannitol	OSMITROLL
Urea	CARMOL,

- Hydrochlorothiazide: combination drug — 12.5mg / 25mg
- Loop diuretics: → most effective [Na⁺ abs most @ loop]
- Furosemide: most used! → emergency
- Potassium-sparing diuretics: w/ hypokalemic patients
- Spironolactone: !
- Acetazolamide: not used as diuretics [weak]
- Osmotic diuretics: Physical activity drug [inert]
- osmotic ← ما بيسوي إشي كدوا بس عشان أطعمه لازم أشرب معه مي كثير


ACETAZOLAMIDE
A carbonic anhydrase inhibitor that inhibits the reabsorption of HCO_3^- in the proximal convoluted tubule.
Weak diuretic properties.
THIAZIDES
Inhibit reabsorption of Na^+ and Cl^- in the distal convoluted tubule, resulting in retention of water in the tubule.
Most commonly used diuretic for the treatment of hypertension.
Glomerular filtrate
1 Proximal convoluted tubule
2 Descending loop of Henle
3 Ascending loop of Henle
4 Distal convoluted tubule
5 Collecting tubule and duct
BUMETANIDE, FUROSEMIDE, TORSEMIDE, ETHACRYNIC ACID
The loop diuretics inhibit the $Na^+/K^+/2Cl^-$ cotransport in the ascending loop of Henle, resulting in retention of Na^+, Cl^-, and water in the tubule.
These drugs are the most efficacious of the diuretics.
SPIRONOLACTONE, AMILORIDE, TRIAMTERENE
Spironolactone, an aldosterone antagonist, inhibits the aldosterone-mediated reabsorption of Na^+ and secretion of K^+.
Amiloride and triamterene block Na^+ channels.
These agents can prevent loss of K^+ that occurs with thiazide or loop diuretics.

1. Thiazides and related agents

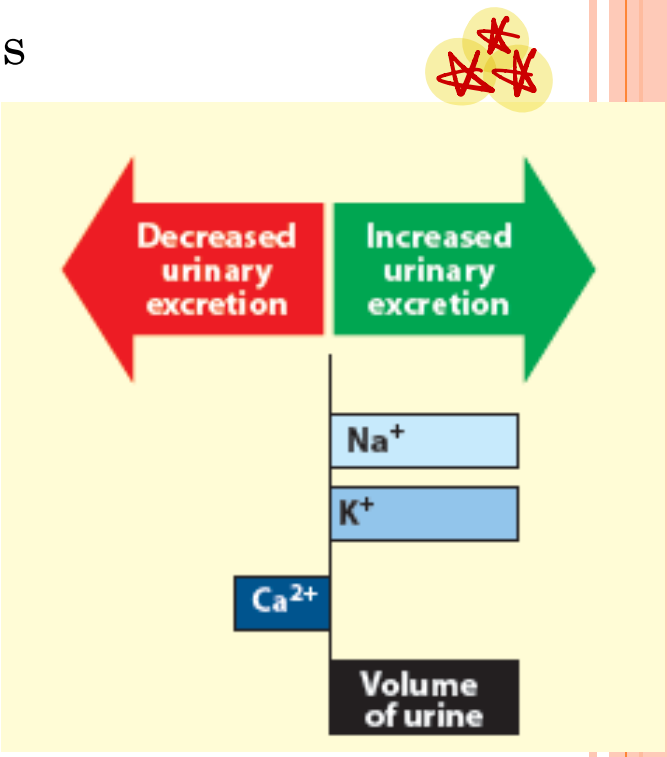
- They are sulfonamide derivatives and their mechanism of action is similar
- They are the most widely used of the diuretic drugs

Mechanism of action

They act mainly in the cortical region of the ascending loop of Henle and the distal tubule to decrease the reabsorption of Na+, apparently by inhibition of Na+/Cl– cotransporter on the luminal membrane of the tubules resulting in

A. Increased excretion of Na^+ and Cl^-

B. Loss of K^+: thiazides increase the Na^+ in the filtrate arriving at the distal tubule, more K^+ is also exchanged for Na^+, resulting in a continual loss of K^+ from the body with prolonged use of these drugs.



C. Loss of Mg^{2+}

D. Decreased urinary calcium excretion: They promote the reabsorption of Ca^{2+}.

E. Reduced peripheral vascular resistance: caused by relaxation of arteriolar smooth muscle.

Therapeutic uses:

Chlorothiazide and hydrochlorothiazide

used more often

1. **Hypertension:** effective in reducing systolic and diastolic blood pressure for extended periods in the majority of patients with mild to moderate essential hypertension
2. **Heart failure:** reduce extracellular volume in mild to moderate heart failure.

thiazide treat Ca oxalate stones, and loop cause it

3. **Hypercalciuria:** treating idiopathic hypercalciuria, because they inhibit urinary Ca^{2+} excretion. This is particularly beneficial for patients with calcium oxalate stones in the urinary tract.
4. **Diabetes insipidus:** Thiazides can substitute for antidiuretic hormone in the treatment of nephrogenic diabetes insipidus. The urine volume of such individuals may drop from 11 L/day to about 3 L/day when treated with the drug.

!

A. **Chlorthalidone:** It has a very long duration of action and, therefore, is often used to treat hypertension. It is given once per day.

B. **Metolazone**: unlike the thiazides, causes Na^+ excretion in advanced renal failure.

C. **Indapamide:** It is less likely to accumulate in patients with renal failure and may be useful in their treatment.

Adverse effects:

Most of the adverse effects involve problems in fluid and electrolyte balance

1. Hypokalemia
2. Hyponatremia: Limiting water intake and lowering the dose of diuretic can prevent this condition.
3. Hyperuricemia: Thiazides increase serum uric acid by decreasing the amount of acid excreted by the organic acid secretory system(risk of gout).
4. Volume depletion: This can cause orthostatic hypotension (most common) or light-headedness.
5. Hypercalcemia: The thiazides inhibit the secretion of Ca^{2+}, sometimes leading to elevated levels of Ca^{2+} in the blood.
6. Hyperglycemia: Patients with diabetes mellitus taking thiazides for hypertension may become hyperglycemic. This is due to impaired release of insulin and tissue uptake of glucose.

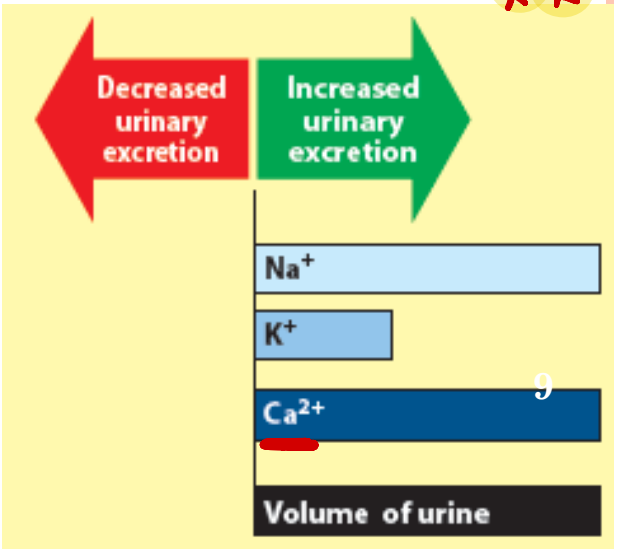
2. Loop or High-Ceiling Diuretics

- Bumetanide, furosemide, torsemide, and ethacrynic acid
- their major action on the ascending limb of the loop of Henle

Mechanism of action:

Loop diuretics inhibit the cotransport of $Na^+/K^+/Cl^-$ in the luminal membrane in the ascending limb of the loop of Henle. Therefore, reabsorption of these ions is decreased

- The loop diuretics are the most efficacious of the diuretic drugs, because the ascending limb accounts for the reabsorption of 25 to 30 percent of filtered NaCl and downstream sites are not able to compensate for this increased Na^+ load.



Therapeutic uses:

1. drugs of choice for reducing the acute pulmonary edema of heart failure. Because of their rapid onset of action, particularly when given intravenously, the drugs are useful in emergency situations, such as acute pulmonary edema, which calls for a rapid, intense diuresis.

2. Loop diuretics (along with hydration) are also useful in treating hypercalcemia, because they stimulate tubular Ca^{2+} excretion.

3. They also are useful in the treatment of hyperkalemia.

Pharmacokinetics:

- Loop diuretics are administered orally or parenterally.
- Their duration of action is relatively brief 2 to 4 hours.

Chronic → thiazide
emergency → loop

Adverse effects:

+ cisplatin

1. Ototoxicity: Hearing can be affected adversely by the loop diuretics, particularly when used in conjunction with the aminoglycoside antibiotics.

2. Hyperuricemia: Furosemide and ethacrynic acid compete with uric acid for the renal and biliary secretory systems, thus blocking its secretion and, thereby, causing or exacerbating gouty attacks.

3. Acute hypovolemia: a severe and rapid reduction in blood volume, with the possibility of hypotension, shock, and cardiac arrhythmias.

4. Potassium depletion: leads to hypokalemic alkalosis.

5. Hypomagnesemia:

same as thiazid EXCEPT: Calcium

3. Potassium-Sparing Diuretics

- They act in the collecting tubule to inhibit Na^+ reabsorption and K^+ excretion .
- They are used alone primarily when aldosterone is present in excess.
- They are not very efficacious diuretics.

A. Aldosterone antagonists: Spironolactone

Mechanism of action:

Spironolactone is a synthetic steroid that antagonizes aldosterone at intracellular cytoplasmic receptor sites leading to inhibition of protein synthesis that stimulates the Na^+/K^+-exchange sites of the collecting tubule and therefore prevents Na^+ reabsorption and, therefore, K^+ and H^+ secretion.

Therapeutic uses:

It is given orally for:

1. Diuretic: it is often given in conjunction with a thiazide or loop diuretic to prevent the K^+ excretion. It is the diuretic of choice in patients with hepatic cirrhosis.
2. Secondary hyperaldosteronism:
3. Heart failure: It prevents the remodeling that occurs as compensation for the progressive failure of the heart.

Adverse effects:

1. It causes gastric upsets and peptic ulcers.
2. Gynecomastia in males
3. Menstrual irregularities in females;
4. At low doses, hyperkalemia, nausea, lethargy, and mental confusion can occur.

B. Epithelial sodium channel blocker :

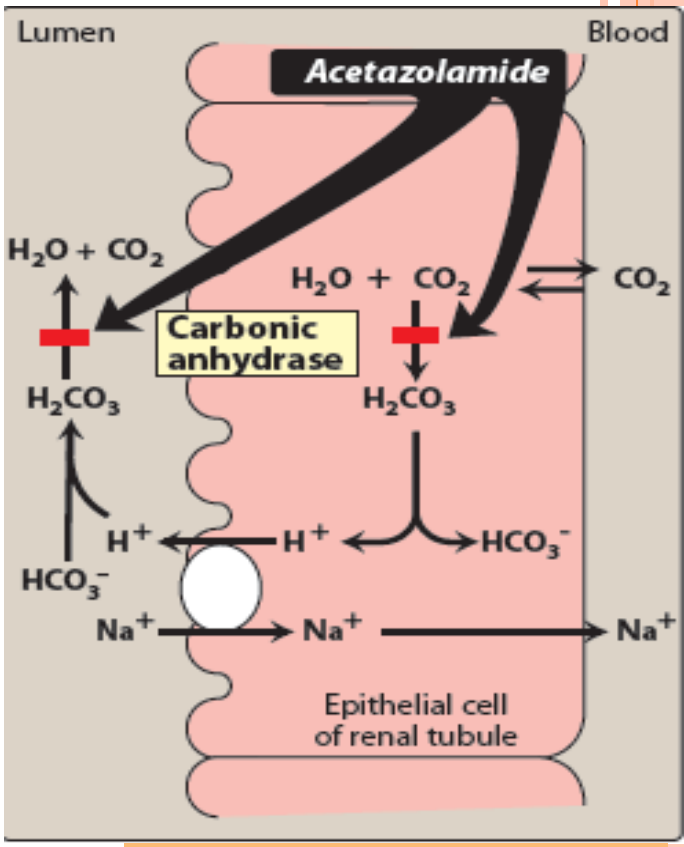
- Triamterene and amiloride block Na^+ transport channels, resulting in a decrease in Na^+/K^+ exchange.
- Both triamterene and amiloride are frequently used in combination with other diuretics, usually for their potassium-sparing properties.
- For example, much like spironolactone, they prevent the loss of K^+ that occurs with thiazides and furosemide.

Side effects

- Triamterene causes leg cramps and the possibility of increased blood urea nitrogen as well as uric acid and K^+ retention.

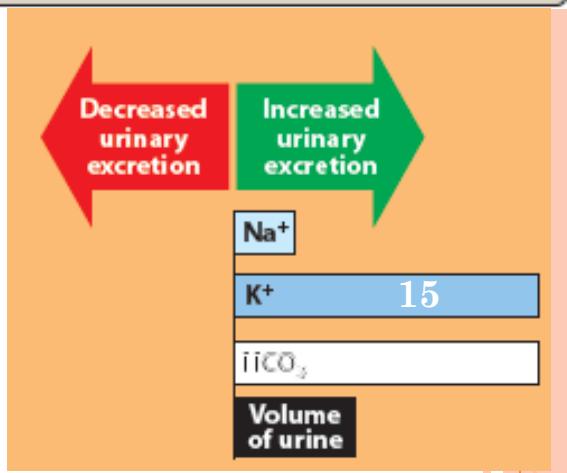
4. Carbonic Anhydrase Inhibitors

- **Acetazolamide**
- Carbonic anhydrase inhibitors are more often used for their other pharmacologic actions rather than for their diuretic effect, because they are much less efficacious than the thiazides or loop diuretics.



Mechanism of action:

- Acetazolamide inhibits carbonic anhydrase located intracellularly (cytoplasm) and on the apical membrane of the proximal tubular epithelium. The decreased ability to exchange Na^+ for H^+ in the presence of acetazolamide results in a mild diuresis.



Therapeutic uses:

1. Treatment of glaucoma (open angle): The most common use of acetazolamide is to reduce the elevated intraocular pressure of open-angle glaucoma. It decreases the production of aqueous humor, probably by blocking carbonic anhydrase in the ciliary.

Pharmacokinetics:

Acetazolamide is given orally/ topically (eye drops) once to four times daily. It is secreted by the proximal tubule.

Adverse effects:

- Metabolic acidosis (mild), potassium depletion, renal stone formation, drowsiness, and paresthesia may occur.

- The drug should be avoided in patients with hepatic cirrhosis, because it could lead to a decreased excretion of NH_4^+.

5. Osmotic Diuretics

- **Mannitol**
- They are agents that are freely filtered at the glomerulus, undergo limited reabsorption by the renal tubule, and are relatively inert pharmacologically.
- They are administered in large enough doses to increase significantly the osmolality of plasma and tubular fluid.
- Given i.v., filtered by glomeruli, but not reabsorbed by proximal tubule, increasing osmolarity of tubular fluid, thus retaining water with little Na+ in lumen of proximal tubule & descending limb of loop of Henle.
- The rate of flow of tubular fluid also increases (Flushing action), causing rapid powerful diuresis

- They also increase plasma osmolality , which can withdraw fluid from brain in cases of cerebral oedema or from anterior chamber of eye in acute glaucoma.

Therapeutic Uses :

1. It decreases cerebral oedema.
2. It decreases intra-ocular pressure in acute narrow angle glaucoma.
3. It increases excretion of drugs & heavy metal chelates in poisoning.
4. Prevent RF in early acute tubular necrosis and in severe haemolysis

Contraindication: heart failure ; established RF; (they may cause pulmonary oedema in these cases)

renal failure

Notable interactions between diuretics and other drugs

Diuretic drug(s)	Drug(s) interacting	Consequence	Comment
Acetazolamide	Phenytoin Phenobarbital Primidone	Osteomalacia and rickets	Uncertain mechanism
Acetazolamide	Aspirin or salicylates	Lethargy, confusion and coma	Acetazolamide-induced acidosis results in more salicylate entering the central nervous system, which can lead to salicylate intoxication
Thiazide, thiazide-like and loop diuretics	Cardiac glycosides	Increased cardiac glycoside-induced arrhythmias	Hypokalemia potentiates action of cardiac glycosides
Thiazide, thiazide-like and loop diuretics	Sulfonylureas (oral hypoglycemic drugs) and insulin	Hyperglycemia	Thiazides and to a lesser extent loop diuretics decrease insulin secretion
Thiazide, thiazide-like and loop diuretics	Lithium	Increased plasma levels of lithium with risk of toxic effects	Increased tubular reabsorption of lithium
Thiazide, thiazide-like and loop diuretics	Uricosuric agents	Reduced effect of uricosuric agents	Decreased tubular secretion of uricosuric agents
Thiazide, thiazide-like and loop diuretics	Nonsteroidal anti-inflammatory drugs	Reduced diuretic response	Interaction a result of inhibition of prostaglandin synthesis
Loop diuretics	Aminoglycosides Cisplatin	Increased risk of ototoxicity	Synergism of ototoxicity
Potassium-sparing diuretics	ACE inhibitors and K supplements	Increased risk of hyperkalemia	Additive hyperkalemic effects

Fig. 17.9 Notable interactions between diuretics and other drugs.