Chapter 6
Diuretics

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Abstract Diuretic medications compose one of the most frequently used drug classes in the care of pediatric cardiology patients. They have a vast range of indications, including congestive heart failure, hypertension and postoperative fluid overload. The main function of this class of medicines is to reduce plasma volume by increasing urine output. Although all have a similar function, diuretics are then grouped by which region of the kidney they act upon. The most commonly used diuretic among pediatric patients is furosemide, which acts upon the loop of Henle. Although furosemide may be used as a single agent, it is commonly used in conjunction with other diuretics for synergy or to negate adverse effects. Most specific diuretic medications have indications for all age ranges and many have intravenous and enteral formulations available. An understanding of the mechanism and specific

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indications of these medications is necessary for optimal care of infants and children with cardiac disease.

Keywords Diuretic • Thiazide diuretic • Loop diuretic • Potassium-sparing diuretic • Carbonic anhydrase inhibitor • Osmotic diuretic • Cardiovascular medication

Diuretic medications compose one of the most frequently used drug classes in the care of pediatric cardiology patients. The main function of this group is to reduce plasma volume by increasing urine output. This reduced plasma volume can help with symptoms of heart failure, postoperative fluid overload, hypertension or renal dysfunction. The general mechanism of action is similar in most diuretics: inhibition of renal ion transporters decreasing the reabsorption of sodium ions (Na^+), causing higher osmolarity in the urine. This leads to increased passive flow of water molecules into the urine causing diuresis. Manipulation of renal tubule ion channels, while effective at eliminating plasma volume, occurs at the cost of electrolyte abnormalities.

The subclasses of diuretic medications are categorized by the component of the renal tubule which they act upon. The potency and side effect profile of each group is based upon the mechanism of that region of the nephron. The more powerful loop diuretics can increase sodium secretion by more than 20 % creating strong diuresis, while the secretion of potassium sparing diuretics may be as little as 1–2 %.

In order to understand how diuretics influence electrolytes and fluid balances, it is important to review the normal electrolyte regulation of the kidneys and the concept of the five zones of the nephron (Fig. 6.1).

Fluid enters the kidney through the glomerular capillaries and filters through Bowman's capsule. This filtrate does not include blood cells or protein, but has high concentrations of glucose, sodium bicarbonate, amino acids and electrolytes. This filtrate is modified as it passes through the nephron system and towards the ureter.

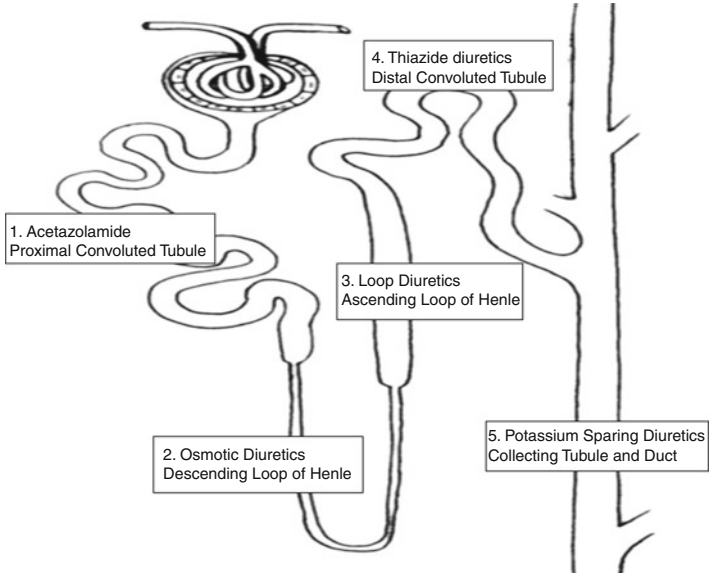

FIGURE 6.1 Schematic of nephron – the regions of the nephron are shown along with the main class of diuretic which acts upon each region

The proximal convoluted tubule is the first zone of the nephron and where the majority of reabsorption of filtered water, glucose, bicarbonate, amino acids and sodium occurs. Sodium is pumped out of filtrate by a Na^+/K^+ ATPase pump. The reabsorption of bicarbonate and organic solutes relies highly on carbonic anhydrase which is in the cell and luminal membrane. Water passively follows these solutes from the lumen into the interstitum.

The descending loop of Henle is the next zone and where urine osmolarity increases as water is reabsorbed into the renal medulla. This results in a net increase in tubular fluid salt concentration. This is the region where osmotic diuretics display their maximal effect. The next zone is the ascending loop of Henle where the tubular epithelium is impermeable to water but has active reabsorption of Na^+, K^+ and Cl^- mediated by a $Na^+/K^+/2Cl^-$ co-transporter. This area is where ¼ of all NaCl is resorbed and therefore loop diuretics, which affect this site, have major modifications on sodium balance.

The fourth zone is the distal convoluted tubule which is also impermeable to water. Here an additional 10 % of NaCl is reabsorbed via a Na^+/Cl^- transporter, along with calcium reabsorption. This zone is affected by thiazide diuretics. The final zone of the nephron is the collecting tubule in which Na^+, K^+ and water are reabsorbed with dependence on Na^+/K^+/ATPase channels. This zone is where aldosterone has its effect, limiting Na^+ reabsorption and K^+ secretion. This is also the zone where vasopressin and antidiuretic hormone (ADH) have their effect. ADH receptors promote reabsorption of water from collecting tubules and ducts and decrease diuresis.

The main therapeutic uses of diuretics within pediatric cardiology are:

- heart failure
- postoperative oliguria
- hypertension
- pulmonary edema
- electrolyte correction(hyper/hypokalemia)
- renal dysfunction
- chronic lung disease.

Heart failure causes decreased effective blood flow to the kidney, making the kidney behave as if it were in a state of hypovolemia, and causes salt and water retention to increase blood volume. The mechanism by which diuretics help with heart failure is by the reduction of plasma volume, which decreases cardiac preload decreasing oxygen demand. Diuretics relieve pulmonary congestion and peripheral edema as well.

Patients who undergo heart surgery with cardiopulmonary bypass have increased body edema for multiple reasons. Bypass induces increased inflammatory states which cause capillary leak, and also may cause renal dysfunction and oliguria. Furthermore, postoperative low cardiac output causes edema by the above mechanism. Diuretics are an integral component of post-surgical treatment and typically are required in aggressive regimens.

The mechanism by which diuretics help with hypertension is the decrease in plasma volume which decreases afterload resulting in a lower blood pressure.

The management of postoperative oliguria and fluid overload after cardiopulmonary bypass is a popular topic. There is growing evidence that suggests the use of peritoneal dialysis early in the course of fluid overload due to postoperative acute kidney injury is a superior means of diuresis compared to medical management [1]. Studies have demonstrated worse clinical outcome with higher degrees of fluid overload [2] and suggest that peritoneal dialysis may be ultimately linked to improved outcomes.

The concept of synergy of medications is especially pertinent among diuretic management, both for potentiating effect and minimizing side effects. Many of the diuretics including loop diuretics and thiazides, have the side effect of potassium wasting. Therefore, a potassium-sparing diuretic is often used in conjunction with higher dosed diuretic regimens, most classically furosemide and spironolactone. Other synergistic combinations are used to potentiate effect. For example loop diuretics and thiazide diuretics are often given in concert, because despite the powerful effect of Na^+ secretion by loop diuretics, sodium is later reabsorbed in the distal convoluted tubule, increasingly as the medication is used for longer term treatments. If a thiazide diuretic is given prior to the loop diuretic, it prevents reabsorbed of sodium, thus maximizing the effect via a "sequential nephron blockade". Although never assessed in children, the addition of a thiazide diuretic in adult heart failure has been studied in more than 50 published reports and can double urine sodium secretion [3].

A consideration when using intravenous diuretics is the use of bolus medications versus continuous infusion. Although it is more common to give medications via bolus administration, there is data that suggests that continuous infusions may be safer. A prospective randomized study among infants after cardiac surgery found that continuous infusions was given at lower doses with similar urine output, and associated with less fluctuation in urinary output and need for fluid replacement [4, 5].

The five subclasses of medications will be discussed individually and key pharmaceutical agents within each subclass will be further described (Table 6.1).

Table 6.1 Mechanisms and representative agents of diuretic classes

Mechanism of action of diuretic classes		
Drug class	**Examples**	**Mechanism of action**
Loop diuretics	Furosemide Bumetanide Torsemide Ethacrynic acid	Inhibition of $Na^+/K^+/2Cl^-$ co-transporter in ascending loop of Henle
Thiazide and thiazide-like diuretics	Chlorothiazide Hydrochlorothiazide Metolazone	Inhibition of Na^+/Cl^- co-transporter in distal convoluted tubule
Potassium sparing diuretics (aldosterone antagonists)	Amiloride (Spironolactone)	Inhibition of aldosterone-responsive Na^+ channel in distal nephron and collecting tubule (aldosterone antagonists reduce Na^+ channel and Na^+/K^+/ ATPase)
Carbonic anhydrase inhibitors	Acetazolamide	Inhibition of proximal convoluted tubule sodium bicarbonate reabsorption
Osmotic diuretic	Mannitol	Increases the osmotic pressure of the glomerular filtrate, which inhibits the tubular reabsorption of water and electrolytes

6.1 Loop Diuretics

6.1.1 Indication

Loop diuretics are commonly used in the management of volume overload in congestive heart failure, postoperative cardiac surgery, acute and chronic renal insufficiency and

hepatic pediatric patients. They may be used alone or in combination with other medication classes to assist in the management of hypertensive patients.

6.1.2 Mechanism of Action

Loop diuretics inhibit the reabsorption of sodium and chloride from the ascending loop of Henle. They interfere with the $Na^+/K^+/2Cl^-$ cotransporter system and cease salt transport. This action causes an increase of excretion of water, sodium, chloride and potassium. The inhibition of the cotransporter system decreases absorption of calcium and magnesium in the ascending limb by eliminating the transepithelial potential difference. Bumetanide is a loop diuretic that is 40 times more potent than furosemide [6].

6.1.3 Monitoring Parameters

Serum sodium, potassium, chloride, and bicarbonate, renal function (BUN and Cr), blood pressure and hearing screening.

6.1.4 Contraindications

Anuria or increasing azotemia. The use of Ethacrynic acid should be avoided if hypotension, metabolic alkalosis with hypokalemia or hyponatremic dehydration is present.

Warning: loop diuretics are potent agents. Excess amounts may lead to profound diuresis with fluid and electrolyte loss. Close medical supervision and dose evaluation is required.

6.1.5 Poison Information

Symptoms of loop diuretic overdose may include acute and profound water loss, volume and electrolyte depletion, dehydration, reduction of blood volume and circulatory collapse

with a possibility of vascular thrombosis and embolism. Electrolye depletion may be manifested by weakness, muscle cramps, fatigue, dizziness, fainting, confusion, irregular pulse, dry mouth, dehydration, nausea, and vomiting. Decontamination using activated charcoal is recommended and other treatment is supportive and symptomatic. Replacement of fluid and electrolyte losses may be necessary.

6.2 Furosemide

6.2.1 Pharmacodynamics/Pharmacokinetics

The onset of action of loop diuretics is 30-60 minutes after oral administration. The peak effects occur within 1–2 h and the duration of action is 6–8 h. After an intravenous injection the diuresis begins in 5 min and typically lasts for 2 h. The hepatic metabolism of the drug is minimal and the half-life is approximately 30 min.

6.2.2 Dosing

Neonates, **Premature**:

Oral (*poor bioavailability*): doses of 1–4 mg/kg/dose once or twice daily have been used

Intramuscular (*I.M.*), *intravenous* (*I.V.*): 1–2 mg/kg/dose administered every 12–24 h

Note: Significant absorption within ECMO circuit; avoid administration directly into circuit; high doses may be required for adequate diuretic effect [7].

Infants and Children:

Oral: 1–6 mg/kg/day divided every 6–12 h

I.M., *I.V.*: 0.25–2 mg/kg/dose every 6–12 h

I.V. continuous infusion: 0.05 mg/kg/h initially, titrate to clinical effect. (Usual dosage range – 0.1–0.4 mg/kg/h.)

Adults:

Oral: initial, 20–80 mg/dose; increase in increments of 20–40 mg/dose at intervals of 6–8 h; usual maintenance dose interval is once or twice daily; may be titrated up to 600 mg/day for severe edematous states

I.M., *I.V.*: 20–40 mg/dose; repeat in 1–2 h as needed and increase by 20 mg/dose until the desired effect has been obtained; usual dosing interval, 6–12 h; for acute pulmonary edema, the usual dose is 40 mg I.V.; if not adequate, may increase dose to 80 mg

Continuous I.V. infusion: initial I.V. bolus dose of 20–40 mg followed by continuous I.V. infusion doses of 0.1 mg/kg/h doubled every 2 h to a maximum of 0.4 mg/kg/h

6.2.3 Precautions/Adverse Effects

Adverse effects of furosemide use include serious depletion of total body Na^+ manifesting in hyponatremia or extracellular fluid volume depletion associated with hypotension, reduced glomerular filtration rate (GFR), or circulatory collapse. Can cause extracellular fluid volume depletion associated with hypotension and fluid and electrolyte imbalances including; hypokalemia, hyponatremia, hypomagnesium and hypocalcemia. Also reported are dizziness, urticaria, hypokalemia, nausea, pancreatitis, headaches, photosensitivity, diarrhea, dehydration, and anemia. Ototoxicity from high doses of furosemide has been reported. Other effects may include hypochloremia, metabolic alkalosis, hypercalciuria, agranulocytosis, thrombocytopenia, nephrocalcinosis, prerenal azotemia, hyperuricemia, and interstitial nephritis. Oral solutions contain sorbitol, which may cause diarrhea. Pregnancy Class: C.

6.2.4 Drug-Drug Interaction

Nonsteroidal anti-inflammatory drugs (NSAIDs) decrease the effect of furosemide. There is increased ototoxicity with aminoglycosides and ethacrynic acid; and drugs affected by potassium depletion, such as digoxin. There is increased

anticoagulation by warfarin; decreased glucose tolerance may increase requirements of oral anti-diabetic agents; and there is decreased lithium excretion with furosemide administration.

6.2.5 Compatible Diluents/Administration

Injection can be administered undiluted or can be diluted in normal saline (NS) or 5 % dextrose in water (D5W) to a concentration of 1–2 mg/mL and will be stable for 24 h at room temperature. Administration is by direct I.V. injection at a maximum rate of 0.5 mg/kg/min.

6.3 Bumetanide

6.3.1 Pharmacodynamics/Pharmacokinetics

Bumetanide has an onset of action for oral or I.M. administration within 30–60 min after the initial dose and within a few minutes after the I.V. injection. The duration of action after a usual dose of the drug is 4–6 h. Bumetanide is almost completely absorbed from the gastrointestinal (GI) tract, with protein binding at 95 %. The drug undergoes partial hepatic metabolism, with the majority of the drug eliminated as the parent molecule or as a metabolite in the urine. The half-life of bumetanide is 1–1.5 h in adults and 2.5 h in infants younger than 6 months of age.

6.3.2 Dosing

Neonates:

Oral, *I.M.*, *I.V.*: 0.01–0.05 mg/kg/dose every 24–48 h

Infants and Children:

Oral, *I.M.*, *I.V.*: 0.01–0.1 mg/kg/dose every 6–24 h (maximum, 10 mg/day)

Continuous I.V. infusion: the total daily I.V. intermittent dose can be administered as a continuous infusion over 24 h (5–50 μg/kg/h)

Adults:

Oral: 0.5–2 mg/dose (maximum, 10 mg/day) once or twice daily
I.M., *I.V.*: 0.5–1 mg/dose (maximum, 10 mg/day)
Continuous I.V. infusion: 0.5–1 mg/h

6.3.3 Precautions/Adverse Effects

The injectable formulation of this drug contains benzyl alcohol and large amounts (>99 mg/kg/day) have been associated with a potentially fatal toxicity ("gasping syndrome") in neonates. This syndrome consists of metabolic acidosis, respiratory distress, gasping respirations, central nervous system (CNS) dysfunction, hypotension, and cardiovascular collapse. In vitro animal studies have shown that benzoate, a metabolite of benzyl alcohol, displaces bilirubin from protein binding sites. Avoid or use injection cautiously in neonates. In vitro studies using pooled sera from critically ill neonates have also shown bumetanide to be a potent displacer of bilirubin. Avoid use in neonates at risk for kernicterus. There is an increased risk of ototoxicity with rapid I.V. administration, renal impairment, excessive doses, and concurrent use with other ototoxins. Use with caution in patients with previous hypersensitivity reactions to sulfonamides or thiazides. Adverse effects that may occur with bumetanide use include hypotension, chest pain, dizziness, headache, encephalopathy, vertigo, and potential rashes. Bumetanide can cause extracellular fluid volume depletion associated with hypotension and fluid and electrolyte imbalances including; hypokalemia, hyponatremia, hypomagnesium and hypocalcemia. Other effects may include urticaria, hypokalemia, nausea, pancreatitis, photosensitivity, diarrhea, dehydration and decreased uric acid excretion. Hypochloremia, arthritic pain, metabolic alkalosis, hypercalciuria, agranulocytosis, thrombocytopenia, hyperuricemia, and cramps have also been reported. Pregnancy Class: C

6.3.4 Drug-Drug Interaction

Hypotension may occur when bumetanide is used with other antihypertensive medications and angiotensin-converting enzyme (ACE) inhibitors. NSAIDs decrease the effect of bumetanide. There is increased ototoxicity when bumetanide is used with aminoglycosides and ethacrynic acid; and drugs affected by potassium depletion, such as digoxin. With bumetanide administration, there is decreased glucose tolerance with anti-diabetic agents; and decreased lithium excretion. Increased potassium losses with torsemide increase the risk of digoxin toxicity.

6.3.5 Compatible Diluents/Administration

Administer undiluted by direct I.V. injection over 1–2 min; may be diluted in D5W or NS and infused over 5 min; dilute in D5W to 0.024 mg/mL for continuous infusion.

6.4 Torsemide

6.4.1 Pharmacodynamics/Pharmacokinetics

Rapidly absorbed; bioavailability, 80–90 %. Peak serum concentrations are reached in 1 h. Torsemide is metabolized by cytochrome P450. The halflife of torsemide is normally 2–4 h, but is increased to 7–8 h in cirrhosis. Of the total dose, 20 % is excreted unchanged in the urine.

6.4.2 Dosing

Neonates, **Infants**, **and Children**: no data is available

Adults:

Edema: *Oral*, *I.V.*: 10–20 mg once daily. Titrate up to maximum dose of 200 mg/day

Hypertension: *Oral*, *I.V.*: 5 mg once daily initially, then increase to 10 mg once daily, if needed, after 4–6 weeks

6.4.3 Precautions/Adverse Effects

Adverse effects that may occur with torsemide use include hypotension, chest pain, dizziness, headache, prerenal azotemia, and rashes. Torsemide can cause extracelluar fluid volume depletion associated with hypotension and fluid and electrolyte imbalances including; hypokalemia, hyponatremia, hypomagnesium and hypocalcemia. Other effects may include hypokalemia, nausea, pancreatitis, photosensitivity, diarrhea, dehydration, and decreased uric acid excretion. Hypochloremia, arthritic pain, metabolic alkalosis, hypercalciuria, agranulocytosis, anemia, hyperuricemia, and cramps have also been reported. Pregnancy Class: B.

6.4.4 Drug-Drug Interaction

Use of torsemide with aminoglycosides or ethacrynic acid increases risk of ototoxicity. Torsemide use increases the anticoagulant effects of warfarin. NSAIDs decrease the diuretic effect of torsemide. Torsemide decreases lithium excretion; and decreased glucose tolerance with torsemide may increase requirements of oral anti-diabetic agents.

6.4.5 Compatible Diluents/Administration

Administer torsemide undiluted by direct I.V. injection over at least 2 min; torsemide may be diluted in D5W or NS to concentrations of 0.1, 0.2, 0.4, or 0.8 mg/mL for continuous infusion, and is stable for 24 h at room temperature.

6.5 Ethacrynic Acid

6.5.1 Pharmacodynamics/Pharmacokinetics

Ethacrynic acid has an onset of action within 30 min of administration of oral doses and within 5 min of I.V. injection. The duration of diuresis is approximately 6–8 h after oral and 2 h after I.V. administration. The drug is rapidly absorbed and hepatically metabolized to an active cysteine conjugate. The half-life ranges from 30–70 min, and the drug and metabolites are eliminated in the bile and urine.

6.5.2 Dosing

Children:

Oral: 1 mg/kg/dose every 24–48 h; adjust dose as needed at 2–3-day intervals to a maximum of 3 mg/kg/day
I.V.: 0.5–2 mg/kg/dose (maximum, 50 mg/dose) administered every 6–12 h

Adults:

Oral: 25–400 mg/day in one to two divided doses
I.V.: 0.5–1 mg/kg/dose (maximum, 100 mg/dose); repeat doses not routinely recommended but may be administered every 8–12 h
Note: Avoid use in patients with a Cr clearance (ClCr) less than 10 mL/min

6.5.3 Precautions/Adverse Effects

Use with corticosteroids may increase risk of GI hemorrhage. Avoid use in patients with severe renal impairment (ClCr < 10 mL/min). Adverse effects of ethacrynic acid can cause extracelluar fluid volume depletion associated with hypotension and fluid and electrolyte imbalances including; hypokalemia, hyponatremia, hypomagnesium

and hypocalcemia. Additional adverse effects can include hypotension, hyperglycemia, thrombocytopenia, neutropenia, agranulocytosis, abnormal liver function test results, GI irritation or bleeding, ototoxicity (higher risk than other loop diuretics), hyperuricemia, phlebitis, headache, rash, and hematuria. Pregnancy Class: B.

6.5.4 Drug-Drug Interaction

Ethacrynic acid administration causes increased potassium losses with amphotericin and steroids. Use of ethacrynic acid with aminoglycosides increases the risk of ototoxicity; increases the anticoagulant effects of warfarin; and decreases lithium excretion. Decreased glucose tolerance with ethacrynic acid may increase requirements of oral anti-diabetic agents.

6.5.5 Compatible Diluents/Administration

Ethacrynic acid is stable for 24 h at room temperature when mixed at 1 mg/mL in D5W or NS; inject slowly over 20–30 min. Ethacrynic acid is a tissue irritant and is not to be administered I.M. or subcutaneously.

6.6 Thiazide and Thiazide-Like Diuretics

6.6.1 Indication

Thiazide and Thiazide-Like diuretics are used for the treatment of mild to moderate hypertension. Additionally, they are used for the treatment of edema caused by CHF, pregnancy, bronchopulmonary dysplasia, nephrotic syndrome, or after cardiac surgery. Metolazone is also commonly used in conjunction with a loop diuretic in the management of edema secondary to CHF [8]. Thiazide is commonly used in conjunction with ACE-Inhibitors to control hypertension to offset potassium retention.

6.6.2 Mechanism of Action

The primary site of action of Thiazide diuretics (Chlorothiazide and Hydrochlorothiazide) is the distal convoluted tubule and the secondary site of action is the proximal tubule. In these regions, Thiazide and Thiazide-like diuretics block sodium reabsorption by inhibition of Na^+/Cl^- co-transporter causing increased excretion of sodium and water as well as potassium, bicarbonate, magnesium, phosphate, and calcium (transiently).

Similarly, Thiazide-like diuretics (Metolazone) primarily act upon the distal convoluted tubule and secondarily upon the proximal tubule. In these regions, metolazone inhibits sodium reabsorption, causing increased excretion of sodium and water as well as potassium and hydrogen ions.

6.6.3 Monitoring Parameters

Serum electrolytes, renal function (BUN and Cr), blood glucose, triglycerides, uric acid, blood pressure and fluid balance.

6.6.4 Contraindications

Anuria or an allergy to thiazide diuretics or sulfonamide. Hepatic coma.

6.6.5 Poison Information

Thiazide and Thiazide-like diuretic overdose is characterized by lethargy, dizziness, drowsiness, muscle weakness, arrhythmias, cramps, and fainting. On onset of these symptoms, drug administration should be stopped and symptomatic treatment should be initiated.

6.7 Chlorothiazide

6.7.1 Pharmacodynamics/Pharmacokinetics

Chlorothiazide has an onset of action of 2 h after oral administration and duration of action of 6–12 h. The duration of action is approximately 2 h after I.V. injection. Oral absorption of the drug is only 10–20 %, and protein binding ranges from 20 to 80 %. Chlorothiazide is not metabolized, and its half-life is 1–3 h. Almost the entire I.V. dose is eliminated unchanged in the urine within 3–6 h, and 35–60 % of the oral dose is excreted within 24 h.

6.7.2 Dosing

Note: I.V. dosage in infants and children has not been established. The following dosages in infants and children are based on anecdotal reports. Lower dosing regimens have been extrapolated from oral dosing recommendations, because 10–20 % of an oral dose is absorbed.

Neonates and Infants Younger than 6 Months:

Oral: 20 mg/kg/day in two divided doses; maximum, 375 mg/day
I.V.: 2–8 mg/kg/day in two divided doses; doses up to 20 mg/kg/day have been used

Infants older than 6 Months and Children:

Oral: 20 mg/kg/day in two divided doses; maximum, 1 g/day
I.V.: 5 mg/kg/dose administered every 6–24 h; doses up to 20 mg/kg/day

Adults:

Hypertension:
Oral: 125–500 mg once daily
Edema:

Oral: 500 mg to 2 g/day divided in one to two doses
I.V.: 100–500 mg/day divided in one to two doses

6.7.3 Precautions/Adverse Effects

Warning: do not administer the injectable formulation I.M. or subcutaneously.

Use cautiously in patients with severe renal disease, reduced hepatic function, and in patients with high triglyceride or cholesterol levels. Side effects of chlorothiazide use include hypotension, rashes, hypokalemia, hypochloremic metabolic alkalosis, hyperglycemia, hyperlipidemia, hyperuricemia, prerenal azotemia, thrombocytopenia, cholestasis, photosensitivity, arrhythmias, nausea, vomiting, diarrhea, pancreatitis, and fevers. Rarely, blood dyscrasias may also occur. Pregnancy Class: C.

6.7.4 Drug-Drug Interactions

NSAIDs may decrease the antihypertensive effect of chlorothiazide. Steroids, loop diuretics, and amphotericin B will cause additive potassium losses. With chlorothiazide use, there is a decreased clearance of lithium; there is increased hyperglycemia with diazoxide; there are increased hypersensitivity reactions to allopurinol; and there is an increased risk of renal toxicity with cyclosporine.

6.7.5 Compatible Diluents/Administration

Do not administer chlorothiazide I.M. or subcutaneously; avoid extravasation; administer chlorothiazide by I.V. injection over 3–5 min or by I.V. infusion over 30 min at a maximum concentration of 25 mg/mL in D5W or NS; reconstituted injectable formulation is stable for 24 h at room temperature.

6.8 Hydrochlorothiazide

6.8.1 Pharmacodynamics/Pharmacokinetics

Hydrochlorothiazide has an onset of action within 2 h of oral administration, with duration of action of 6–12 h. The oral absorption in the GI tract is approximately 60–80 %. The half-life of hydrochlorothiazide is 5–15 h, and hydrochlorothiazide is eliminated almost completely via the kidneys as unchanged drug.

6.8.2 Dosing

Neonates and Infants Younger than 6 Months:

Oral: 2–4 mg/kg/day in one to two doses; maximum daily dose, 37.5 mg

Infants Older than 6 Months and Children:

Oral: 2 mg/kg/day in one to two doses; maximum daily dose, 200 mg

Adults:

Oral: 12.5–100 mg/day in one to two doses; maximum, 200 mg/day

Note: Daily dosages should be decreased if used with other antihypertensive agents.

6.8.3 Precautions/Adverse Effects

Use cautiously in patients with severe renal disease, reduced hepatic function, diabetes mellitus, systemic lupus erythematosus, and gout. Adverse side effects of hydrochlorothiazide may include drowsiness, paresthesia, hypokalemia, hyponatremia, hypochloremic metabolic alkalosis, hyperglycemia, nausea, vomiting, anorexia, pancreatitis, cholestasis,

hypotension, agranulocytosis, thrombocytopenia, leukopenia, prerenal azotemia, polyuria, and photosensitivity. Pregnancy Class: B.

6.8.4 Drug-Drug Interactions

There is a decreased antihypertensive effect with NSAIDS. With hydrochlorothiazide use, there are increased potassium losses with steroids and amphotericin B; and increased hypersensitivity reactions to allopurinol. With hydrochlorothiazide use, there is increased hyperglycemia with diazoxide; a decreased effectiveness of anti-diabetic agents; a decreased clearance of lithium; increased hypotension with ACE inhibitors; and increased renal toxicity with cyclosporine.

6.9 Metolazone

6.9.1 Pharmacodynamics/Pharmacokinetics

Metolazone has an onset of action of approximately 1 h and duration of action of 12–24 h. Oral absorption of the drug is dependent on the preparation used, and protein binding is 95 %. The half-life is 6–20 h and 70–95 % of the drug is eliminated unchanged in the urine.

6.9.2 Dosing

Metolazone is only available for oral/enteral administration.

Children:

0.2–0.4 mg/kg/day divided every 12–24 h

Adults:

Edema: 5–20 mg/dose every 24 h
Hypertension: 2.5–5 mg/dose every 24 h

6.9.3 Precautions/Adverse Effects

Use cautiously in patients with severe renal disease, reduced hepatic function, diabetes mellitus, systemic lupus erythematosus, gout, and in patients with high triglyceride or cholesterol levels.

Common adverse reactions with metolazone use include palpitations, chest pain, hypotension, headaches, drowsiness, rash, and GI irritation. Hypokalemia, hyponatremia, hypochloremia, metabolic alkalosis, hyperglycemia, thrombocytopenia, leukopenia, aplastic anemia, and hyperuricemia have also been reported. Patients may experience sensitivity to light, chills, and abdominal bloating. Pregnancy Class: B.

6.9.4 Drug-Drug Interactions

There is a decreased antihypertensive effect with NSAIDs. There are also increased potassium losses with steroids and amphotericin B; and increased hypersensitivity reactions to allopurinol. There is increased incidence of digoxin toxicity caused by hypokalemia and hypomagnesium.

6.10 Potassium-Sparing Diuretics

6.10.1 Indication

Potassium-Sparing diuretics are commonly used to prevent potassium loss caused by the usage of Loop and Thiazide-like diuretics for the management of edema. Spironolactone is more commonly used and has been shown to increase success in the treatment of patients with CHF in animal models [9]. It is used in the management of neonatal chronic lung disease. Potassium-Sparing Diuretics are also used to treat edema associated with hepatic cirrhosis and nephrotic syndrome as well as hypertension, hypokalemia, and primary aldosteronism.

6.10.2 Mechanism of Action

Potassium-sparing diuretics inhibit sodium reabsorption in the distal nephron and collecting tubule by either competing with, or inhibiting the aldosterone-responsive Na^+ channels in the distal nephron and collecting tubule. They increase the excretion of sodium, chloride, and water and inhibit the excretion of potassium and hydrogen. The effect of aldosterone on arteriolar smooth muscle may also be blocked.

6.10.3 Poisoning Information

Symptoms include nausea, vomiting, diarrhea, dehydration and electrolyte imbalances (hyperkalemia). Severe toxicity causes altered mental status, tachycardia, acute renal injury and arrhythmias secondary to hyperkalemia. Treatment of minor intoxication is oral rehydration and monitoring of hyperkalemia. Severe toxicity causing severe potassium abnormalities requires aggressive treatment with rehydration with IV fluids, calcium chloride, sodium bicarbonate, insulin, IV glucose and sodium polystyrene. Dialysis may be necessary.

6.10.4 Monitoring Parameters

Serum potassium, blood pressure, renal function (BUN and Cr), fluid balance

6.10.5 Contraindications

Anuria, hyperkalemia, diabetic nephropathy, renal failure

6.10.6 Drug-Drug Interactions

Potassium sparing diuretics increases serum potassium when used with potassium supplements, potassium-sparing

diuretics, ACE inhibitors, angiotensin receptor blockers, arginine, tacrolimus, sotolol, and cyclosporine. Amiloride decreases digoxin and lithium clearance. NSAIDs decrease the effects of amiloride. Spironolactone use may decrease clearance of digoxin; may cause a decreased response to norepinephrine; and may decrease the effects of oral anticoagulants.

6.11 Spironolactone

6.11.1 Mechanism of Action

Spironolactone is a potassium-sparing diuretic that competes with aldosterone for binding to receptor sites in the distal tubule of the kidneys. It increases the excretion of sodium, chloride, and water and prevents the excretion of potassium and hydrogen. The effect of aldosterone on arteriolar smooth muscle may also be blocked.

6.11.2 Pharmacokinetics

Spironolactone is well absorbed after oral administration, with bioavailability at approximately 90 %. The protein binding of the drug is greater than 90 % with hepatic metabolism to multiple metabolites, including the active agent, canrenone. The half-life of spironolactone is 1.4 h and the half-life of canrenone is 13–24 h. The duration of action is 2–3 days.

6.11.3 Dosing

Spironolactone is only available for oral/enteral administration.

Neonates:

Diuretic: 1–3 mg/kg/day divided every 12–24 h

Children:

Diuretic, *hypertension*: 1.5–3.5 mg/kg/day or 60 mg/m^2/day in one to four divided doses daily

Adults:

Edema, *hypokalemia*: 25–200 mg/day in one to two divided doses

Hypertension: 25–50 mg/day in one to two doses daily

6.11.4 Precautions/Adverse Effects

Warning: severe hyperkalemia may result when used with ACE inhibitors, potassium supplements, and NSAIDs; monitor potassium levels and renal function closely.

Use with caution in patients with decreased renal function, hyponatremia, dehydration, or reduced hepatic function.

Adverse reactions associated with spironolactone include hyperkalemia, dehydration, hyponatremia, hyperchloremic metabolic alkalosis, headaches, fever, diarrhea, vomiting, nausea, lethargy, rash, anorexia, gynecomastia (in males), irregular menses, agranulocytosis, coughing, and decreased renal function. Pregnancy Class: C.

6.12 Amiloride

6.12.1 Mechanism of Action

Amiloride inhibits sodium-potassium ion exchange in the distal convoluted tubule, cortical collecting tubule and collecting tubule. Unlike spironolactone, this does not depend on aldosterone and has effect by inhibiting cellular sodium transport mechanisms and inhibits hydrogen ion secretion.

6.12.2 Pharmacokinetics

Amiloride has an onset of action of 2 h and peak at 3–4 h. Oral bioavailability is 15–25 %. The half-life in normal renal function is

6–9 h and up to 144 h in severe renal disease. Amiloride is eliminated in the urine and feces and not metabolized by the liver

6.12.3 Dosing

Amiloride is only available for oral/enteral administration.

Children 6–20 kg:

0.625 mg/kg/day administered once daily (maximum dose, 10 mg/day)

Children Greater than 20 kg and Adults:

5–10 mg/day (maximum dose, 20 mg/day)

In Patients with Renal Impairment: Reduce dose 50 % for ClCr 10–50 mL/min. Avoid use if ClCr is less than 10 mL/min

6.12.4 Precautions/Adverse Effects

Warning: Use with caution with potassium supplements or other potassium sparing diuretics; reduce dose in patients with renal insufficiency, hyponatremia, dehydration, electrolyte imbalance, diabetes, or decreased hepatic function. Adverse effects include hypotension, arrhythmias, hyperkalemia, hyponatremia, dehydration, hyperchloremic metabolic acidosis, nausea, vomiting, diarrhea, GI bleeding, liver function abnormalities, muscular weakness, paresthesias, neutropenia, aplastic anemia, headache, dizziness, confusion, insomnia, rash, and bladder spasms. Pregnancy Class: B.

6.13 Carbonic Anhydrase Inhibitors

6.13.1 Acetazolamide

The main indication of Acetazolamide within pediatric cardiology is to treat secondary metabolic alkylosis , however, it is also a weak diuretic. It is also is used to reduce intraocular pressure in glaucoma and in the treatment of neurologic illness including hydrocephalus, seizures, and altitude sickness [10].

6.13.2 Mechanism of Action

As a diuretic, acetazolamide initiates competitive, reversible inhibition of carbonic anhydrase, which results in increased renal secretion of sodium, potassium, sodium bicarbonate, and water. It is the secretion of bicarbonate which is clinically important in treating metabolic alkylosis. Acetazolamide also inhibits carbonic anhydrase in the CNS, thus, reducing discharges from CNS neurons.

6.13.3 Pharmacokinetics

Acetazolamide has an onset of action of 2 min after I.V. injection, 1–2 h after tablet ingestion, and 2 h after extended-release capsule administration. The duration of action of the drug is 4–5 h if administered I.V., 8–12 h after a tablet, and 18–24 h after an extended-release capsule. Absorption of acetazolamide is dose dependent, and acetazolamide distributes into erythrocytes and the kidneys. The half-life ranges from 2.4 to 5.8 h, with 70–100 % of the I.V. or tablet dose eliminated unchanged in the urine within 1 day.

6.13.4 Dosing

Children:

Edema:
Oral, *I.V.*: 5 mg/kg/dose or 150 mg/m^2/dose once every day
Secondary metabolic alkalosis:
Oral, *I.V.*: 3–5 mg/kg/dose every 6 h for four doses

Adults:

Edema:
Oral, *I.V.*: 250–375 mg once daily
Urine alkalinization:
Oral: 5 mg/kg/dose repeated two to three times over 24 h

In Patients with Renal Impairment:

ClCr 10–50 mL/min: administer every 12 h
ClCr less than 10 mL/min: avoid use

6.13.5 Monitoring Parameters

CBC, platelets, serum electrolytes. Liver enzymes and ASA/acetaminophen levels in symptomatic patients.

6.13.6 Contraindications

Allergy to sulfonamides, hyperchloremic acidosis, severe renal disease, hepatic insufficiency, low serum sodium or potassium

6.13.7 Precautions/Adverse Effects

Warning: sulfonamides have caused fatalities caused by toxic epidermal necrolysis, Stevens-Johnson syndrome, hepatic necrosis, aplastic anemia, and other blood dyscrasias. Discontinue use at the first sign of rash or adverse reaction.

Use with caution in patients with chronic obstructive pulmonary disease, respiratory acidosis, gout, and diabetes mellitus; reduce dosage in patients with renal dysfunction.

The most common adverse effects include: paresthesias, renal calculi, metabolic acidosis, bone marrow depression, and rashes. Other more rare adverse effects include: taste disturbances, ataxia, gastritis, cholestatic hepatitis, and renal failure. Acetazolamide is basic and may be implicated in extravasation injury. Pregnancy Category: C.

6.13.8 Poisoning Information

Symptoms of acetazolamide overdose include confusion, drowsiness, nausea, vomiting, tachycardia, tachypnea and electrolyte abnormalities. Severe toxicity yields lethargy and severe metabolic acidosis.

6.13.9 Drug-Drug Interactions

Acetazolamide may decrease the rate of excretion of other drugs, such as sotalol, arsenic trioxide, droperidol, procainamide, flecainide, quinidine, cyclosporine, digoxin, high dose ASA, acetaminophen, amphetamines, and tricyclic antidepressants leading to toxicity. When available, levels should be followed. Acetazolamide may increase the risk of developing osteomalacia in patients receiving phenytoin or phenobarbital. Concomitant topiramate is not recommended due to the increase the risk of nephrolithiasis and paresthesia. Acetazolamide may increase or decrease lithium excretion.

6.13.10 Compatible Diluents/Administration

Reconstituted injectable formulation at 100 mg/mL concentration is stable for 1 week refrigerated. It may be diluted further in D5W or NS for I.V. infusion, with a stability of 5 days at room temperature and 44 days refrigerated.

6.14 Osmotic Diuretics

6.14.1 Mannitol

Mannitol is occasionally used to promote diuresis in the treatment of oliguria caused by acute renal failure. Mannitol is also used to reduce increased intracranial pressure associated with cerebral edema and to facilitate the urinary excretion of toxic substances.

6.14.2 Mechanism of Action

Mannitol is an osmotic diuretic that increases the osmotic pressure of the glomerular filtrate, which inhibits the tubular reabsorption of water and electrolytes, thus increasing urinary output.

6.14.3 Pharmacokinetics

The onset of action of mannitol begins within 1–3 h after injection and persists for 3–8 h. The drug remains confined to the extracellular space except in high concentrations or acidosis. The half-life of mannitol is 1.1–1.6 h and it is primarily eliminated in urine by glomerular filtration.

6.14.4 Dosing

Children:

Test dose (*to assess adequate renal function*): 200 mg/kg (maximum 12.5 g) over 3–5 min to produce urine flow of at least 1 mL/kg/h for 1–3 h
Initial: 0.5–1 g/kg over 20 min as a 20 % solution
Maintenance: 0.25–0.5 g/kg administered every 4–6 h

Adults:

Test dose: 12.5 g (200 mg/kg) over 3–5 min to produce urine flow of at least 30–50 mL of urine per hour over the next 2–3 h
Initial: 0.5–1 g/kg (50–100 g)
Maintenance: 0.25–0.5 g/kg administered every 4–6 h

6.14.5 Monitoring Parameters

Serum electrolytes, renal function (BUN and Cr), fluid balance, serum and urine osmolality (maintain serum osmolality 310–320 mOsm/kg for high intracranial pressure)

6.14.6 Contraindications

Severe pulmonary edema or congestion, severe renal disease, progressive oliguria after administration, dehydration, and active intracranial bleeding

6.14.7 Precautions/Adverse Effects

Mannitol should not be administered until adequate renal function and urine flow is established with test doses and cardiovascular status is evaluated. High doses may cause renal dysfunction—use caution in patients taking other nephrotoxic agents, with severe dehydration, with sepsis, or underlying renal disease. To minimize adverse renal effects, serum osmolality should be kept under 320 mOsm/L. Adverse reactions associated with mannitol include circulatory overload, CHF, headache, convulsions, fluid and electrolyte imbalance, dehydration, hypovolemia, plasma hyperosmolality, hyponatremia or hypernatremia, increased osmolar gap, blurred vision, and pulmonary edema. Pregnancy Category: C

6.14.8 Poisoning Information

Symptoms of mannitol overdose include acute renal failure, hypotension, pulmonary edema, cardiovascular collapse, polyuria, oliguria, seizures, hyponatremia, and hypokalemia. Replacement of fluid and electrolyte losses may be necessary. Hemodialysis will clear mannitol and reduce osmolality.

6.14.9 Drug-Drug Interactions

Mannitol use increases lithium toxicity. Its use may potentiate the effects of other medications that cause electrolyte abnormalities.

6.14.10 Compatible Diluents/Administrations

Do not administer mannitol with blood. Inspect mannitol for crystals before administration. Use a filter in administration set. Avoid extravasation.

References

1. Pedersen KR, Hjortdal VE, Christensen S, et al. Clinical outcome in children with acute renal failure treated with peritoneal dialysis after surgery for congenital heart disease. Kidney Int Suppl. 2008;108:S81–6.
2. Sutherland SM, Zappitelli M, Alexander SR, et al. Fluid overload and mortality in children receiving continuous renal replacement therapy: the prospective pediatric continuous renal replacement therapy registry. Am J Kidney Dis. 2010; 55(2):316–25.
3. Jentzer JC, Dewald TA, Hernandez AF. Combination of loop diuretics with thiazide-type diuretics in heart failure. J Am Coll Cardiol. 2010;56(19):1527–34.
4. Luciani GB, Nichani S, Chang AC, Wells WJ, Newth CJ, Starnes VA. Continuous versus intermittent furosemide infusion in critically ill infants after open heart operations. Ann Thorac Surg. 1997;64(4):1133–9.
5. Singh NC, Kissoon N, Almofada S, Bennett M, Bohn DJ. Comparison of continuous versus intermittent furosemide administration in postoperative pediatric cardiac patients. Crit Care Med. 1992;20(1):17–21.
6. Schwartz J, Bloch R, Imbs JL, Spach MO. Diuretics. Pathol Biol (Paris). 1986;34(7):861–85.
7. Buck ML. Pharmacokinetic changes during extracorporeal membrane oxygenation – implications for drug therapy of neonates. Clin Pharmacokinet. 2003;42(5):403–17.
8. Sica DA. Metolazone and its role in edema management. Congest Heart Fail. 2003;9(2):100–5.
9. Brilla CG, Schencking M, Scheer C, Rupp H. Spironolactone: renaissance of anti-aldosterone therapy in heart failure? Praxis (Bern 1994). 1997;86(14):566–74.
10. Poca MA, Sahuquillo J. Short-term medical management of hydrocephalus. Expert Opin Pharmacother. 2005;6(9):1525–38.