Postnatal Corticosteroids for Bronchopulmonary Dysplasia

Alan H. Jobe, MD, PhD

KEYWORDS

• Lung injury • Alveoli • Premature • Neurodevelopment
• Mechanical ventilation

All who drink of this treatment recover in a short time, except those whom it does not help, who all die. Therefore, it is obvious that it fails only in incurable cases.
—Galen, 200 AD

A PERSPECTIVE

Are corticosteroids being used today in the uninformed way that Galen used his potion to treat patients almost 2000 years ago, and are treatment failures the result of the disease or the drug? Galen seemed to discount drug toxicity for those unfortunate incurable cases. There really are only two core questions that need to be asked about the use of postnatal corticosteroids for bronchopulmonary dysfunction (BPD): do they work, and do they have clinically concerning adverse effects? The challenge is to define what "work" means, what adverse effects are of concern, and what "they" are, because multiple corticosteroids are used in different doses at different postnatal ages for different treatment durations. The use of postnatal corticosteroids for BPD has been widely evaluated by randomized, controlled trials, but these trials have multiple treatment schedules and have produced limited and inconsistent information about outcomes. Ultimately, the clinician must weigh the statistical and population-based evidence and decide if corticosteroids might help a particular infant and if the risks are acceptable.

The Food and Drug Administration has not approved the use of corticosteroid drugs for the treatment of bronchopulmonary dysplasia.

Division of Pulmonary Biology, Cincinnati Children's Hospital, University of Cincinnati, 3333 Burnet Avenue, Cincinnati, OH 45229-3039, USA
E-mail address: alan.jobe@cchmc.org

Clin Perinatol 36 (2009) 177–188
doi:10.1016/j.clp.2008.09.016 **perinatology.theclinics.com**
0095-5108/08/$ – see front matter

HOW FREQUENTLY ARE CORTICOSTEROIDS USED?

The use of postnatal corticosteroids has been a bit like women's hemlines, rising and falling based on fashion or perceived benefits and risks. In 1990, about 17% of very low birth weight (VLBW) infants cared for in the Vermont Oxford Network received postnatal corticosteroids, and the rate of use was 7% for VLBW infants in the National Institute for Child Health and Human Development Neonatal Research Network.[1] The peak rate of use was 28% for Vermont Oxford Network and 23% for the Neonatal Research Network in 1997. As follow-up information about adverse effects of corticosteroids on neurodevelopment began to appear, the American Academy of Pediatrics and the Canadian Pediatric Association strongly recommended against the use of corticosteroids to prevent or treat BPD in 2002.[2] Since then, use has decreased. In 2006 8% of VLBW infants overall in the Vermont Oxford Network registry and 23% of the infants in the group at highest risk (those with birth weights between 501 and 750 g) received postnatal corticosteroids (R. Soll, personal communication, 2008). Therefore, postnatal corticosteroids continue to be used selectively in infants. Infants also receive corticosteroids for indications other than BPD. In 62 neonatal ICUs in California in 2003, 19% of VLBW infants received postnatal steroids, but only 3.6% received steroids for BPD alone; the other uses were for treatment of hypotension, airway management after extubation, or a combination of indications.[3] Some ICUs also use aerosolized corticosteroids. Thus the risks and benefits of corticosteroid use remain a concern. Corticosteroids are used preferentially in the smaller and earlier gestational age infants because those infants are at highest risk for developing severe BPD.

DO CORTICOSTEROIDS WORK FOR BRONCHOPULMONARY DYSPLASIA?

One way of interpreting the question whether corticosteroids work for BPD is whether the use of corticosteroids improves lung function in ventilator-dependent infants at risk for BPD sufficiently to permit extubation. Corticosteroids now are used less frequently soon after birth to ''prevent'' BPD because of concerns about the risk and interactions with other drugs such as indomethacin.[4,5] The summary conclusions of the meta-analyses by Halliday and colleagues[6–8] indicate that postnatal corticosteroids do not decrease death, although there is a trend for a death benefit for treatments started at 7 to 14 days of age (**Table 1**). Corticosteroids decrease BPD and decrease extubation failures independently of the age at which treatments are started. The trials included in these meta-analyses dated mostly from the era before surfactant treatment was available, and some of the trials were done before the use of antenatal corticosteroids was common. The infants in these studies were larger than many of the infants who receive postnatal corticosteroids today. Also, there have been changes in the techniques used for mechanical ventilation and in ventilatory goals. Higher P_{CO_2} values may be accepted for infants requiring mechanical ventilation for severe respiratory failure. A therapy that was effective in a different era and in a different patient population may not work now. If postnatal corticosteroids do not work in current practice, a further discussion of their use is not relevant.

The American Academy of Pediatrics and Canadian Pediatric Association joint condemnation of postnatal corticosteroid use for BPD curtailed enthusiasm for further studies.[2] Nevertheless, two studies were attempted, and both were closed before full enrollment. Watterberg and colleagues[5] randomly assigned ventilated infants with birth weights between 500 and 999 g to a 15-day tapered course of hydrocortisone or placebo within 2 days of birth. The hypothesis was that hydrocortisone would treat the adrenal insufficiency that commonly occurs soon after birth, would improve survival, and would decrease BPD. The trial was stopped because of increased