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The Role of Hydrocortisone in the Management of Bronchopulmonary Dysplasia

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Although the clinical landscape of bronchopulmonary dysplasia (BPD) has shifted over the years, BPD remains the most common form of chronic lung disease in infants.[1] Historically BPD was seen in preterm infants who had suffered vasotrauma from aggressive mechanical ventilation. With advancements in medical care and the resultant survival of extremely premature infants delivered during the late canalicular and early saccular stage of lung development, today's BPD has become more of a developmental disorder. [1,2]

Low cortisol levels in premature infants have correlated to increased severity of illness, mortality, and subsequent development of BPD, thus leading to the proposed option of glucocorticoids for prevention and treatment of BPD.[3] However, mixed results from clinical studies combined with their potential for neurologic adverse events have created controversy around their use in the neonatal population. Despite this fact, hydrocortisone is one of the 15 most frequently prescribed medications in extremely low birth weight (ELBW) infants in neonatal intensive care units and is a continued topic of study and discussion.[4]

Mechanism of Action

The clinically significant role of inflammation in BPD development led to the consideration of corticosteroids as a treatment modality, with rapid improvement in lung mechanics.[2] The primary anti-inflammatory effect is mediated by glucocorticoid synthesis of annexin-1, which suppresses phospholipase A3 expression. This suppression blocks eicosanoids such as prostaglandins, thromboxanes, leukotrienes, and their resulting inflammatory processes including adhesion and migration. Additional anti-inflammatory effect is attributed to the suppression of cyclooxygenase I and II. Furthermore, the decrease in circulating prostaglandins after postnatal steroid therapy has been associated with decreased incidence of patent ductus arteriosus (PDA). The decreased responsiveness of this ductal tissue prevents endothelial damage caused by left-to-right shunting through a PDA. Closure of the PDA may also lower the risk of pulmonary edema and reduce the need for mechanical ventilation.[5,6]

Dexamethasone vs Hydrocortisone

Dexamethasone is a potent, long-acting steroid with exclusive corticosteroid effect. In adults, it has a half-life of 36-54 hours and its potency is 25-50 times that of its alternative, hydrocortisone, which has a half-life of only 8 hours. These agents have different binding affinities within the hippocampus. This area of the brain, responsible for memory and spatial processing, is comprised of both mineralocorticoid and glucocorticoid receptors. Dexamethasone can only bind to the glucocorticoid receptors, which animal models have suggested may lead to degeneration and necrosis of hippocampal neurons.[6] In contrast, hydrocortisone can bind to both classes of receptors due to its similar binding profile to native cortisol. This binding profile is the reason that hydrocortisone is the preferred anti-inflammatory agent for BPD.

Pharmacokinetics

Glucocorticoids are readily absorbed from the gastrointestinal tract with average oral bioavailability of 96%.[7] Hydrocortisone is highly protein bound with 80% bound to corticosteroid-binding globulin and approximately 10% bound to albumin, leaving only 5-10% unbound and therefore biologically active. Neonates and infants have hypoproteinemia, exacerbated by critical illness, which may result in higher concentrations of unbound drug. Hepatic metabolism occurs by 11-beta hydroxysteroid dehydrogenase. The resulting metabolites are

excreted in the urine and through the bile.[8] The effects of hydrocortisone administered intravenously are typically seen in adults within one hour of administration.[9]

A pharmacokinetic study of hydrocortisone in 62 critically ill neonates and infants (median gestational age 27 weeks and median postnatal age 0.7 weeks) found that population estimates for clearance and volume of distribution were 20.2 L/hr (95% CI 15.9-24.5) and 244 L (95% CI 160-328) respectively.[7] Using the median weight and postmenstrual age of their subjects (1.2 kg and 27 weeks), the typical unbound hydrocortisone clearance was 1.0 L/h with a volume of distribution of 4.2 L. This corresponded to a half-life for unbound hydrocortisone of 2.9 hours. The study found that there was a sharp and continuous increase in unbound hydrocortisone clearance at 35 weeks postmenstrual age.

Clinical Experience

Efficacy and Neurologic Outcomes

A Cochrane review examined the outcome of corticosteroids started within the first 7 days of life in 3750 preterm infants.[10] A similar review was performed in 1424 preterm infants with evolving chronic lung disease, examining the effects of late (>7 days) initiation of postnatal steroids.[11] Each of these analyses found that the use of steroids decreased rates of failure to extubate and decreased risks of chronic lung disease at both 28 days and 36 weeks postmenstrual age.

A subgroup analysis was performed by type of corticosteroid used in the early postnatal period which found that most of the beneficial effects on chronic lung disease were attributable to dexamethasone (typical risk ratio (RR) dexamethasone 0.85, 95% CI 0.79 to 0.92; 16 studies and 2621 infants; hydrocortisone 1.00, 95% CI 0.85 to 1.18; one study and 253 infants).[10] However, dexamethasone was also the main driver of the harmful effects with a higher incidence of hyperglycemia and gastrointestinal hemorrhage. Additionally, cerebral palsy (CP) and the combined outcome of death or CP were more common with dexamethasone but not hydrocortisone (CP typical RR dexamethasone 1.75, 95% CI 1.2 to 2.55; seven studies and 921 infants; hydrocortisone 0.97, 95% CI 0.55 to 1.69; five studies and 531 infants). Both agents were associated with a higher rate of gastrointestinal (GI) perforation and lower rates of PDA compared to placebo. The discordance amongst the size of the treatment groups makes comparison analysis difficult, however, it suggests that neurological outcomes are impacted more by dexamethasone.

In 2015, Parikh and colleagues reported the results of their randomized parallel group double-blind trial comparing a tapering 7-day course of stress dose hydrocortisone to saline placebo.[4] A total of 57 extremely low birth weight infants (median gestational age 25 weeks) between the ages of 10 and 21 days were eligible, 28 of whom were given hydrocortisone sodium succinate 3 mg/kg/day for the first 4 days, 2 mg/kg/day for 2 days, and 1 mg/kg/day for the final day, with preference for the IV route of administration. The primary outcome measure was a composite of mortality and survival with neurodevelopmental impairments (defined as one of the following: cognitive delay, language delay, cerebral palsy, hearing loss, and bilateral blindness). Of those in the hydrocortisone treatment arm at 18 to 22 months (n=28), 68% died or survived with impairment compared with 76% in the placebo arm (n=29) (RR 0.83; 95% CI 0.61-1.14). Although also not statistically significant, the rates of cognitive delay (defined as cognitive score < 80 on the Bayley Scales of Infant and Toddler Development, Third Edition) was 21% (4/19) in the hydrocortisone arm and 47% (8/17) in the placebo arm (RR 0.46; 95% CI 0.18 to 1.17). The rates of death were also lower in the hydrocortisone group, 31% in the hydrocortisone group vs 41% in the placebo group, although this difference was not significant (P= 0.42).

Renault and colleagues compared treatment rates between two institutions, one of which had a permissive policy with routine use of hydrocortisone (Center P) versus another that had a restrictive policy where corticosteroid use was strongly discouraged (Center R).[12] This retrospective study included premature infants (<27 weeks gestation) who were requiring mechanical ventilation at 14 days of life. Center P consisted of 62 infants (median age 16 days), 92% of whom received hydrocortisone at a median (IQR) cumulative dose of 27.2 (26.2-52.5) mg/kg. Center R consisted of 48 infants (median age 36.5 days), only 13% of whom received betamethasone at a median dose (IQR) of 3.0 (3.0-3.0) mg/kg. The rate of BPD was significantly lower in Center P (30% vs 71%, p<0.001) with significantly shorter duration of non-invasive ventilation. Poor neurodevelopmental outcomes at two years of corrected age occurred in 9 of the 51 assessed infants (18%) at center P compared with 11 of 27 assessed infants (30%) at Center R (p=0.18), however there was a difference in height Z-

scores with a median of -0.1 and 0.6 for center P and R respectively (P=0.055).

A longer hydrocortisone treatment in ELBW infants was examined at Rush University Medical Center. Their cohort consisted of 175 infants, 86 on hydrocortisone and 89 steroid naïve, who were assessed at 8 and 20 months in terms of their comparative mortality, morbidity, and neurodevelopmental outcome.[13] Indications for hydrocortisone included: persistent hypotension despite dopamine (8%) and inability to successfully wean from mechanical ventilation (88%). Patients received up to a maximum daily dose of 3 mg/kg divided every 8 hours and had a wean initiated at 2-5 days of treatment. Outcome measures included neurologic exam and results of the Bayley Scales of Infant and Toddler Development-III (BSITD-III). BSITD-III outcome measures include: cognitive, language and motor index scores. The mean for index scores is 100 ± 15. The median age at treatment duration was 14 days, with treatment initiated in 48% of infants at <14 days of life. The median total duration of treatment was 43 days (25^{th}-75^{th} percentile: 24-61.5). Patients in the hydrocortisone group had significantly lower motor mean index scores at 8 months (87 $\pm$ 18 vs 95 $\pm$ 15; P<0.05) and a higher percentage with a subnormal motor index (44 vs 15% P<0.01). No differences were found in neurodevelopmental outcome between the treatment groups at 20 months. Multivariate analysis demonstrated that length of hydrocortisone exposure was associated with worse fine motor performance at 8 months, with those exposed >7 days having significantly worse motor skills (P<0.05). Each additional day of hydrocortisone exposure increased the risk of both subnormal expressive language and subnormal motor scores by 2%.

New Directions

Recently, Baud and colleagues initiated the discussion of steroids and BPD once more, focusing the attention away from the long-term neurodevelopmental studies that had become more the standard when discussing the use of steroids in BPD, and instead returning to the efficacy of low-dose hydrocortisone for the prevention of BPD.[14] This double-blind, placebo-controlled, randomized trial enrolled 521 neonates <28 weeks of gestation and utilized a hydrocortisone dose of 1 mg/kg/day divided every 12 hours for 7 days, followed by 0.5 mg/kg/day for 3 days. The cumulative dose of 8.5 mg/kg is the lowest used thus far in preterm neonates for this indication. Early ibuprofen and glucocorticoids were not permitted during the treatment course.

The primary outcome, survival without BPD at 36 weeks, occurred in significantly more infants assigned to hydrocortisone (153/255; 60%) than placebo (136/266; 51%) (odds ratio [OR] adjusted for gestational age group and interim analyses 1.48, 95% CI 1.02-2.16, p=0.04). This effect was more pronounced in infant girls (65% girls on hydrocortisone vs 53% of girls on placebo). More infants on hydrocortisone were extubated on day 10 (60% vs 44%, OR 2.07, p=0.0002) and they were less likely to require PDA ligation (15% vs 21%, OR 0.63, p=0.03). These benefits coincided with no significant differences in other adverse effects such as GI perforation, necrotizing enterocolitis, or late-onset sepsis. Unfortunately, due to financial considerations by the funder, the trial by Baud and colleagues stopped enrollment prematurely, truncating the procedure for sequential analysis.

The approach used by Baud and colleagues focused on prevention of BPD rather than delaying treatment until clinically necessary, at which point the benefit of steroids may not be fully achieved. This trial has been referred to as a supplementation therapy trial[15] with its low doses focused on maintenance of cortisol in a normal range. While these results re-fuel interest in the early use of hydrocortisone, the withdrawal of support by the funding agency prevented recruitment of the intended number of patients. Additionally, long-term outcomes of this dosing strategy and treatment initiation at less than 24 postnatal hours have not been assessed.

Adverse Effects

Watterberg and colleagues were forced to end enrollment of their study examining a 15 day course of hydrocortisone to 360 ELBW infants due to an increase in spontaneous gastrointestinal perforation in study subjects (17 patients [9%] on hydrocortisone vs 4 patients [2%] on placebo).[16] This significant risk was seen predominantly in patients also receiving indomethacin. Other reviews have demonstrated that while there is an increase in gastrointestinal bleeding with steroid use, this difference is not statistically significant.[10, 11] Other adverse effects of concern with the systemic use of corticosteroids include hyperglycemia, hypertension, and infection.

Drug Interactions

Drugs that induce hepatic enzymes, such as barbiturates, phenytoin, and carbamazepine, may enhance the metabolism of hydrocortisone. The co-administration of hydrocortisone and warfarin may decrease the degree of anticoagulation secondary to inhibition of the response to

warfarin. Patients requiring potassium-depleting agents should be observed closely for development of hypokalemia.[9] Use of nonsteroidal anti-inflammatory drugs increases the risk of gastrointestinal effects such as intestinal perforation.[16]

Availability and Dosing Recommendations

Hydrocortisone is available as an injectable solution (Solu-CORTEF), which comes in 100 mg (50 mg/mL), 250 mg (125 mg/mL), 500 mg (125 mg/mL), 1 g (125 mg/mL) vials. These ACT-O-VIAL® systems are single use and do not contain any preservatives. There is also a 100 mg vial that does not contain diluent, and includes preservatives. Oral doses include 5 mg, 10 mg, and 20 mg tablets, and a 2 mg/mL oral solution. Hydrocortisone may be administered with food to decrease the possibility of GI upset. When possible, administering doses earlier in the day may help to prevent sleep interference.

The preferred dose of hydrocortisone in neonates and infants at risk for BPD has not been established. Studies suggest that lower doses, similar to those used for physiologic replacement, are effective and suggest that these doses do not carry risk of poor long-term neurodevelopmental outcomes. The literature supports cumulative hydrocortisone doses of 8-20 mg/kg.[4,14] Limiting treatment to shorter courses is preferable, with treatment durations longer than 14 days demonstrating negative outcomes.[13] Treatment courses lasting longer than 7 days should be tapered, rather than stopping therapy abruptly.

Summary

While progress has been made in the treatment and prevention of BPD, the prevalence has not decreased. Hydrocortisone's mineralocorticoid and glucocorticoid properties are beneficial in decreasing inflammatory processes that may be harmful to the developing lung. Studies indicate that hydrocortisone improves BPD-free survival and may decrease ventilation time.[4,12,14] Hydrocortisone appears to be a safer alternative to dexamethasone, which historically demonstrated efficacy in the prevention of BPD, but was associated with short- and long-term adverse effects that may outweigh its benefit.

Additional studies are needed to further investigate the preferred dosing, time of initiation, and duration of therapy of hydrocortisone for prevention of BPD in extremely preterm infants. Continued follow-up from studies utilizing smaller, supplemental doses will be beneficial to dispel the association between hydrocortisone and poor neurologic outcomes as infants develop.

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