Treatment

Review: insufficient evidence exists for regular use of loop diuretics in preterm infants with chronic lung disease


QUESTION: In premature infants who have, or are developing, chronic lung disease (CLD), what are the short and long term benefits and risks of loop diuretics?

Data sources
Studies were identified by searching Medline (1966 to August 2000); EMBASE/Excerpta Medica (1974–98); and the Cochrane Controlled Trials Register (1998, issue 3). Abstracts from 4 national and international societies (1991–8) and 4 annual scientific meetings were handsearched.

Study selection
Randomised controlled trials were selected if they included preterm infants (<37 weeks gestation) with oxygen dependency or ventilator dependency secondary to lung disease beyond 3 days of life and compared intravenous or enteral administration of a loop diuretic with placebo or no treatment, administration of an additional loop diuretic, different diuretics, or different administration routes. Trials were selected if they reported short term outcomes (changes in mean airway pressure, need for artificial ventilation, need for continuous positive airway pressure, failure to tolerate extubation, and oxygen supplementation), long term outcomes (mortality, duration of need for oxygen supplementation and respiratory support, need for oxygen at 28 d, CLD at 36 weeks postconceptional age, length of stay, and hospital readmission), complications, or pulmonary function.

Data extraction
Data were extracted on study methods and quality indicators, mean postnatal and gestational age, presence of an endotracheal tube, and outcomes.

Main results
6 studies (n = 109) met the inclusion criteria. Most assessed physiological outcomes and none assessed the primary clinical outcomes of need for continuous positive airway pressure, CLD at 36 weeks postconceptional age, mortality, length of stay, and number of readmissions to hospital during the first year. Where possible, outcomes were assessed on an intention to treat basis. 5 studies compared furosemide with placebo. 1 study of infants <3 weeks postnatal age (n = 20) found inconsistent effects on oxygenation. In infants >3 weeks postnatal age, a 2 day course of furosemide did not affect oxygen requirements (1 study, n = 17), but a 7–8 day course improved percentage inspired oxygen (2 studies, n = 39, weighted mean difference [WMD] –2.7%, 95% CI –1.0 to –4.4). One study examining the effects of furosemide on pulmonary mechanisms (n = 20) found that a single dose improved pulmonary compliance (WMD 0.5 ml/cm water/kg, CI 0.3 to 0.7) and resistance (WMD 25 cm water/L/sec, CI –5 to –15) at 1 hour, but not 2 hours. A 1–2 day course did not improve compliance (3 studies, n = 59), tidal volume (1 study, n = 17), or resistance (2 studies, n = 59), and a 4–6 day course did not improve compliance or resistance (1 study, n = 22). A 7–8 day course, however, improved pulmonary compliance (2 studies, n = 39, WMD 0.4 ml/cm water/kg, CI 0.1 to 0.7) and minute ventilation (1 study, n = 17, WMD 126 ml/kg/min, CI 19 to 233). Only 1 study (n = 18) compared continuous infusion with bolus administration of furosemide and found no difference between the 2 administration methods.

Conclusions
Evidence from a few small trials suggests that a single dose of a loop diuretic, furosemide, transiently improves pulmonary compliance and reduces resistance in preterm infants >3 weeks postnatal age who have, or are developing, chronic lung disease. A 7–8 day course improves compliance and oxygenation. Insufficient data exist of the effects on clinical outcomes.

COMMENTARY
Limited research is available on the clinical effects of diuretics for preterm infants who develop CLD. The 6 studies in this systematic review by Brion and Primhak had 2 different study designs: parallel and crossover. In the parallel design, infants were randomly assigned to receive the diuretic or not, and the results were compared across the 2 groups. In the crossover design, each infant was exposed to the treatment and control conditions sequentially and the order of exposure was randomly assigned. Of importance is the washout period—that is, the time required for the diuretic to clear from the infant’s system. Because of the long half life of loop diuretics in immature infants, a prolonged washout period is required to eliminate all diuretic effect between exposures. Several studies had a short washout period or none at all, which could decrease the apparent effect of diuretic administration. The analyses yield few clinically useful results. Most improvements in infants receiving furosemide were not sustained beyond the duration of treatment. The only sustained effects were associated with a 7–8 day course of furosemide during which infants had improved lung compliance and minute ventilation. Of more importance is that most of the studies did not evaluate clinically relevant outcomes such as mortality, duration of oxygen administration, length of stay, electrolyte imbalances, and nephrocalcinosis. This review makes an important contribution to our knowledge of the effectiveness of loop diuretics in preterm infants who have, or are developing, CLD. Neonatal nurses will be more aware of the clinical changes that may occur in an infant’s condition such as need for less ventilatory support and a reduction in the number of desaturation spells. This study is also relevant to neonatal nurse practitioners who prescribe loop diuretics to improve respiratory status. Not enough evidence is available, however, to support regular use of loop diuretics in preterm infants with CLD. Further research is needed to evaluate all clinically relevant outcomes related to loop diuretics.

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