Editorial

Diuretics and Chronic Lung Disease of Prematurity

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Babies leaving today's neonatal nurseries with chronic lung disease of prematurity (CLD) are very different to those initial survivors followed by Northway et al.¹ The definition of the disease has changed; most now consider an oxygen requirement beyond 36 weeks post conceptional age to be a more important defining criterion than the 28 days of oxygen dependency used initially for bronchopulmonary dysplasia.² Early stages of the disease are associated with alveolar and interstitial edema,^{1,3} which could reduce lung compliance as well as increase airway resistance by narrowing terminal airways.³ Diuretic administration could improve pulmonary mechanics by three mechanisms: (1) immediate diuresis-independent reabsorption of lung fluid, (2) decrease in bronchospasm in patients with reactive airway disease, and (3) reabsorption of lung fluid mediated by a decrease in extracellular volume secondary to increased diuresis.⁴⁻⁶ The first two mechanisms may occur during systemic or aerosolized administration, whereas the third mechanism requires systemic absorption or administration. Potential complications of diuretic use⁴⁻⁶ include patent ductus arteriosus (furosemide), nephrocalcinosis, osteopenia, hearing loss, hypovolemia, hypotension, and electrolyte and acid base disturbances.

When treatment is given for CLD, the crucial clinical question is whether it will affect long-term prognosis. Key outcomes might include mortality, duration of ventilation, and overall duration of oxygen therapy. We have recently concluded three systematic reviews of the use of diuretics in infants with oxygen or ventilator dependency secondary to lung disease beyond 5 days of age.⁴⁻⁶ We only considered randomized trials that assessed effects of diuretics on one of predetermined outcome variables. Primary outcome variables included changes in need for respiratory support and oxygen

supplementation, mortality, oxygen dependency at 28 days or 36 weeks, length of stay, and number of hospitalizations during the first year of life. The complete list of eligible randomized trials and details of selection criteria and methods of analyses are all available at {<http://www.nichd.nih.gov/cochrane/neonatal>}.

Despite the widespread use of diuretics in CLD, there have been surprisingly few randomised clinical trials of their clinical safety or efficacy. The 20 eligible studies used very variable outcome measures, and most concentrated on short-term physiological measures such as pulmonary mechanics. Only three of the studies extended beyond 8 days duration: two compared thiazide and spironolactone to placebo,^{7,8} and a third evaluated the addition of spironolactone to thiazide treatment.⁹ The studies spanned a 16-year period, during which the pattern of disease and survival in preterm infants have changed, and the assumptions made to calculate summary statistics from the often limited data available may have underestimated real differences between treatments. Furthermore, virtually no data are available about long-term morbidity due to side effects, such as nephrocalcinosis and bone mineral washout.

LOOP DIURETICS

There have been 14 studies of furosemide, 8 using the systemic route and 6 the inhaled route. All were short-term studies and none assessed important outcomes as defined above. We found no evidence that systemic furosemide had a useful effect in infants <3 weeks of age developing CLD. In older infants with established CLD systemic furosemide transiently improves pulmonary mechanics, and a 1-week course also improves oxygenation.^{10,11} Before routine or sustained use of systemic loop diuretics are recommended we need studies that demonstrate effects on long-term outcome (survival, duration of oxygen and ventilator dependency, length of stay) and complications.

When aerosolised furosemide is given to infants with CLD there is evidence of improvement in pulmonary mechanics after a single dose;^{12,13} strangely, a daily dose given for a week does not appear to have significant effects.¹⁴ Given these very limited data there is currently no place for aerosolized furosemide in clinical practice. Investigators planning randomized trials should consider (1) using double-blinded design, (2) analyzing factors likely to affect the response to aerosolized furosemide, e.g., washout period and delivery of furosemide to distal airways, and (3) assessing, in addition to short-term outcome, the effects of chronic administration of aerosolized furosemide on the main outcome variables defined above.

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DIURETICS ACTING ON THE DISTAL TUBULES (DISTAL DIURETICS)

We have found six eligible studies of distal diuretics, of which only two involved prolonged treatment and assessed important outcomes. In preterm infants with CLD the chronic administration of a thiazide with spironolactone improves lung compliance after 4 weeks treatment, and reduces the need for bolus doses of furosemide.^{7,8} In nonintubated infants this regimen decreases oxygen requirement at 4 weeks, but does not improve mortality, or total duration of supplemental oxygen.⁷ In contrast, the single study assessing the effect of distal diuretics in intubated patients published by Albersheim et al.⁸ in 1989 and not exposed to systemic corticosteroids showed a decreased need for furosemide and a significant decrease in mortality. However, mortality in the placebo group (8/15 patients) was unusually high. Another study showed that adding spironolactone to thiazide did not improve oxygen requirement or pulmonary function.⁹ Maintenance of potassium levels may be important in avoiding excessive acid–base disturbance.¹⁵

In summary, in view of the paucity of evidence about the benefits and toxicity of chronic administration of diuretics for the treatment of CLD we cannot recommend their routine use at present. The long-term effect of loop diuretics on primary outcomes has not been evaluated in randomized trials, and risks of such therapy may include reopening of a pharmacologically treated ductus arteriosus, nephrocalcinosis, and bone mineral washout. Standard long-term diuretic therapy is the combined administration of hydrochlorothiazide and spironolactone;⁸ nevertheless, this protocol carries the risk of nephrocalcinosis and osteopenia. An alternative might be the use of hydrochlorothiazide without spironolactone; this protocol would be expected to prevent hypercalciuria in the absence of other diuretics and of sodium supplementation.^{16,17}

During the last decade, several strategies have been assessed to prevent and treat CLD, including prenatal administration of glucocorticoids, early administration of surfactant, early closure of the ductus arteriosus, limitation of volutrauma and barotrauma, permissive hypercapnia, vitamin A, antioxidants, anti-inflammatory agents, and prophylaxis of respiratory syncytial virus infection.^{18–24} Interventions in neonatal care must be rigorously evaluated for both efficacy and safety; the recent concern about developmental outcome after administration of glucocorticoids^{25,26} has highlighted the risks of doing harm inadvertently. In this context, the role of diuretics in CLD needs to be reassessed. Additional studies are needed (1) to confirm that routine administration of distal diuretics improves main outcome variables in intubated patients, and (2) to compare the effects on main outcome variables and potential risks (e.g., nephrocalcinosis) of hydrochlorothiazide alone with the combined administration of hydrochlorothiazide and spironolactone.

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