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Furosemide: A Review of Its Use in Infants and Children

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Furosemide, the first of the loop diuretics, was introduced in the United States in 1966. After nearly half a century of use, furosemide has become one of the most frequently prescribed medications in the United States.[1,2] In pediatric patients, furosemide is used to reduce edema in both acute and chronic cardiovascular, pulmonary, and kidney diseases.[3,4] This issue of *Pediatric Pharmacotherapy* will review the basic pharmacology of furosemide and describe recent studies of its use in infants and children.

Mechanism of Action

Furosemide (4-chloro-N-furfuryl-5-sulfamoylanthranilic acid), like other loop diuretics, reversibly binds to a chloride binding site on the $Na^+2Cl^-K^+$ cotransporter present on the luminal cell membrane of the thick ascending limb of the loop of Henle. This cotransporter is responsible for the movement of sodium out of the urinary space and into the tubular cell via a concentration gradient. The primary effect of blocking $Na^+2Cl^-K^+$ cotransporter activity is the reduction of sodium reabsorption by approximately 20 to 30% resulting in natriuresis. Significant diuresis occurs because water reabsorption is inhibited in the collecting duct due to reduction in the medullary interstitial concentrating gradient.[1-4]

To a lesser degree, furosemide also inhibits sodium reabsorption in the proximal tubule, likely through carbonic anhydrase inhibition and prostaglandin-mediated changes in renal hemodynamics. A number of other actions have been proposed as additional mechanisms for the drug's diuretic effect. The ability of furosemide to accumulate in the adrenals, lung, spleen, and liver, in addition to the kidneys, has led to the theory that it may influence fluid status by inhibiting endogenous corticosteroid production or stimulating metabolism. Other studies have suggested that furosemide administration results in stimulation of the renin-angiotensin-aldosterone system and prostaglandin production, as well as increased release of endogenous atrial naturetic factor and endothelin-1. These effects are tightly interconnected in compensatory pathways making isolated effects of furosemide difficult to assess in the intact organism. Very importantly, adaptation in the distal tubule to the increased sodium concentration produced by prolonged furosemide administration may result in increased sodium and water reabsorption, leading to diuretic tolerance.[1-4]

Pharmacokinetics and Pharmacodynamics

Pharmacokinetic studies of furosemide have revealed considerable interpatient variability. After oral administration, peak serum furosemide concentrations occur at approximately 1 to 1.5 hours. The oral bioavailability of furosemide in adults has been estimated at 40 to 60% in most studies. Peak serum concentrations do not differ significantly between tablets and the oral solution. Estimates of the volume of distribution in adults range from 4 to 13 L. Furosemide is highly protein bound (91 to 99%). It is primarily metabolized in the liver to furosemide glucuronide. The half-life of furosemide in adults is approximately 1 to 2 hours, but is prolonged in patients with hepatic disease.[1,2,5]

The pharmacokinetic profile of furosemide has also been evaluated in infants and children. Mirochnick and colleagues evaluated furosemide clearance in 10 preterm infants (mean birthweight 0.829 ± 0.217 kg, mean gestational age 26.6 ± 2.9 weeks).[6] All patients received an initial dose of 1 mg/kg followed by doses of 1 to 2 mg/kg every 12 or 24 hours, based on clinical response. Serum sampling was conducted at timed intervals after dose administration. The average volume of distribution in the sample patients was 0.48 ± 0.14 L/kg. Bioavailability of oral furosemide (assessed in three patients) was approximately 84%. Protein binding was nearly 95%. Clearance was significantly prolonged in this patient population, with half-life values ranging from 1.8 to 67.3 hours. The half-life of furosemide in infants born at less than 31 weeks gestation often exceeded 24 hours. In these patients, dosing every 12 hours frequently

resulted in furosemide accumulation to potentially ototoxic levels (≥ 25 mcg/mL). Renal clearance of furosemide increased with increasing postconceptional age. By 36 weeks, the average half-life had declined to 4 hours, similar to that of term neonates.

The pharmacodynamic response to furosemide is influenced by the patient's renal function and hydration status. The efficacy of the drug is dependent on the amount of furosemide excreted into the proximal tubular lumen. In older children and adults, the typical onset of diuresis after intravenous (IV) administration is 5 minutes, with a peak effect within 30 minutes and a duration of 2 to 6 hours.[1-4] A delayed response is seen in preterm infants or in infants after cardiac surgery, with an onset within an hour after IV dosing, peak action occurring over a 3 hour period, and a duration of 6 hours.[7,8]

Clinical Trials in Infants and Children

Furosemide is used in the treatment of many pediatric disease states. In the acute setting, it is used to treat edema associated with shock or traumatic brain injury, as well as postoperative volume overload. Long-term furosemide therapy is used in infants with chronic lung disease or children with nephrotic syndrome or cardiac failure. A wide variety of pediatric studies have been conducted with furosemide over the past 40 years.[3] Early studies were primarily conducted in preterm infants with chronic lung disease. More recent papers have focused on the use of furosemide as a continuous infusion in critically ill infants after cardiac surgery.[8-12] Continuous infusions of furosemide have been suggested as a means of optimizing sodium and water excretion while avoiding wide fluctuations in serum furosemide concentrations and volume status.

The initial study in this population was published in 1992 by Singh and colleagues.[8] They conducted a prospective, randomized clinical trial to compare the effects of intermittent and continuous administration of furosemide in 20 children (newborn to 4 years of age) after cardiac surgery. The intermittent group was given 1 mg/kg furosemide IV every 4 hours. This dose was increased by 0.25 mg/kg increments if urine output was less than 1 mL/kg/hr, up to a maximum of 1.5 mg/kg. The continuous infusion group received a loading dose of 0.1 mg/kg (up to 1 mg) followed by an infusion starting at 0.1 mg/kg/hr. The infusion was titrated by doubling the rate at 2 hour intervals for a urine output less than 1 mL/kg/hr, to a maximum of 0.4 mg/kg/hr. Although the 24-hour urine output was no different between the two groups (3.36±1.79 mL/kg/day in the infusion group and 3.53±4.10 mL/kg/day in the intermittent group), the infusion group had a lower total daily furosemide dose compared to the intermittent group (4.90±1.78 mg/kg/day versus 6.23±0.62 mg/kg/day, p=0.045). Sodium and chloride loss was greater in the intermittent group, but by relatively small amounts. Serum sodium decreased by 0.29±0.15 mmol/kg/day in the intermittent group and 0.20±0.06 mmol/kg/day in the infusion group (p=0.0007). Chloride decreased by 0.40±0.20 mmol/kg/day and 0.30±0.12 mmol/kg/day, respectively (p=0.045). Potassium loss was similar in both groups.

In 2002, Schoemaker and colleagues utilized quantitative modeling techniques to assess the relationship between furosemide dosing, serum concentrations, and urinary excretion.[12] The goal was to create a dosing regimen that would optimize urine output while maintaining serum furosemide concentrations < 50 mcg/mL. To develop the model, the authors collected urine and blood samples from 18 infants (ages 0.5-48.4 weeks) given furosemide at a rate of 0.1 mg/kg/hr after cardiac surgery. Using nonlinear mixed effects modeling to simulate alternative dosing strategies, the authors found that a regimen of a 1 to 2 mg/kg bolus dose, followed by an infusion of 0.2 mg/kg/hr, would maximize diuresis. This regimen was evaluated in a follow-up study with another 18 cardiac patients. The infusion was adjusted by 0.1 mg/kg/hr increments for a urine output outside of the desired 2 to 6 mL/kg/hr goal. Twelve infants completed the follow-up phase. Three patients required titration to 0.3 mg/kg/hr and two required 0.4 mg/kg/hr. Serum furosemide concentrations remained below 50 mcg/mL. Based on the follow-up results, the use of higher initial doses to promote greater furosemide tubular excretion in the face of reduced urine output, with subsequent downward titration as function improves, appears warranted.

Contraindications and Precautions

Furosemide is contraindicated in anuric patients or those with a history of hypersensitivity to it. Patients with allergies to sulfonamides should be monitored for cross-sensitivity to furosemide. Furosemide should be used with caution in patients with significant hepatic dysfunction; doses should be adjusted based on individual response. It should also be used with caution in patients with systemic lupus erythematosus or hyperuricemia, where it may precipitate gout.[1,2]

Adverse Effects

When used in recommended doses, furosemide is generally well tolerated. High-dose therapy may produce excessive diuresis, resulting in

hypotension, dehydration, and placing susceptible patients at increased risk for vascular clot formation. Careful attention to fluid and electrolyte status is necessary when high-dose therapy is used. All patients should be monitored for signs and symptoms of a hypochloremic metabolic alkalosis, hyponatremia, hypokalemia, hypomagnesemia, or hypercalciuria.[1-4]

Nephrocalcinosis, a consequence of the high urinary calcium excretion rate and an alkaline urine pH caused by furosemide, is a well known risk of long-term therapy, particularly in infants.[3,4,13] Saarela and colleagues compared the rate of nephrocalcinosis in 36 term infants (mean age 2.9 months) with cardiac failure receiving furosemide versus an age-matched control group. Patients were followed for up to 2 years or until resolution of the calcifications was established by ultrasound. Nephrocalcinosis was observed in 5/36 (14%) of the furosemide group, but none of the controls (p=0.03). Within the furosemide group, the patients with nephrocalcinosis had received a higher average daily dose than those who did not develop calcifications (1.3±0.4 mg/kg/day versus 1.0±0.6 mg/kg/day, p=0.01). As anticipated, urinary calcium was significantly higher in the furosemide group, 1.56 mmol/L compared to 0.82 mmol/L in the controls (p=0.005). Nephrocalcinosis resolved in three of the patients by the end of the study, but two had persistent calcifications at 2 years of age. The authors recommend renal ultrasonography to evaluate for nephrocalcinosis within the first several months of long-term furosemide therapy in infants and consideration of alternative diuretic regimens in those with evidence of calcifications.

Ototoxicity is a rare, but serious adverse effect associated with the loop diuretics. Cases of tinnitus, as well as reversible and irreversible sensorineural hearing loss have been documented in the literature. While the mechanism for ototoxicity is not well understood, several studies have shown alterations in ion transport in the marginal cells of the cochlear duct with high concentrations of furosemide, resulting in reduced endocochlear potentials. Hearing loss has most frequently been associated with elevated serum furosemide concentrations (typically defined as > 50 mcg/mL). Other factors predisposing patients to ototoxicity include rapid IV injection (> 4 mg/min), concomitant use of other ototoxic drugs or drugs that inhibit furosemide clearance, use in patients with significant renal or hepatic dysfunction, and use in preterm neonates.[14]

Dermatologic reactions with furosemide include phototoxicity and conditions ranging from mild pruritic rash to purpura, exfoliative dermatitis, and erythema multiforme. Other adverse effects reported with furosemide include paresthesias, dizziness, headache, blurred vision, rash, pruritus, pancreatitis, jaundice, abdominal cramping or upset, nausea, vomiting, diarrhea, constipation, muscle spasm, including urinary bladder spasms, interstitial nephritis, and systemic vasculitis. There are also case reports of furosemide-induced thrombocytopenia, hemolytic anemia, aplastic anemia, and agranulocytosis. Anaphylaxis following furosemide administration is rare, but has been reported several times in the medical literature.[1,2]

Drug Interactions

Concomitant administration of furosemide with other loop diuretics (bumetanide or torsemide), ethacrynic acid, cisplatin, or aminoglycosides may increase the risk for ototoxicity. Use of furosemide with salicylates may produce salicylate toxicity, as a result of competitive renal excretion. A similar inhibition of renal clearance may occur when furosemide is given with lithium. Furosemide may potentiate the effects of other antihypertensive agents, resulting in significant hypotension. While it antagonizes the effects of nondepolarizing neuromuscular blocking agents, furosemide potentiates the effect of succinylcholine. Potentiation may also occur when it is given with ganglionic or peripheral adrenergic blocking drugs.[1,2]

Administration of indomethacin with furosemide may reduce diuresis. Sucralfate may reduce the absorption of furosemide tablets and reduce its effectiveness. Doses of furosemide and sucralfate should be separated by at least 2 hours. Phenytoin, probenecid, and methotrexate also have the potential to reduce the efficacy of furosemide. The interaction between furosemide and methotrexate alters both drugs: furosemide impairs the tubular secretion of methotrexate, resulting in higher serum methotrexate serum concentrations and a greater risk for toxicity. Concomitant use of furosemide and cyclosporine may result in hyperurecemia.[1,2]

In a small number of cases, administration of IV furosemide within 24 hours of a dose of chloral hydrate has resulted in flushing, diaphoresis, restlessness, nausea, hypertension, and tachycardia. Although not widely documented in the literature, the manufacturer recommends that these drugs not be used in combination.[1,2]

Availability and Dosing Recommendations

Furosemide is marketed as the brand name product (Lasix®, sanofi-aventis U.S., LLC) and as a generic product from a number of manufacturers. It is available in 20, 40, and 80 mg tablets, 8 mg/mL (40 mg/5 mL) and 10 mg/mL oral solutions, and a 10 mg/mL injection. The typical starting dose for furosemide in infants and children is 1 mg/kg IV or PO given every 6 to 24 hours, with the dosing interval determined by the patient's age, renal function, and clinical status. The recommended maximum single dose is 6 mg/kg. Continuous furosemide infusions typically range from 0.05 to 0.5 mg/kg/hr. The initial dose for furosemide in adults is 20 to 80 mg IV or PO, with subsequent doses administered at 6 to 8 hour intervals, as needed. Maintenance therapy is typically given once or twice daily, with adjustment based on clinical response.[1-4,8-12]

Intravenous injections should be given over at least 1-2 minutes, or at a rate no more than 0.5 mg/kg/min. Furosemide is compatible with sodium chloride and dextrose solutions. Its pH of 9, however, makes it incompatible with many drugs commonly used in the pediatric or neonatal intensive care setting. Oral furosemide doses may be given with or without food.[1,2]

Summary

Furosemide remains to be one of the most widely used therapies in pediatric and neonatal intensive care and is a mainstay in the long-term management of cardiac, pulmonary, and kidney diseases in children. New research has helped to refine our understanding of its mechanisms of action and its application in the pediatric population.

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Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee at their meeting on 7/24/09:

1. *Saccharomyces boulardii* (Florastor®), a non-colonizing, non-systemic yeast probiotic, was added to the Inpatient and Outpatient Formularies for the prevention or treatment of acute or chronic infectious diarrhea and antibiotic-associated diarrhea.
2. Bromfenac 0.09% ophthalmic solution (Xibrom™) was added to the Inpatient and Outpatient Formularies for the treatment of inflammation after cataract removal.
3. A generic form of mycophenolate mofetil was added to the Inpatient and Outpatient Formularies as an alternative to Cellcept®.
4. Felbamate (Felbatol®) was returned to the Inpatient Formulary for use in patients with refractory seizures. Prescribing is restricted to the Neurology division.

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