CHAPTER 14
Use of Diuretics in the Newborn
Jean-Pierre Guignard, MD

Body Fluid Homeostasis
Clinical Use of Diuretics
Adverse Effects of Diuretics

Diuretics are pharmacologic agents that increase the excretion of water and electrolytes. They are primarily used in states of inappropriate salt and water retention. Such states can be the consequence of congestive heart failure (CHF), renal diseases, and liver disease. Diuretics are also used in various conditions not evidently associated with salt retention. Such conditions include oliguric states, respiratory disorders, electrolyte disorders, and nephrogenic diabetes insipidus. Diuretics can also be valuable tools in the laboratory differential diagnosis of congenital tubulopathies.

The rationale use of diuretics in newborn infants requires a clear understanding of the physiology and physiopathology of immature kidneys.¹,2

Body Fluid Homeostasis

The kidney is responsible for maintaining the extracellular fluid (ECF) volume and osmolality constant despite larges variations in salt and water intake.

Extracellular Fluid Volume

NaCl, the major osmotically active solute in ECF, determines its volume. The overall balance between sodium intake and its urinary excretion thus regulates ECF volume and consequently cardiac output and blood pressure. Volume receptors are distributed in the low-pressure capacitance vessels (great veins and atria) as well as in the high-pressure resistance vessels (arterial vascular tree). Arterial sensors perceive the adequacy of blood flow in the arterial circuit, a parameter coined as effective arterial circulating volume. This volume is also monitored by baroreceptors located in the juxtaglomerular apparatus of the kidney. When sensed by these receptors, a decrease in renal perfusion pressure leads to the activation of the renin–angiotensin–aldosterone system (RAAS). Aldosterone stimulates sodium reabsorption and potassium excretion. Although aldosterone is the main hormone regulating long-term changes in sodium excretion, other hormones and paracrine factors, including angiotensin II, the prostaglandins, dopamine, the catecholamines, and atrial natriuretic peptide (ANP), also modulate sodium renal handling. The release of the latter, a potent vasodilator and natriuretic agent, is modulated by sensors (the stretch receptors) that sense the atrial filling volume.³

Plasma Osmolality

The plasma osmolality is maintained within narrow limits.³ Small 2% to 3% changes in plasma osmolality are sensed by osmoreceptors located in the hypothalamus, which by stimulating or inhibiting the release of vasopressin, lead to increases or decreases in the excretion of free water. By acting on the baroreceptors, the effective
circulating volume also influence the release of vasopressin. Dilution of urine depends on sodium delivery to the distal nephron diluting site, and the concentration of urine, modulated by vasopressin, requires the presence of a hypertonic renal medullary interstitium.3

**Clinical Use of Diuretics**

**Sodium-Retaining States**

Sodium retention is the primary target of diuretics. Salt and water retention with or without edema formation can occur as a primary event or as a consequence of reduced effective circulating volume with secondary hyperaldosteronism. CHF is the main neonatal condition associated with sodium retention.4 The increased pressure in the venous circulation and capillaries favors the movement of fluid into the interstitium and leads to the formation of edema. Failure of the heart to provide normal tissue perfusion is sensed as a decrease in effective circulating volume by the kidney, which retains sodium and water. Treatment of the condition consists in restoring normal cardiac output. By mobilizing the edematous fluid, diuretics improve the symptoms of CHF. The pulmonary edema secondary to left heart failure requires the urgent use of diuretics to reduce the life-threatening pulmonary congestion.5,6 The use of diuretics can be lifesaving when the ECF volume is expanded.

Diuretics may on the contrary further compromise the patient’s condition when sodium retention occurs in response to homeostatic mechanisms mobilized to defend the circulating volume. The same reasoning applies to states of nephrotic or liver cirrhosis edemas.7,8 The use of diuretics (loop diuretics, thiazides, and potassium-sparing diuretics) in these conditions requires a clear understanding of the patient’s underlying pathophysiologic condition and careful monitoring of the hemodynamic state.5,6

**Oliguric States**

Loop diuretics are often administered to patients with oliguric renal insufficiency in the hope of promoting diuresis and improving renal perfusion and glomerular filtration rate (GFR). When present, the diuretic response may actually worsen the renal hypoperfusion.9,10

**Respiratory Disorders**

Interstitial and alveolar edema is present in idiopathic respiratory distress syndrome (RDS) of preterm babies as well as in transient tachypnea of term neonates. Inadequate fetal lung fluid clearance is partly responsible for the edema. Administration of diuretics (loop diuretics) could accelerate the reabsorption of lung fluid and ameliorate pulmonary recovery in these patients with lung edema.11

**Central Nervous System Disorders**

Large hemorrhages into the brain ventricles may result in fluid retention and dilatation of the fluid-producing brain cavities. Diuretics (acetazolamide, furosemide) are sometimes used to prevent or reduce the accumulation of fluid in the ventricles.12

**Electrolyte Disorders**

Diuretics can be used in various situations associated with dyselectrolytemia. They can increase potassium excretion in hyperkalemic states (loop diuretics, thiazides), increase calcium excretion in hypercalcemia (loop diuretics), or decrease the rate of calcium excretion in hypercalciuric states (thiazides). Increased bicarbonate excretion can be achieved by acetazolamide, and increased excretion of hydrogen ions can be stimulated by loop diuretics.5,13,14

**Nephrogenic Diabetes Insipidus**

Diuretics (thiazides) can paradoxically decrease urine output in nephrogenic diabetes insipidus.15
Arterial Hypertension

Arterial hypertension may be a consequence of or aggravated by sodium retention and consecutive expansion of the ECF volume. This type of hypertension responds to diuretic-induced natriuresis.15

Differential Diagnosis of Congenital Tubulopathies

Diuretics such as acetazolamide, furosemide, and hydrochlorothiazide can be used to test distal tubular acidification or distal sodium reabsorption defects in patients with congenital tubulopathies.

Classification of Diuretics According to the Site of Action

Diuretics can be classified according to their site and mode of action (Fig. 14-1 and Table 14-1). They all increase sodium and water excretion and variably modify the excretion of other electrolytes (Table 14-2). Filtration diuretics increase salt and water excretion by primarily increasing GFR. Osmotic diuretics depress salt and electrolyte reabsorption in the proximal tubule and in Henle loop. Carbonic anhydrase inhibitors act primarily on the proximal tubule. Loop diuretics, the most potent diuretics, inhibit Na⁺ reabsorption in the ascending limb of Henle loop. The thiazide and thiazide-like diuretics act in the distal convoluted tubule and potassium-sparing diuretics in the late distal tubule and collecting duct.13,14 New diuretics with different modes of action (adenosine antagonists, natriuretic peptides, vasopressin antagonists) are being developed and tested. All diuretics share adverse effects that are actually extensions of their primary effects on electrolyte excretion (Table 14-3), as well as non-electrolyte adverse effects (Table 14-4).

Although diuretics are very widely used in intensive care neonatal units, the extent of and expectations for diuretic therapy by neonatologists caring for low birth weight neonates may, as stated in a recent survey,17 exceed evidence for efficacy (Table 14-5). The dosages of diuretics commonly used in neonates are given in Table 14-6.

**Figure 14-1**  Sites 1 to 5: sites of sodium transport along the nephron. Numbers 1 to 5 represent the sites and mechanisms of Na⁺ transport. The group of diuretics acting at the different sites is indicated in brackets. 1, Na⁺ / H⁺ exchanger NHE1. 2, Na⁺glucose cotransporter SLGT2. 3, Na⁺, K⁺, 2Cl⁻ cotransporter (furosemide receptor): NKCC2 (loop diuretics). 4, Na⁺, Cl⁻ cotransporter (thiazide receptor): NCC (thiazides). 5, H⁺, K⁺ ATPase and epithelial sodium channel (amiloride receptor): ENaC (potassium-sparing diuretics). The aquanetcs act on the collecting duct V₂R arginine vasopressin receptor. CAI, carbonic anhydrase inhibitor; ENaC, sodium epithelium channel.
Table 14-2  ACUTE EFFECTS OF DIURETICS ON ELECTROLYTE EXCRETION*

<table>
<thead>
<tr>
<th></th>
<th>Na⁺</th>
<th>K⁺</th>
<th>Ca²⁺</th>
<th>Mg²⁺</th>
<th>H⁺</th>
<th>Cl⁻</th>
<th>HCO₃⁻</th>
<th>H₂PO₄⁻</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbonic anhydrase inhibitors</td>
<td>↑</td>
<td>↑↑</td>
<td>=</td>
<td>~</td>
<td>↓</td>
<td>(↑)</td>
<td>↑↑</td>
<td>↑↑</td>
</tr>
<tr>
<td>Loop diuretics</td>
<td>↑↑</td>
<td>↑↑</td>
<td>↑↑</td>
<td>↑↑</td>
<td>↑</td>
<td>↑↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Thiazide diuretics</td>
<td>↑</td>
<td>↑↑</td>
<td>~</td>
<td>(↑)</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>K⁺-sparing diuretics</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
<td>(↑)</td>
<td>=</td>
</tr>
</tbody>
</table>

*In the absence of significant volume depletion, which would trigger complex adjustments.
(↑), slight increase; ↑, moderate increase; ↑↑, marked increase; ↓, decrease; =, no change; ~, variable effects.

Filtration Diuretics

Agents that increase diuresis by increasing GFR are called filtration diuretics. These agents include the glucocorticoids; theophylline; and inotropic agents such as isoproterenol, dopamine, and dobutamine. By increasing GFR, these drugs only moderately increase Na⁺ excretion. Dopamine and theophylline are sometimes used in neonates in the hope of improving renal perfusion and GFR rather than for their natriuretic and diuretic effect. They are discussed in Chapter 5.
### Table 14-3  
**ELECTROLYTE DISTURBANCES INDUCED BY DIURETICS COMMONLY USED IN NEONATES**

<table>
<thead>
<tr>
<th>Electrolyte Disturbance</th>
<th>Loop</th>
<th>Thiazides</th>
<th>K⁺-Sparing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypovolemia</td>
<td>+++</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>++</td>
<td>+++</td>
<td>-</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>+++</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>-</td>
<td>-</td>
<td>++</td>
</tr>
<tr>
<td>Hypercalciuria</td>
<td>++</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Hypercalcemia</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Hypomagnesemia</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>*</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Hyperuricemia</td>
<td>++</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Metabolic acidosis</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Metabolic alkalosis</td>
<td>++</td>
<td>++</td>
<td>-</td>
</tr>
</tbody>
</table>

***, marked increase in electrolyte disturbances; ***, moderate increase in electrolyte disturbances; *, mild increase in electrolyte disturbances. A, indicates no effects. Adapted from ref 13.

### Table 14-4  
**GENERAL NON-ELECTROLYTE SIDE EFFECTS OF DIURETICS**

<table>
<thead>
<tr>
<th>Diuretic</th>
<th>Non-electrolyte Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbonic anhydrase inhibitors</td>
<td>CNS depression, paresthesia, calculus formation</td>
</tr>
<tr>
<td>Loop diuretics</td>
<td>Ototoxicity (usually reversible), nephrocalcinosis in neonates, PDA in neonates, hyperuricemia, hyperglycemia, hyperlipidemia, hypersensitivity</td>
</tr>
<tr>
<td>Thiazides</td>
<td>Hyperglycemia, insulin resistance, hyperlipidemia, hypersensitivity (fever, rash, purpura, anaphylaxis, interstitial nephritis), hyperuricemia</td>
</tr>
<tr>
<td>K⁺-sparing</td>
<td>Amiloride Diarrhea, headache</td>
</tr>
<tr>
<td>Amiloride</td>
<td></td>
</tr>
<tr>
<td>Triamterene</td>
<td>Glucose intolerance, interstitial nephritis, blood dyscrasias</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>Gynecomastia, hirsutism, peptic ulcers, ataxia, headache</td>
</tr>
</tbody>
</table>

CNS, central nervous system; PDA, patent ductus arteriosus.

### Table 14-5  
**SPECIFIC INDICATIONS WITH QUESTIONABLE BENEFITS IN CLINICAL TRIALS**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Diuretic(s)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oliguric prerenal failure</td>
<td>Mannitol, Furosemide</td>
<td>Better et al, Rigden et al, Kellum, Dubourg et al</td>
</tr>
<tr>
<td>Respiratory distress syndrome</td>
<td>Furosemide</td>
<td>Jain and Eaton</td>
</tr>
<tr>
<td>Transient tachypnea of the newborn</td>
<td>Furosemide</td>
<td>Wiswell et al, Lewis and Whitelaw</td>
</tr>
<tr>
<td>Posthemorrhagic ventricular dilatation</td>
<td>Furosemide + acetazolamide</td>
<td>International PHVD Drug Trial Group, Kennedy et al, International PHVD Drug Trial Group, Whitelaw et al</td>
</tr>
</tbody>
</table>

Continued
### Table 14-6 DOSAGES OF DIURETICS COMMONLY USED IN NEONATES

<table>
<thead>
<tr>
<th>Drug</th>
<th>Route/Interval (qh)</th>
<th>Dosage (mg/kg/day)</th>
<th>Half-life (h)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Furosemide</td>
<td>PO: 12–24</td>
<td>1–2</td>
<td>≈1.5 idem</td>
<td>Effective at GFR &lt;10 Doses may be increased up to 5 mg/kg in CRF Hypokalemia; Mg, Ca depletion Ototoxicity; metabolic alkalosis</td>
</tr>
<tr>
<td></td>
<td>IV: 12–24 CIVI</td>
<td>0.5–1.5</td>
<td>≈3.5</td>
<td>Longer half-life and larger duration than furosemide Effective at GFR &lt;10 Idem furosemide</td>
</tr>
<tr>
<td>Torasemide</td>
<td>PO</td>
<td>0.5–1</td>
<td>≈1</td>
<td>Effective at GFR &lt;10 Idem furosemide</td>
</tr>
<tr>
<td>Ethacrynic acid</td>
<td>PO: 12–24</td>
<td>1–2</td>
<td>≈1</td>
<td>Effective at GFR &lt;10 Idem furosemide</td>
</tr>
<tr>
<td>Bumetanide</td>
<td>PO: 12–24 IV: 12–24 CIVI</td>
<td>0.01–0.10 0.01–0.05 5–10 µg/kg/h</td>
<td>≈1 idem</td>
<td>Effective at GFR &lt;10 Idem furosemide</td>
</tr>
<tr>
<td>Hydrochlorothiazide</td>
<td>PO: 12–24</td>
<td>1–3</td>
<td>≈2.5</td>
<td>Not effective at GFR &lt;20 Hypokalemia metabolic alkalosis</td>
</tr>
<tr>
<td>Chlorthalidone</td>
<td>PO: 24–48</td>
<td>0.5–2.0</td>
<td>45</td>
<td>Not effective at GFR &lt;20 Hypokalemia metabolic alkalosis</td>
</tr>
<tr>
<td>Metolazone</td>
<td>PO: 12–24</td>
<td>0.2–0.4</td>
<td>8–10</td>
<td>Effective at GFR &lt;20 Hypokalemia</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>PO: 6–12</td>
<td>1–3</td>
<td>≈1.6</td>
<td>Delayed effect. Cave CRF or K suppl. Hyperkalemia, acidosis</td>
</tr>
<tr>
<td>Canrenoate-K</td>
<td>IV: 24</td>
<td>4–10</td>
<td>≈16</td>
<td>Single IV dose Hyperkalemia, acidosis</td>
</tr>
<tr>
<td>Triamterene</td>
<td>PO: 12–24</td>
<td>2–4</td>
<td>≈4.2</td>
<td>Cave RF or K suppl. Hyperkalemia, acidosis</td>
</tr>
<tr>
<td>Amiloride</td>
<td>PO: 24</td>
<td>0.5</td>
<td>≈21</td>
<td>Cave RF or K suppl. Hyperkalemia, acidosis</td>
</tr>
</tbody>
</table>

CIVI, constant IV infusion; CRF: chronic renal failure; GFR: glomerular filtration rate (mL/min/1.73 m²); IV, intravenous; PO, oral.

Osmotic Diuretics

Osmotic diuretics are agents that inhibit the reabsorption of solute and water by altering osmotic driving forces along the nephron.

Chemistry

Mannitol, a hexahydric alcohol related to mannose with a molecular weight of 182 d, is the main representative of this class of agents.\textsuperscript{18}

Mechanisms and Sites of Action

Freely filtered and (mostly) not reabsorbed, osmotic diuretics increase the tubular fluid osmolality, thus impairing the diffusion of water out of the tubular lumen, as well as that of NaCl by a solvent drag effect. The osmotic diuretics act in the proximal tubule and in the loop of Henle. By attracting water from the intracellular compartment, osmotic diuretics increase ECF volume and renal blood flow. Increased medullary blood flow washes out the hypertonic medulla, thus impairing the concentrating mechanism. By inhibiting NaCl reabsorption out of the water-impermeable thick ascending limb, osmotic diuretics also impair the dilution of urine. Osmotic diuretics increase nonspecifically the excretion of all electrolytes. The natriuresis induced by osmotic diuretics is only about 10% of the filtered load.

Efficacy and Therapeutic Uses

Osmotic diuretics increase the excretion of Na\textsuperscript{+}, K\textsuperscript{+}, Cl\textsuperscript{−}, Mg\textsuperscript{2+}, Ca\textsuperscript{2+}, Cl\textsuperscript{−}, and HCO\textsubscript{3}−. They improve renal perfusion without significantly affecting GFR. Mannitol has been used to increase urine flow rate in patients with prerenal failure,\textsuperscript{18,19} promote the excretion of toxic substances by forced diuresis, and reduce elevated intracranial and intraocular pressures.

Adverse Effects: Interactions

Circulatory overload, acute renal tubular necrosis, intracranial hemorrhage, and CHF have been described in patients given intravenous (IV) mannitol. Mannitol is presently not recommended in neonates.

Carbonic Anhydrase Inhibitors

Agents in this group act by inhibiting the carbonic anhydrase in renal tubular cells and in the brush border of proximal tubular cells.

Chemistry

Acetazolamide, a sulfonamide derivative, is the main inhibitor of carbonic anhydrase used in humans.

Mechanisms and Sites of Action

Inhibition of carbonic anhydrase results in depressed cellular formation and subsequent secretion of H\textsuperscript{+}. As a consequence, the HCO\textsubscript{3}− ions that are normally reabsorbed by combining to H\textsuperscript{+} in the tubular lumen are excreted in the urine. Acetazolamide is a weak diuretic agent, at best producing the excretion of 5% of the Na\textsuperscript{+} and water filtered load.

Pharmacokinetic Properties

Acetazolamide is readily absorbed and is eliminated in the urine. It crosses the placental barrier and is secreted in breast milk.

Efficacy and Therapeutic Uses

Acetazolamide increases the urinary excretion of HCO\textsubscript{3}−, Na\textsuperscript{+}, and K\textsuperscript{+}, promoting alkaline diuresis with consequent systemic metabolic acidosis. Acetazolamide may be useful to alkalinate the urine when necessary, such as when chemotherapy is given. Acetazolamide can also be used to assess reliably the distal acidification ability by measuring the urine minus blood PCO\textsubscript{2} in alkaline urine.\textsuperscript{20}
Specific Indications with Questionable Benefits (Table 14-5)

Posthemorrhagic Ventricular Dilatation. Acetazolamide has been used alone or in association with furosemide in the treatment of posthemorrhagic ventricular dilatation (PHVD) in the hope of avoiding the need for surgical management. Randomized controlled studies have led to the conclusion that this treatment was ineffective in decreasing the rate shunt placement and that it was associated with increased neurologic morbidity. The use of diuretics in PHVD is thus not recommended.21,22

Adverse Effects: Interactions
The occurrence of metabolic acidosis is common if the urinary losses of \[ \text{HCO}_3^- \] are not substituted. Side effects include paresthesias, drowsiness, rash, fever, and the formation of renal calculi. Blood dyscrasias and hepatic failure are occasionally seen.

Loop Diuretics: Inhibition of Na\(^+\), K\(^+\), 2Cl\(^-\) Cotransport
Loop diuretics induce natriuresis by inhibiting the active reabsorption of NaCl in Henle loop.

Chemistry
Loop diuretics form a group of diuretics with diverse chemical structures.23,24 Furosemide and bumetanide are sulfonamide derivatives, torsemide is a sulfonylurea, and ethacrynic acid is a phenoxyacetic acid derivative.

Mechanisms and Sites of Action
Loop diuretics block the Na\(^+\), K\(^+\), 2Cl\(^-\) cotransporter in the thick ascending limb of Henle loop, where 25% of NaCl filtered load are usually reabsorbed. They are consequently highly efficacious because only a small proportion of the filtered Na\(^+\) that escapes reabsorption in the loop can be reabsorbed downstream. Loop diuretics act from within the tubular lumen where they are actively secreted by the organic acid pump. The effect of loop diuretics is more closely related to their urinary excretion rate than to their plasma concentration. By inhibiting NaCl reabsorption in Henle loop, loop diuretics abolish the lumen-positive voltage and thus the driving force for Ca\(^{++}\) and Mg\(^{++}\) reabsorption. They consequently increase Ca\(^{++}\) and Mg\(^{++}\) excretion. Inhibition of NaCl transport upstream of the distal tubule results in increased Na\(^+\) delivery to the late portion of the distal tubule and cortical collecting duct. This part of the nephron responds by increasing the tubular secretion of \[ \text{K}^+ \] and \[ \text{H}^+ \], thus decreasing urine pH and increasing the urinary excretion of \[ \text{K}^+ \]. This secretion is also stimulated by the state of secondary hyperaldosteronism usually present as a consequence of diuretic-induced decrease in ECF volume.3 By inhibiting NaCl reabsorption in the water-impermeable thick ascending limb of Henle loop, loop diuretics interfere with both the diluting and the concentrating mechanism.

Pharmacokinetic Properties
Furosemide is rapidly reabsorbed from the gastrointestinal (GI) tract and is mainly excreted unchanged in the urine. It is 99% bound to plasma albumin and has a bioavailability close to 60% to 70%. Furosemide and ethacrynic acid displace bilirubin from albumin-binding sites.13 Loop diuretics cross the placental barrier and are secreted in breast milk. The diuretic response to loop diuretics appears within a few minutes after IV administration and within 30 to 60 minutes after oral administration. The effect does not last over 2 hours after IV injection and 6 hours after oral administration. Compared with furosemide, torsemide’s release and half-life are prolonged.25-27 The nonrenal clearance of loop diuretics is increased in patients with chronic renal failure. The half-life is prolonged in patients with renal and liver insufficiency and in premature and term neonates in whom half-lives as long as 45 hours have been observed.28 Although the pharmacology of furosemide has been well studied in children29 and neonates,28 that of other loop diuretics is not as well defined. The pharmacokinetics
and pharmacodynamics of bumetanide have been studied in critically ill children\textsuperscript{30} and infants.\textsuperscript{31}

**Efficacy and Therapeutic Uses**

Loop diuretics are the most potent natriuretic agents, also markedly increasing $\text{Cl}^-$, $\text{K}^+$, $\text{Ca}^{++}$, and $\text{Mg}^{++}$ excretion.\textsuperscript{32} They have steep dose-response curves. They remain active in patients with advanced renal failure. Loop diuretics are the most frequently used diuretics in neonates, infants, and children.\textsuperscript{32}

**Continuous Intravenous Infusion of Loop Diuretics**

Clinical trials in infants indicate that continuous infusion therapy can produce more efficient and better-controlled diuresis with less fluid shifts and greater hemodynamic stability.\textsuperscript{33} Administration of a small loading dose of the diuretic before starting the continuous infusion accelerates the diuretic response.\textsuperscript{34} Alternatively, starting with a relatively high continuous infusion dose (0.2 mg/kg/h) of furosemide has been claimed to be optimal.\textsuperscript{34} In hemodynamically stable postoperative cardiac patients, intermittent furosemide has been shown to be more efficacious than continuous infusion of furosemide.\textsuperscript{35}

**Indications**

**Edematous States.** CHF is the most common indication to the use of loop diuretics in neonates and infants. In infants with severe CHF, the diuretic effect of furosemide is inversely related to the serum aldosterone level. The concomitant administration of a $\text{K}^+$-sparing diuretic improves the response to loop diuretics.\textsuperscript{36} Furosemide increases the peripheral venous capacitance and can thus be useful independently from its diuretic effect. In adults, torsemide has been shown to be at least as effective as furosemide in reducing salt and water retention,\textsuperscript{37} to have a longer duration of action, and to reduce the overall treatment costs of CHF compared with furosemide.\textsuperscript{38}

**Nephrotic Syndrome.** In hypovolemic infants with massive nephrotic edema, IV furosemide can be used to promote sodium and water excretion. Furosemide (1–2 mg/kg) should only be given after careful expansion of the extracellular space with IV albumin (5 mL/kg of 20% albumin in 60 min). The dose can be repeated. The effect is transient but may be useful in patients with severe ascites or pulmonary edema. The therapy may be associated with potentially serious complications such as CHF or RDS.\textsuperscript{39}

**Specific Indications with Questionable Benefits (Table 14-5)**

**Oliguric States.** Furosemide is frequently used in oliguric states secondary to prerenal or renal failure in the hope of promoting diuresis and improving renal function. Although furosemide may increase urine output and facilitate the clinical management of the patient, it is unlikely to improve GFR. By inducing diuresis and possibly hypovolemia, loop diuretics carry the risk of further stressing the oliguric kidney. There is as yet no clinical or experimental evidence that loop diuretics can prevent acute renal failure or improve the outcome of patients with acute renal failure.\textsuperscript{9,40}

**Respiratory Distress Syndrome.** Furosemide administration has produced conflicting results in preterm neonates with RDS. Although furosemide usually acutely induces diuresis and a transient improvement in pulmonary function, a recent critical review of the literature failed to find evidence for long-term benefits of routine administration of furosemide (or any diuretic) in preterm infants with RDS.\textsuperscript{41} The review also concluded that elective administration of furosemide should be weighed against the risk of precipitating hypovolemia or of developing a symptomatic patent ductus arteriosus (PDA) by stimulating prostaglandin synthesis.

**Transient Tachypnea of the Newborn.** Transient tachypnea of the newborn (TTN), sometimes called wet lungs, is a common self-limited disease of term
newborns that results from delayed lung fluid clearance. This deficit is probably secondary to immature sodium epithelium channel (ENaC). Furosemide has been proposed to hasten fluid lung clearance and thus improve the pulmonary condition. In a randomized study, the oral administration of 2 mg/kg followed by 1 mg/kg 12 hours later increased weight loss but did not improve the severity or duration of symptoms. A Cochrane analysis of the study concluded that oral furosemide could not be recommended as treatment of TTN. Whether infants with TTN could benefit from IV furosemide remains to be demonstrated.

Preterm Infants with or Developing Chronic Lung Disease. Loop diuretics have been given to preterm infants with chronic lung disease (CLD) in the hope of decreasing the need for oxygen or ventilatory support. A critical review of the available literature has concluded that (1) furosemide has very inconstant effects in preterm infants younger than 3 weeks of age developing CLD and (2) in infants older than 3 weeks of age with CLD, the acute IV administration of furosemide (1 mg/kg) improved lung compliance and airway resistance for only 1 hour. The chronic administration of furosemide improved both oxygenation and lung compliance. The overall conclusion of the authors of the Cochrane review was that the routine use of loop diuretics in infants with or developing CLD, whether administered IV or enterally, cannot be recommended until randomized trials assessing their effects on survival, duration of oxygen administration and ventilatory support, and long-term outcome are available.

A similar conclusion was drawn by the thorough analysis of studies on the effect of aerosolized furosemide in preterm infants with CLD. Although data in preterm infants older than 3 weeks of age with CLD showed that a single dose of aerosolized furosemide improved pulmonary mechanisms, the data in premature infants younger than 3 weeks of age were too scarce to confirm this effect. Based on current available evidence, the routine or sustained use of IV or aerosolized furosemide cannot be recommended. The suggestion that adding metolazone to furosemide would overcome tolerance to the latter awaits confirmation.

Posthemorrhagic Ventricular Dilatation. PHVD is a common complication of intraventricular hemorrhage in preterm infants. It carries a high risk of long-term disability. Combined furosemide–acetazolamide treatment has been used in the hope of avoiding the need of placing a ventriculoperitoneal shunt. A large trial in 177 infants showed that acetazolamide and furosemide treatment resulted in a borderline increase in the risk for motor impairment at 1 year and in an increased risk for nephrocalcinosis without evidently decreasing the risk for disability, chronic motor impairment, or death. A critical review of the three available randomized trials in newborn infants with PHVD concluded that combined furosemide–acetazolamide therapy is neither effective nor safe in treating preterm infants with PHVD.

Indomethacin-Induced Oliguria. Oliguria occurs frequently after administration of indomethacin to close a PDA. Inhibition of prostaglandin synthesis by indomethacin is responsible for the oliguria. Because furosemide increases the production of prostaglandins, it could potentially help prevent the indomethacin-related toxicity while at the same time decreasing the ductal response to indomethacin. A Cochrane analysis of studies available in 2001 demonstrated that furosemide increased urine output in all patients, leading to a 5% weight loss during a three-dose course. This diuretic response was considered as being risky in dehydrated neonates. The review concluded that there was as yet not enough evidence to support the administration of furosemide to preterm infants with PDA treated with indomethacin. This conclusion has been confirmed by more recent studies showing that (1) furosemide given before each indomethacin dose resulted in a significant increase in serum creatinine and worsening of hyponatremia without increasing urine output and (2) furosemide increased the incidence of acute renal failure without, however, affecting the PDA closure rate. A delay in ductus arteriosus closure has recently been
demonstrated in neonatal rats given furosemide.\textsuperscript{54} Noteworthy is also the conclusion that there is as yet no evidence from randomized trials to support the use of dopamine to prevent renal dysfunction in indomethacin-treated preterm infants.\textsuperscript{55} The same conclusion probably applies to the premature infants presenting with ibuprofen-induced oliguria.

**Hypercalcemic States.** Loop diuretics can promote calcium excretion and decrease hypercalcemia. Isotonic saline must be infused concomitantly to prevent volume depletion.

**Severe Hyponatremia.** Severe hyponatremia can be treated by loop diuretics and the concomitant isovolumetric infusion of hypertonic saline.

**Asthma and Compromised Lung Mechanics.** Direct intratracheal administration of furosemide has been claimed to produce beneficial effects in patients with asthma, in infants with bronchopulmonary dysplasia, and in toddlers with compromised lung mechanics after cardiac surgery. In the latter study, a systemic effect was observed within 15 minutes after intratracheal instillation of the agent.\textsuperscript{56} This technique has not yet been validated.

**Laboratory Investigation: Assessment of Distal Tubular Acidification.** The simultaneous administration of furosemide and fludrocortisone has been shown to be an easy, effective, and well-tolerated alternative to standard ammonium chloride loading to assess distal tubular urine acidification and confirm the diagnosis of distal renal tubular acidosis.\textsuperscript{57}

**Drug Dosage**

See Table 14-6.

**Adverse Effects: Interactions**

Adverse effects, including volume depletion, postural hypotension, dizziness and syncope, hyponatremia, and hypokalemia, are commonly observed when using loop diuretics. These effects are dose dependent and often occur after overzealous use of large doses of diuretics or chronic administration.

**Hypochloremic Metabolic Alkalosis**

This occurs frequently as a consequence of direct stimulation by loop diuretics of $\text{H}^+$ secretion in the collecting tubule.

**Hypercalciuria and Nephrocalcinosis**

Elevated Ca\textsuperscript{++} urinary losses after chronic furosemide administration may lead to nephrocalcinosis in term\textsuperscript{58} and premature infants\textsuperscript{59} secondary hyperparathyroidism, bone resorption, and rickets. When prolonged, hypercalciuria may lead to renal impairment.\textsuperscript{60} Although thiazide diuretics decrease calcium and oxalate excretion, adding thiazides to loop diuretics does not appear beneficial.\textsuperscript{61}

**Patent Ductus Arteriosus**

The beneficial renal effect of combining furosemide and indomethacin is still controversial.\textsuperscript{24} The suggestion that stimulating prostaglandin synthesis furosemide could promote PDA has not been confirmed (see earlier discussion).

**Ototoxicity**

The use of furosemide has been identified as an independent risk factor for sensorineural hearing loss in preterm infants.\textsuperscript{62} Hearing loss may be transient or permanent. It is usually associated with elevated blood concentrations of loop diuretics. The coadministration of loop diuretics and aminoglycosides increases the risk of ototoxicity. By avoiding elevated peak concentrations of furosemide, the continuous infusion may decreases the risk of ototoxicity.\textsuperscript{24}
Miscellaneous

Pancreatitis, jaundice, impaired glucose tolerance, thrombocytopenia, and serious skin disorders are occasionally observed. The majority of adverse effects occur with the use of high doses of the diuretics.

Interactions

Drug interactions may occur with the coadministration of nephrotoxic antibiotics, nonsteroidal antiinflammatory drugs, anticoagulants, and cisplatin.

Distal Convoluted Tubule: Inhibitors of Na⁺Cl⁻ Cotransport

The thiazides inhibit NaCl reabsorption in the distal convoluted tubule.

Chemistry

The benzothiadiazide derivatives are sulfonamides. They are weak diuretics that inhibit the reabsorption of NaCl at the diluting site in the early distal tubule. The main thiazides include chlorothiazide and hydrochlorothiazide. Thiazide-like agents such as chlorthalidone and metolazone belong to this group.

Mechanisms and Sites of Action

The thiazide diuretics are organic anions. They gain access to the tubular lumen by filtration and by secretion in the proximal tubule. They decrease NaCl reabsorption in the distal convoluted tubule by inhibiting the Na⁺-Cl⁻ apical cotransporter. This cotransporter, sometimes called “thiazide-sensitive sodium chloride cotransporter (TSC)” is predominantly expressed in the epithelial cells of the distal convoluted tubule. Its expression is upregulated by aldosterone. To reach their site of action on the luminal side of the tubular cells, the thiazides must be secreted by the anionic organic acid pathway in the proximal tubule. Approximately 4% to 5% of the Na⁺ filtered load being reabsorbed in the distal tubule, inhibition of Na⁺ reabsorption at this site can only modestly increase NaCl excretion. Some of the thiazides also slightly increase the excretion of HCO₃⁻ by weakly inhibiting the carbonic anhydrase. By increasing Na⁺ delivery to the late distal tubule, the thiazides lead to increased reabsorption of Na⁺ at this site in exchange for K⁺ and H⁺ which are then excreted in the urine. By inhibiting NaCl reabsorption in the early distal tubule, the thiazides blunt the ability to dilute the urine. They do not interfere with the concentrating mechanism. The thiazides stimulate Ca²⁺ reabsorption in the distal tubule, probably by opening the apical membrane Ca²⁺ channels. The thiazides (but not metolazone) are ineffective at GFRs below 30 mL/min/1.73 m².

Pharmacokinetic Properties

The thiazides are rapidly absorbed after oral administration. They variably bind to plasma proteins. They are eliminated unchanged, exclusively (chlorothiazide, hydrochlorothiazide, chlorthalidone) or in great part (∼80%) (metolazone) in the urine. Administration of thiazides initiates diuresis in 2 hours, an effect that lasts for 12 hours. The response to metolazone is somewhat more rapid (1 hour) and lasts longer (12–24 hours). The thiazides cross the placental barrier and are secreted in breast milk.

Efficacy and Therapeutic Uses

Thiazide diuretics moderately increase the excretion of Na⁺, Cl⁻, and water. All thiazides (chlorothiazide, hydrochlorothiazide) and thiazide-like diuretics have overall similar effects when used in maximal doses. When administered chronically, they decrease the excretion of Ca²⁺, as well as that of uric acid, probably as a consequence of increased proximal reabsorption because of volume depletion. The excretion of Mg²⁺ is somewhat increased, as is the excretion of K⁺ and fixed acids. The prophylactic coadministration of K⁺-sparking diuretics can prevent the occurrence of severe hypokalemia. Alternatively, potassium and magnesium supplementation may be useful in patients at risk of symptomatic hypokalemia. The thiazides (but not metolazone) increase the excretion of HCO₃⁻. In the absence of significant volume
depletion, the thiazides do not normally influence renal hemodynamics and GFR. In contrast with the thiazides and chlorthalidone, metolazone remains effective at GFRs below 30 mL/min/1.73 m².

**Indications**

The main indications for the administration of thiazide diuretics include edematous states, hypertension, and a few specific indications.

**Specific Indications with Questionable Benefits (Table 14-5)**

**Hypercalciuria**

The thiazides decrease calcium excretion and this effect may be useful in states of idiopathic hypercalciuria, as well as to prevent calcium losses in patients receiving glucocorticoids. They have been associated to loop diuretics in the hope of decreasing the risk of hypercalciuria and nephrocalcinosis in very low birth weight infants; disappointing results have been observed. In young rats with established furosemide-induced nephrocalcinosis, thiazides failed to improve the calcinosis.

The use of thiazides has been associated with an increase in total serum cholesterol and in the ratio of low-density lipoprotein (LDL) to high-density lipoprotein (HDL). In children with X-linked hypophosphatemia on renal phosphate and vitamin D therapy, hydrochlorothiazide decreased the urinary excretion of calcium but did not reverse the nephrocalcinosis.

**Proximal Renal Tubular Acidosis**

The thiazides have been used to raise the plasma bicarbonate concentration in proximal renal tubular acidosis. This effect on bicarbonate reabsorption is the consequence of the chronic volume contraction induced by the thiazides, a condition that is deleterious for body growth.

**Nephrogenic Diabetes Insipidus**

The thiazides have been successfully used in children with nephrogenic diabetes insipidus. By inducing volume contraction, they enhance the proximal tubular reabsorption of water and electrolytes, thus significantly decreasing urine output. Although usefully decreasing urine output, volume contraction may inhibit growth in young children with nephrogenic diabetes insipidus. The concomitant use of hydrochlorothiazide and amiloride obviates the need for the K⁺ supplementation and has been shown as useful as the standard treatment with hydrochlorothiazide and indomethacin in reducing urine output.

**Chronic Lung Disease**

The thiazide and thiazide-like diuretics have been used in the hope of improving pulmonary mechanisms and clinical outcome in preterm infants with CLD. A critical analysis of available well-planned studies led to the conclusion that in preterm infants older than 8 weeks of age with CLD, a 4-week treatment with thiazides and spironolactone reduced the need for furosemide, improved lung compliance, decreased the risk of death, and tended to decrease the risk for lack of extubation after 8 weeks in intubated infants without access to corticosteroids, bronchodilators, or aminophylline. There was little evidence to support any benefit on the need for ventilatory support, length of hospital stay, or long-term outcome in infants receiving current therapy. There was also no evidence to support the hypothesis that adding spironolactone to thiazides or metolazone to furosemide improved the outcome of preterm infants. The addition of K⁺-sparing diuretics to thiazide did, however, decrease the risk of hypokalemia.

**Laboratory Investigation: Diagnosis of Renal Hypokalemic Tubulopathies**

Assessment of the maximal diuretic response induced by the administration of hydrochlorothiazide (1 mg/kg orally) allows to differentiate Bartter from Gitelman syndrome, the former presenting with a blunted response to the diuretic agent.
Drug Dosage

See Table 14-6.

Adverse Effects: Interactions

The thiazides may adversely affect water balance and induce electrolyte imbalances (See Table 14-3). They induce an increase in total serum cholesterol and in the LDL-to-HDL ratio.65 Other side effects include GI disturbances, hypersensitivity reactions, cholestatic jaundice, pancreatitis, thrombocytopenia, and hyperglycemia in diabetic and susceptible patients and hyperlipidemia. Precipitation of hepatic encephalopathy has been observed in patients with hepatic cirrhosis. The thiazides displace bilirubin from albumin and should be cautiously administered to patients with jaundice.

Cortical Collecting Duct: K⁺-Sparing Drugs

Diuretics that inhibit Na⁺ reabsorption in the cortical collecting duct decrease the urinary excretion of K⁺ and H⁺ and can produce hypokalemia and metabolic acidosis.14

Chemistry

Two types of diuretics form the group of K⁺-sparing diuretics: the inhibitors of a renal epithelial Na⁺ channels (ENaC) and the antagonists of mineralocorticoid receptors. The overall effects of these two groups of diuretics differ only in their mode of action.

Mechanisms and Sites of Action

The antagonists of the action of aldosterone on the principal cells of the collecting duct increase Na⁺ excretion and decrease K⁺ and H⁺ secretion. Spironolactone, the main agent in this group, competitively inhibits the binding of aldosterone to the mineralocorticoid receptor, thus decreasing the synthesis of aldosterone-induced proteins. The aldosterone antagonists have greater effects in situations of hyperaldosteronism. They do not modify the renal hemodynamics. Highly selective antagonists of the mineralocorticoid receptor are currently under investigation.72

The K⁺-sparing diuretics amiloride and triamterene block the entry of Na⁺ into the cell through the ENaC Na⁺ in the apical membrane. Because of changes in electrical profile across the apical membrane, the diffusion of both H⁺ and K⁺ from cells into tubular fluid decreases. Activation of the RAAS by the diuretics also impairs the excretion of K⁺, H⁺, Ca²⁺, and Mg²⁺. The ENaC blockers do not affect renal hemodynamics.

Pharmacokinetic Properties

Spironolactone is rapidly absorbed from the GI tract with a bioavailability close to 90%. It is 90% bound to plasma proteins and is excreted mainly in the urine and to a lesser extent in the feces. Spironolactone has a slow onset of action, requiring 2 to 3 days for maximum effect.73 Canrenoate potassium has actions similar to those of spironolactone. It is available for IV administration.

Amiloride is incompletely absorbed from the GI tract with a bioavailability of only 50%. It is not bound to plasma proteins and is excreted unchanged in the urine. Its half-life is 6 to 9 hours. It is prolonged in patients with hepatic or renal failure. Triamterene is unreliably absorbed. It is metabolized by hepatic conjugation. One-fifth of the dose is excreted unchanged in the urine. Its half-life is 1 to 3 hours.

All K⁺-sparing diuretics cross the placental barrier and are secreted in breast milk.

Efficacy and Therapeutic Uses

The overall effects on electrolyte excretion are similar for spironolactone, amiloride, and triamterene. They are weak natriuretic agents that reduce the excretion of potassium and hydrogen ions. K⁺-sparing diuretics are mainly used in Na⁺-retaining states in association with loop or thiazide diuretics. They enhance the natriuretic effect
while at the same time limiting $K^+$ losses. Refractory edema secondary to CHF, cirrhosis of the liver, and the nephrotic syndrome represent the most common indications for the use of $K^+$-sparing diuretics. In these conditions associated with secondary hyperaldosteronism, spironolactone is the first choice agent provided renal function is not impaired. Because they induce $K^+$ retention, $K^+$-sparing diuretics should not be used in patients with impaired renal function or in those receiving $K^+$ supplementation. They should also be avoided in patients prone to developing metabolic acidosis. Amiloride has been successfully used in association with hydrochlorothiazide in patients with nephrogenic diabetes insipidus, obviating the need for using indomethacin.

**Specific Indications with Questionable Benefits (Table 14-5)**

$K^+$-sparing diuretics are often used in association with thiazide diuretics in the management of preterm infants with CLD. Although they certainly decrease the risk of hypokalemia and facilitate the clinical management of the infants, there is as yet no definite proof that their association to thiazide improve the long-term outcome of preterm infants with CLD.

The respiratory function of patients with cystic fibrosis has been improved by the inhalation of amiloride, possibly by the blocking effect of ENaC in pulmonary tissue. Such a beneficial effect has not been confirmed in placebo-controlled trials.

**Drug Dosage**

See Table 14-6.

**Adverse Effects: Interactions**

The main adverse effects of $K^+$-sparing diuretics is to increase the $K^+$ plasma concentration to harmful levels. Close monitoring of $K^+$ concentration is thus mandatory. GI disturbances, dizziness, photosensitivity, and blood dyscrasias have been reported after the use of triamterene.

Significant adverse effects have been observed with spironolactone; gynecomastia, hirsutism, impotence and menstrual irregularities can occur. Gynecomastia in men is related to both the dose and duration of treatment. Breast enlargement and tenderness occur in women. The pathogenesis of the adverse effects of spironolactone on the endocrine system is probably related to an antiadrenergic action and to reduced 17 hydroxylase activity.

**Interactions**

$K^+$-sparing diuretics should not be used in patients receiving angiotensin-converting enzyme inhibitors because the association can worsen the risk of hyperkalemia.

**New Developments in Diuretic Therapy**

Three categories of diuretics are under investigation: the adenosine A1 receptor antagonists, the natriuretic peptides, and the arginine-vasopressin antagonists.

**Adenosine A1 Receptor Antagonists**

Theophylline, an A1 adenosine nonspecific receptor antagonist, presents with natriuretic and diuretic properties. It has been shown, both in experimental studies and clinical trials, to protect newborn kidneys in conditions of asphyxia and RDS. The effect and the use of theophylline are described in Chapter 5.

**Natriuretic Peptides**

ANP and B-type natriuretic peptide (BNP) are two peptides with natriuretic and diuretic properties. Both are released by cardiac cells in the atria in response to increased blood volume. ANP (28 amino acids) and BNP (32 amino acids) act via the natriuretic peptide receptor A (NPR-A). In addition to increasing the excretion of Na+, both peptides inhibit the sympathetic system and the RAAS. They also relax vascular smooth muscle. ANP and BNP are degraded by the metalloproteinase neutral endopeptidase 24.11 (NEP). Urodilatin is a noncirculating natriuretic peptide
Special Problems

(32 amino acids) secreted by distal tubular cells that is not degraded by the NEP located in the proximal tubular cells. ANP favors filtration by relaxing the afferent artery and the mesangial cells. The NPs inhibit Na⁺ proximal reabsorption and decrease distal Na⁺ reabsorption indirectly by blunting angiotensin II and aldosterone synthesis and directly by inhibiting the thiazide-sensitive Na⁺ channel. ANP increases diuresis by inhibiting the V2 receptor-mediated action of arginine vasopressin (AVP) on water permeability.

The natriuretic peptides have not yet been used as diuretic agents in neonates but may have interesting properties in patients presenting with inappropriate salt and water retention.

Arginine Vasopressin Antagonists

AVP acts on three type of receptors: (1) the V₁A receptors mediating vasoconstriction, (2) the V₁B mediating the release of ACTH, and (3) the V₂ receptors mediating free water reabsorption in the collecting duct. AVP also stimulates Na⁺, K⁺, 2Cl⁻ cotransport in the ascending limb of Henle loop via V₂ receptors. By selectively increasing the excretion of free water, the AVP antagonists may prove useful in the treatment of severe hyponatremic states.

References