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REVIEW

Diuretics in pediatrics

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Abstract

Diuretics are frequently prescribed drugs and help managing several pathological conditions, including acute and chronic kidney disease, nephrotic syndrome, congestive heart failure, ascites, systemic and pulmonary hypertension. Diuretic classes include among others osmotic diuretics and carboanhydrase inhibitors, loop diuretics, thiazides, and potassium-sparing diuretics. In this educational article, we aim at reviewing indications, mechanisms of action, and side effects, as well as basic pharmacokinetics considerations and data on diuretics in children, supporting practicing clinicians in choosing (and understanding the background of) the best-suited diuretic regimen for the individual patient. Newer diuretic classes like vaptans and sodium glucose type 2 cotransporter inhibitors, the recent controversies on hydrochlorothiazide, and the issue of diuretic resistance, will also be briefly addressed.

Conclusion: This educational review offers a didactical overview of diuretics in Pediatrics.

What is Known:

- *Diuretics are frequently prescribed drugs in both adults and children.*
- *They increase water and sodium excretion, reducing fluid overload.*

What is New:

- *This article reviews indications, mechanisms of action, side effects, and basic pharmacokinetics facts on diuretics in Paediatrics.*
- *It also addresses current issues, like the management of diuretic resistance, the recent controversy on hydrochlorothiazide, and the novel classes vaptans and gliflozins.*

Keywords Diuretic · Child · Fluid overload · Furosemide · Hydrochlorothiazide · Spironolactone

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Introduction

Diuretics are widely used drugs in both adults and children [1–3]. Over the last years, a diatribe on thiazide diuretics has animated scientific discussions [4], and two new diuretic classes, namely the vaptans [5] and the sodium glucose cotransporter 2 (SGLT2) inhibitors [6], have appeared on the market, stimulating some fresh curiosity. In this concise guide, we aim at reviewing indications, mechanisms of action, side effects, basic pharmacokinetics considerations, and data on diuretics in children, supporting practicing pediatricians in choosing the best diuretic for the individual patient. Additionally, four typical vignettes and four multiple-choice questions are provided as supplementary material.

Indications

Diuretics mainly act through an increase in water and sodium excretion, reducing fluid overload.

Sodium and water retention can derive either directly from volume overload (e.g., acute kidney injury, chronic kidney disease, nephrotic syndrome, capillary leak states, …) or indirectly from a reduced effective arterial circulating volume and decreased renal perfusion, which triggers a state of hyperaldosteronism (e.g., congestive heart failure, liver failure, nephrotic syndrome) [3] (Table 1).

Acute kidney injury

In acute kidney injury, fluid retention from oliguria or anuria can benefit from diuretic therapy. Due to their efficacy and rapidity of effect, loop diuretics are generally the first choice [7]. They can be combined with thiazides for a stronger natriuresis through distal sodium reabsorption blockade.

It might appear surprising that, in front of an acutely suffering kidney, a forced diuresis turns out to be protective for the kidney, preventing the complications of fluid overload. However, there is a clear pathophysiological rationale for such "renal salvage" strategies [7]. First, by reducing the transporter activity, loop diuretics reduce oxygen and energy consumption in the vulnerable, tubular cells. Second, they increase prostaglandin production, leading to vasodilation, which upregulates renal blood flow. Notably, in acute kidney injury following hypoxia, hypovolaemia, hypotension, and the resulting vasomotor nephropathy, prostaglandins can be critical in supporting glomerular blood flow [8]. Finally, the reduced salt and water reabsorption in the proximal tubule results in increased intratubular urine flow. This helps to dislodge brush border debris after tubular ischemia, thus preventing tubular obstruction [8].

Chronic kidney disease

Chronic kidney disease reflects a constant, often progressive decline of renal function. Uremic complications generally occur when the GFR is < 30 mL/min/1.73m^2. This condition progressively leads to a diminished capacity to increase urine output and, with some residual renal function, diuretics can be helpful. Loop diuretics are the first choice and can be combined with thiazides to inhibit the compensatory distal sodium reabsorption [7].

Congestive heart failure

In congestive heart failure (CHF), diuretics aim to decrease extracellular volume overload and to reduce right and left ventricular end-diastolic pressures. In chronic heart failure, diuretic therapy should not be used continuously, but just intermittently to reach euvolemia and relieve symptoms [9, 10].

Table 1 Indications for diuretic use in Pediatrics

Disease	Main aim	Treatment
Arterial hypertension	Decrease arterial blood pressure by increasing Na^+ and fluid loss	Thiazides Loop diuretics for rapid and short action + Spironolactone (if hypokalaemia)
Chronic heart failure	Decrease volume overload Negative NaCl and H_2O balance	(Hydro)Chlorothiazide or Furosemide + Spironolactone or Eplerenone Consider Tolvaptan for resistant cases
Pulmonary hypertension	Fluid overload treatment	Loop or thiazide diuretics + Spironolactone
Nephrotic syndrome	Oedema treatment	Loop diuretics + Spironolactone Thiazides if resistant oedema
Acute kidney injury	Oliguria treatment, "Renal salvage"	Loop diuretics Thiazides Sometimes consider mannitol
Hyperkalaemia	Excretion of K^+, diminish total body stores	Loop diuretics
Diabetes insipidus	(Distal) sodium loss stimulates proximal water reabsorption (paradoxical antidiuretic effect)	Thiazide diuretics
Ascites	Excretion of accumulated liquid	Thiazides or loop diuretics + Spironolactone (mainstay of therapy)
Post-traumatic cerebral oedema	Decrease intracerebral fluid, prevent bleeding	Osmotic diuretics
Idiopathic intracranial hypertension (Pseudotumor cerebri)	Reduce intracranial hypertension by decreasing intracerebral fluid	Carboanhydrase inhibitors

In heart failure, a decreased cardiac output leads to a blunted effective circulating arterial blood volume, which stimulates the renin–angiotensin–aldosterone system. That is why, in addition to the pivotal role of angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARBs), among the diuretic classes, mineralocorticoid antagonists play an important role in heart failure therapy. Additionally, mineralocorticoid antagonists are known to have antifibrotic effects, likely the main mechanism by which, in adults, they demonstrated a mortality benefit as well as reduced hospitalization rates [11].

The duration of a diuretic effect is limited by compensatory mechanisms in more distal parts of the tubule (e.g., in the case of loop diuretics) and by the activation of the renin–angiotensin–aldosterone system. These features require a careful dose management during the treatment course. Monitoring of weight, potassium levels, and renal function are important, for example before initiation of therapy, approximately 7–14 days thereafter, and following relevant dose adaptations [12].

Nephrotic syndrome, ascites, liver failure

Further edematous states such as nephrotic syndrome are also usually treated with loop diuretics. Thiazides are a secondary option for those cases because of their weaker efficacy, as compared to loop diuretics. However, because of compensatory sodium reabsorption in the distal tubule under chronic loop diuretic use, thiazides are recommended for a prolonged treatment course (starting from an anticipated period of approximately 7–10 days).

In the setting of liver failure, spironolactone is a mainstay of treatment [13]. Diuretics, combined with a dietary salt restriction, are indeed important in the treatment of hepatic cirrhosis- causing ascites. In absence of renal failure, aldosterone antagonists are the first option [13]. In fact, liver failure is characterized by splanchnic vasodilation, with resultant activation of the renin–angiotensin–aldosterone system [14].

Systemic arterial hypertension

In arterial hypertension, diuretics are not first-line drugs. However, they can help in decreasing extracellular fluid volume and are probably underused [15]. Thiazides (less prone to distal compensatory mechanisms) are the best diuretic class in this context [16], and are the only diuretic class that has consistently been shown to effectively lower high blood pressure [17]. Interestingly, the anti-hypertensive effect of thiazide diuretics ensues slowly, with most of the response appearing by 4–6 weeks [16]. The addition of spironolactone (both as distal addition and as a potassium-sparing molecule) is frequently used.

Pulmonary hypertension

Pulmonary hypertension may lead, over time, to right ventricular failure. Diuretic treatment can benefit this condition, by reducing liquid retention and optimizing right ventricular preload, as well as by decreasing right and left ventricular end-diastolic pressures, even if randomized controlled trials are not available.

Cerebral oedema and Idiopathic intracranial hypertension (Pseudotumor cerebri)

Post-traumatic cerebral edema is more frequent in children than in adults: a head injury leads to hyperemia and diffuse cerebral swelling, with a subsequent risk of intracerebral hypertension and hemorrhage. Osmotic diuretics increase serum osmolality pulling water out of (cerebral) cells. Furthermore, mannitol also reduces the production of intracerebral fluid [2]. Caution is mandated, obviously, in polytrauma patients, since mannitol can aggravate hypovolemia [2]. Exploiting the same mechanisms, acetazolamide and topiramate (which are, in addition, also weakly analgesic) are used in the therapy of *Pseudotumor cerebri* [18].

Bronchopulmonary dysplasia

Although controversial, diuretics are often used also among newborns and infants with bronchopulmonary dysplasia to accelerate lung fluid reabsorption [3, 19–21].

Dyselectrolytaemias and diabetes insipidus

Taking advantage from their mechanisms of action, diuretics are used to modulate some dyselectrolytaemic states. (1) In hyperkalemia, loop diuretics and thiazides increase potassium excretion (and they are an important armamentarium for hyperkalemia management both in acute and chronic kidney disease). (2) In hypercalcemia, loop diuretics can be used to reduce calcium reabsorption and, therefore, increasing calcium excretion. (3) Conversely, in hypercalciuric states, thiazide diuretics can increase calcium reabsorption and therefore diminish calcium excretion. (4) Also, the acid–base balance can be modulated by diuretics: acetazolamide increases bicarbonate excretion, loop diuretics increase potassium and hydrogen excretion, and aldosterone antagonist increase potassium (and, therefore, hydrogen) reabsorption. (5) Thiazide diuretics induce sodium loss and stimulate proximal tubule water reabsorption and are therefore very

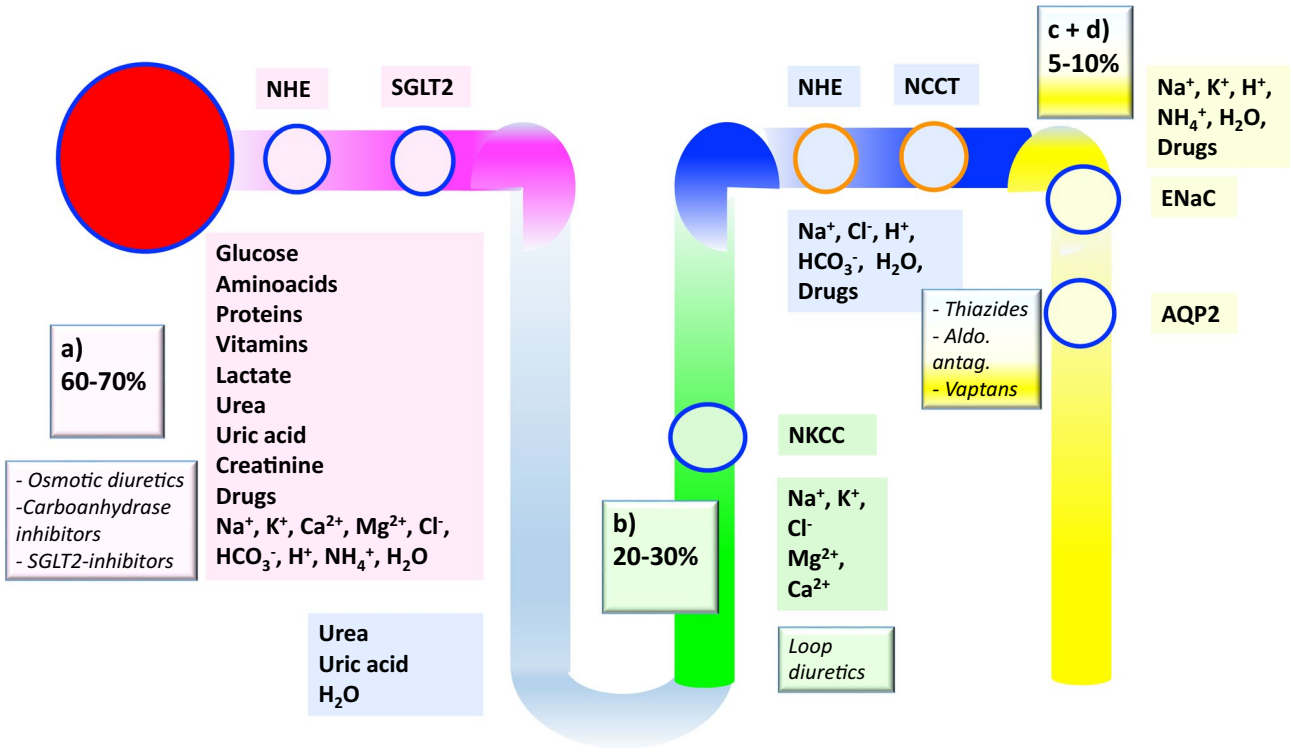

Fig. 1 Renal tubule and Na^+ reabsorption. The figure depicts the channels and transporters involved in Na^+ handling, as well as further substances that are reabsorbed along the renal tubule. The boxes with the percentages indicate the approximate contribution in renal Na^+ reabsorption of the several tubule segments in a healthy (diuretic-naïve) individual. **a** In the proximal tubule, Na^+ reabsorption is partly coupled with the reabsorption of bicarbonate (HCO_3^-) by means of the Na^+/H^+ exchanger (NHE) and with the reabsorption of chloride and glucose, by means of the Na^+/glucose co-transporter SGLT2. The function of the Na^+/H^+ exchanger (NHE) is indirectly inhibited by carboanhydrase inhibitors such as acetazolamide. The *SGLT2 inhibitors* (so called "*gliflozins*") block the renal sodium–hydrogen exchanger 3 (NHE3) and therefore the sodium-glucose co-transporter SGLT2, thereby enhancing diuresis of both sodium and glucose. **b** In the thick ascending limb of the Henle's loop, sodium is reabsorbed through the $Na^+/K^+/2\ Cl^-$ cotransporter (NKCC2, encoded by SLC12A1), which is inhibited by *loop diuretics*. **c** In the distal convoluted tubule, Na^+ reabsorption is coupled with that of Cl^- by means of the Na^+/Cl^- cotransporter (NCC(T), encoded by SLC12A3), which is inhibited by *thiazide diuretics*. **d** In the collecting duct, several transporters are present. (1) Principal cells reabsorb Na^+ and secrete K^+. They are stimulated by aldosterone and therefore inhibited by *aldosterone antagonists*. (2) Type A intercalated cells reabsorb K^+ in exchange with H^+ secretion. They modulate acid–base balance, are also stimulated by aldosterone and therefore inhibited by aldosterone antagonists. (3) The epithelial sodium channel (ENaC) is responsible for active Na^+ transport in the collecting duct and is *amiloride*-sensitive. (4) Finally, also the water channel aquaporin-2 (AQP2) resides in the collecting duct. This ADH-sensitive channel can be inhibited by *vaptans*

effective in the management of diabetes insipidus ("paradoxical antidiuretic effect").

Mechanisms of action and side effects

After being filtered by the glomerulus, 99% of filtered urine and sodium are reabsorbed along the renal tubule [3]: 60–70% in the proximal tubule, 20–30% in the ascending limb of the loop of Henle, and 5–10% in the distal tubule and collecting duct [3, 22, 23] (Fig. 1). The driving force for sodium reabsorption is the Na^+/K^+-ATPase, located in the basolateral membrane of tubular cells. On the apical membrane, several transporters and channels help the reabsorption of different ions (Fig. 1).

With the exception of spironolactone, diuretics exert their effect from the tubular lumen, which is reached by glomerular filtration (osmotic diuretics) or tubular secretion (loop diuretics and thiazides). Therefore, in front of a reduced renal function, (1) diuretic concentration at the site of action is reduced and (2) its delivery is slower. This occurs in renal failure, but also in healthy infants. Indeed, glomerular and tubular ontogeny and immaturity are responsible for a delayed onset of action as well as for an increased elimination time and therefore a prolonged effect, especially in the first 2 years of life [2, 24].

The maximal diuretic effect is generally reached after the first dose, while the induced compensatory response decreases the effect of subsequent doses. The more proximal the diuretic action site, the more important this phenomenon is.

Table 2 Diuretic classes, sites, and mechanisms of action, with examples of specific substances

Type	Site of action		Target canal/reaction	Specific substances	Prescribed in pediatrics?
Osmotic diuretics	Proximal tubule and loop of Henle		Osmotic effect	Mannitol	Yes, rarely (cerebral oedema)
SGLT2 inhibitors	Proximal tubule, S1 segment		Inhibition of the low-affinity, high-capacity SGLT2 transporter: natriuretic and glucosuric effect	Dapagliflozin Empagliflozin Canagliflozin, Ipragliflozin Ertugliflozin, Sotagliflozin	Yes, but use just started in children, still very rarely (mainly in type 2 diabetes mellitus and glycogen storage disease type Ib)
Carbonic Anhydrase Inhibitors	Proximal tubule		Carbonic anhydrase inhibition (CA II)	Acetazolamide Topiramate	Yes, rarely
Loop diuretics	Thick ascending limb of the loop of Henle and *Macula densa*		Na–K-2Cl carrier: NKCC1 and 2 (Cl^- site)	Furosemide Bumetanide Tor(a)semide Ethacrynic acid	Yes, often
Thiazide diuretics	Distal convoluted tubule		Na^+Cl^- membrane carrier: NCC (Cl^- site)	Hydrochlorothiazide Chlorothiazide Metolazone	Yes, often
Potassium-sparing diuretics	Distal nephron (collecting tubule and duct)	Epithelial Na^+ channel blockers	Epithelial Na^+ channel (ENaC)	Amiloride Triamterene	Yes, often in association with thiazide or loop diuretics
		Aldosterone antagonists	Mineralocorticoid receptor (MR)	Spironolactone Eplerenone Finerenone Canrenone	
Aquaretics	Collecting duct		Vasopressin receptor (selective water diuresis)	Tolvaptan	Yes, rarely
Aminophylline/ teophylline	Macula densa Renal vessels		*Macula densa*: Adenosine receptor blockade (low dose) *Vessels*: phosphodiesterase type IV inhibition (high dose)	Aminophylline (the ethylenediamine salt of Theophylline)	Yes, very rarely

Loop diuretics

Loop diuretics are powerful drugs because they block sodium reabsorption in the thick ascending tubule of the loop of Henle (Fig. 1). The most common molecules are furosemide, torasemide, and bumetanide (Table 2). The electrolyte balance is altered, because of the decreased reabsorption of the cations Na^+, K^+, Ca^{2+}, and Mg^{2+} and the anion Cl^- (Fig. 1). This mechanism anticipates the known side effects of hyponatremia, hypokalemia, hypocalcemia, and hypomagnesemia (Table 3).

Of note, reduced sodium reabsorption in the thick ascending limb of the Henle's loop leads to increased sodium delivery to the distal and collecting tubules, with a compensatory increase in sodium reabsorption at this location, which is accompanied (for electroneutrality reasons) by an increased potassium secretion [2]. Furthermore, loop diuretics inhibit the $Na^+/K^+/2\ Cl^-$ (NKCC) symporter also in the *macula densa*, thereby stimulating renin secretion and activating the renin–angiotensin–aldosterone system, which results in increased sodium reabsorption and potassium secretion in the distal tubule [25].

The onset of action is rapid (< 1 h), as it is the reaching of a new steady state. The blockage of a second isoform of NKCC1, present throughout the body and notably in the *stria vascularis* of the ears, can lead to complications like ototoxicity [1, 25].

The half-lives of most loop diuretics (approximately 1 h for bumetanide, 3 h for furosemide, and 6 h for torasemide [23]) are shorter than their administration intervals, these drugs being typically administered twice a day. Thus, while a loop diuretic dose increases sodium excretion for some hours, this is followed by a period of low sodium excretion: "post-diuretic sodium retention" [25]. With high dietary sodium intake and long (e.g., once or twice a day) dosing intervals of short half-life drugs (like bumetanide or furosemide), the post-diuretic sodium retention might offset the initial natriuretic effect [1, 25].

Upon chronic diuretic administration, a new steady state is rapidly reached, characterized by a combination of increased distal sodium and solute delivery, hypertrophy of the distal nephron, activation of the renin–angiotensin–aldosterone system, and of the sympathetic nervous system [23, 25]. In this new state, sodium input and output are equal, but the set-point is lowered (at a smaller extracellular fluid volume) as compared to baseline [1]. This new equilibrium characterizes the efficacy of a chronic diuretic treatment but also represents the basis for the development of diuretic resistance [25]. Treatment of diuretic resistance is tricky. High-dose diuretics and continuous diuretic infusions have traditionally been used. Recognizing that up to ¾ of diuretic resistance might be due to activation of NaCl transport in the distal nephron [25], a tempting approach is to block NaCl reabsorption in the distal nephron (e.g., with thiazides), the "sequential nephron blockade" approach [23]. Interestingly, also proximally acting drugs, like the carbonic-anhydrase inhibitor acetazolamide (which works in the proximal tubule by inhibiting pendrin, a chloride-bicarbonate exchanger) and the new SGLT2 inhibitors have been used with some success [26, 27]. Vaptans can increase diuresis, but it is unclear whether this translates into better outcomes in children [5]. Finally, a recent meta-analysis suggested that, in children with fluid overload, adding aminophylline/theophylline to furosemide may increase urine output and help in achieving a negative fluid balance [28].

Potassium-sparing diuretics

There are two targets for potassium-sparing diuretics: (1) epithelial Na^+ channels, directly inhibited by amiloride and triamterene, and (2) the intracellular mineralocorticoid receptor, inhibited by spironolactone and eplerenone (Table 2). Because of their site of action, their efficacy with respect to volume regulation is limited in an otherwise untreated patient (Fig. 1). However, aldosterone antagonists are particularly efficacious in situations of effective intra-arterial volume depletion (only when diuretic treatment is indicated and safe in these patients with already depleted effective fluid volume), i.e., situations, where the mineralocorticoid axis is activated.

Vaptans

The previously mentioned diuretics are "natriuretic," as they increase sodium and water excretion. On the opposite, vasopressin receptor antagonists, also called aquaretics (like Tolvaptan and Conivaptan), increase water excretion by blocking the vasopressin receptor on tubule cells, leading to dilution of the produced urine [5]. Their use may be interesting in diuretic resistance and, particularly, in front of volume overload concurrent with hyponatremia, as it is sometimes found in heart failure and in some cases of nephrotic syndrome [10, 29]. Vaptans are also proposed in some types of hyponatremia (like the syndrome of inappropriate antidiuretic hormone). Finally, tolvaptan slows disease progression in adult patients with autosomal dominant polycystic kidney disease and there is hope to see similar results in children [5].

Sodium glucose transporter type 2 inhibitors

Very recently, SGLT2 inhibitors (or gliflozins) have brought in adult medicine novel approaches in the treatment of type 2 diabetes mellitus [30], chronic kidney disease [31], and heart failure [32]. This class of drug exhibits natriuretic and glucosuric properties, inhibiting sodium (> 60%) and glucose (> 90%) reabsorption in the proximal tubule [33] (Fig. 1). Interestingly, they appear to have a more pronounced effect on interstitial fluid than on plasma volume [34], which may be particularly appealing in patients with congestive heart failure [35]. Of note, as opposed to other diuretics, gliflozins appear not to be associated with sympathetic activation and heart rate increase [36]. Intriguingly, besides their role in osmotic sodium handling, SGLT2 inhibitors might also modulate the non-osmotic sodium compartment [34, 37, 38], with potential impact on the endothelial glycocalix and therefore high appeal in heart failure. Their role in children just started to be explored [39–41].

Side effects

The side effects of the several diuretic classes mirror their mechanisms of action and are listed in Table 3. A special note deserve the recent concerns on the possibly increased incidence of non-melanoma skin cancers among adult patients on chronic thiazide diuretics [42]. Epidemiological studies based on health registries from Northern Europe suggested an increased incidence of such tumors among elderly patients on long-lasting thiazide therapy and prompted regulatory agencies to issue pertaining warnings. While these drugs have known photosensitizing potential, such epidemiological studies have inherent methodological limitations and deserve confirmation in well-designed observational studies [43]. Furthermore, the extrapolation of such data to children is problematic, since the cumulative dose of both thiazide molecules and ultraviolet exposure is significantly lower in children.

Doses and some basic pharmacokinetics considerations

Accepted dose recommendations and some basic pharmacokinetic data are summarized in Table 4.

Table 3 Main side effects of diuretics used in Pediatrics

	Urate	Magnesium	Calcium	Sodium	Potassium	Further side effects
Osmotic diuretics			Hypercalciuria	Hyponatremia (acute) Hypernatremia (chronic)	Hypokalaemia	Hyperosmolarity
Carboanhydrase inhibitors			Hypercalciuria, Nephrolithiasis, Nephrocalcinosis	Hyponatremia	Hypokalaemia	Metabolic acidosis Nephrocalcinosis / lithiasis
SGLT2 inhibitors		Slight increase	Increased calciuria, small increase in serum phosphate, FGF-23 and PTH, small decrease in serum 1,25$(OH)_2$-Vitamin D (clinically not significant)	No significant change	No significant change (mild increase with Canagliflozin, no change with Dapa-/ Empagliflozin)	Urinary tract infection Mycotic genital infections Euglycemic ketoacidosis Small and transient reduction in eGFR
Thiazide diuretics	Hyperuricemia	Hypermagnesuria, Hypomagnesemia	Hypocalciuria (and hypercalcemia)	Hyponatremia ++	Hypokalaemia	Hyperglycemia and insulin resistance, Hyperlipidemia, Hypophosphatemia, Drug fever, Cholestasis, Hypersensitivity reactions (including dermatitis and vasculitis), Metabolic alkalosis
Loop diuretics	Hyperuricemia	Hypermagnesuria, Hypomagnesemia	Hypercalciuria (and Hypocalcemia), nephrolithiasis, nephrocalcinosis, bone demineralization	Hyponatremia	Hypokalaemia	Nephro / Ototoxicity, Cholestasis (bilirubin displacement from albumin), Hyperglycemia, Hyperlipidemia, drug fever, Hypersensitivity reactions (including Steven-Johnson syndrome), Metabolic alkalosis, Hypophosphatemia
Potassium-sparing diuretics		Hypomagnesuria	Nephrocalcinosis		Hyperkalaemia	Metabolic acidosis, Gynecomastia, Vaginal bleeding, Hirsutism, Ovarian cyst(s) Glucose intolerance, Interstitial nephritis
Vaptans				Increase or normalization (if hyponatraemia at baseline)/small, non-significant increase (if normal at baseline)		Thirst Xerostomia Dry skin Skin rash Increased aminotransferases
Aminophylline						Arrhythmia Dizziness Vomiting / Nausea

Table 4 Pharmacokinetics data of diuretics used in Pediatrics. Data for aminophylline and SGLT2 inhibitors, still in an early phase of research, are scanty and therefore consciously not reported

	Adult dosage	Pediatric dosage	Bioavailability	Time to peak concentration (Tmax)	Volume of distribution (Vd)	Half-life ($t_{1/2}$)	Metabolites
Acetazolamide	100–250 mg, q6–8H 500–1000 mg/day	5–10 mg/kg q6–8h		1–4h (PO) 15 min (IV)	0.2 L/kg	2–9h (mostly approx. 4h)	
Mannitol	1.25–2 g/kg IV	0.25– 0.5 g/kg q2h	7%	1.5h	34.3 L	1.5–5h	Glycogen
Furosemide	20–40 mg (i.v./i.m.), 20–80 mg (p.o.) q6–24H	0.5–2 mg/kg/dose, q6–24h	47–90%	1–2 h (PO) < 15 min (IV)	0.16–0.27 L/kg	Preterm: 12–24 h Term: 4–8h Children: 1–2 h Adults: 1–4h	Furosemide glucuronide, 4-chloro-5-sulfamoylanthranilic acid (saluamine)
Torasemide	5–20 mg q24h	0.1–1 mg/kg/24h	68–100%, mostly around 80–90%	1 h (PO)	0.2 L/kg 12–15 L	3–4h	Active metabolites M1, M3; inactive metabolite M5
Bumetanide	0.5–2 mg (p.o.), 0.5–1 mg (i.v./i.m.) q12–24h	0.01–0.1 mg/kg/24h	58–100%, mostly 80–100%	1–2 h (PO), 30 min (IM), 5 min (IV)	Adults: 9–25L Children: 0.1–0.4 L/kg	1–2 h (Neonates: 2–6h)	Bumetanide conjugates, Desbutyl bumetanide, Primary alcohols, Aliphatic acid
Metolazone	2.5–10 mg/24h	0.1–0.4 mg/kg/24h	40–65%	2–4h	N.A	14–20h	
Chlorothiazide	0.5–1 g q12–24h	5–20 mg/kg q12–24h	15–65%	Approx.. 1h (4 h PO, 30 min IV)	0.3–1 L/kg	Adult: 1.5–2.5h Preterm: 45 min–27h	-
Hydrochlorothiazide	12.5–50 mg q12–24h	1–3 mg/kg/24h (1–1.5 mg/kg q12–24h)	36–77%, mostly 60–70%	1.5–5h mostly 1.5–2.5	0.8–4.2 L/kg, mostly 2.5–3 L/kg	6–15h, mostly 6–10 h	-
Chlortalidone	12.5–25(−100) mg/day PO	2 mg/kg, 3×/week	61–72%	1.5–6h	3–5 L/kg	24–60h, mostly 40–60h	
Spironolactone	20–100 mg PO q12–24h	1–3 mg/kg/2h (divided in 1 or 2 daily doses)	60–95%	2.6–4.3h (PO)		1.4–1.5h, Canrenone 16.5h	Canrenone, 7-alpha-thiomethylspirolactone, 6-beta-hydroxy-7-alpha-thiomethyl-spironolactone
Amiloride	5 mg q12–24h 5–10 mg/day PO	0.625 mg/kg/24h 0.2 mg/kg q12–24 h	30–90%, mostly approx. 50%	3–4h	350–380 L 5 L/kg	6–26h, mostly 6–9h	
Triamterene	50–100 mg q8–24h	1–4 mg/kg/24h 2 mg/kg q8–24h	30–70%, mostly approx. 52%	1.5–3h	1.5–13 L/kg	1.5–5h, mostly 1.5–2.5h	Hydroxytriamterene sulfate
Tolvaptan	15 mg/24h	15 mg/24h	Unknown, minimum 40%	2–4h	3L/kg	12h	

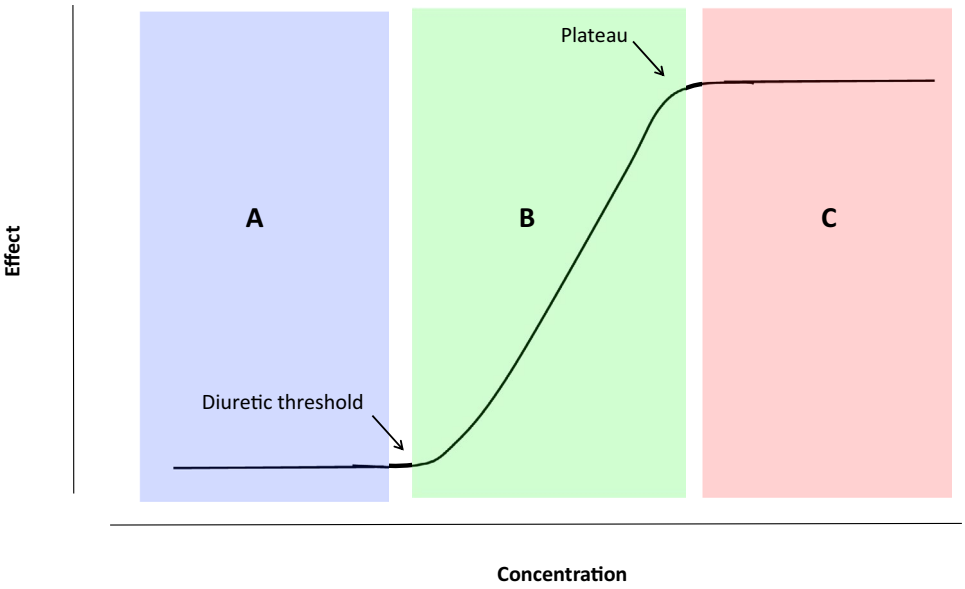

Fig. 2 Pharmacodynamic dose response curve of (loop) diuretics. The diuretic threshold needs to be reached (**A**) before a diuretic effect can be appreciated. A nearly linear phase follows (**B**), until a plateau is reached (**C**), where a further increase in dose will not lead to a gain in diuretic effect any more

Absorption-limited kinetics

The loop diuretics torasemide and bumetanide are rapidly absorbed. While the bioavailability of torasemide is high (> 80% [17]), that of furosemide is lower (on average approximately 50%) [1, 17] and, most importantly, very variable, from approximately 10% to about 90%, depending among others on food consumption, age, and presence of edema [1]. Intriguingly, even if the half-life of furosemide is short, its duration is longer after oral administration, because its absorption can be equal to or even slower than its elimination half-life. This phenomenon is called *absorption-limited kinetics* and explains the mnemonic name "Lasix®" (the market name of the originator drug): "it lasts for six hours". This phenomenon is not encountered with torasemide and bumetanide [1].

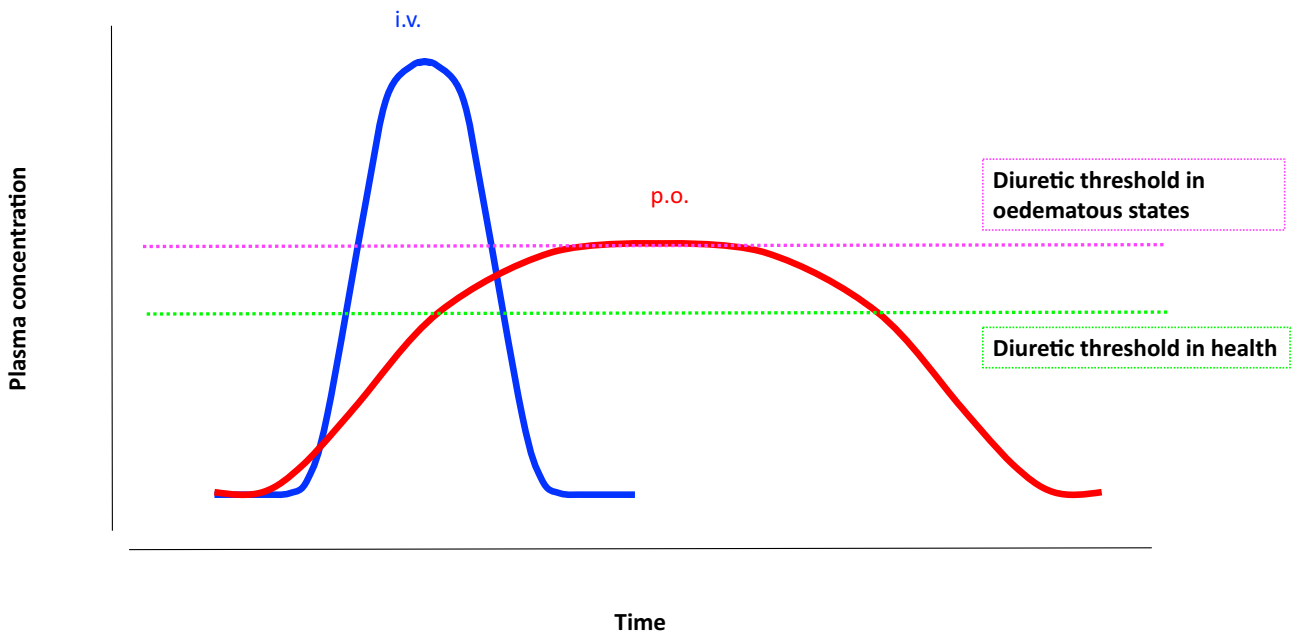

Fig. 3 Plasma concentration of a loop diuretic after i.v. and p.o. administration. Note the shallower curve after p.o. administration, which implies a lower and later peak. This might cause a delayed and limited time above the diuretic threshold in edematous states

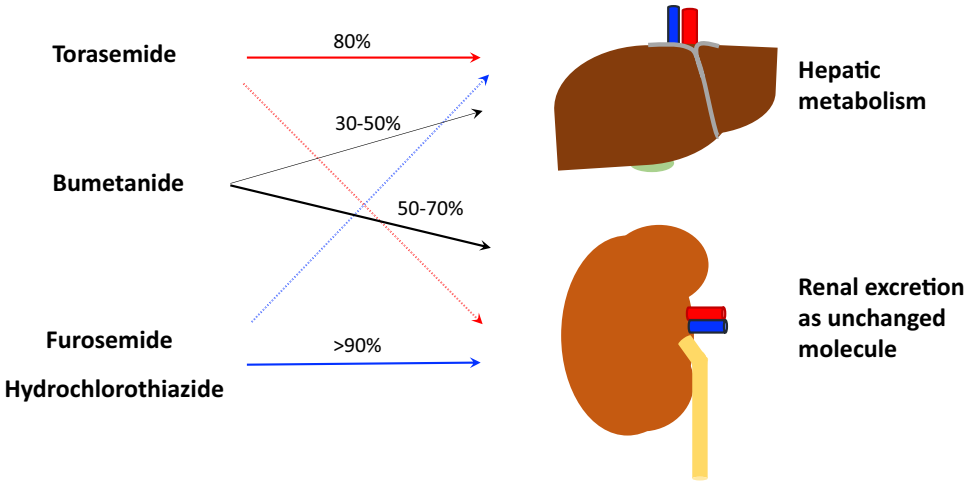

Fig. 4 Relative contribution of hepatic metabolism and direct renal excretion of unchanged substance for furosemide, bumetanide, torasemide, and hydrochlorothiazide

Dose-concentration and Dose–response curves of loop diuretics, natriuretic threshold

All loop diuretics share similar sigmoid-shaped dose–response curves: no natriuretic effect below a certain threshold (A in Fig. 2), steep, roughly linear increase after having reached that threshold (B in Fig. 2) and, finally, a ceiling effect (plateau phase, box C in Fig. 2), where a further increase in the drug plasma concentration does not lead to any response increase any more [25].

Notably, in edematous states, the absorption is slowed and the diuretic threshold increased [25]. This translates into a limited time during which the diuretic concentration is above the natriuretic threshold. In this situation, the i.v. administration (and even more so the continuous i.v. administration) becomes particularly interesting, since it allows to increase in the time above the diuretic threshold and therefore rise the net diuretic effect (Fig. 3).

Renal excretion versus hepatic metabolism

Furosemide is excreted to approximately 50% unchanged in the urine, with the other half eliminated through glucuronidation, which also mainly takes place in the kidneys. Its half-life is therefore increased in renal disease. It might be interesting to note that also hydrochlorothiazide is mostly excreted as the original compound (without significant metabolism). This happens by active tubular secretion through organic anion transporters 1 (OAT1) and 3 (OAT3) [44].

In contrast, torasemide, which is extensively hepatically metabolized [17], presents a more preserved half-life in acute and chronic kidney disease [1].

Bumetanide takes an intermediate position, as it is metabolized for approximately 40% and excreted unchanged for the remaining 60% [1, 45] (Fig. 4).

Conclusion

Diuretics are frequently used and mainly serve to counteract sodium and water retention, either from volume overload or from hyperaldosteronism subsequent to reduced effective circulating volume. In this review aimed at practicing pediatricians, we reviewed indications, mechanisms of action, side effects, posology, and some clinically relevant pharmacokinetic characteristics of the most frequently used diuretics. Drug classes in the pipeline, like vaptans and gliflozins, were briefly addressed. An understanding of the mechanisms and key pharmacological properties of these drugs is pivotal for their effective and safe use in children.

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Authors' contributions SAGL and SDB conceptualized and designed the study. CZ, supervised by SAGL, performed the literature search. SAGL contributed to data interpretation and critically analyzed and summarized the data. SAGL drafted the initial manuscript. SAGL, CZ, HC, DS, NS, and SDB critically reviewed the manuscript. All authors approved the final manuscript as submitted.

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