Pediatric Pharmacotherapy

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DIURETICS IN CHILDREN

Pharmacology Literature Reviews

Formulary Update

Diuretics are used for a wide variety of conditions in infancy and childhood, including the management of pulmonary diseases such as respiratory distress syndrome (RDS) and bronchopulmonary dysplasia (BPD)(1-5). Both RDS and BPD are often associated with underlying pulmonary edema and clinical improvement has been documented with diuretic use.6 Diuretics also play a major role in the management of congestive heart failure (CHF), which is frequently the result of congenital heart disease (7). Other indications, include hypertension due to the presence of cardiac or renal dysfunction. Hypertension in children is often resistant to therapy, requiring the use of multidrug regimens for optimal blood pressure control (8).

Control of fluid and electrolyte status in the pediatric population remains a therapeutic challenge due to the profound effects of age and development on renal function. Although diuretics have been used extensively in infants and children, few controlled studies have been conducted to define the pharmacokinetics and pharmacodynamics of diuretics in this population.

Nonetheless, diuretic therapy has become an important part of the management of critically ill infants and children. This issue will review the mechanisms of action, monitoring parameters, and indications for use of diuretics in the pediatric population (1-5).

Loop Diuretics

Loop diuretics are the most potent of the available diuretics (4). These agents work by blocking the Na^+ -K^+ -$2Cl^-$ transporter in the ascending loop of Henle, inhibiting reabsorption of these ions. Because reabsorption of approximately 25% of the filtered sodium occurs in this tubular segment, use of loop diuretics results in significant diuresis (3). Potassium reabsorption in the ascending limb also is reduced, resulting in increase loss of potassium. With increased presentation of sodium to the distal tubule, secretion of potassium is enhanced thus contributing to the potassium loss. Magnesium and calcium excretion are also enhanced by mechanisms not completely understood (1-3).
Currently available loop diuretics include furosemide, bumetanide, and torsemide. Both furosemide and bumetanide have been studied in children. Unlike bumetanide, furosemide inhibits not only the Na^+ -K^+ -$2Cl^-$ pump but other ion channels as well. Thus, bumetanide seems to be a more specific inhibitor of the Na^+ -K^+ -$2Cl^-$ transporter. In vitro comparisons of furosemide and bumetanide have shown bumetanide to be 15 to 100 fold as potent as furosemide (9).
The pharmacokinetics of furosemide and bumetanide have been studied in children. In neonates, volume of distribution and half-life are significantly greater than in adults. In preterm infants the half-life of furosemide ranges from 24 to 46 hours, whereas in term neonates the half-life is generally less than 12 hours. As renal and hepatic functions mature, clearance increases and elimination half-life is shortened (3). In critically ill infants and children, the half-life of bumetanide is approximately two hours and one hour respectively (10, 11).
Furosemide is the most extensively used and studied diuretic in the pediatric population (1) Due to the continual maturation of the kidney and the changes in fluid distribution in the pediatric population, it is especially important to monitor electrolytes during therapy. Following extended use of furosemide, hyponatremia, hypokalemia, and volume contraction may occur. Enhanced urinary calcium loss resulting from chronic furosemide use in neonates can cause nephrocalcinosis. Concurrent use of chlorothiazide has reportedly decreased hypercalciuria and dissolved some of the calculi (12). Furosemide is highly protein bound and may displace bilirubin from albumin, although a causal relationship between furosemide-induced bilirubin displacement and the development of kernicterus has not been shown (3).
Premature infants appear to be at increased risk for development of furosemide-induced ototoxicity from the accumulation of furosemide due to its longer t1/2 in these babies. Beermann and associates found that high plasma levels of

furosemide (above 50 mcg/ml) are associated with a higher incidence of auditory disturbances (13). Rupp calculated that injection of furosemide at a rate slower than 4 mg/min would not produce serum concentrations greater than 40 mcg/ml (14). This was substantiated by blood level measurements in patients with renal disease and no hearing loss was reported. Ototoxicity due to furosemide may be avoided with several methods. Continuous slow infusion of IV furosemide has been found to be a more effective method of drug administration to elicit a diuretic response in patients with CHF and avoids high peaks associated with ototoxicity. Divided oral doses are recommended as well as keeping blood levels < 50 mcg/ml to reduce the risk of ototoxicity (12) In both clinical trials and animal studies, bumetanide appears to be less ototoxic than furosemide (9). In patients receiving other ototoxic drugs, bumetanide may be a safer alternative (3).

Bumetanide and furosemide have significant structural and pharmacodynamic similarities. Although direct comparison of the agents with respect to the incidence, prevalence, and clinical significance of adverse effects in children have not been done, bumetanide therapy appears to offer only marginal theoretic advantages when compared with furosemide (3). Bumetanide reaches the site of action by passive diffusion due to its high lipid solubility and therefore is much less dependent than furosemide on tubular secretion for reaching its site of action (1,5). When the dose response to bumetanide and furosemide are compared in terms of natriuresis and kaliuresis, the relative potency of bumetanide in promoting potassium excretion was significantly lower than its relative natriuretic response. The potential for decreased hypokalemia may be a potential advantage to bumetanide (9). At plasma concentrations above those achieved during routine therapeutic use, the binding of bumetanide to neonatal plasma proteins is approximately 97%. Hence, saturation of albumin-binding sites is unlikely at therapeutic doses (3).

In neonates, loop diuretics may be used with indomethacin to prevent NSAID-induced nephrotoxicity during therapeutic closure of a patent ductus arteriosus (1,5,15). However, these agents stimulate renal synthesis of prostaglandin E and may interfere with closure of the PDA when given to premature infants. Adverse effects associated with loop diuretics include gastric irritation, diarrhea, weakness, fatigue, dizziness, muscle cramps, photosensitivity, anemia, leukopenia, thrombocytopenia, hyperglycemia, agranulocytosis, and various cutaneous eruptions (3,15).

Thiazide Diuretics

The thiazide diuretics are sulfonamide derivatives which differ primarily in their duration of action. Thiazides work by inhibiting Na^+ -Cl^- transport in the distal convoluted tubule. Prior to the site of action of the thiazides, 90% of the filtered sodium is absorbed, thus explaining why thiazides are only moderately effective natriuretic drugs (4,5). In contrast to the loop diuretics, the therapeutic efficacy

of the thiazides diminishes as GFR decreases (1). Thiazide diuretics also have some carbonic anhydrase inhibitory properties and are able to decrease peripheral vascular resistance (PVR) (4,5). Thiazides prevent 5-8% of filtered sodium from being reabsorbed. Thus, sodium presentation to the distal portion of the nephron is increased, enhancing Na+ - K+ exchange. This results in increased potential for hypokalemia. Hyponatremia and hypomagnesemia may also occur with the use of thiazides. Unlike loop diuretics, the thiazides can decrease renal calcium excretion. Sodium intake must be restricted to favor the renal calcium reabsorbing mechanism of the thiazides (3-5).

The thiazide diuretics most commonly used in pediatric practice are chlorothiazide and hydrochlorothiazide. These agents are often used in combination with loop diuretics or spironolactone in the management of infants with pulmonary edema associated with RDS or BPD.

Reported adverse effects of the thiazides include hyperuricemia, hypersensitivity reactions, cholestasis, muscle cramps, dizziness, nausea, and vomiting. Rarely, severe shaking chills and fever have accompanied administration of hydrochlorothiazide.[1,5] Like the loop diuretics, thiazides have been shown to displace bilirubin from albumin-binding sites. In adults, thiazide diuretics have been found to have an adverse effect on lipids and glucose metabolism; however, little information of these effects is available in children (4).

Due to a problem in manufacturing, the makers of chlorothiazide oral suspension are unable to supply their product. Hydrochlorothiazide differs from chlorothiazide in one aspect of the central ring structure, saturation of the carbon-nitrogen bond allowing for greater potency. If substituting hydrochlorothiazide in place of chlorothiazide, the difference in dosing of these agents should be noted. There are no differences in efficacy or adverse effects at equivalent dosages.

Metolazone

Metolazone has a mechanism of action similar to the thiazides. Unlike the thiazides, it acts in both the proximal and distal convoluted tubule making it somewhat more potent than thiazides. Metolazone has no carbonic anhydrase inhibitory activity. There is minimal loss of potassium with this agent (1,4,5). Like the loop diuretics metolazone maintains the ability to produce diuresis in advanced renal failure (1). Within the pediatric population, metolazone is most often used in conjunction with furosemide. In this case, metolazone is most effective when given 30 minutes to one hour prior to furosemide so that the Na+ Cl- transporter downstream may be completely inhibited and thus unable to reabsorb the increased Na+ presentation that will accompany the administration of furosemide (3,16). To its disadvantage, metolazone is only available orally.

Potassium-sparing Diuretics

Spironolactone is the most widely used potassium-sparing diuretic in pediatrics.1 Spironolactone is an inhibitor of the action of aldosterone, which enhances potassium secretion and sodium reabsorption by the distal nephron. This mechanism of action requires approximately three days before a maximal effect is achieved (3). It is not considered a potent diuretic; however, it is used with other diuretics to reduce urinary potassium loss (1-5). Spironolactone accumulates in renal failure; thus, dosage adjustment is needed. In general, spironolactone should not be used in children when GFR decreases below 10 ml/min. Adverse effects of spironolactone include hyperkalemia, nausea, vomiting, abdominal pain or cramping, mild azotemia, and gynecomastia (3). Spironolactone is only available in tablet form; however, it can be compounded into a suspension for young children.

Diuretic Dosages (17)			
furosemide	neonates	p.o.	1-4 mg/kg/dose, 1-2 times daily
		iv/im	1-2 mg/kg/dose q 12-24 hrs
	children	p.o./iv/im	1-2 mg/kg/dose q 6-12 hrs
	adults	p.o./iv/im	20-80 mg/day divided q 6 12 hrs
bumetanide	< 6 mos	p.o./iv/im	doses not established
	> 6 mos	p.o./iv/im	0.015 mg/kg/dose qd or qod; max 0.1 mg/kg/dose
	adults	p.o.	0.5-2 mg/dose 1-2 times daily
		iv/im	0.5-1 mg/dose
HCTZ	< 6 mos	p.o.	2-3.3 mg/kg/dose divided bid
	> 6 mos	p.o.	2 mg/kg/day divided bid
	adults	p.o.	25-100 mg/day in 1 or 2 doses
Chlorthiazide	< 6 mos	p.o.	20-40 mg/kg/d divided bid
		iv	2-8 mg/kg/day divided bid
	> 6 mos	p.o.	20 mg/kg/day divided bid
		iv	4 mg/kg/day
	adults	p.o.	500 mg - 2 g divided in 1 or 2 doses
		iv	100-500 mg/day
Metolazone	children	p.o.	0.2-0.4 mg/kg/day divided q 12-24 hr
	adults	p.o.	edema: 5-10 mg/dose q 24 hrs
			HTN: 2.5-5 mg/dose q 24 hrs

spironolactone	children	p.o.	1.5-3.5 mg/kg/day divided q6 - 24 hrs
	adults	p.o.	25-200 mg/day in 1-2 divided doses

Efficacy of Diuretics in Pulmonary Disease

Although diuretics have been studied in infants with pulmonary disease for more than 20 years, the role of these agents in minimizing fluid excess in RDS remains controversial. Many investigators have attempted to identify the optimal method for minimizing pulmonary edema. Green et al (18) conducted a study in premature neonates with RDS comparing prophylactic furosemide 1 mg/kg q12h given for four doses to furosemide given as treatment once the presence of edema or oliguria had been established. It was determined that prophylactic administration of furosemide produced no additional benefit on pulmonary function over that seen with standard treatment. In patients with established intravascular volume overload, diuretics may be of benefit in improving pulmonary function; however, the prophylactic use of diuretics to prevent pulmonary edema may not be beneficial (19).

Several studies have demonstrated acute improvement in lung function in infants with BPD after diuretic use, including furosemide, chlorothiazide or hydrochlorothiazide, and spironolactone. Although the exact mechanisms by which diuretic therapy improves lung function in patients with BPD are incompletely understood, they most likely involve a combination of diuresis and local pulmonary effects (20). Rush and colleagues conducted a placebo-controlled trial of alternate-day furosemide therapy in infants with BPD. The authors found that alternate-day furosemide therapy increased lung compliancy and decreased total pulmonary resistance compared with placebo (p=0.032 for both variables) (21). Segar et al concluded that the administration of metolazone with furosemide enhanced diuresis, natriuresis, and chloruresis and overcame the rapid development of tolerance to furosemide in infants with BPD by blocking the compensatory increase in renal sodium and chloride absorption (22). Recently, Kao and coworkers conducted a randomized trial to determine the long-term effects of spironolactone plus chlorothiazide verses placebo in infants with oxygen-dependent BPD. Both groups received furosemide as needed. It was determined that long-term diuretic therapy in these infants improved their pulmonary function and decreased their fractional inspired oxygen requirement; however, therapy did not decrease the number of days that the infants required supplemental oxygen nor did the improvement in pulmonary function associated with diuretic therapy remain after discontinuation (23). As a result of these trials and a number of similar reports, diuretic therapy has become an established part in the management of infants with pulmonary disease.

Summary

Due to growth and development of the kidney during childhood frequent monitoring of diuretic use is needed. In addition to monitoring renal function, blood pressure, and electrolyte status, clinicians should also be aware of the potential for other adverse effects such as ototoxicity, blood dyscrasias, and hyperbilirubinemia. The variety of diuretics available allows for individualization of therapy and offers the potential for maximizing diuresis with combination therapy.

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Ibuprofen Overdose

Shock, metabolic acidosis, and coma occurring after accidental ibuprofen ingestion by a 6-year-old boy are described. The child experienced a full recovery with supportive care consisting of fluid and electrolyte supplementation. The authors summarize additional cases of ibuprofen ingestions reported in the medical literature. Zuckerman GB, Uy CC. Shock, metabolic acidosis, and coma following ibuprofen overdose in a child. **Ann Pharmacother 1995;29:869-71.**

Predicting Creatinine Clearance

The authors investigated the accuracy of equations based on length and serum creatinine used to predict creatinine clearance in critically ill children. These equations are used to determine the appropriate dosage of medications in patients with renal dysfunction. A comparison of estimated clearance to measured creatinine clearance (24-hour urine collection) revealed considerable variation. In 84 of the 100 children studied, the estimated creatinine clearance was greater than the actual value. This difference could potentially result in errors in medication dosing. Fong J, Johnston S, Valentino T et al. Length/serum creatinine ratio does not predict measured creatinine clearance in critically ill children. **Clin Pharmacol Ther 1995;58:192-7.**

Formulary Update

The following actions were taken by the Pharmacy and Therapeutics committee at their meeting on 9/22/95:

Medications added to the formulary include:

- tramadol (Ultram®) a nonopioid analgesic for moderate pain
- oxaprozin (DayPro®) a nonsteroidal anti-inflammatory agent
- nabumetone (Relafen®) a nonsteroidal anti-inflammatory agent
- Rh Immune globulin (WinRho®) for use in idiopathic thrombocytopenic purpura
- mycophenolate mofetil (CellCept®) an alternative to azathioprine for preventing rejection after kidney transplantation
- isosorbide monotritate SR (Imdur®) for angina
- sevoflurane (Ultane®) an inhalational anesthetic

The UVa approved uses for enoxaparin, a low-molecular weight heparin, were extended to include patients with spinal cord injury.

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