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EDITORIAL

Routine use of diuretics in very-low birth-weight infants in the absence of supporting evidence

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In this issue of Journal of Perinatology, Hagadorn *et al.*[1] confirm the known variability of therapeutic approach among neonatologists and demonstrate the willingness of some neonatologists to routinely prescribe diuretics to very-low birth-weight infants in the first 28 days of life. They also show that some neonatologists overestimate the benefits (eg, sustained improvement in pulmonary mechanics, decreased ventilator days and decreased length of stay) of diuretic administration during the first 4 weeks of life and underestimate potential risks (eg, patent ductus arteriosus, hearing loss or renal failure) of diuretic administration. This study adds to the growing body of literature suggesting that diuretics may be one of the most commonly abused drugs in the neonatal intensive care unit.[2–4]

The 39% response rate in this survey is within the range (23–85%; 52 ± 18% (mean ± s.d.)) observed in 13 surveys involving US neonatologists and preterm infants published in 2005 to 2010 (unpublished data, Stewart and Brion), and similar to that of academic studies in behavioral sciences (56 ± 20%).[5] However, a limitation of this study is lack of assessment for possible non-response bias and lack of any procedures to minimize such bias.

Lung edema occurs in respiratory distress syndrome as a result of delayed sodium channel (ENaC) expression and may occur in chronic lung disease because of increased capillary permeability resulting from lung injury and inflammation, congestive heart failure due to patent ductus arteriosus, and fluid overload.[6–10] Diuretics might improve lung function by improving fluid absorption, by reducing lung congestion and by reducing lung fibrosis.[6–12] However, diuretics have many potential complications: (A) electrolyte imbalance such as hyponatremia, hypomagnesemia, hyperuricemia and either hypokalemic alkalosis (thiazides, loop diuretics) or hyperkalemia and acidosis (potassium-sparing diuretics); (B) reduction in extracellular volume, dehydration, hypovolemia, hypotension and pre-renal failure; (C) intrinsic renal failure potentially increasing toxicity of other medications; (D) mineral changes including either (most diuretics) osteopenia, phosphaturia, hypercalciuria, nephrocalcinosis and nephrolithiasis (associated with reduced glomerular and tubular function in childhood); or (thiazides, metolazone and potassium-sparing diuretics other than spironolactone) hypocalciuria and hypercalcemia; (E) persistent patent ductus arteriosus due to increased formation of prostaglandin E (furosemide); (F) metabolic: cholelithiasis (loop diuretics) and glucose intolerance (thiazides); (G) reduction of alveolar fluid absorption (amiloride and spironolactone);[13] (H) binding to androgen receptors with anti-androgen effects, disturbed gonadal and adrenal steroidogenesis, estrogen-like side effects, elevated gonadotrophin levels, interference with newborn screening for congenital adrenal hyperplasia (spironolactone);[14,15] (I) hearing loss, associated with a potential synergism of loop diuretics and aminoglycosides;[16,17] (J) worse neurodevelopmental outcome (acetazolamide and furosemide for treating post hemorrhagic ventricular dilatation).[18]

There is very little evidence to support routine use of diuretics in very-low birth-weight infants with respiratory distress syndrome or developing or established chronic lung disease.[6–10] The three trials that addressed mostly infants with postnatal ages of 7 to 28 days[19–21] looked at short-term renal and/or pulmonary outcomes varying from 24 to 96 h post treatment and not at long-term outcomes. Most trials of diuretics in preterm infants have only shown short-term effects on lung mechanics or oxygen requirement; these effects disappear as soon as the diuretics are stopped and do not shorten the duration of oxygen administration, long-term lung function or length of stay. Only one trial showed that chronic diuretic administration improved important outcomes.[22] This trial showed that an 8-week administration of thiazide and spironolactone in intubated very-low birth-weight infants who were at least 1 month of age and requiring a minimum of 30% O_2 improved survival at discharge, but did not affect the duration of ventilator support and length of stay. The patients did not receive prenatal steroids or surfactant. In addition, aminophylline, corticosteroids and bronchodilators were not allowed.[18] Another trial showed that chronic addition of spironolactone to thiazide for 8 weeks did not affect lung mechanics, serum sodium and potassium nor FiO_2.[23]

It is surprising that neonatologists are willing to routinely prescribe diuretics during the first 4 weeks of life[1] or for a long duration after extubation,[4] despite lack evidence for benefit from randomized controlled trials and for lack of information about long-term complications. A large randomized trial is needed to assess important and long-term outcomes including risks and benefits of diuretic administration to very-low birth-weight infants using current standard of care including prenatal steroids, caffeine and vitamin A.[24]

Conflict of interest

The authors declare no conflict of interest.

AL Stewart and LP Brion
Division of Neonatal-Perinatal Medicine, The University of Texas Southwestern Medical School Program, Medical Center at Dallas, Dallas, TX, USA
E-mail: luc.brion@utsouthwestern.edu

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