Journal of Perinatology (2008) 28, 789–790

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EDITORIAL

Corticosteroids and hypotension: altered response states and human disease

Journal of Perinatology (2008) **28,** 789–790; doi:10.1038/jp.2008.191

The story of steroid use in the neonatal population continues to fascinate neonatologists. Early in our specialty's history, dexamethasone was observed to have an almost magical effect in the chronically ventilated preterm infant, with rapid decreases in support requirements over just a few days. The earliest studies suggested many powerful effects of these drugs, warned of potential dangers to their use, and unfortunately reported prolonged therapy for bronchopulmonary dysplasia (BPD), which was rapidly adopted around the world.[1,2] In addition, though the early impact of steroid therapy was not subtle, the mechanisms were very poorly defined. After a long period of widespread use, further study demonstrated that the price for this rapid respiratory response was exacted in worsened neurodelopmental outcomes, at least for some babies; currently, the Committee on Fetus and Newborn of the American Academy of Pediatrics does not recommend routine use of corticosteroids in BPD.[3]

As use of steroid treatment for chronic lung disease declined, a different kind of problem became a focus for steroids—hypotension. Using much lower doses than those used for BPD, a few studies suggested efficacy of steroid treatment for hypotension.[4–6] This lead to evaluation of a much larger question—do small preterm infants actually suffer from a relative adrenal insufficiency, similar to that seen in adults? Would replacement of physiologically essential hydrocortisone in this population have an impact not just on blood pressure, but on pulmonary and neurologic development? In very preterm infants, at least partial answers are being revealed.[7] These infants do have characteristics of relative adrenal insufficiency. Physiologic hydrocortisone replacement improves blood pressure, decreases evidence of chronic lung disease in babies exposed to *in utero* inflammation, and positively impacts neurodevelopmental outcomes in babies without evidence of *in utero* inflammation.[8] As often happens, unexpected problems were also identified in these trials: gastrointestinal perforation was more common in hydrocortisone-treated extremely low birth weight (ELBW) infants, especially in conjunction with indomethacin therapy, and in babies with high initial serum cortisol levels.[7]

But what about in the older infant with hypotension? In this issue of the *Journal of Perinatology*, Dr Fernandez and co-workers describe the response of the hypothalamic/pituitary axis in critically ill and noncritically ill late-preterm and term neonates. Dr Watterberg, the study's senior author, has been dogged in her pursuit to better understand the neonatal hypothalamic/pituitary axis; this study lays a foundation for continued investigation in the older preterm and term infant. Expanding on previous data, this study prospectively evaluates cortisol and adrenocorticotropin (ACTH) responses in a group of critically ill infants $\geqslant 34$ weeks gestation, and compares them to a similar, though slightly older and larger control infants. Cortisol levels in the critically ill babies were low and did not increase as expected in response to their illness, consistent with the concept of relative adrenal insufficiency. Unexpectedly, they found that cortisol levels were similar whether the sick infants required vasopressor treatment or not, were not related to severity of illness as assessed by score for neonatal acute physiology (SNAP) scores, that cortisol levels responded appropriately to ACTH stimulation, and that ACTH levels were much lower than expected for critically ill neonates. These findings led the authors to postulate an altered response state, likely due to the *in utero* exposure of the infant to placental corticototropin-releasing hormone (CRH). They suggest that either the hypothalamus is unable to appropriately secrete CRH, resulting in low pituitary secretion of ACTH and adrenal cortisol, or the pituitary is relatively insensitive to hypothalamic CRH, with the same end effect. More study is needed to ask these questions, and to define the duration of this altered state of responsiveness.

This variant on the theme of relative adrenal insufficiency adds to an expanding list of human disorders potentially caused by altered responsiveness of organ systems. In the very preterm infants, there is increasing evidence that *in utero* and immediately post-natal exposure to inflammatory stimuli—infection, improper lung inflation, endotracheal intubation, prolonged oxygen exposure among others—result in alterations in developmental responses, some of which may be difficult or impossible to counteract.[9] The Barker hypothesis of the developmental origins of adult disease is based on the concept that early developmental events alter end-organ responses in adulthood.[10] In addition to providing new information about the late-preterm and term infant, this study reminds us that 'normal' and 'healthy' are tricky terms. When we study a problem, asking, 'What is the answer?' it is most important to step back and ask, 'What is the question?' and even 'Why is this a question at all?' Fernandez and co-workers, by

posing these types of questions, get the most from their data and point the way for more work.

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