Neonatal Diuretic Therapy: Furosemide, Thiazides, and Spironolactone

Jeffrey L. Segar, MD

KEYWORDS

• Bronchopulmonary dysplasia • Diuretic • Neonate
• Prematurity • Sodium

Diuretics are one of the most frequently prescribed medications in the neonatal intensive care unit (NICU). In a study using the Pediatrix Medical Group data warehouse, Clark and colleagues[1] reported that furosemide was the seventh most commonly reported medication in the NICU, with more than 8% of all NICU patients being exposed to the agent. This high usage rate exists despite a relative paucity of studies supporting routine use in this population. Because of this lack of data, furosemide, metolazone, a thiazidelike diuretic, hydrochlorothiazide, and spironolactone have at various times, in response to the Best Pharmaceuticals for Children Act, been placed on US Food and Drug Administration and National Institutes of Health lists of drugs for which pediatric studies are needed.

Rational use of diuretics requires an understanding of developmental renal physiology and function in the neonate, knowledge of the mechanisms of action of various diuretic agents as well as the limitations and potential adverse effects. Randomized trials of diuretics for the prevention and treatment of lung disease, including respiratory distress syndrome (RDS) and bronchopulmonary dysplasia (BPD), have been performed, providing the practitioner with some guidance regarding the use of these drugs. However, these trials primarily took place before routine use of antenatal steroids and surfactant replacement therapy. Extrapolation of these data to infants with the new BPD may not be logical or justified.[2]

FUNCTIONAL DEVELOPMENT OF THE KIDNEY

The human renal excretory system passes through 3 stages of morphogenic development. The first stage is characterized by the emergence of paired tubules to form the nonfunctional pronephros. The second stage is the development of the mesanephros,

Division of Neonatology, Department of Pediatrics, University of Iowa Children's Hospital, 200 Hawkins Drive, Iowa City, IA 52242, USA
E-mail address: jeffrey-segar@uiowa.edu

Clin Perinatol 39 (2012) 209–220
doi:10.1016/j.clp.2011.12.007 **perinatology.theclinics.com**
0095-5108/12/$ – see front matter

consisting of approximately 20 pairs of glomeruli and tubules, which are able to form urine. The mesanephros degenerates by the 12th week of gestation and is followed by the appearance of the metanephros, the development of which is dependent on interaction between the ureteric bud and the undifferentiated mesenchyme containing the nephrogenic blastema. After the formation of the metanephric nephron, the first evidence of renal tubular function appears between 9 and 12 weeks of gestation. New nephrons continue to form up to the 36th week of gestation in the human fetus. Nephrogenesis is complete at birth in full-term infants, but continues after birth in preterm infants.[3,4]

During the last trimester of gestation, the fetal kidneys receive only 2% to 4% of the combined ventricular blood output. After birth, there is a decrease in renal vascular resistance associated with an increase in arterial pressure, both contributing to the increase in renal blood flow during the weeks after birth such that the newborn kidney receives 8% to 10% of cardiac output at the end of the first week of life and 15% to 18% by a few months of age. In comparison, 25% of cardiac output is distributed to the kidneys in the normal adult. In addition to an increase in renal blood blow, there is a redistribution of blood flow to the superficial cortex, a process that continues with maturation. The mechanisms regulating these developmental changes in renal blood flow include anatomic, hemodynamic, and neurohumoral factors. Studies performed in animals, primarily the sheep fetus and newborn rabbits and piglets, provide evidence for important roles of the renin-angiotensin system, prostaglandins, nitric oxide and renal sympathetic nerves, and adrenergic function.[5]

Accompanying postnatal changes in blood flow are marked increases in glomerular filtration rate (GFR) and renal sodium reabsorption. It is estimated that GFR increases at least 50% during the first day of life in the term infant and doubles by 2 weeks of age. In premature infants, GFR, measured as clearance of inulin or creatinine correlates closely with gestational age, increasing from $\sim$5 mL/min/m^2 at 28 weeks' gestation to $\sim$12 mL/min/m^2 at term.[6] Developmental changes in renal sodium excretion also occur during the perinatal period. Fractional excretion of sodium (FENa), or urinary sodium excretion as a percentage of the amount of sodium filtered at the glomerulus, is widely used to estimate the excretory capacity of sodium by the kidney. In utero, urinary sodium excretion is high, averaging 10% to 15%. In the full-term infant, FENa decreases to 2% to 4% in the first few hours of life and to even lower values in the subsequent 48 hours. In the first few days of life, urine sodium excretion typically exceeds dietary sodium intake, resulting in a state of negative sodium balance coincident with loss of body weight. As urinary sodium losses decrease further (FENa $\sim$0.2–0.3%) and sodium intake increases, a state of positive weight and water gain occurs. In premature infants, FENa during the first few days of life is proportionate to gestational age and decreases with maturation. By 36 weeks' post-conceptional age, FENa is typically less than 1%.

SODIUM AND CHLORIDE REABSORPTION IN THE KIDNEY

Sodium and chloride reabsorption normally occur at 4 major sites in the nephron: the proximal tubule (50%–70%), the loop of Henle (25%–30%), the distal tubule (5%), and the collecting duct (3%). The proximal tubule and thick ascending loop of Henle are responsible for the reabsorption of a large amount of filtered sodium to maintain constancy of total body sodium, whereas the distal tubule and collecting duct are responsible for fine regulation of sodium balance. Within the proximal tubule, active transport of sodium by the sodium-potassium-adenosine triphosphatase (Na^+K^+-ATPase) system drives passive transport of chloride and water. Because the process