Postnatal steroids: the way forward

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Chronic lung disease (bronchopulmonary dysplasia) remains a major problem for neonatologists caring for very preterm infants, with rates in Europe varying from 10% in one Italian region to 25% in the northern region of the UK in the Models of Organizing Access to Intensive Care for Very Preterm Births (MOSAIC) cohort study; infants in this study had gestational ages ranging from 23 to 31 weeks. Similar or even higher rates are found in the USA, with a recent study reporting a rate of bronchopulmonary dysplasia of 45% of survivors at 22–28 weeks’ gestation. As the pathogenesis of neonatal chronic lung disease is thought to involve a perinatal inflammatory process, corticosteroid treatment has been proposed as a rational intervention for both prevention and therapy.

In the late 1960s and early 1970s, hydrocortisone was given to preterm infants with respiratory distress syndrome with the aim of modifying the course of this disease. No acute benefits were noted, but follow-up studies pointed towards potentially harmful effects on the developing central nervous system. Dexamethasone was first used to treat infants with bronchopulmonary dysplasia in 1978, but the study was never published in full. In the 1980s, two small studies of dexamethasone for the treatment of bronchopulmonary dysplasia were reported with apparent short-term beneficial effects. The use of dexamethasone increased exponentially during the 1990s, until three follow-up studies were published showing at least a twofold increased risk of cerebral palsy in surviving infants. The risk was subsequently shown to be associated primarily with early dexamethasone treatment during the first week of life. Systematic reviews also showed that later treatment after the first week of life was associated with not only reduced rates of bronchopulmonary dysplasia but decreased neonatal mortality, posing a dilemma for neonatologists. In 2001, I suggested that in infants with chronic lung disease much lower doses of dexamethasone, such as 0.05 mg/kg/day, may lead to improvement in lung function. This regimen seems to have been adopted in Leeds and Belfast and the experience of the former is reported in this issue of the journal (see page 190).

Yates and Newell from Leeds report the short-term effects of dexamethasone 0.05 mg/kg/day on 50 babies of less than 30 weeks’ gestation who were ventilator-dependent for more than 2 weeks. The outcomes of these babies were compared retrospectively with a matched cohort of 26 babies who had standard dose (0.5 mg/kg/day) dexamethasone therapy deferred due to concerns about neurodevelopmental sequelae. The ultra-low dose dexamethasone group (called ‘Minindex’ by the authors) received a cumulative dose of dexamethasone of 0.65 mg/kg, less than one-tenth of the so-called standard dose dexamethasone course. Yates and Newell reported faster extubation and more rapid improvement in lung function with no increased risk of clinical hypertension or hyperglycaemia. Disappointingly, there was no difference in the rate of chronic lung disease at 36 weeks’ corrected age and the trend was even towards an increase in the ultra-low dose group (OR 1.61; 95% CI 0.62 to 4.22). The authors sensibly call for a randomised controlled trial to further assess efficacy and long-term outcomes. In Belfast we have been using ultra-low dose dexamethasone under similar circumstances for about 10 years and have reported comparable short-term outcomes in a preliminary communication.

So, what is the way forward? There is no doubt that concerns about neurodevelopmental sequelae in the early 2000s led to a reduction in the use of postnatal dexamethasone with a consequent increase in the rate of bronchopulmonary dysplasia. The US study showed that postnatal steroid use remains relatively high among the most immature infants of less than 29 weeks’ gestation, with about 7% receiving dexamethasone and about 7% hydrocortisone. There is, however, no evidence that early hydrocortisone prevents chronic lung disease and there are no randomised trials of this steroid for treatment of bronchopulmonary dysplasia. In contrast, inhaled steroids may have a role in the prevention of chronic lung disease. In 2001, we showed that inhaled budesonide was as effective as systemic dexamethasone in the prevention of bronchopulmonary dysplasia and at follow-up aged 7 years there were similar neurodevelopmental outcomes, although the budesonide-treated children were less likely to have high systolic blood pressure or a diagnosis of asthma. One way forward is further assessment of early inhaled budesonide in an attempt to prevent chronic lung disease in very preterm infants and a large European randomised trial, the Neonatal European Study of Inhaled Steroids (NEUROSIS), is currently underway.

Very recently, the American Academy of Pediatrics (AAP) published an updated policy statement on postnatal steroids to prevent or treat bronchopulmonary dysplasia. This concludes that high dose dexamethasone (0.5 mg/kg/day) does not seem to confer additional therapeutic benefit over lower doses and is not recommended. The AAP statement continues to say that evidence is insufficient to make recommendations on other steroid doses and preparations, and the clinician must use clinical judgement when attempting to balance the potential adverse effects of steroids with those of bronchopulmonary dysplasia. The AAP statement despite discussing implications for practice, makes no mention of implications for research. However, I believe that neonatologists in the UK are keen to take part in randomised clinical trials to help determine the optimal management of extremely preterm infants at risk of developing bronchopulmonary dysplasia. Apart from the NEUROSIS study which is testing inhaled budesonide for the prevention of chronic lung disease, Yates and Newell suggest a randomised placebo controlled trial of ultra-low dose dexamethasone to treat infants with bronchopulmonary dysplasia and this would have a similar sample size of 800 subjects. Such a trial could include an arm with low dose hydrocortisone (1–3 mg/kg/day) and this has been discussed recently at a national meeting organised by the neonatal clinical study group of the Medicines for Children Research Network. So watch...
this space. Our colleagues from Leeds deserve our gratitude for their attempts to improve management of very preterm infants at risk of developing bronchopulmonary dysplasia.

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REFERENCES


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