Research Briefings

Neonatology
formerly Biology of the Neonate

Neonatology 2010;97:52–55
DOI: 10.1159/000227294

Received: February 10, 2009
Accepted after revision: April 21, 2009
Published online: July 7, 2009

The Neonatal European Study of Inhaled Steroids (NEUROSIS): An EU-Funded International Randomised Controlled Trial in Preterm Infants

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Introduction

Survival of extremely low birth weight infants has improved in recent decades, but bronchopulmonary dysplasia (BPD) remains a major health care problem [1]. BPD not only contributes to the mortality of preterm infants, but is also associated with impaired neurosensory development in survivors [2, 3]. Furthermore, a diagnosis of BPD has been associated with respiratory morbidity later in life [4–8]. This puts an enormous burden not only on individual patients and their families, but also on collective health resources.

Genetic background and antenatal environmental factors play an important, yet poorly defined role in the pathogenesis of BPD [9, 10]. Central is the exposure of the developing lung to inflammation [10–12]. Most infants that develop BPD encounter the first serious inflammatory event early after birth [12]. Corticosteroids have anti-inflammatory properties, and early inhalation of corticosteroids may provide beneficial local effects on the lungs prior to development of a full inflammatory response with a lower risk of undesirable systemic side effects.

Inhaled Postnatal Steroids

The efficacy of inhaled steroids to prevent BPD has already been investigated in several randomised trials, both in comparison with systemic steroids [13] and with placebo [14–20]. According to recent systematic reviews on inhaled drugs for the prevention and treatment of BPD, there are 7 fully published controlled trials in which infants were either randomised to inhaled steroids or placebo within 2 weeks of life [21, 22]. However, these trials have not provided a definite answer to the question of best timing of inhalation of steroids.

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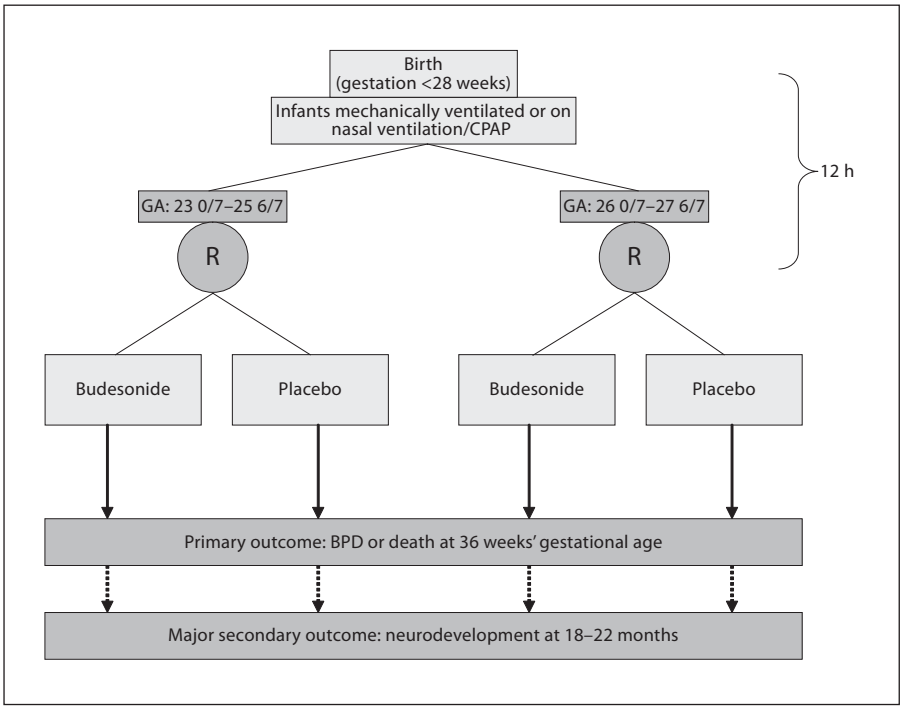

Fig. 1. Diagram showing the study design for NEUROSIS. GA = Gestational age; R = randomisation.

In 5 trials, inhaled corticosteroids were initiated at day 3 of life or later [14–18]. Among these trials is the largest randomised placebo-controlled trial (RCT) on inhaled corticosteroids for the prevention of BPD published to date that included 253 preterm infants [14]. In this study, inhaled beclomethasone was initiated at an average of 5.5 days and did not prevent BPD, but was associated with a reduced use of systemic glucocorticoid therapy and mechanical ventilation.

In the 6th study, therapy with inhaled fluticasone proprionate was started in the first 24 h of life in 53 ventilated infants [19]. Inhaled steroids resulted in a significantly higher success rate for extubation within the first 2 weeks of life and a more pronounced improvement in lung compliance. Six infants in the fluticasone group and 12 in the placebo group either died or were oxygen dependent at 36 postconceptional weeks, a difference that was not statistically significant.

In the 7th study, a pilot study, the first dose of beclomethasone or placebo was initiated at birth in 47 preterm infants [20]. This study also failed to show a statistically significant reduction in BPD rates at 36 weeks, but inhaled steroids reduced the need for supplemental oxygen at 30 weeks.

Open Questions

Most of the studies mentioned above only included ventilator-dependent preterm infants [14, 15, 17–20], but BPD also develops in preterm infants who require relatively little ventilatory support in the first few days of life [23–25]. An RCT enrolling mechanically ventilated infants and also those on continuous positive airway pressure (CPAP) that investigates the efficacy and safety of very early inhalation of budesonide might therefore help to improve survival without BPD in preterm infants. The long-term safety and efficacy of inhaled steroids, however, has not been adequately studied [22, 26], and since early *systemic* corticosteroids affect neurodevelopmental outcomes in preterm infants [27, 28], a new RCT of inhaled budesonide should include a long-term follow-up.

Summary of Study

The Neonatal European Study of Inhaled Steroids (NEUROSIS) is a randomised placebo-controlled, international clinical trial. 850 infants of 23–27 weeks' postmenstrual age (either mechanically ventilated or on CPAP) will be randomised during the first 12 h of life

to budesonide or placebo (fig. 1). Study drugs will be administered via a spacer device and continued until infants no longer need either supplemental oxygen or positive pressure support or have reached a postmenstrual age of 32 0/7 weeks regardless of ventilatory status. The primary outcome of survival without BPD will be determined at 36 weeks' postmenstrual age, and BPD will be defined according to the physiological definition [29]. Study patients will be followed and neurodevelopmental outcomes assessed at a corrected age of 18–22 months.

The severity of BPD according to 3 different definitions will be determined as an exploratory analysis. Candidate genes related to absorption, distribution, metabolism, and excretion of budesonide will be investigated including pharmacokinetic data. Moreover, a sub-study on genetic susceptibility to BPD will be performed.

NEUROSIS is funded by the European Union in its 7th framework program. Infants are planned to be randomised starting from September 2009, and units are invited to participate. The results of NEUROSIS will provide useful indications about the efficacy and safety of inhaled steroids in very preterm infants.

Acknowledgement

NEUROSIS is supported by the European Union (Grant Award HEALTH-F5-2009-223060).

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