Pediatric Nephrology (2021) 36:2687–2695
https://doi.org/10.1007/s00467-021-04921-3

EDUCATIONAL REVIEW

Use of diuretics in the neonatal period

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Received: 2 October 2020 / Revised: 6 November 2020 / Accepted: 5 January 2021 / Published online: 22 January 2021

Abstract
The use of diuretics is extremely frequent in sick neonates, the more so in very premature newborn infants. The use of diuretics in patients whose kidney function is immature necessitates a thorough knowledge of renal developmental physiology and pathophysiology. This review presents the basic aspects of body fluid homeostasis in the neonate, discusses the development of kidney function, and describes the mechanisms involved in electrolyte and water reabsorption along the nephron. Diuretics are then classified according to the site of their action on sodium reabsorption. The use of diuretics in sodium-retaining states, in oliguric states, in electrolyte disorders, and in arterial hypertension, as well as in a few specific disorders, is presented. Common and specific adverse effects are discussed. Recommended dosages for the main diuretics used in the neonatal period are given. New developments in diuretic therapy are briefly mentioned.

Keywords Neonates · Diuretics · Furosemide · NICU · VLBW · AKI · Bronchopulmonary dysplasia

Introduction

Diuretics are pharmacologic agents that promote the excretion of water and electrolytes. They represent one of the most common classes of drugs administered to sick neonates, for whom they are primarily used in the treatment of illnesses associated with inappropriate water and sodium retention, such as congestive heart failure, kidney disorders, and liver disease. The use of diuretics is extended to various clinical conditions not evidently related to salt retention (i.e., respiratory diseases, unwanted fluid excess or oliguric states, electrolyte disorders). According to a recent study, furosemide is one of the 20 medications most prescribed during the neonatal period, with an overall exposure rate of 6.9% in infants cared for in neonatal wards and up to 44.2% in preterm infants of gestational age less than 27 weeks [1]. It is evident that expectations for diuretic therapy by neonatologists caring for very low birth weight (VLBW) infants may exceed evidence of efficacy [2].

This article reviews the actions of the diuretic agents commonly used in neonates, the rationale for the use of diuretics in preterm and term infants, and the adverse effects of diuretic therapy.

Body fluid homeostasis in neonates

The kidney is the main organ responsible for maintaining the extracellular fluid (ECF) volume and osmolality within narrow limits. In neonates, the functional capacity of the kidney is clearly influenced by the infant's gestational and postnatal ages. Thus, a precise knowledge of both the physiology of the fluid balance and the pathophysiology of the immature kidney provides an adequate basis for the rational prescription of diuretics in newborn infants.

Body fluid homeostasis

NaCl is the major osmotically active solute in the ECF and determines its volume. The overall balance between the intake and the renal excretion of Na^+ regulates the ECF volume, and as a consequence the cardiac output and pressure. Pressure receptors within the vasculature and flow receptors within the kidney trigger a coordinated response for maintaining the

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"effective arterial circulating volume," a term that describes the critical blood flow for an adequate organ perfusion.

Aldosterone is the main hormone regulating long-term changes in sodium excretion, though renal sodium handling is also modulated by other factors, such as changes in glomerular filtration rate (GFR) and various intrarenal hormones and paracrine factors. The plasma renin activity generated by the fetal kidney is elevated and is essential for the maintenance of blood pressure in the fetus. It slowly decreases after birth. While sodium is the main solute regulating ECF volume, the antidiuretic hormone (ADH, or vasopressin) plays a central role in the defense of the plasma osmolality.

The reabsorption of Na along the nephron

Up to 99% of the filtered sodium is reabsorbed by the kidney tubule. To achieve this, 65% is reabsorbed in the proximal tubule, 25% in the ascending limb of Henle's loop, and ~ 10% in the distal tubule and collecting duct. The key sites of sodium transport along the nephron are shown in Fig. 1.

Throughout the nephron, the driving force for Na^+ reabsorption is the Na^+, K^+- ATPase in the basolateral membrane of tubular epithelial cells. In the early portion of the proximal tubule, the luminal reabsorption of Na^+ is primarily coupled to that of the filtered load of bicarbonate, with the help of the Na^+/H^+ exchanger (NHE). In the late proximal tubule, sodium is mostly reabsorbed with chloride. In the loop of Henle, the majority of the sodium is reabsorbed by the Na^+, K^+, $2Cl^-$ cotransporter (NKCC). This is the transporter that is inhibited by furosemide and bumetanide. Sodium, but not water, is reabsorbed in the ascending limb, thus allowing the generation of a hyperosmolar medullary interstitium necessary for urinary concentration. In the distal convoluted tubule, sodium reabsorption primarily occurs with chloride, via the Na^+Cl^- cotransporter (NCC), which is inhibited by thiazides. The collecting duct has two types of cells. The principal cells reabsorb Na^+ and water and secrete K^+, under the control of aldosterone. Neighboring type A intercalated cells reabsorb K^+ and secrete H^+ in the tubular lumen, playing an important role in acid-base balance. They are also affected by aldosterone. The active sodium transport that occurs in the collecting duct is mediated by the amiloride-sensitive ENaC channel. The principal cells of the collecting duct also express the vasopressin-sensitive water channel aquaporin-2 (AQP2) which represents the chief target of the ADH for the regulation of water permeability. AQP2 is translocated from intracellular vesicles to the apical membrane of collecting duct cells after ADH stimulation. Under physiological conditions, urinary AQP-2 excretion is a marker of the kidney concentrating ability.

Body fluid homeostasis and kidney function after birth

The amount of total body water and its distribution between the body fluid compartments is very different in the fetus and in the neonate as compared to the adult. The transition from fetal to neonatal life is associated with major changes in water and sodium homeostasis. The ECF volume in the neonate is affected by antenatal factors, gestational age, birth weight, adaptation to extra-uterine environment, and postnatal age. The ECF amount per body weight is greater at lower gestational ages. A physiologic contraction of ECF volume occurs after birth, and, under normal conditions, a net water and

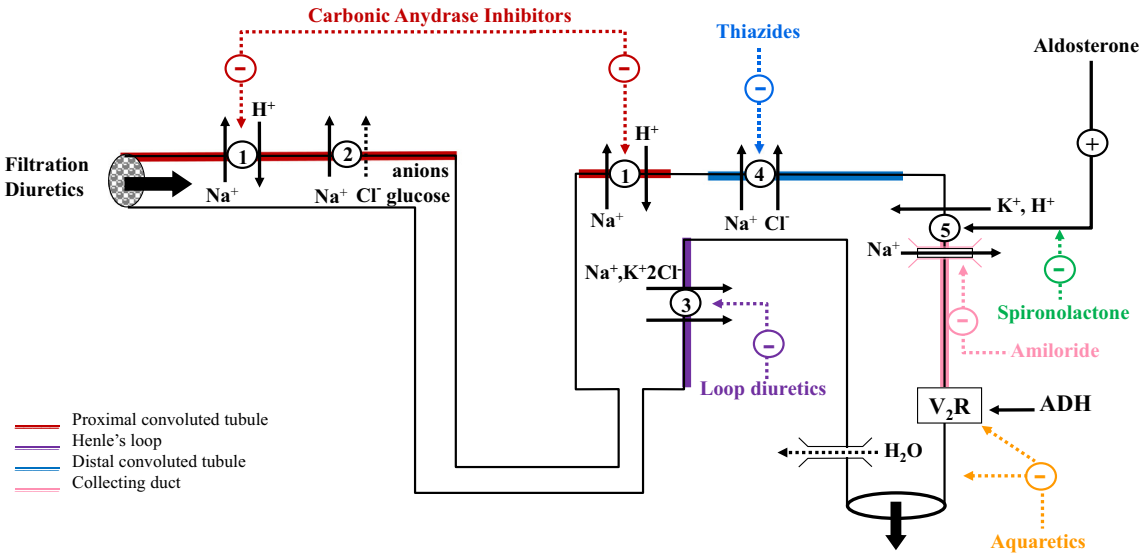

Fig. 1 Sites of sodium reabsorption and diuretic site of action along the nephron. (1) sodium hydrogen exchanger (NHE); (2) sodium glucose cotransporter (SGLT2); (3) sodium potassium chloride cotransporter (furosemide receptor)(NKCC2); (4) sodium chloride cotransporter (thiazide receptor)(NCC); (5) proton ATPase and epithelial sodium channel (ENaC) (amiloride receptor). V2R = arginine vasopressin receptor. ADH = antidiuretic hormone

sodium loss occur appropriately in the first week of life, especially in the most preterm infants. From a value of 60% of body weight in neonates of 24 weeks of gestational age, the ECF volume decreases to 44% of body weight near term. The ECF volume decreases to 30% in the infant and stabilizes at a value of 20% in the grown-up child. At birth GFR is low, both in term and preterm infants, and this limits the newborn infant's ability to excrete a water and sodium load. After birth, renal blood flow (RBF) and GFR mature rapidly according to gestational and postnatal ages [3]. The abrupt increase of GFR largely contributes to contract the ECF volume and increases the filtered load of sodium and the diuresis. Postnatal variations in ECF volume and GFR are paralleled by maturational changes in tubular transport and marked changes in tubular sodium handling occur with and following birth (the reader is referred to [4, 5] for a more detailed description). These developmental changes are mostly dependent upon gestational age more than upon postnatal age, thus inducing a certain degree of glomerulotubular imbalance, especially in VLBW infants. Briefly, several factors are responsible for the reduced sodium renal handling: (i) the activity of the basolateral Na^+, K^+- ATPase presents with a rapid increase during the first 24 h of life, but is completely mature at 35 weeks of gestational age; (ii) the NHE activity in the proximal tubular increases immediately after birth, but this is not paralleled by corresponding mRNA abundance and protein activity; (iii) plasma aldosterone levels at birth increase significantly with gestational age but, despite levels higher than adults, preterm infants are less responsive to aldosterone; and (iv) there is a paucity of conducting ENaC channels in principal cells of the collecting duct.

Concerning the newborn's ability to regulate urine concentration, noteworthy is the fact that the immature kidney can produce urine as diluted as 50 mOsm/kg H_2O, after prolonged decrease of serum osmolality. Conversely, the ability to concentrate urine is deeply impaired by the limited concentration of urea in the medullary interstitium. Despite the huge increase of ADH in response to augmented serum osmolality or reduced effective arterial circulating volume, and even though urinary AQP2 excretion increases under these circumstances [6], the immature neonatal kidney can only concentrate urine up to 600 mOsm/kg H_2O. This places neonates at risk of volume depletion. Furthermore, urinary water losses may also be augmented by other conditions in sick or preterm infants, such as caffeine or theophylline therapy, glycosuria, and, of course, diuretic therapy.

Classification of diuretics

All diuretics are natriuretic agents. Diuretics can variably modify electrolyte excretion. Diuretic drugs can be classified according to their site of action on Na^+ transport along the nephron, as shown in Fig. 1.

From a clinical point of view, diuretics can be classified according to their mode of action (Table 1). Table 1 also describes the most commonly used diuretic agents in neonates.

Indications of diuretics

Diuretics are used in sodium-retaining states with or without the formation of edema, in oliguric kidney failure, in situations of electrolyte imbalances or arterial hypertension, and in nephrogenic diabetes insipidus. Diuretics can be used to test the integrity of distal tubular function (Table 1).

Sodium-retaining states

Sodium retention is the primary indication of diuretics. Salt and water retention may result either from primary excessive volume or pressure overload, or from a reduced effective circulating volume. This latter triggers a secondary hyperaldosteronism, with the result of restoring perfusion of the vital organs.

The most common sodium-retaining state in neonates is congestive heart failure (CHF). In CHF systemic and pulmonary congestion arises from the inability of the heart to pump as much blood as required for an adequate organ metabolism. The decrease of effective circulating volume is sensed by the kidney which retains sodium and water. A newborn infant with CHF carries the risk of rapid deterioration, and even if the chief treatment of CHF consists in restoring an adequate cardiac output, the use of diuretics can be life-saving in reducing pulmonary edema and congestion. The loop diuretic furosemide is the most used diuretic in neonates worldwide, and CHF is its main therapeutic indication [1, 11, 12]. Several studies provide strong evidence that, in case of volume overload after cardiac surgery and in critically ill patients, continuous intravenous furosemide is effective, well tolerated, and safe [13, 14]. In the postoperative management of hemodynamically stable infants following open heart surgery, intermittent infusion should be preferred [15]. Furosemide increases the peripheral venous capacitance and can thus be useful independently from its diuretic effect. In infants with severe CHF, the diuretic effect of furosemide is inversely related to serum aldosterone levels. The concomitant administration of a K^+- sparing diuretic improves the response to loop diuretics [16], and oral spironolactone is often associated with furosemide in the mid-long-term treatment of neonatal CHF.

Few pharmacokinetic studies provide evidence that intermittent administration of bumetanide is effective and tolerated in volume overloaded, critically ill newborn infants, with no data available, to date, on its continuous infusion [17]. It is

Table 1 Diuretic classification according to mechanism of action, most commonly used drugs, clinical uses, and questionable indications for diuretics in neonates

	Actions	Drugs	Clinical uses	Questionable indications
Osmotic diuretics	Increase of ECF, RBF Freely filtered, Not reabsorbed ↑ water diuresis ↑ natriuresis	Mannitol	Intracranial hypertension [7]	Oliguric prerenal failure
Carbonic anhydrase inhibitors	Inhibit proximal tubular H^+ secretion ↑ HCO_3^- excretion ↑ water and Na excretion (weak)	Acetazolamide	Assessment of distal acidification Hypochloremic metabolic alkalosis [8, 9]	PHH
Loop diuretics	Inhibit NaCl active reabsorption ↑ natriuresis	Furosemide Bumetanide	Edematous states Prerenal failure Electrolyte disorders Assessment of distal acidification	Respiratory disorders PHH
Thiazides	Inhibit NaCl active reabsorption ↑ water excretion (weak)	Hydrochlorothiazide Chlorothiazide	Edematous states pRTA Hypercalciuria NDI	CLD BPD Nephrocalcinosis [10]
K^+-sparing diuretics	Inhibit Na reabsorption in the cortical collecting duct	Amiloride Spironolactone	Adjuvant therapy with loop or thiazide diuretics Prevention of hypokalemia NDI	CLD BPD
Xanthines	Inhibit intrarenal adenosine	Theophylline Aminophylline, Caffeine	RDS, hypoxemic or asphyxic kidney failure	RDS

BPD bronchopulmonary dysplasia, *CLD* chronic lung disease, *ECF* extracellular fluid, *GFR* glomerular filtration rate, *NDI* nephrogenic diabetes insipidus, *PHH* post-hemorrhage hydrocephalus, *pRTA* proximal renal tubular acidosis, *RBF* renal blood flow, *RDS* respiratory distress syndrome

interesting to note that in neonates undergoing extra-corporeal membrane oxygenation (ECMO), substantial pharmacokinetic alterations in loop diuretics occur [18]. These alterations, along with the variable kidney function, make the dosing schedule for furosemide and bumetanide in newborn infants under ECMO very empirical (see dosage drug table here below).

Nephrotic and liver failure edemas are less frequent in neonatal life. In these conditions, sodium retention occurs in order to defend the circulating volume which can be very low, and the use of diuretics (loop diuretics, thiazides, and K^+-sparing diuretics) requires a careful assessment of the infant intravascular volume. In severe forms of congenital nephrotic syndrome (CNS) generalized edema, urine protein concentration > 20 g/L, and serum albumin level < 10 g/L can be detected since the neonatal period [19]. Intravenous furosemide can be used to promote sodium and water excretion and should be given together with the expansion of the extracellular space with intravenous albumin [20]. In the management of edema associated with CNS, amiloride has been studied in conjunction with loop diuretics and has been shown to have an additive effect [21]. Broadly, refractory edema secondary to CHF, cirrhosis of the liver or nephrotic syndrome, represents a common indication for the use of K^+-sparing diuretics. In all conditions associated with secondary hyperaldosteronism, spironolactone is the first-choice agent, provided kidney function is not impaired. Because they induce K^+ retention, K^+-sparing diuretics should not be used in patients with impaired kidney function or in those receiving potassium supplementation. They should also be avoided in patients prone to develop metabolic acidosis.

Oliguric states

There are no specific guidelines regarding the use of diuretics in newborn infants with acute kidney injury (AKI), and there is no evidence that this treatment can ameliorate kidney function or improve the outcome of infants with AKI. Among diuretics, the osmotic diuretic mannitol is presently not recommended in neonates with the indication of improving diuresis in oliguric states, due to several reported adverse effects (see paragraph 6). With a lack of consensus from human adult studies [22], and based on animal models of the immature kidney [23], there is no evidence that loop diuretics can prevent the evolution from prerenal to intrinsic kidney failure or that they can improve the outcome of patients with established kidney failure.

Nevertheless, in neonates with oliguric AKI, standard practice includes a trial with loop diuretic therapy (often furosemide) to improve diuresis and avoid fluid overload [24–27]. Moreover, in neonates undergoing cardiopulmonary bypass surgery, it has been proven that urine output response to furosemide administered intraoperatively predicts cardiac surgery-induced AKI development and other important morbidities [28].

Very few studies have reported results on the use of bumetanide in preterm or LBW infants, and they do not allow a definite conclusion on the usefulness of bumetanide in AKI [29–31].

Finally, since the late 80s, experimental studies have explored the role of adenosine in the immature kidney and in functional kidney insufficiency and the protective effects of theophylline, a xanthine derivative with strong adenosine antagonistic properties [32, 33]. They provided evidence of natriuretic and diuretic properties of theophylline when used in oliguric acute hypoxemic vasomotor nephropathy in rabbits [34]. In recent years, aminophylline and theophylline have been tested in several randomized controlled trials for their prophylactic and curative use in kidney impairment in critically ill neonates. Systematic reviews and meta-analyses conclude that prophylactic theophylline helps in prevention of AKI/severe kidney dysfunction in term neonates with severe birth asphyxia [35, 36]. Asphyxia is the most frequent cause of severe oligo-anuric kidney failure. Inhibition of intrarenal adenosine seems promising for improving kidney outcome of asphyxiated neonates undergoing therapeutic hypothermia and deserves further investigation [37].

Electrolyte disorders

Diuretics are used in clinical situations associated with electrolyte disorders.

In hyperkalemic states, loop diuretics and thiazides can increase potassium excretion; in hypercalcemia, loop diuretics can be used to increase calcium excretion; in hypercalciuric states, thiazides decrease the rate of calcium excretion. Increased bicarbonate excretion can be achieved by acetazolamide, and increased excretion of hydrogen ions can be stimulated by loop diuretics.

Arterial hypertension

Loop diuretics, thiazides, and aldosterone antagonists can be used in treatment of slow onset neonatal hypertension (NH), especially if arterial hypertension is a consequence of, or is aggravated by, sodium and water retention. This type of hypertension responds to diuretic-induced natriuresis. Furosemide and hydrochlorothiazide have modest effects on blood pressure, but they can be used in association with K^+-sparing diuretics in NH related to bronchopulmonary dysplasia (BPD). Diuretics do not represent the first-line treatment for NH, and they should not be used as antihypertensive drugs in the treatment of malignant, fast onset crisis [38].

Specific indications

Acetazolamide, furosemide, and hydrochlorothiazide have been used in the past to test distal tubular acidification or distal sodium reabsorption defects in neonatal onset kidney tubulopathies [39]. In the newborn infant with congenital Bartter syndrome, amiloride (or triamterene) and spironolactone can be added for the treatment of hypokalemia as they will also improve the metabolic alkalosis [40]. Potassium-sparing diuretics should however be administered with caution because they carry the risk of inducing hypovolemia. Thiazides can be used to create mild hypovolemia which encourages salt and water uptake in the proximal tubule and thus improve polyuria in nephrogenic diabetes insipidus [41].

Dosages of diuretics in newborn infants

While not the object of this review, it is important to remember that the age-related establishment and maturation of RBF and GFR, and the kidney tubular secretory capacity, affect the delivery of diuretics to their sites of action and, as a consequence, condition the pharmacodynamics and neonatal response.

With the exception of furosemide, pharmacokinetic and pharmacodynamic of diuretics have been poorly studied in human newborn infants [17, 42–44]. Most of the available data on dosages of diuretics in neonates are derived from studies conducted in pediatric or adult patients, without logical or justified extrapolation [45].

Table 2 reports the dose of the diuretics most often used during the neonatal period according to pharmacokinetic and pharmacodynamic data or clinical pharmacology studies.

The use of diuretics in neonatal intensive care—where is the evidence?

Diuretic drugs, especially loop diuretics, are often used in the neonatal intensive care unit as off-label treatments for several clinical conditions. This occurs despite significant side effects and also despite that, to date, studies have not demonstrated a positive impact of diuretic therapy upon important clinical outcomes. These conditions are discussed below.

Diuretics for respiratory distress syndrome of the newborn infant

As it can produce an acute diuresis, furosemide may induce a transient improvement in pulmonary function. However, the most recent critical review of the literature [46] failed to support the routine administration of furosemide (or any diuretic) in preterm infants with RDS and concluded that elective administration of diuretics should be weighed against the risk of inducing cardiovascular complications. Recent results from the PROP (prematurity and respiratory outcomes program)

Table 2 Dosages of the most used diuretics in neonatal life

Drug	Route/ interval (qh)	Dosage (mg/kg/day) (unless otherwise noted)	Comments
Furosemide	PO: 12–24 IV: 12–24 CIVI	1–2 (up to 6) 0.5–1.5 0.1–0.4 mg/kg/h	• Plasma half-life as long as 72 h has been observed in premature neonates, and plasma half-life decreases with increasing postnatal age • Effective at GFR < 10 mL/min • After cardiac surgery the administration of a loading dose (1–2 mg/kg) of the diuretic before starting continuous infusion accelerates the diuretic response [13] • Some oral liquid furosemide formulations contain ethanol as excipient and may induce moderate alcohol exposure
Ethacrynic acid	PO: 12–24	1–2	• Effective at GFR < 10 mL/min per 1.73 m^2
Bumetanide	PO: 12–24 IV: 12–24 CIVI	0.01–0.10 0.01–0.05 5–10 μcg/kg/h	• Plasma half-life ranges from 1.74 to 7 h • High variable half-life during ECMO
Hydrochlorothiazide	PO: 12–24	1–3	• Not effective at GFR < 30 mL/min per 1.73 m^2
Metolazone	PO: 12–24	0.2–0.4	• Effective at GFR < 20 mL/min per 1.73 m^2
Spironolactone	PO: 6–12	1–3	• Delayed diuretic effect
Canrenoate-K	IV: 24	4–10	• Plasma half-life around 11 h
Triamterene	PO: 12–24	2–4	• Contraindicated in CKD and in conditions associated to hyperkalemia
Amiloride	PO: 24	0.5	• idem triamterene

CKD chronic kidney disease, *GFR* glomerular filtration rate, *CIVI* continuous intravenous infusion, *IV* intravenous infusion, *PO* per OS

cohort did not support the ability of diuretics to substantially improve the extremely premature infant's respiratory status [47]. Diuretics cannot even be recommended for the treatment of transient tachypnea of the newborn at term [48].

Diuretics for preterm infants with evolving or established BPD

Diuretics are used as symptomatic therapy in the management of BPD. Loop diuretics increase re-absorption of the interstitial fluid and pulmonary vasodilation, decrease filtration of transpulmonary fluid, and systemic vasodilation [49]. So, enteral and aerosolized administration of furosemide have been studied, but Cochrane meta-analyses [50, 51] conclude that they are not recommended for routine management of the early or late phases of BPD. Noteworthy is however the recent observation demonstrating that more days on furosemide between postnatal day 7 and 36 weeks were associated with decreased risk of BPD and of combined outcome of BPD or death [52].

Acute and chronic administration of thiazides improve pulmonary mechanics. However, their positive effects should be interpreted with caution as the numbers of patients studied are small in surprisingly few randomized controlled trials [53]. To date, there is no evidence to support that combined diuretic treatments (i.e., adding spironolactone to thiazide or adding metolazone to furosemide) improve the outcome of preterm infants with BPD.

It is important to note that caffeine has unequivocal beneficial effects in prevention of BPD due to several mechanisms, among which is its diuretic effects [54].

Furosemide in preterm infants with patent ductus arteriosus

Oliguria occurs frequently after administration of indomethacin or ibuprofen to close a PDA, and AKI is also a complication of these drugs. On the one side, there is no evidence that furosemide can prevent the incidence of AKI in infants treated by non-steroidal anti-inflammatory drugs for PDA closure [55]. On the other side, the suggestion that by stimulating prostaglandin synthesis furosemide could promote PDA has not been confirmed. On the contrary, in a large cohort of VLBW infants, furosemide exposure was recently associated with decreased odds of PDA treatment [56]. According to a recent study in preterm infants born before 32 weeks of gestation and treated for PDA [57], furosemide exposure reaches about 25% and increases with decreasing gestational age, and individual cumulative doses can reach as much as 10 mg per kg bodyweight, which is considered an independent risk factor for nephrocalcinosis in VLBW infants.

Despite all the above conclusions, diuretics administration remains recommended in severe chronically ill patients for the management of accumulation of interstitial lung fluid, such as in cases of pulmonary edema which may occur in respiratory and cardiac acute and chronic morbidities. Repeated doses of the diuretic are often needed to restore the fluid balance.

Common side effects of diuretics

Electrolyte disturbances and frequent side effects of diuretics commonly used in neonates are shown in Table 3.

New developments in diuretic therapy

Among the three categories of diuretics under development (natriuretic peptides, adenosine A1 receptor antagonists, and ADH antagonists), only adenosine receptor antagonists have been studied in newborn infants. The diuretic effects of the methylxanthines theophylline and caffeine, two nonselective antagonists of adenosine receptors, have been briefly discussed in this article.

Key summary points

1. Diuretics promote the excretion of electrolytes and water. They are primarily used in states of inappropriate salt and water retention.
2. Diuretics can also be used in a variety of conditions where an increase in sodium excretion is not the primary goal of treatment, as for instance electrolyte disturbances and nephrogenic diabetes insipidus.
3. Loop diuretics are the used in acute states of sodium retention. Their prolonged use in neonates and infants can impair growth, induce nephrocalcinosis, and lead to deleterious hypokalemic states.
4. Among the new diuretics under development, adenosine A1 receptor antagonists appear the most promising agents.

Multiple choice questions (answers are given after the references)

1. Which of the following is not a therapeutic indication of loop diuretics?

   a) Sodium-retaining states
   b) Hyperkalemic states
   c) Hypercalcemic states
   d) Nephrogenic diabetes insipidus
   e) Assessment of distal acidification

2. Which of the following is not a side effect of loop diuretics?

   a) Ototoxicity
   b) Hyperglycemia
   c) Hyperuricemia
   d) Gynecomastia
   e) Nephrocalcinosis

3. Which of the following is a possible side effect of inhibitors of carbonic anhydrase?

   a) Metabolic alkalosis
   b) Hyperkalemia
   c) Hypercalcemia

Table 3 Electrolyte disturbances and frequent side effects of diuretics commonly used in neonates

Diuretics	Side effects	Electrolyte disorders
Loop diuretics	Ototoxicity, nephrocalcinosis hyperuricemia, hyperglycemia, hyperlipidemia, hypersensitivity	Hypovolemia +++ Hyponatremia ++ Hypokalemia +++ Hypercalciuria ++ Hypomagnesemia + Hypophosphatemia + Metabolic alkalosis++
Thiazides	Hyperglycemia, insulin resistance, hyperlipidemia, hypersensitivity (fever, rash, purpura, anaphylaxis, interstitial nephritis), hyperuricemia	Hypovolemia + Hyponatremia +++ Hypokalemia ++ Hypercalcemia + Hypomagnesemia + Hypophosphatemia+ Hyperuricemia ++ Metabolic alkalosis ++
K^+- sparing		Hypovolemia +
• Amiloride	• Diarrhea	Hyperkalemia ++
• Triamterene	• Glucose intolerance, interstitial nephritis, blood dyscrasias	Metabolic acidosis +
• Spironolactone	• Gynecomastia, hirsutism, peptic ulcers, ataxia	

d) Hypokalemia
e) Hirsutism

4. Which diuretic among the following inhibits the sodium-potassium-chloride cotransporter NKCC?

a) Acetazolamide
b) Spironolactone
c) Amiloride
d) Hydrochlorothiazide
e) Furosemide

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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Answers: 1: d, 2: d, 3: d, 4: e