In the Name of GOD

Diuretics lecture note

Prepared and summarized by
M.R. Panjehshahin, Ph.D
Professor of Pharmacology
Shiraz Medical School

At the end of this lecture the students should be able to:

1- Describe the renal tubule transport mechanisms at proximal, loop of Henle, distal, collecting tubules and collecting duct.
2- Classify different diuretic agents and define the pharmacokinetics, mechanism of action, clinical uses and side effects of each different diuretic agents.
3- Name some important clinical situations in which the use of diuretics are vital.

Abnormalities in fluid volume and electrolyte composition arecommon and important clinical disorders. Drugs that block specific transport functions of the renal tubules are valuable clinicaltools in the treatment of these disorders. This chapter is divided into three sections.

The first sectioncovers major renal tubule transport mechanisms. The nephron isdivided structurally and functionally into several segments(Figure 15–1, Table 15–1) The second section describes thepharmacology of diuretic agents. Many diuretics exert their effectson specific membrane transport proteins in renal tubular epithelialcells. Other diuretics exert osmotic effects that prevent water reabsorption (mannitol), inhibit enzymes acetazolamide), or interferewith hormone receptors in renal epithelial cells (vaptans, or vasopressin antagonists). The physiology of each nephron segment isclosely linked to the basic pharmacology of the drugs acting there,which is discussed in the second section. The third section of thechapter describes the clinical applications of diuretics

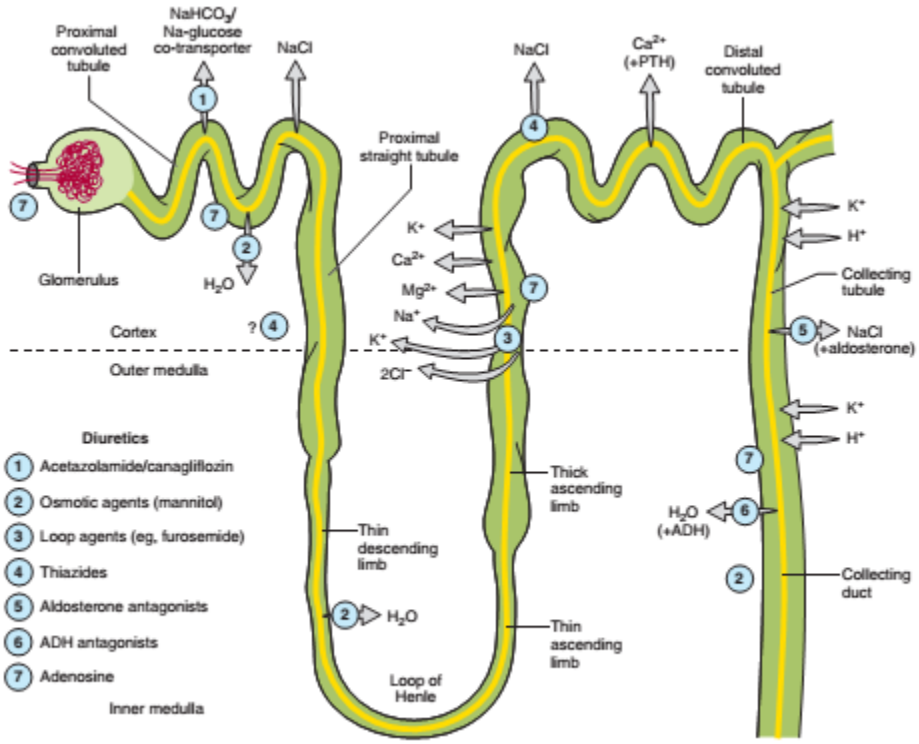

FIGURE 15–1 Tubule transport systems and sites of action of diuretics. ADH, antidiuretic hormone; PTH, parathyroid hormone.

■ RENAL TUBULE TRANSPORT MECHANISMS

PROXIMAL TUBULE

Approximately66% of filtered sodium ions (Na+), 85% of the NaHCO3, 65% ofthe K+, 60% of the water, and virtually all of the filtered glucoseand amino acids are reabsorbed in the proximal tubule.Of the various solutes reabsorbed in the proximal tubule, themost relevant to diuretic

action are NaHCO3 and NaCl. The H+ secreted intothe lumen combines with bicarbonate (HCO3−) to form H2CO3(carbonic acid), which is rapidly dehydrated to CO2 and H2O bycarbonic anhydrase. Carbon dioxide produced by dehydration ofH2CO3 enters the proximal tubule cell by simple diffusion, whereit is then rehydrated back to H2CO3, facilitated by intracellularcarbonic anhydrase. After dissociation of H2CO3, the H+ is available for transport by the Na+/H+ exchanger, and the HCO3− istransported out of the cell by a basolateral membrane transporter(Figure 15–2). Bicarbonate reabsorption by the proximal tubule is thus dependent on carbonic anhydrase activity.

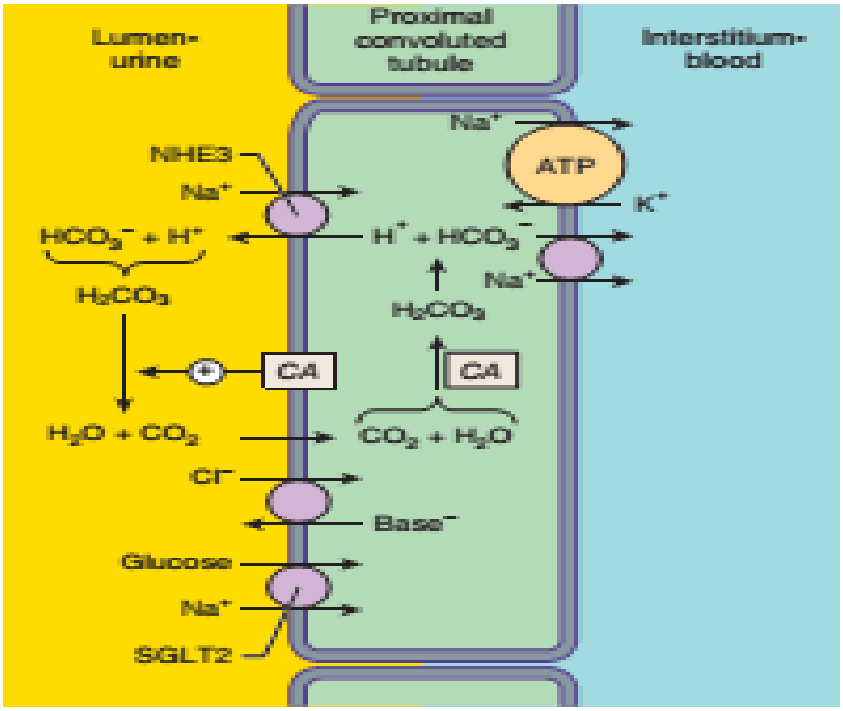

FIGURE 15–2 Apical membrane Na^+/H^+ exchange (via NHE3) and bicarbonate reabsorption in the proximal convoluted tubule cell. Na^+/K^+-ATPase is present in the basolateral membrane to maintain intracellular sodium and potassium levels within the normal range. Because of rapid equilibration, concentrations of the solutes are approximately equal in the interstitial fluid and the blood. Carbonic anhydrase (CA) is found in other locations in addition to the brush border of the luminal membrane. SGLT2, Na^+/glucose transporter.

Organic acid secretory systems are located in the middle third ofthe straight part of the proximal tubule (S2 segment). These systemssecrete a variety of organic acids (uric acid, nonsteroidal anti-inflammatory drugs [NSAIDs], diuretics, antibiotics, etc) into the luminalfluid from the blood. These systems thus help deliver diuretics tothe luminal side of the tubule, where most of them act. Organicbase secretory systems (creatinine, choline, etc) are also present, inthe early (S1) and middle (S2) segments of the proximal tubule.

LOOP OF HENLE

The proximal tubule empties into the thin descendinglimb of Henle's loop. Water is extracted from the descending limbof this loop by osmotic forces found in the hypertonic medullary interstitium. The **thick ascending limb (TAL)**, which follows the thinlimb of Henle's loop, actively reabsorbs NaCl from the lumen(about 25% of the filtered sodium). It is nearly impermeable to water. Salt reabsorption in the TAL thereforedilutes the tubular fluid, and it is called a *diluting segment*.The NaCl transport system in the luminal membrane of theTAL is a **Na+/K+/2Cl− cotransporter**(called **NKCC2** or **NK2CL**)(Figure 15–3). Backdiffusion of K+ into the tubular lumen (via the ROMK channel) causes a lumen-positive electrical potential that provides thedriving force for reabsorption of cations—including magnesiumand calcium—via the paracellular pathway.

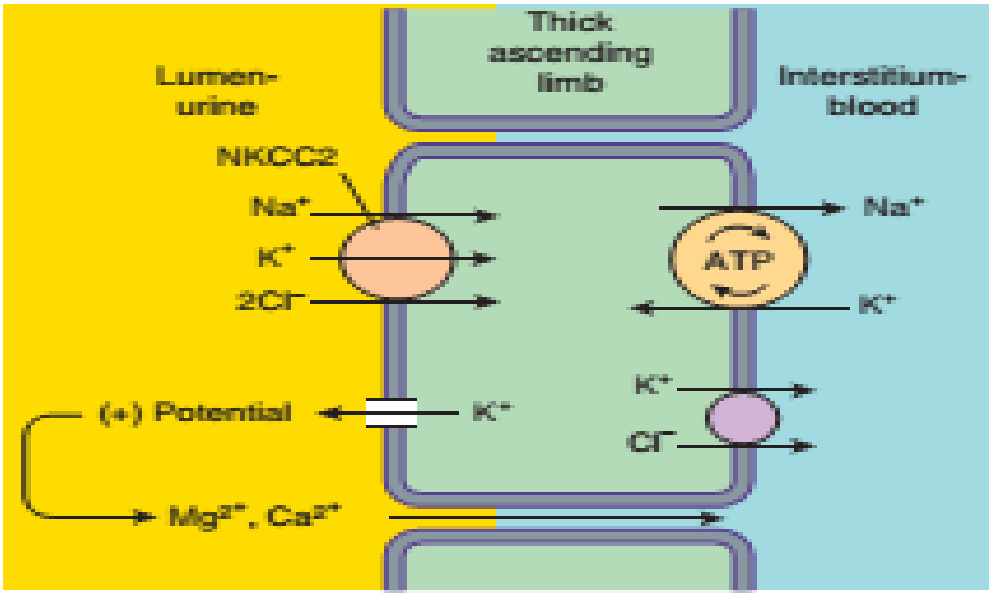

FIGURE 15–3 Ion transport pathways across the luminal and basolateral membranes of the thick ascending limb cell. The lumen positive electrical potential created by K^+ back diffusion drives divalent (and monovalent) cation reabsorption via the paracellular pathway. NKCC2 is the primary transporter in the luminal membrane

DISTAL CONVOLUTED TUBULE

Only about 10% of the filtered NaCl is reabsorbed in the distalconvoluted tubule (**DCT**). Like the TAL of Henle's loop, this segment is relatively impermeable to water, and NaCl reabsorption further dilutes the tubular fluid. The mechanism of NaCl transport in the DCT is an electrically neutral thiazide-sensitive **Na+/Cl− cotransporter (NCC**; Figure 15–4).Instead, Ca2+ is ctively reabsorbed by the DCT epithelial cell via an apical Ca2+ channel andbasolateral Na+/Ca2+ exchanger (Figure 15–4). This process isregulated by parathyroid hormone.

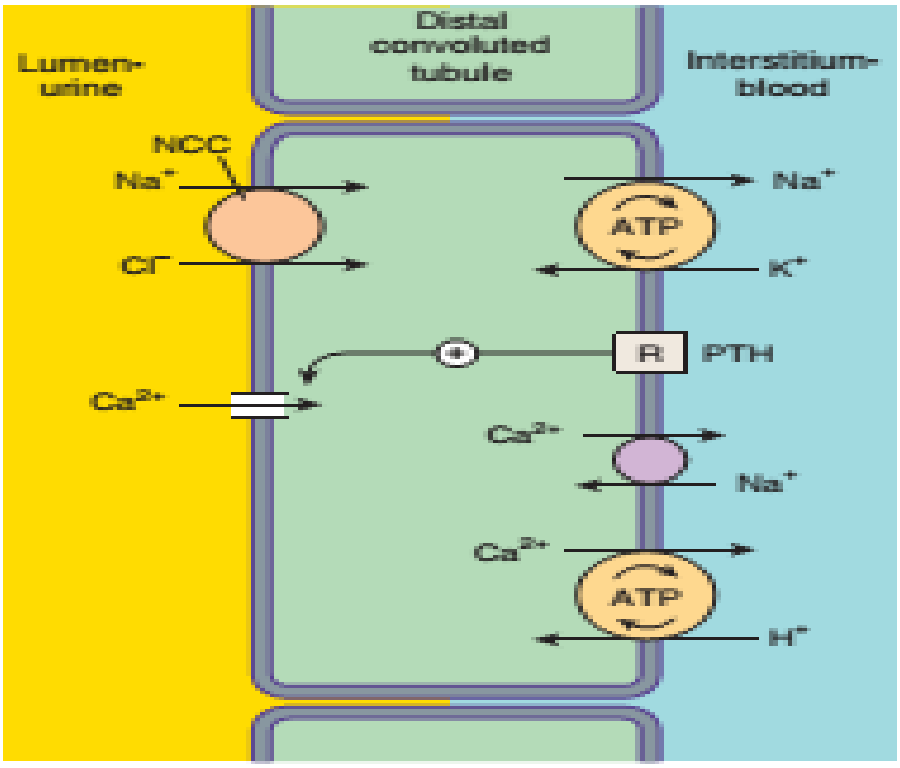

FIGURE 15–4 Ion transport pathways across the luminal and basolateral membranes of the distal convoluted tubule cell. As in all tubular cells, Na^+/K^+-ATPase is present in the basolateral membrane. NCC is the primary sodium and chloride transporter in the luminal membrane. (R, parathyroid hormone [PTH] receptor.)

COLLECTING TUBULE SYSTEM

Thecollecting tubule system is responsible for only 2–5% of NaClreabsorption by the kidney. Despite this small contribution, it plays an important role in renal physiology and in diuretic action.As the final site of NaCl reabsorption, the collecting system isresponsible for tight regulation of body fluid volume and fordetermining the final Na+ concentration of the urine. Furthermore,the collecting system is the site at which mineralocorticoids exerta significant influence. Lastly, this is the most important site of K+secretion by the kidney and the site at which virtually all diureticinduced changes in K+ balance occur.The collecting tubule system is also the site at which the finalurine concentration is determined. In addition to their role in control of Na+ absorption and K+ secretion (Figure 15–5), principal cellsalso contain a regulated system of water channels (Figure 15–6).Antidiuretic hormone (ADH) controls the permeability of these cells to water by regulating the insertion of pre-formed water channels **aquaporin-2,AQP2**) into the apical membrane. In the absence ofADH, the collecting tubule (and duct) is impermeable to water,and dilute urine is produced.

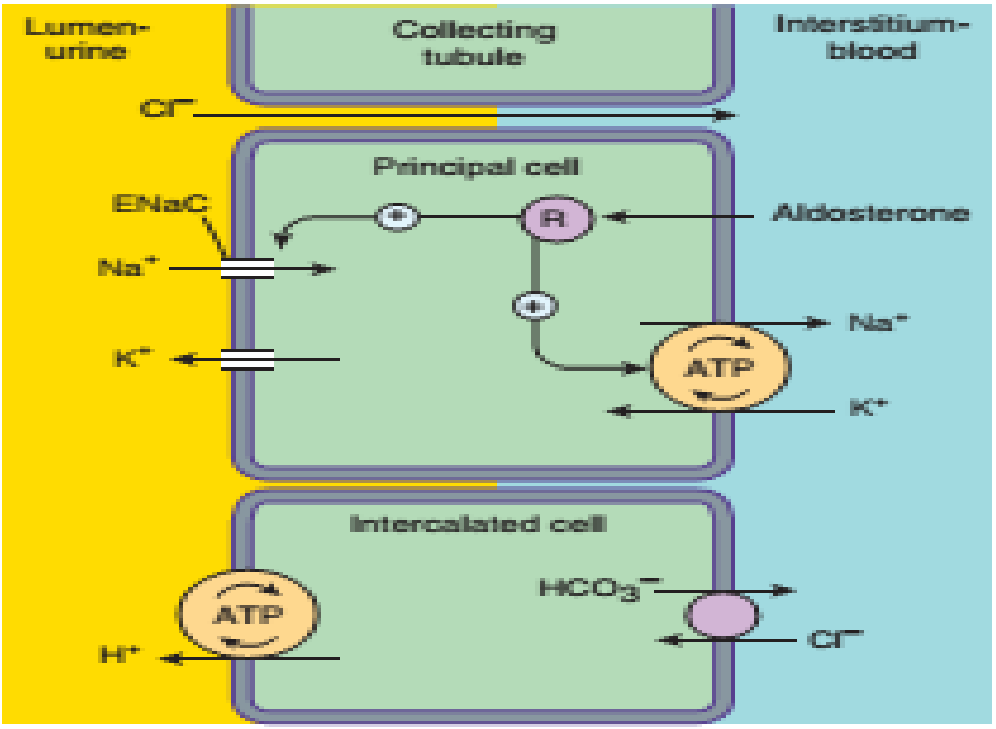

FIGURE 15–5 Ion transport pathways across the luminal and basolateral membranes of collecting tubule and collecting duct cells. Inward diffusion of Na^+ via the epithelial sodium channel (ENaC) leaves a lumen-negative potential, which drives reabsorption of Cl^- and efflux of K^+. (R, aldosterone receptor.)

TABLE 15–2 Changes in urinary electrolyte patterns and body pH in response to diuretic drugs.

	Urinary Electrolytes			
Group	**NaCl**	**$NaHCO_3$**	**K^+**	**Body pH**
Carbonic anhydrase inhibitors	+	+++	+	↓
Loop agents	++++	0	+	↑
Thiazides	++	+	+	↑
Loop agents plus thiazides	+++++	+	++	↑
K^+-sparing agents	+	(+)	–	↓

+, increase; –, decrease; 0, no change; ↓, acidosis; ↑, alkalosis.

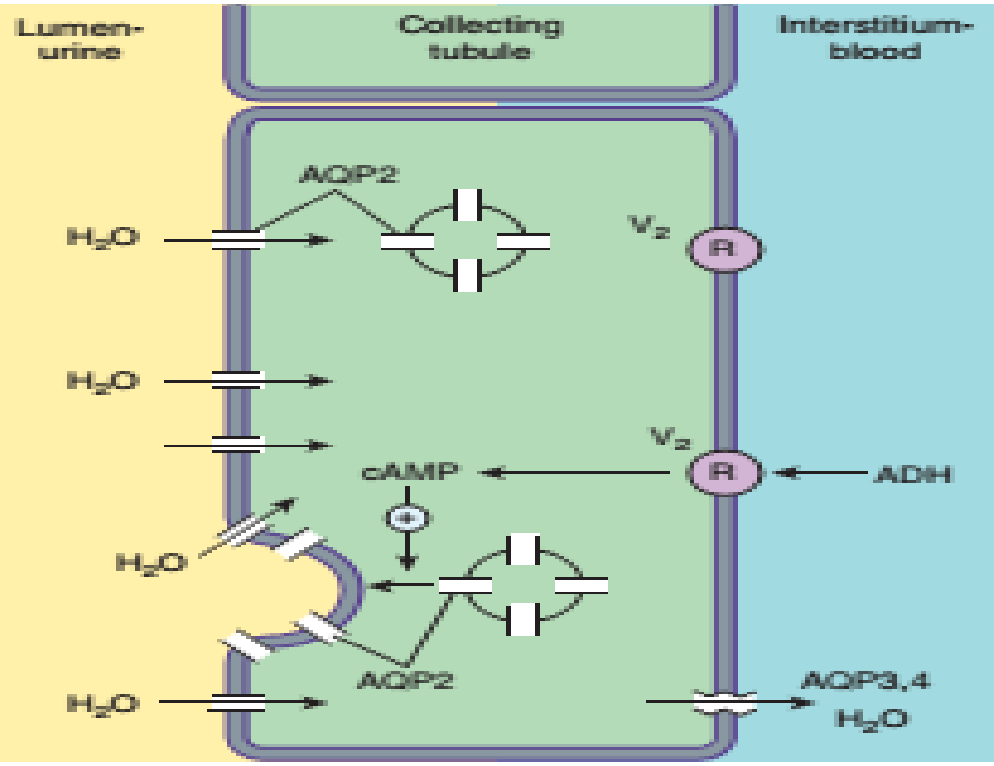

FIGURE 15–6 Water transport across the luminal and basolateral membranes of collecting duct cells. Above, low water permeability exists in the absence of antidiuretic hormone (ADH). Below, in the presence of ADH, aquaporins are inserted into the apical membrane, greatly increasing water permeability. (AQP2, apical aquaporin water channels; AQP3,4, basolateral aquaporin water channels; V_2, vasopressin V_2 receptor.)

■ BASIC PHARMACOLOGY OF DIURETIC AGENTS

CARBONIC ANHYDRASEINHIBITORS

Carbonic anhydrase is present in PCT and catalyzes the dehydration of H2CO3to CO2 at the luminal membrane and rehydration of CO2 toH2CO3 in the cytoplasm. By blockingcarbonic anhydrase, inhibitors blunt NaHCO3 reabsorption andcause diuresis (Figure 15–2).Carbonic anhydrase inhibitors are now rarely used asdiuretics, but they still have several specific applications that arediscussed below. The prototypical carbonic anhydrase inhibitor is **acetazolamide**.

Pharmacokinetics

The carbonic anhydrase inhibitors are well absorbed after oraladministration. An increase in urine pH from the HCO3− diuresisis apparent within 30 minutes, is maximal at 2 hours, and persistsfor 12 hours after a single dose. Excretion of the drug is by secretion in the proximal tubule S2 segment. Therefore, dosing must bereduced in renal insufficiency.

Pharmacodynamics

Inhibition of carbonic anhydrase activity profoundly depressesHCO3− reabsorption in the PCT. At its maximal safe dosage, 85%of the HCO3− reabsorptive capacity of the superficial PCT is inhibited. Some HCO3− can still be absorbed at other nephronsites by carbonic anhydrase–independent mechanisms, so theoverall effect of maximal acetazolamide dosage is only about 45%inhibition of whole kidney HCO3− reabsorption.

Clinical Indications & Dosage (Table 15–3)

A. Glaucoma

The reduction of aqueous humor formation by carbonic anhydrase inhibitors decreases the intraocular pressure. This effect isvaluable in the management of glaucoma in some patients. Topically active agents, which reduceintraocular pressure without producing renal or systemic effects, are available (**dorzolamide, brinzolamide**).

B. Urinary Alkalinization

Uric acid and cystine are relatively insoluble and may form stonesin acidic urine. Therefore, in cystinuria, solubility of cystine can be enhanced by increasing urinary pH to 7-7.5 with carbonic anhydrase inhibitors. Excessiveurinary alkalinization can lead to stone formation from calciumsalts (see below), so urine pH should be followed during treatmentwith acetazolamide.

C. Metabolic Alkalosis When the alkalosis is due to excessive use ofdiuretics in patients with severe heart failure, acetazolamide can be useful in correcting the alkalosis as well as producing a small additional diuresis for correction of volumeoverload. Acetazolamide can also be used to rapidly correct the
metabolic alkalosis that may appear following the correction ofrespiratory acidosis.

D. Acute Mountain Sickness

Weakness, dizziness, insomnia, headache, and nausea can occur inmountain travelers who rapidly ascend above 3000 m. In more serious cases,rapidly progressing pulmonary or cerebral edema can be lifethreatening. By decreasing CSF formation and by decreasing thepH of the CSF and brain, acetazolamide can increase ventilationand diminish symptoms of mountain sickness. This mild metabolic central and CSF acidosis is also useful in the treatment of
sleep apnea.

E. Other Uses

Carbonic anhydrase inhibitors have been used as adjuvants in thetreatment of epilepsy

Toxicity

A. Hyperchloremic Metabolic Acidosis

Acidosis predictably results from chronic reduction of bodyHCO3− stores by carbonicanhydrase inhibitors.

B. Renal Stones

Calcium phosphate salts are relatively insoluble at alkaline pH,which means that the potential for renal stone formation fromthese salts is enhanced.

C. Renal Potassium Wasting

Potassium wasting can occur because the increased Na+ presentedto the collecting tubule (with

HCO3−) is partially reabsorbed,increasing the lumen-negative electrical potential in that segmentand enhancing K+ secretion. This effect can be counteracted by simultaneous administration of potassium chloride or a K+-sparing diuretic. Potassium wasting is theoretically a problem withany diuretic that increases Na+ delivery to the collecting tubule.

D. Other Toxicities

Drowsiness and paresthesias are common following large doses ofacetazolamide. Carbonic anhydrase inhibitors may accumulate inpatients with renal failure, leading to nervous system toxicity.Hypersensitivity reactions (fever, rashes, bone marrow suppression,and interstitial nephritis) may also occur.

Contraindications

Carbonic anhydrase inhibitor–induced alkalinization of the urinedecreases urinary excretion of NH4+ (by converting it to rapidlyreabsorbed NH3) and may contribute to the development of **hyperammonemia**and **hepatic encephalopathy** in patients withcirrhosis.

LOOP DIURETICS

Loop diuretics selectively inhibit NaCl reabsorption in the TAL.and are the most efficacious diuretic agentscurrently available.The two prototypical drugs of this group are **furosemide** and **ethacrynic acid.** New drugs are**torsemide**and**bumetanide,**

Pharmacokinetics

The loop diuretics are rapidly absorbed. They are eliminated bythe kidney by glomerular filtration and tubular secretion.The duration of effect for furosemide is usually2–3 hours. Half-lifedepends on renal function. Since loop agents act on the luminalside of the tubule, their diuretic activity correlates with their secretionby the proximal tubule. Metabolites of ethacrynic acid and furosemide have been identified, but it is not known whetherthey have any diuretic activity.

Pharmacodynamics

Loop diuretics inhibit NKCC2, the luminal Na+/K+/2Cl− transporterin the TAL of Henle's loop. By inhibiting this transporter,the loop diuretics reduce the reabsorption of NaCl and also diminish the lumen-positive potential that comes from K+ recycling(Figure 15–3). Therefore, loop diuretics cause an increase in Mg2+and Ca2+ excretion. Prolonged use can cause significant hypomagnesemiain some patients. In disorders that cause hypercalcemia, Ca2+ excretion can be enhanced by treatment with loop diureticscombined with saline infusion. Loop agents have direct effects on blood flow through severalvascular beds. Furosemide increases renal blood flow via prostaglandinactions on kidney vasculature. Both furosemide and ethacrynic acid have also been shown to reduce pulmonary congestionand left ventricular filling pressures in heart failure beforea measurable increase in urinary output occurs. These effects on peripheral vascular tone are also due to release of renal prostaglandinsthat are induced by the diuretics.

Clinical Indications & Dosage

The most important indications for the use of the loop diureticsinclude **acute pulmonary edema, other edematous conditions,**and **acute hypercalcemia.** Other indications for loop diuretics include hyperkalemia, acute renal failure,and anion overdose.

A. Hyperkalemia

In mild hyperkalemia—or after acute management of severehyperkalemia by other measures—loop diuretics can significantlyenhance urinary excretion of K+. This response is enhanced by

Simultaneous NaCl and water administration.

B. Acute Renal Failure

Loop agents can increase the rate of urine flow and enhance K+retion in acute renal failure. However, they cannot prevent orshorten the duration of renal failure.

C. Anion Overdose

Loop diuretics are useful in treating toxic ingestions of bromide,fluoride, and iodide, which are reabsorbed in the TAL. Salinesolution must be administered to replace urinary losses of Na+ and to provide Cl−, so as to avoid extracellular fluid volumedepletion. The only exception is that loop diuretics should not be used in lithium overdose

Toxicity

A. Hypokalemic Metabolic Alkalosis

By inhibiting salt reabsorption in the TAL, loop diuretics increaseNa+ delivery to the collecting duct. Increased Na+ delivery leads toincreased secretion of K+ and H+ by the duct, causing hypokalemicmetabolic alkalosis (Table 15–2). This toxicity is a function of themagnitude of the diuresis and can be reversed by K+ replacementand correction of hypovolemia.

B. Ototoxicity

Loop diuretics occasionally cause dose-related hearing loss that isusually reversible. It is most common in patients whoare also receiving other ototoxicagents such as aminoglycoside antibiotics.

C. Hyperuricemia

Loop diuretics can cause hyperuricemia and precipitate attacks ofgout. This is caused by competition with uric acid in tubular secretion and also hypovolemia-associated enhancement of uric acid reabsorption in the proximal tubule.

D. Hypomagnesemia

Magnesium depletion is a predictable consequence of the chronicuse of loop agents and occurs most often in patients with dietarymagnesium deficiency. It can be reversed by administration of oralmagnesium preparations.

E. Allergic and Other Reactions

All loop diuretics, with the exception of ethacrynic acid, are sulfonamides.Therefore, skin rash, eosinophilia, and less often,interstitial nephritis are occasional adverse effects of these drugs. Allergic reactions are much less common with ethacrynic acid. Loop diuretics cancause severe dehydration. Patients who increase waterintake in response to hypovolemia-induced thirst can become severely hyponatremic with loop agents. Loop agents can cause hypercalciuria, which can lead to mild hypocalcemia and secondary hyperparathyroidism.

Contraindications

Furosemide, bumetanide, and torsemide may exhibit allergiccross-reactivity in patients who are sensitive to other sulfonamides,but this appears to be very rare. Overzealous use of any diuretic is dangerous in hepatic cirrhosis, borderline renal failure, or heart failure.

THIAZIDES

The thiazide diuretics were discovered in 1957, as a result of efforts to synthesize more potent carbonic anhydrase inhibitors. Some members of this group retain significant carbonic anhydrase inhibitory activity (eg, chlorthalidone). The prototypical thiazide is **hydrochlorothiazide (HCTZ).**

Pharmacokinetics

All thiazides can be administered orally, but there are differences in their metabolism. HCTZ is considerably more potent and should be used in much lower doses. **Chlorthalidone** is slowly absorbed and has a longer duration of action. All thiazides are secreted by the organic acid secretary 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 from the luminal side of epithelial cells in the DCT by blocking the Na^+/Cl^- transporter (NCC). In contrast to the situation in the TAL, in which loop diuretics inhibit Ca^{2+} reabsorption, thiazides actually enhance Ca^{2+} reabsorption. Thiazides are sometimes useful in the prevention of calcium-containing kidney stones caused by hypercalciuria.

Clinical Indications

The major indications for thiazide diuretics are (1) hypertension, (2) heart failure, (3) nephrolithiasis due to idiopathic hypercalciuria, and (4) nephrogenic diabetes insipidus.

Toxicity

A. Hypokalemic Metabolic Alkalosis and Hyperuricemia

These toxicities are similar to those observed with loop diuretics

B. Impaired Carbohydrate Tolerance

Hyperglycemia may occur in patients who are overtly diabetic or who have even mildly abnormal glucose tolerance tests. The effect is due to both impaired pancreatic release of insulin and diminished tissue utilization of glucose. This effect is exacerbated by hypokalemia, and thus thiazide-induced hyperglycemia may be partially reversed with correction of hypokalemia.

C. Hyperlipidemia

Thiazides cause a 5–15% increase in total serum cholesterol and low-density lipoproteins (LDLs). These levels may return toward baseline after prolonged use.

D. Hyponatremia

Hyponatremia is an important adverse effect of thiazide diuretics. It is caused by a combination of hypovolemia-induced elevation of ADH, reduction in the diluting capacity of the kidney, and increased thirst. It can be prevented by reducing the dose of the drug or limiting water intake.

E. Allergic Reactions

The thiazides are sulfonamides and share cross-reactivity with other members of this chemical group. Photosensitivity or generalized dermatitis occurs rarely. Serious allergic reactions are extremely rare but do include hemolytic anemia, thrombocytopenia, and acute necrotizing pancreatitis.

F. Other Toxicities

Weakness, fatigability, and paresthesias similar to those of carbonic anhydrase inhibitors may occur. Impotence has been reported but is probably related to volume depletion.

Contraindications

Excessive use of any diuretic is dangerous in patients with hepatic cirrhosis, borderline renal failure, or heart failure (see text that follows).

POTASSIUM-SPARING DIURETICS

Potassium-sparing diuretics prevent K^+ secretion by antagonizing the effects of aldosterone in collecting tubules. Inhibition may occur by direct pharmacologic antagonism of mineralocorticoid receptors **(spironolactone, eplerenone)** or by inhibition of Na^+ influx through ion channels in the luminal membrane **(amiloride, triamterene).**

Pharmacokinetics

Spironolactone is a synthetic steroid that acts as a competitive antagonist to aldosterone. Overall, spironolactone has a rather slow onset of action, requiring several days before full therapeutic effect is achieved. Eplerenone is a spironolactone analog with much greater selectivity for the mineralocorticoid receptor. It is several hundredfold less active on androgen and progesterone receptors than spironolactone, Amiloride and triamterene are direct inhibitors of Na+ influx in the CCT. Triamterene is metabolized in the liver, but renal excretion is a major route of elimination for the active form and the metabolites. Because triamterene is extensively metabolized, it has a shorter half-life and must be given more frequently than amiloride (which is not metabolized).

Pharmacodynamics

Potassium-sparing diuretics reduce Na+ absorption in the collecting tubules and ducts. Sodium absorption (and K+ secretion) at this site is regulated by aldosterone. Aldosterone antagonists interfere with this process. Similar effects are observed with respect to H+ handling by the intercalated cells of the collecting tubule, in part explaining the metabolic acidosis seen with aldosterone antagonists (Table 15–2). Amiloride and triamterene do not block aldosterone but instead directly interfere with Na+ entry through the epithelial Na+ channels (ENaC; Figure 15–5) in the apical membrane of the collecting tubule. Since K+ secretion is coupled with Na+ entry in this segment, these agents are also effective K+-sparing diuretics.

Clinical Indications

Potassium-sparing diuretics are most useful in states of mineralocorticoid excess or hyperaldosteronism or other conditions associated with diminished effective intravascular volume). Use of diuretics such as thiazides or loop agents can cause or exacerbate volume contraction and may cause secondary hyperaldosteronism. In the setting of enhanced mineralocorticoid secretion and excessive delivery of Na+ to distal nephron sites, renal K+ wasting occurs. Potassium-sparing diuretics of either type may be used in this setting to blunt the K+ secretory response.

Toxicity

A. Hyperkalemia

Unlike most other diuretics, K+-sparing diuretics reduce urinary excretion of K+ and can cause mild, moderate, or even life-threatening hyperkalemia. With fixed-dosage combinations of K+-sparing and thiazide diuretics, the thiazide-induced hypokalemia and metabolic alkalosis are ameliorated

B. Hyperchloremic Metabolic Acidosis

By inhibiting H+ secretion in parallel with K+ secretion, the K+- sparing diuretics can cause acidosis similar to that seen with type IV renal tubular acidosis.

C. Gynecomastia

Synthetic steroids may cause endocrine abnormalities by actions on other steroid receptors. Gynecomastia, impotence, and benign prostatic hyperplasia (very rare) all have been reported with spironolactone. Such effects have not been reported with eplerenone, presumably because it is much more selective than spironolactone for the mineralocorticoid receptor and virtually inactive on androgen or progesterone receptors.

D. Acute Renal Failure
The combination of triamterene with indomethacin has been reported to cause acute renal failure. This has not been reported with other K+-sparing diuretics.
E. Kidney Stones
Triamterene is only slightly soluble and may precipitate in the urine, causing kidney stones.

Contraindications
Potassium-sparing agents can cause severe, even fatal, hyperkalemia in susceptible patients. Patients with chronic renal insufficiency are especially vulnerable and should rarely be treated with these diuretics.

AGENTS THAT ALTER WATER EXCRETION (AQUARETICS)

OSMOTIC DIURETICS
The proximal tubule and descending limb of Henle's loop are freely permeable to water. Any osmotically active agent that is filtered by the glomerulus but not reabsorbed causes water to be retained in these segments and promotes a water diuresis. The prototypic osmotic diuretic is **mannitol.**

Pharmacokinetics
Mannitol is poorly absorbed by the GI tract, and when administered orally, it causes osmotic diarrhea rather than diuresis. For systemic effect, mannitol must be given intravenously. Mannitol is not metabolized and is excreted by glomerular filtration within 30–60 minutes, without any important tubular reabsorption or secretion.

Pharmacodynamics
Osmotic diuretics have their major effect in the proximal tubule and the descending limb of Henle's loop. Through osmotic effects, they also oppose the action of ADH in the collecting tubule. The presence of a nonreabsorbable solute such as mannitol prevents the normal absorption of water by interposing a countervailing osmotic force. As a result, urine volume increases.

Clinical Indications
Reduction of Intracranial and Intraocular Pressure
Osmotic diuretics alter Starling forces so that water leaves cells and reduces intracellular volume. This effect is used to reduce intracranial pressure in neurologic conditions and to reduce intraocular pressure before ophthalmologic procedures. Intracranial pressure, which must be monitored, should fall in 60–90 minutes.

Toxicity
A. Extracellular Volume Expansion
Mannitol is rapidly distributed in the extracellular compartment and extracts water from cells. Prior to the diuresis, this leads to expansion of the extracellular volume and hyponatremia. This effect can complicate heart failure and may produce florid pulmonary edema. Headache, nausea, and vomiting are commonly observed in patients treated with osmotic diuretics.
B. Dehydration, Hyperkalemia, and Hypernatremia
Excessive use of mannitol without adequate water replacement can ultimately lead to severe dehydration, free water losses, and hypernatremia.

As water is extracted from cells, intracellular K+ concentration rises, leading to cellular losses and hyperkalemia. These complications can be avoided by careful attention to serum ion composition and fluid balance.

C. Hyponatremia

When used in patients with severe renal impairment, parenterally administered mannitol cannot be excreted and is retained in the blood. This causes osmotic extraction of water from cells, leading to hyponatremia

ANTIDIURETIC HORMONE ANTAGONISTS

A variety of medical conditions, including congestive heart failure (CHF) and the syndrome of inappropriate ADH secretion (SIADH), cause water retention as a result of excessive ADH secretion. Until recently, two nonselective agents, lithium and demeclocycline, were used for their well-known interference with ADH activity. Demeclocycline is used more often than lithium because of the many adverse effects of lithium administration. However, demeclocycline is now being rapidly replaced by several specific ADH receptor antagonists **(vaptans)**, which have yielded encouraging clinical results.

Pharmacokinetics

The half-lives of demeclocycline is 5–10 hours,

Pharmacodynamics

Antidiuretic hormone antagonists inhibit the effects of ADH in the collecting tubule. Both lithium and demeclocycline reduce ADH-induced cAMP by mechanisms that are not yet completely clarified.

Clinical Indications

A. Syndrome of Inappropriate ADH Secretion

Antidiuretic hormone antagonists are used to manage SIADH when water restriction has failed to correct the abnormality.

B. Other Causes of Elevated Antidiuretic Hormone

Antidiuretic hormone is also elevated in response to diminished effective circulating blood volume, as often occurs in heart failure. When treatment by volume replacement is not desirable, hyponatremia may result.

Toxicity

A. Nephrogenic Diabetes Insipidus

If serum Na+ is not monitored closely, any ADH antagonist can cause severe hypernatremia and nephrogenic diabetes insipidus. If lithium is being used for a psychiatric disorder, nephrogenic diabetes insipidus can be treated with a thiazide diuretic or amiloride

B. Renal Failure

Both lithium and demeclocycline have been reported to cause acute renal failure. Long-term lithium therapy may also cause chronic interstitial nephritis.

C. Other

Dry mouth and thirst are common with many of these drugs. Demeclocycline should be avoided in patients with liver disease and in children younger than 12 years.

Reference:

Basic & Clinical Pharmacology, Katzung- 13th Edition, 2015, Mc Graw Hill pp. 249-269