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EDITORIAL

Postnatal Steroids to Treat Chronic Lung Disease in Preterm Infants: Is it Ever Justified?

Peter Gal, PharmD,[1,2,3] and Mary Ann V. T. Dimaguila, MD[1]

[1]Women's Hospital, Greensboro, North Carolina, [2]Pharmacy Division, Greensboro AHEC, Greensboro, North Carolina, and [3]School of Pharmacy, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina

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The use of postnatal steroids became popular after an initial study by Avery et al. showed marked short-term improvement in pulmonary status.[1] A subsequent study showed that a 42-day course of dexamethasone resulted in better pulmonary and neurological developmental outcomes than either 18 days of dexamethasone or placebo.[2] For clinicians dealing with the frustration of watching a ventilator-dependent baby with chronic lung disease intermittently taking one step forward, only to take a step back afterward, the dramatic improvement in respiratory status observed early in a dexamethasone treatment course was truly gratifying.

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Clinicians caring for a ventilator-dependent baby with chronic lung disease are frequently frustrated when the infant takes one step forward, only to take a step back. The dramatic improvements in respiratory status that are observed early in a dexamethasone treatment course were truly gratifying. These short-term gains were enough to encourage most clinicians to get on the steroid bandwagon, especially when reduced chronic lung disease rates were also confirmed in many studies.[2-6] In the face of such apparent benefits, acute toxicities of hypertension, glucose intolerance, gastrointestinal bleeding, and increased infection risks seemed well worth the risk. Unfortunately, several subsequent studies showed that dexamethasone caused a decrease in brain growth[7] and impairment in neurological development.[8-10]

In an attempt to resolve this controversy, the American Academy of Pediatrics and Canadian Pediatric Society developed a joint statement of the use of postnatal corticosteroids to treat or prevent chronic lung disease in preterm infants.[11] With the exception of controlled trials, these groups advocated against the use of systemic corticosteroids for the prevention or treatment of neonatal chronic lung disease. To put perspective on the initial enthusiasm for corticosteroid use, an elegant letter by Kaplan[12] reminded us that the type of neonates with bronchopulmonary dysplasia (BPD) at that time were larger and often had radiographic changes consistent with stage 3 or 4 disease.

ABBREVIATIONS: BPD, bronchopulmonary dysplasia

Lung disease in these larger babies had a significant inflammatory process and features of airway injury such as fibroproliferation and hyperplasia. Indeed, the nature of chronic lung disease has changed so that the smaller babies (often referred to as micropremies) have immature alveolar development and reduced number of alveoli as their primary pathologic feature.[13] Whether this form of BPD also benefits from systemic steroids is an issue, especially since steroids are known to impair alveolar growth.[14]

Address correspondence to: Peter Gal, PharmD, Greensboro AHEC, 200 E Northwood St, Suite 100, Greensboro, NC, 27401, e-mail: peter.gal@mosescone.com

Others debate that most centers are not in a position to participate in controlled trials and may not have the resources available to fulfill all the expectations needed to participate in a controlled trial. Does this mean that systemic steroids should be totally avoided in all but the elite centers that would carry out clinical trials, or should clinicians make decisions based on their best interpretation of the literature and individual patient circumstances?

While some neonatal practitioners avoid steroids because of concerns over neurological development and the cautionary position taken by the American Academy of Pediatrics, it is apparent from the report by Porter and Garner in this issue that many neonatologists continue to believe that some clinical circumstances warrant systemic glucocorticoids to treat BPD.[15] This recent survey reinforces the results of prior surveys in the United States and Europe, which indicate that neonatologists continue to use systemic steroids despite recommendations to the contrary.[16,17] But, perhaps the opinions from the American Academy of Pediatrics and other experts reflected a pendulum that had swung farther in opposition of systemic steroids than practicing clinicians felt were justified and thus willing to accept.

Although systemic steroids are effective in improving lung function, they have been associated with an increased risk for the development of cerebral palsy. Doyle et al. published a very thoughtful approach to the use of systemic corticosteroids in neonates who had worsening lung disease and a high likelihood of progression to chronic lung disease.[18] The authors used previously published randomized placebo controlled trials of postnatal corticosteroids to categorize the risk of chronic lung disease and the development of cerebral palsy. The confounding effect of steroid use in the control group (referred to as contamination rate) was considered, since the differences between steroid-treated and control groups could be muted by the high use of steroids as rescue medicine in control patients. These authors make a compelling case that the benefits of dexamethasone outweigh the adverse consequences once some level of risk for chronic lung disease or death occurs. In their analysis, the authors place this risk of chronic lung disease at 65% for a conservative practitioner and 50% for a less conservative practitioner. As the accompanying editorial points out, none of the studies of dexamethasone thus far has used an a priori tool for determining chronic lung disease risk, and it is difficult to know the true risk for an individual patient.[19] Thus one must decide somewhat arbitrarily what the risk of chronic lung disease might be.

Initiating steroids after the newborn is at least 7 days old has not been proven to cause cerebral palsy when meta-analyses of these data are performed.[18,20] A reduction in the incidence of chronic lung disease at 28 days postnatal age and 36 weeks postconceptional age was observed. It is important to remember that in neonates with BPD, neurological development is also delayed.[21,22] Thus at some point benefit-to-risk may favor steroids because pulmonary outcomes are better with steroids, and detrimental neurological development is comparable when steroids are compared to placebo. In fact, chronic ventilator use appears to be strongly associated with neurological developmental problems.[23,24] Thus, the trade off for use of systemic steroids requires one to consider the risks for two evils (i.e., steroids, chronic ventilator dependency) that are associated with similar neurotoxicity. It is understandable then that clinicians, while waiting for appropriate studies to provide useful answers, take initiative to make their own decisions.

While mechanistically one could reason how steroids may be neurotoxic, the use of systemic steroids after the first week of life has unproven neurotoxicity. Other inflammatory mechanisms explain how ventilator use can have the same impact on neurological development. Interestingly, a recent 15-year follow-up of persistently ventilator dependent neonates who received dexamethasone after 2 weeks of age showed superior long-term neurological developmental outcome in infants treated with steroid for 42 days compared to those treated 18 days or the control group.[25]

Dexamethasone has been the main corticosteroid administered for BPD, but other corticosteroids may be less neurotoxic.[26] Although hydrocortisone may be less neurotoxic, a recent trial using hydrocortisone for prophylaxis of BPD was stopped early due to excessive spontaneous gastrointestinal perforations, especially

when combined with indomethacin.[27]

Is there a need for prophylaxis of BPD with steroids? This strategy will result in unnecessary treatment of some patients who would not get BPD, and expose patients to steroids at a time when they are most likely to be receiving concurrent indomethacin. Thus, evidence would favor avoiding corticosteroids, except perhaps in cases where histologic evidence of chorioamnionitis and neonatal adrenal insufficiency were observed. Perhaps guidelines from authoritative sources should emphasize avoiding prophylaxis in the absence of chorioamnionitis, rather than later treatment of moderate to severe disease. Certainly research is still needed to determine the best steroid to use, dosage, and duration of therapy. Experts and clinicians usually have strong opinions about which therapeutic strategies provide the greatest benefit-to-risk ratio, and what can be done to minimize steroid toxicities. Those stating that evidence-based medicine clearly dictates avoiding steroids except as part of controlled clinical trials, appear to have overstated the case against long-term effects if steroids are used after one week postnatal age. This delayed use may also prove more neurotoxic than chronic ventilator exposure in later trials. But in the interim, the diversity of approaches to corticosteroid use to treat active BPD seems reasonable for the lack of compelling data favoring any one opinion.

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