Hydrocortisone Dosing for Hypotension in Newborn Infants: Less Is More

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Debate surrounds all aspects of hypotension in newborn infants, including the definition, the questions of whether and when to treat it, the choice of treatments, and their possible benefits and risks.[1,2] To date, no randomized trials have evaluated the long-term risks and benefits of any of these treatment strategies. Despite this, hydrocortisone has become widely used to treat hypotension in critically ill newborn infants.[3] Low cortisol concentrations in critically ill newborns have been associated with several markers of illness, including the use of surfactant, positive pressure ventilation, and vasopressors, as well as with vasopressor-resistant hypotension.[4-7] Furthermore, hydrocortisone treatment of newborn infants with hypotension results in an increase in blood pressure, suggesting that one etiology of hypotension in these infants may be relative adrenal insufficiency.[7-10] If so, hydrocortisone would be a more suitable treatment for these patients than vasopressors. Whether or not that is the case, hydrocortisone has been shown to increase the blood pressure of most patients in this population, particularly in patients with vasopressor-resistant hypotension.[8-10] Despite uncertainties about long-term benefits and risks, the demonstrated efficacy of hydrocortisone has been a strong stimulus for its use.

Although hydrocortisone may be a reasonable therapeutic choice, data to guide its dosing in this population are very limited. Several factors complicate the acquisition of useful data, including: (1) hydrocortisone is identical to native cortisol, limiting our ability to differentiate endogenous from exogenous hormone; (2) only free cortisol is active, but only total cortisol is usually measured; (3) cortisol is secreted in a pulsatile manner, which can result in variable serum concentrations over a short period of time; and (4) serum concentrations are a result of production and elimination; thus, high concentrations in critically ill patients may be the result of increased production, decreased metabolism, and/or decreased excretion.

The paucity of pharmacokinetic data has resulted in the use of a broad range of "stress doses" to treat hypotensive newborn infants, ranging from 20-100 mg/m^2/d.[11,12] One protocol, for example, described using 45 mg/m^2/d as "3 × the dose accepted as physiologic in general practice,"[13] and another used a dose of 1 mg/kg every 8 hours "to simulate endogenous physiologic secretion of cortisol under stressful situations (1.22 ± 0.22 mg/kg/d "physiologic" secretion of cortisol × [3-5 times] for patients under stress)."[8] Administration of these "stress doses" may result in unnecessary excess hydrocortisone exposure in newborn infants, particularly in extremely preterm newborns, resulting in adverse consequences. Several lines of evidence from human studies supporting this statement are discussed below: (1) humans have a lower cortisol production rate than previously thought; (2) hydrocortisone has a prolonged half-life in newborns; (3) stress doses of hydrocortisone result in high serum cortisol concentrations; (4) lower doses have been shown to result in an increase in blood pressure; and (5) excess glucocorticoid exposure has adverse effects. This discussion is followed by a suggested pragmatic approach to hydrocortisone dosing in this population.

First, humans appear to have a lower rate of endogenous cortisol production, both basal and in response to critical illness, than previously thought. Although the basal production rate was described in 1966 by Kenney et al[14] to be about 12 mg/m^2/d in children and adults, and higher in newborns, studies using newer techniques have found production to be considerably lower, about 5-7 mg/m^2/d in adults and children, and 2-5 mg/m^2/d in preterm infants less than 30 weeks gestation.[15-17] Furthermore, a new study using an isotope tracer in critically ill adults found that the increase in production during critical illness may be less than 2 times basal production, rather than 3- to 5-fold as previously estimated.[18] In that study, higher serum concentrations in critically ill patients were due in large part to decreased clearance, rather than increased production.[18] The authors also found reduced inactivation of cortisol in the liver and kidney, which contributed to higher concentrations. This phenomenon could be particularly relevant to newborns.

Second, newborn infants have a longer hydrocortisone serum half-life than children or adults. Previously, very limited data indicated a prolonged serum half-life following hydrocortisone administration in newborn infants: approximately 3.5-4 hours in term infants and more than twice that long in preterm infants, compared with less than 2 hours in adults.[19-22] These data were considerably strengthened by a population pharmacokinetic study of hydrocortisone in infants treated for vasopressor-resistant hypotension.[13] In this study, unbound hydrocortisone concentrations were measured in 62 infants with a median gestational age of 28 weeks (range 23-41) and postnatal age of 5 days (range 1-65). Using a 1-compartment model, the authors reported that the "typical half-life for unbound hydrocortisone" was

BPD	Bronchopulmonary dysplasia
ELBW	Extremely low birth weight
RCT	Randomized controlled trial

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The author declares no conflicts of interest.

http://dx.doi.org/10.1016/j.jpeds.2016.04.005

2.9 hours and that a "sharp and continuous increase in unbound hydrocortisone clearance was observed at 35 weeks gestational age; therefore, older infants are expected to have a shorter unbound hydrocortisone half-life." Their typical half-life of 2.9 hours (174 minutes) was 3-fold longer than the median 61-minute half-life reported for free hydrocortisone in normal adult volunteers after dexamethasone suppression.[23] These data are not surprising, as newborn infants commonly have much longer half-lives than adults for drugs that undergo renal and/or hepatic clearance.[24]

Third, commonly used stress doses are likely to result in very high serum concentrations. Serum cortisol in healthy adults has a circadian rhythm, with a morning peak of ~10-20 mcg/dL.[25] Higher concentrations and loss of circadian rhythms are seen in critically ill adults, with mean values generally reported in the range of 20-30 mcg/dL.[18,25,26] In clinically well preterm infants less than 31 weeks gestation, median values in the first postnatal week have been reported in the range of 5-9 mcg/dL.[27,28] Somewhat higher values have been reported in sick preterm infants, with median values of about 8-12 mcg/dL in small studies.[28,29] In a large study of serum cortisol concentrations in sick extremely low birth weight (ELBW) infants, median values were 16 mcg/dL at less than 48 postnatal hours (n = 265), and 13 mcg/dL at the end of the first postnatal week (n = 124).[10] Similar values have been noted in small studies of hypotensive term and late preterm infants (median of 5-13 mcg/dL).[6,30]

Administration of hydrocortisone at "stress doses" substantially increases these typical serum concentrations in both adults and infants. In one study of critically ill adults, a 10 mg/h hydrocortisone infusion (total daily dose 240 mg, ~3 mg/kg) resulted in a rise in serum cortisol from a mean pre-infusion baseline of 30 mcg/dL to a post-dose mean of 121 mcg/dL at steady state.[26] In another study, a 100 mg total hydrocortisone dose administered to normal volunteers after dexamethasone suppression resulted in peak values of approximately 100 mcg/dL.[22]

In 8 term newborn infants, a 1-time dose of 5 mg/kg resulted in an average peak serum concentration of 577 mcg/dL (range 507-675 mcg/dL).[19] The mean half-life for hydrocortisone in that study was about 3.5 hours, suggesting that serum concentrations may have remained above 20 for almost 18 hours. Similar data have been reported in extremely preterm infants. In one pilot study of 6 ELBW infants treated with hydrocortisone at 0.4 mg-0.8 mg/kg/dose, 5 of 6 trough concentrations remained above 20 mcg/dL at 8-12 hours.[20] In the pharmacokinetic study of unbound hydrocortisone discussed above, the population estimate for baseline unbound hydrocortisone concentration was 1.37 ng/mL; values at variable times after a hydrocortisone dose of 45 mg/m^2/d divided q 6 hours were greater than 10 times higher than baseline in most infants.[13] Finally, in a randomized controlled trial (RCT) of early hydrocortisone treatment to prevent bronchopulmonary dysplasia (BPD), ELBW infants were treated with 0.5 mg/kg/dose q 12 hours (~8-10 mg/m^2/d). After ≥5 doses, serum samples were obtained in 130 infants at variable time points, which revealed a median cortisol value of 18 mcg/dL (25th-75th percentile: 12-40), 5 mcg/dL higher than the median in the placebo-treated infants (n = 124), with wide individual variation.[10] It was not possible to ascertain the contributions of endogenous cortisol and exogenous hydrocortisone to the total concentrations observed.

Fourth, hydrocortisone given at lower doses can achieve an increase in blood pressure. One RCT in 48 very low birth weight preterm infants with vasopressor resistant hypotension showed a significant increase in blood pressure with a hydrocortisone dose of 3 mg/kg/d,[8] prompting many practitioners to use that dose; however, lower doses have also been shown to be effective. A small RCT of hydrocortisone to prevent hypotension in ELBW infants used a dose of 2 mg/kg/d and found that by postnatal day 2 only 7% of the hydrocortisone group were receiving vasopressors compared with 39% of the placebo group ($P < .05$).[9] The large RCT of hydrocortisone to prevent BPD discussed above showed a significantly higher blood pressure in the hydrocortisone-treated group compared with placebo, using a dose of 0.5 mg/kg every 12 hours ($P = .02$ for area under the curve).[10]

Fifth, and most importantly, there are clear adverse consequences from sustained exposure to high concentrations of glucocorticoid, making it prudent to use the lowest effective dose. For example, in adults maintained on long-term hydrocortisone therapy for pituitary insufficiency, higher maintenance doses of hydrocortisone (>30 mg/d or >0.35 mg/kg/d) have been associated with increased mortality.[31,32] In preterm infants, early dexamethasone treatment for BPD has been associated with serious short- and long-term adverse effects, including growth restriction and neurodevelopmental impairments.[33] High doses of hydrocortisone also may have adverse effects. For example, a recent study reported a high incidence of oliguria (24%) and low blood pressure during weaning of hydrocortisone in 54 very low birthweight infants being treated for hypotension or ventilator dependence.[34] The mean starting dose of hydrocortisone in these infants was 2.8 ± 1 mg/kg/d, and infants who developed oliguria had been exposed to higher doses and a longer duration of therapy, suggesting suppression of adrenal function. In contrast, a dose of 0.5 mg/kg every 12 hours for 12 days followed by 0.5 mg/kg every day for 3 days did not suppress adrenal function, confirmed by adrenocorticotropin hormone testing 3 days after completion of therapy.[35] Follow-up of 411 children enrolled in RCTs using lower doses of hydrocortisone (1-2 mg/kg/d) did not show adverse effects on growth or neurodevelopment at 18-22 months adjusted age.[36,37] However, one RCT has reported follow-up of 35 children at school age, which showed "nonsignificant correlation between early hydrocortisone treatment and later neurocognitive impairment," emphasizing the continuing need for long-term follow-up.[38]

As described above, data are still limited, and, unfortunately, RCTs of antihypotensive therapies have proven difficult to conduct.[39] Despite the clear need for these types of studies,[1] such difficulties may hinder their successful