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Population pharmacokinetics of unbound hydrocortisone in critically ill neonates and infants with vasopressor-resistant hypotension

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Abstract

Objective—To determine the population pharmacokinetics of unbound hydrocortisone (HC) in critically ill neonates and infants receiving intravenous HC for treatment of vasopressor-resistant hypotension and to identify patient-specific sources of pharmacokinetic variability.

Design—Prospective observational cohort study.

Setting—Level 3 neonatal intensive care unit.

Patients—Sixty-two critically ill neonates and infants receiving intravenous HC as part of standard of care for the treatment of vasopressor-resistant hypotension: median gestational age 28 weeks (range, 23 to 41), median weight 1.2 kg (range, 0.5 to 4.4), 29 females.

Interventions—None.

Measurements—Unbound baseline cortisol and post-dose HC concentrations measured from blood samples being drawn for routine laboratory tests.

Main Results—A one compartment model best described the data. Allometric weight and postmenstrual age (PMA) were significant covariates on unbound HC clearance (CL) and volume of distribution (V). Final population estimates for CL, V, and baseline cortisol concentration were 20.2 L/h, 244 L, and 1.37 ng/mL, respectively. Using the median weight and PMA of our subjects (i.e. 1.2 kg and 28 weeks) in the final model, the typical unbound HC CL and V were 1.0 L/h and 4.2 L, respectively. The typical half-life for unbound HC was 2.9 hours. A sharp and continuous increase in unbound HC CL was observed at 35 weeks PMA.

Conclusions—We report the first pharmacokinetic data for unbound HC, the pharmacologically active moiety, in critically ill neonates and infants with vasopressor-resistant hypotension. Unbound HC CL increased with body weight and was faster in children with an older PMA. Unbound HC CL increased sharply at 35 weeks PMA and continued to mature thereafter. This study lays the groundwork for evaluating unbound HC exposure-response relationships and drawing definitive conclusions about the dosing of intravenous HC in critically-ill neonates and infants with vasopressor-resistant hypotension.

Keywords

neonates; infants; hydrocortisone; unbound; hypotension; pharmacokinetics

INTRODUCTION

Critically ill premature and full-term neonates and infants are at high risk of morbidity and mortality due in part to the inability of the immature hypothalamic-pituitary-adrenal (HPA) axis to mount an adequate cortisol response (1-4). Conditions in the perinatal period that may further contribute to morbidity and mortality include sepsis, chorioamnionitis, respiratory distress, and chronic lung disease all of which are characterized by an underlying inflammatory process (5-8). In addition, systemic hypotension is common in this patient population and has been associated with cardiovascular instability and death (1, 2, 9).

The normal gestational and postnatal age-dependent blood pressure range is unknown; however, in clinical practice and research settings systemic hypotension is frequently defined as mean arterial blood pressure (MAP) below the 5th or 10th percentile of normative data for gestational age, postnatal age, and weight (10). Standard empiric treatment for systemic hypotension consists of volume expansion and blood pressure support. In many patients hypotension and poor perfusion persist despite the receipt of adequate fluids and the use of two or more vasopressor agents (i.e. dopamine and dobutamine).

Vasopressor-resistant hypotension in neonates and infants is often associated with relative adrenal insufficiency (RAI) and adrenergic receptor downregulation due to critical illness complicated by an immature HPA axis (11-14). While the presence of RAI is well recognized, its definition remains controversial (15-17). There is no consensus on what constitutes a low cortisol level in this population and consequently values of total plasma cortisol ranging from 5 to 15 mcg/dL are often used to define RAI (15, 18, 19). In adults, treatment with low-dose exogenous intravenous (IV) hydrocortisone (HC) reduces the need for vasopressors by increasing blood pressure and improving cardiovascular function and outcomes (20). It should be noted that cortisol and HC are structurally identical; therefore, we refer to the endogenous glucocorticoid as cortisol and the exogenously administered glucocorticoid as HC. Treatment of vasopressor-resistant hypotension with IV HC is also the standard of care in neonates and infants because of its perceived efficacy and lack of neurodevelopmental side effects (21, 22). However, the doses are highly variable and dosing strategies differ across institutions. In a recent meta-analysis of IV HC for vasopressor resistant hypotension in premature infants the effects of HC on increasing blood pressure and decreasing vasopressor requirements were determined to be robust even though the

actual clinical benefits of these effects remain unknown. The long-term sequelae of IV HC administration have yet to be fully elucidated (23). Furthermore, total plasma cortisol concentrations are used to determine the extent of adrenal insufficiency and to guide IV HC dosing in most studies published to date. Hydrocortisone is highly bound to corticosteroid-binding globulin ($\approx 80\%$) and albumin ($\approx 10\%$) with only 5 to 10% unbound and biologically active (24). Neonates and infants experience hypoproteinemia by virtue of their age as well as their critical illness, which could result in higher concentrations of unbound HC (16, 17, 25). Dosing IV HC based on total plasma cortisol concentrations may underestimate or overestimate the amount of exogenous glucocorticoid needed and lead to ineffective treatment regimens or adverse effects in an already vulnerable population.

The pharmacokinetics of unbound plasma HC in critically ill premature and full-term neonates and infants receiving treatment for vasopressor-resistant hypotension are unknown. Our group previously developed a liquid chromatography mass spectrometry method to measure unbound plasma HC in this patient population and evaluate drug disposition (26). The objectives of the present study were to determine unbound HC plasma pharmacokinetics during receipt of IV HC and to identify patient-specific characteristics associated with variability using a population analysis approach. An improved understanding of the disposition of unbound HC in critically ill neonates and infants could lead to better IV HC dosing strategies and outcomes for the treatment of vasopressor-resistant hypotension.

MATERIALS AND METHODS

Subjects and Study Design

This study was conducted between September 2005 and August 2008. The study was approved by the Institutional Review Board at the University of Michigan and qualified for waiver of consent. Residual plasma from blood samples already being collected for routine laboratory tests before and during IV HC treatment were used for this study. Critically ill premature and full-term neonates and infants in the Mott Children's Hospital Neonatal Intensive Care Unit (NICU) receiving stress and maintenance doses of IV HC as standard of care for the treatment of vasopressor-resistant hypotension secondary to RAI according to a predetermined protocol were included. Vasopressor-resistant hypotension was defined as severe hypotension (MAP $\leq$ gestational age in the first week of life or resulting in inadequate end organ perfusion defined as urine output < 0.5 mL/kg/h for > 3 hours during an 8 hour period) despite dopamine and/or dobutamine therapy at doses of 20 mcg/kg/min. Relative adrenal insufficiency was defined as a total plasma cortisol concentration < 5 mcg/dL as measured by the hospital's Clinical Laboratory. Intravenous HC was administered as a bolus according to a standard clinical protocol in place in the NICU during the study period (Figure 1) (27). Briefly, baseline total serum cortisol concentrations were measured prior to administration of the first stress dose of IV HC. The baseline concentration was used to determine the extent of adrenal dysfunction, and to guide the maintenance dose regimen following stress dose treatment for the first 48 hours. A total cortisol concentration < 5 mg per 100 mL at baseline or at the scheduled check time during administration of IV HC was considered adrenal insufficiency. The IV HC stress dose was

defined as 45 mg/m² per day (3 times the dose accepted as physiologic in general practice) divided every 6 hours. The stress dose was administered for the first 48 hours regardless of baseline total cortisol concentration. The IV HC maintenance dose was 15 mg/m² per day divided every 6 hours. After completing the first 48 hours of treatment with the stress dose, infants were either placed on maintenance dose regimens or IV HC was discontinued. Infants in the 5 to 15 mg per 100 mL baseline total cortisol concentration group had total cortisol concentrations re-evaluated 12 hours after the end of the stress dose. If the concentration was < 5 mg per 100 mL and/or if the infant was hemodynamically unstable, the maintenance regimen was started; otherwise, IV HC was discontinued. Infants on maintenance dosing were evaluated once per week to determine continued need. Two doses of IV HC were withheld on a Sunday evening and a total cortisol concentration was measured on a Monday morning. If the concentration was > 5 mg per 100 mL then the weaning schedule was instituted provided that the infant was hemodynamically stable. The weaning schedule consisted of 50% of the maintenance dose divided every 6 hours for 24 hours followed by 25% of the maintenance dose divided every 6 hours for 24 hours. Neonates and infants were not included in the study if they had major congenital abnormalities such as cyanotic congenital heart disease, lesions involving the left ventricular outflow tract, and apparent end organ unresponsiveness secondary to adrenal glucocorticoids (i.e. vasopressor-resistant hypotension despite adequate cortisol production).

Residual plasma samples from the baseline cortisol measurement and from up to 3 post-dose blood samples drawn for routine laboratory tests were obtained for each patient. Plasma samples were batched and frozen until the time of analysis. For each post-dose blood sample, the draw time and IV HC dosing history including the dose, and the date and time of the last dose were recorded. Additional clinical data were collected from each patient's medical record and included sex, gestational age, postnatal age (i.e. chronological age) at treatment, treatment weight, serum creatinine, liver function tests, and concomitant medications including vasopressor therapy. Postmenstrual age was calculated as the sum of gestational age and postnatal age at treatment.

Quantification of Unbound Hydrocortisone in Plasma

Unbound HC concentrations were measured using a liquid chromatography tandem mass spectrometry with protein ultrafiltration method developed for this study by Medtox Laboratories (St. Paul, Minnesota) (26). The assay was validated over a concentration range of 0.5 to 1000 ng/mL. The assay's lower limit of quantification (LLOQ) was 0.5 ng/mL (or 0.05 mcg/dL). Accuracy and precision at the LLOQ was 116% and within 3.4%, respectively. The mean internal standard recovery was 97.3% and analyte recovery ranged from 86.2 to 91.2%. Within and between assay variability expressed as a coefficient of variation (CV%) was 6.8% and 9.3%, respectively.

Population Pharmacokinetic Analysis

Unbound HC pharmacokinetic parameters were determined by nonlinear mixed-effects modeling (NONMEM® version 7.2 with PDx-PoP® version 5.0, Icon Development Solutions, Ellicott City, MD). Pharmacokinetic parameter estimates (i.e. clearance and volume of distribution terms) and estimates of interindividual and residual variability were

obtained using the first order conditional estimation with interaction method (FOCE-I). Several pharmacokinetic structural models were fit to the concentration-time data including one- and two-compartment IV bolus models with baseline cortisol concentrations incorporated as a constant and by fitting a circadian rhythm function. A circadian rhythm function was tried because cortisol follows a diurnal pattern in adults and older children and this rhythmicity was identified recently in newborn infants hospitalized in a NICU (28-31). Interindividual variability in the pharmacokinetic parameters was described using an exponential error model in the form:

$$P_i = \theta_j \exp(\eta_{ij})$$

where P_i is the parameter estimate for the individual patient i ; θ_j is the typical population value of the pharmacokinetic parameter j ; and η_{ij} is the interindividual variability for the individual patient i and parameter j . Residual variability (e.g. analytical errors, dosing history errors) was evaluated using additive, proportional, and combined (additive and proportional) error models. During structural model development, the likelihood ratio test, which is approximately χ^2 distributed, was the primary statistic used to compare two nested models. In maximum likelihood regression, the objective function value (OFV) is a type of sum of squares and is used as a measure of goodness of fit. During structural model development, a change in the OFV of 3.84 units ($p < 0.05$, $df = 1$) was considered statistically significant.

After the pharmacokinetic structural model was identified, potential sources of biologic variability in unbound HC pharmacokinetic parameters (i.e. covariates) were evaluated. Available covariate data consisted of the continuous variables weight in kilograms, gestational age (GA) in weeks, postnatal age (PNA) in weeks, and postmenstrual age (PMA) in weeks, and the categorical variables sex, renal function (i.e. serum creatinine $\leq$ or > 1.1 mg/dL), and dose type (i.e. stress or maintenance). Liver function test results were unavailable for approximately 25% of the population and could not be evaluated as a covariate. Covariate models were developed by assessing the clinical importance of the covariate, visually inspecting plots of covariate-parameter relationships, and likelihood ratio testing during the standard process of stepwise forward inclusion and backward elimination. During stepwise forward inclusion and backward elimination, a change in the OFV of 10.8 units was regarded as significant ($p < 0.001$, $df = 1$). Briefly, during forward inclusion covariates were added to the model one at a time, checked for significance, and removed. The covariate that produced the largest statistically significant drop in objective function value was retained in the model and forward inclusion was repeated until no significant covariates remained. A full model with all significant covariates from forward inclusion was constructed. During backward elimination covariates in the full model were removed one at a time, checked for significance, and added back. The covariate with the smallest impact was removed and backward elimination was repeated until removal of any other covariate resulted in a statistically inferior model. In the present analysis the impact of body size (i.e. weight) was examined first using an allometric model:

$$TVP = \theta_j \cdot (WT_i / WT_{ref})^{\theta_{allo}}$$

where TVP is the typical value of a pharmacokinetic parameter described as a function of body weight; θ_j is an estimated pharmacokinetic parameter describing the typical value for an individual patient with weight equivalent to WT_{ref} ; WT_i is the weight of the individual patient i ; WT_{ref} is the reference weight of 70 kg; and θ_{allo} is the allometric exponent that takes on a value of 0.75 when modeling clearance terms and 1.0 when modeling volume of distribution terms (32-34). After incorporating body size, relationships with age and categorical covariates were investigated.

Throughout model development, model comparisons were based on changes in OFV, standard goodness-of-fit plots, and precision of the parameter estimates. Standard goodness-of-fit plots included the observations versus the concentrations predicted under the regression model, the observations versus the concentration predictions based on individual parameter estimates, and the distribution of residuals versus the concentration predictions and over time. The final model was selected by carefully evaluating all goodness-of-fit measures. The stability of the final model and the precision of the parameter estimates were evaluated by a bootstrap re-sampling technique. Briefly, each individual patient was randomly sampled with replacement from the original dataset to generate new datasets with the same number of patients as in the original dataset. The final model was applied to each of the bootstrap datasets to obtain bootstrap parameter estimates and standard errors. The results from 1000 bootstrap runs were obtained, and the median and 95% confidence intervals were determined and compared with the final parameter estimates and 95% confidence intervals from the original dataset.

RESULTS

Study Population

Residual plasma samples from 64 critically ill premature (n=39) and full-term (n=25) neonates and infants receiving IV HC for the treatment of vasopressor-resistant hypotension were available for the study. Sixty-two neonates and infants contributed suitable samples for the population pharmacokinetic analysis. Concentration data from 2 patients were excluded because only plasma from the baseline cortisol measurement was collected. The median (range) baseline demographic characteristics for the 62 patients included in the study are summarized in Table 1. The median (range) stress and maintenance doses of IV HC administered to the patients were 1.4 (0.4 to 3.0) and 0.46 (0.2 to 1.0) mg/m²/day divided every 6 hours, respectively.

Unbound Hydrocortisone Population Pharmacokinetics

A total of 194 unbound HC concentrations from 62 neonates and infants were used in the population pharmacokinetic analysis. Four baseline cortisol concentrations drawn erroneously during IV HC administration were excluded. The unbound HC plasma concentration-time data used for model development are presented in Figure 2. A one-compartment model with first-order elimination best described these data. Baseline cortisol

modeled as a constant and added to the individual concentration predictions fit the data better than the circadian rhythm function. Interindividual variability was modeled exponentially for clearance (CL) and baseline cortisol but was fixed to zero for volume of distribution (V). It is not biologically plausible that there is no interindividual variability in V; however, the sparseness of the data made it difficult to reliably estimate this pharmacokinetic parameter for each patient. During the process of stepwise forward inclusion and backward elimination allometric weight and PMA modeled by an exponential function centered at the population median value of 28 weeks were found to be significant covariates on CL and V. None of the categorical covariates were statistically significant. There were also no covariate effects on baseline cortisol concentrations. The estimated population baseline unbound cortisol concentration was 1.37 ng/mL. Given these findings, the final pharmacokinetic model is as follows:

$$CL \text{ (L/h)} = 20.2 \cdot (\text{weight}/70)^{0.75} \cdot \exp^{(0.11 \cdot (PMA-28))}$$

$$V \text{ (L)} = 244 \cdot (\text{weight}/70) \cdot \exp^{(0.11 \cdot (PMA-28))}$$

Plots of the observations versus the concentrations predicted under the final regression model in and observations versus the concentration predictions based on individual parameter estimates are shown in Figure 3. Allometric weight and PMA accounted for 24.1% and 17.7% of the interindividual variability in CL, respectively; however, the remaining interindividual variability was still high at 54.1%. We further examined the change in unbound HC CL as a function of PMA (Figure 4). A sharp and continuous increase in CL was observed at approximately 35 weeks PMA. Residual variability was best described by a combined error model. The proportional and additive components of this variability were 57.3% and 0.049, respectively. Final pharmacokinetic and variability parameter estimates, relative standard errors, and 95% confidence intervals (CIs), as well as the median bootstrap estimates and 95% CIs are shown in Table 2. Successful estimation and covariance steps were achieved in 98% of the bootstrap runs indicating a robust model. Using the median weight and PMA of the study population (i.e. 1.2 kg and 28 weeks, respectively) in the final model, the typical unbound HC CL and V were 1.0 L/h and 4.2 L, respectively. The typical half-life for unbound HC was 2.9 hours.

DISCUSSION

Unbound cortisol is the effector molecule that binds to the HPA axis and influences the body's response to stress (35-37). Unbound cortisol concentrations may be more useful than total cortisol concentrations for identifying patients with vasopressor-resistant hypotension who may benefit from IV HC treatment and for following response to therapy. Despite this understanding, there is no information on cortisol pharmacokinetics in neonates and infants. To our knowledge this is the first report of the pharmacokinetics of unbound HC in premature and full-term critically ill neonates and infants under 3 months of age who had baseline cortisol measured and were receiving IV HC for the treatment of vasopressor-resistant hypotension. Given the blood sampling restrictions for this patient population, a

sparse sampling study design and population pharmacokinetic analysis were applied in this study. The final population pharmacokinetic model informs us that unbound HC clearance and volume of distribution increase with body size and postmenstrual age. Upon further examination of unbound HC clearance, a sharp and continuous increase was observed at 35 weeks postmenstrual age; therefore, older infants are expected to have a shorter unbound HC half-life compared with younger infants and neonates. This information could inform the clinical monitoring of unbound HC concentrations and the subsequent dosing of IV HC.

A one-compartment model with first order elimination adequately described the unbound HC concentration-time data from our study. Baseline cortisol concentrations were incorporated into the pharmacokinetic model as a constant and could not be modeled with a circadian rhythm function. This was not surprising because only one baseline cortisol measurement was available per patient and it was not always collected when diurnal changes in cortisol concentrations were expected. Iwata and colleagues identified recently a 24-h adrenal circadian rhythm in newborn infants in a NICU who were 2 to 11 days postnatal age (31). The investigators observed increases in salivary cortisol concentrations from 3 o'clock p.m. to approximately 9 o'clock p.m. and from 0 to approximately 6 hours after birth (31). Future investigations should consider these time windows when measuring cortisol concentrations in an attempt to capture diurnal variability.

In our population, the most important biological covariates for predicting unbound HC clearance and volume of distribution were body size (i.e. weight) and postmenstrual age. We chose to scale weight allometrically using well-established principles that fix the allometric exponents to 0.75 for clearance and 1.0 for volume of distribution and use a standard reference weight of 70 kg (32-34). Given that there are no published pharmacokinetic data for HC in neonates and infants, this approach allows us to compare our results to limited data reported previously in adults (38). Perogamvros and colleagues evaluated the role of corticosteroid-binding globulin on total and unbound cortisol and cortisone pharmacokinetics in serum and saliva after IV and oral HC administration to female adults (n=14) (38). Endogenous cortisol production was suppressed in all individuals prior to the study by administration of dexamethasone (38). Following IV HC administration to healthy participants (n=6), the median clearance and half-life of free cortisol were 202.8 L/h and 61 minutes, respectively (38). The clearance was 10-fold faster and the half-life almost 3-fold shorter compared with our findings in neonates and infants in whom the mean clearance scaled to an adult value was 20.2 L/h and the median half-life was 2.9 hours. It is not uncommon for premature and full-term neonates and infants to have 3- to 9-fold longer half-lives than adults for a range of drugs that undergo hepatic or renal elimination (39). This difference is reported to disappear by 2 to 6 months of age after which time, half-lives may be shorter compared with adults (39). All the subjects in our study were less than 3 months of age and we observed a sharp and continuous increase in unbound HC clearance at 35 weeks postmenstrual age. As clearance continues to mature, half-life values are expected to shorten and more closely resemble adult values. The mean volume of distribution for unbound HC in neonates and infants in our study was less than the reported median adult value (i.e. 244 L vs. 341.6 L), which is expected given the body size differences between groups (38).

No other biological covariates were statistically significant; however, after accounting for body size and age, over 50% of the interindividual variability in HC clearance was still unexplained. Additional covariates not available in this study that could be investigated in the future include corticosteroid binding protein and albumin concentrations, liver function tests, and host genetics related to protein binding and pathways responsible for HC metabolism. During critical illness there are significant changes in the amount and structure of circulating plasma proteins including corticosteroid binding protein and albumin that can influence the distribution of hydrocortisone (40, 41). Hydrocortisone also undergoes extensive hepatic metabolism by the 11-beta hydroxysteroid dehydrogenase system (11-beta HSD), which consists of 11-beta HSD1 and 11-beta HSD2, and 5-beta reductase and the resulting metabolites are excreted in urine and through the bile (42). It is plausible that these metabolic pathways are not fully developed in neonates and infants and could also exhibit genetic variation. Residual variability in our study was also high with the proportional error component estimated at just over 57%. This can be explained by the clinical nature of the study design, potential recording errors when IV HC dosing histories were obtained, and the dynamic underlying health of our patients that could not be captured by biological covariates.

These pharmacokinetic data are the first of their kind and provide rationale for investigating pharmacokinetic-pharmacodynamic relationships in critically ill neonates and infants receiving IV HC for vasopressor-resistant hypotension. We were also able to characterize the maturation of unbound HC clearance over the age range of the study population and identified an increase in clearance beginning at 35 weeks postmenstrual age. This may have important implications for the monitoring of unbound HC concentrations and the dosing of IV HC. The limitations of our research were its sparse sampling study design, particularly for evaluating diurnal variations in cortisol, and the limited number of biological covariates available for model development. We were also unable at this time to evaluate unbound HC exposure-response relationships because our data did not include pharmacodynamic outcomes. Future prospective studies that incorporate a more robust sampling strategy and novel, biologically-based covariates could identify new sources of variability in unbound HC pharmacokinetics that refine and expand upon our model. Evaluating relationships between unbound HC pharmacokinetics and pharmacodynamic outcomes such as mean arterial blood pressure or regional blood flow changes are useful next steps in assessing IV HC dosing strategies. Our long-term goal is to identify an optimal dosing regimen for IV HC in neonates and infants with vasopressor resistant hypotension and prospectively study the safety and efficacy of this approach.

Conclusions

In critically ill neonates and infants, IV HC is the most frequently used corticosteroid for the treatment of vasopressor-resistant hypotension because of its effectiveness and perceived lack of adverse neurodevelopmental outcomes; however, dosing is variable and regimens are derived from previous studies conducted in adults and older children. In order to draw definitive conclusions about efficacy and safety in this patient population, a solid understanding of HC pharmacokinetics and factors that affect pharmacokinetic variability is needed. We characterized the pharmacokinetics of unbound HC, the pharmacologically

active drug moiety, for the first time in critically ill neonates and infants with vasopressor-resistant hypotension. Importantly, unbound HC clearance increased with treatment weight and was faster in children with an older PMA. These findings are valuable for better understanding IV HC dosing regimens in critically ill neonates and infants. Given our data, prospective studies that investigate relationships between unbound HC pharmacokinetics and clinical response to IV HC treatment are warranted.

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References

1. Fernandez E, Schrader R, Watterberg KL. Prevalence of low cortisol values in term and near-term infants with vasopressor-resistant hypotension. *J Perinatol.* 2005; 25:114–118. [PubMed: 15526013]
2. Martins PG, Procianny RS. Cortisol and 17-alpha-hydroxy-progesterone concentrations in infants with refractory hypotension born at 30 weeks of gestation or less. *Braz J Med Biol Res.* 2007; 40:577–582. [PubMed: 17401502]
3. Scott SM, Cimino DF. Evidence for developmental hypopituitarism in ill preterm infants. *J Perinatol.* 2004; 24:429–434. [PubMed: 15129226]
4. Huysman MW, Hokken-Koelega AC, De Ridder MA, et al. Adrenal function in sick very preterm infants. *Pediatr Res.* 2000; 48:629–633. [PubMed: 11044483]
5. Scott SM, Watterberg KL. Effect of gestational age, postnatal age, and illness on plasma cortisol concentrations in premature infants. *Pediatr Res.* 2000; 48:629–633. [PubMed: 11044483]
6. Watterberg KL, Gerdes JS, Cook KL. Impaired glucocorticoid synthesis in premature infants developing chronic lung disease. *Pediatr Res.* 2001; 50:190–195. [PubMed: 11477202]
7. Watterberg KL, Gerdes JS, Gifford KL, et al. Prophylaxis against early adrenal insufficiency to prevent chronic lung disease in premature infants. *Pediatrics.* 1999; 104:1258–1263. [PubMed: 10585975]
8. Watterberg KL, Scott SM, Naeye RL. Chorioamnionitis, cortisol, and acute lung disease in very low birth weight infants. *Pediatrics.* 1997; 99:E6. [PubMed: 9099763]
9. Matthews TJ, Maenacker F, MacDorman MF, et al. Infant mortality statistics from the 2000 period linked birth/infant death data set. *Natl Vital Stat Rep.* 2002; 50:1–28.
10. Cunningham S, Symon AG, Elton RA, et al. Intra-arterial blood pressure reference ranges, death and mortality in very low birth weight infants during the first seven days of life. *Early Hum Dev.* 1999; 56:151–165. [PubMed: 10636594]
11. Cooper MS, Stewart PM. Corticosteroid insufficiency in acutely ill patients. *N Engl J Med.* 2003; 348:727–734. [PubMed: 12594318]
12. Annane D, Bellissant E, Bollaert PE, et al. Corticosteroids for severe sepsis and septic shock: a systematic review and meta-analysis. *BMJ.* 2004; 329:480. [PubMed: 15289273]
13. Hausdorff WP, Caron MG, Lefkowitz RJ. Turning off the signal: desensitization of beta-adrenergic receptor function. *FASEB J.* 1990; 4:2881–2889. [PubMed: 2165947]
14. Collins S, Caron MG, Lefkowitz RJ. Regulation of adrenergic receptor responsiveness through modulation of receptor gene expression. *Annu Rev Physiol.* 1991; 53:497–508. [PubMed: 2042970]
15. Bouchier D, Weston PJ. Randomized trial of dopamine compared with hydrocortisone for the treatment of hypotensive very low birth weight infants. *Arch Dis Child Fetal Neonatal Ed.* 1997; 76:174–178.

16. Hamrahian AH, Oseni TS, Arafah BM. Measurements of free cortisol in critically ill patients. *N Engl J Med*. 2004; 350:1629–1638. [PubMed: 15084695]
17. Rokicki W, Forest MG, Loras B, et al. Free cortisol of human plasma in the first three months of life. *Biol Neonate*. 1990; 57:21–29. [PubMed: 2302434]
18. Tantivit P, Subramanian N, Garg M, et al. Low serum cortisol in term newborns with refractory hypotension. *J Perinatol*. 1999; 19:352–357. [PubMed: 10685256]
19. Fernandez E, Schrader R, Watterberg K. Prevalence of low cortisol values in term and near-term infants with vasopressor-resistant hypotension. *J Perinatol*. 2005; 25:114–118. [PubMed: 15526013]
20. Annane D, Sebille V, Charpentier C, et al. Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients in septic shock. *JAMA*. 2002; 288:862–871. [PubMed: 12186604]
21. Lattimore KA, Vazquez DA, Barks JD, et al. Developmental outcomes of very low birth weight infants treated with hydrocortisone for refractory hypotension. *J Neonatal-Perinatal Med*. 2008; 4:225–232.
22. Pellicer A, Bravo MC, Madero R, et al. Early systemic hypotension and vasopressor support in low birth weight infants: impact on neurodevelopment. *Pediatrics*. 2009; 123:1369–1376. [PubMed: 19403504]
23. Higgins RD, Friedlich P, Seri I. Hydrocortisone for hypotension and vasopressor dependence in preterm neonates: A meta-analysis. *J Perinatol*. 2010; 30:373–378. [PubMed: 19693023]
24. Micromedex® Healthcare Series [Internet database]. Greenwood Village, Colorado: Thomson Healthcare; Updated periodically
25. Derendorf H, Molman H, Barth J, et al. Pharmacokinetics and oral bioavailability of hydrocortisone. *J Clin Pharmacol*. 1991; 31:473–476. [PubMed: 2050835]
26. Bhatt-Mehta V, Barks JD. Relationship between free and total cortisol concentrations in the serum of newborn infants. *J Neonatal-Perinatal Med*. 2011; 4:247–252.
27. Baker CFW, Barks JDE, Engmann C, et al. Hydrocortisone administration for the treatment of refractory hypotension in critically ill newborns. *J Perinatol*. 2008; 28:412–419. [PubMed: 18337742]
28. Friberg LE, Vermeulen AM, Petersson KJF, et al. An agonist-antagonist interaction model for prolactin release following risperidone and paliperidone treatment. *Clin Pharmacol Ther*. 2009; 85:409–417. [PubMed: 19109590]
29. Morselli PL, Marc V, Garattini S, et al. Metabolism of exogenous cortisol in humans–1: diurnal variation in plasma disappearance rate. *Biochem Pharmacol*. 1970; 19:1643–1647. [PubMed: 5513944]
30. Potts AL, Cheeseman JF, Warman GR. Circadian rhythms and their development in children: implications for the pharmacokinetics and pharmacodynamics in anesthesia. *Paediatr Anaesth*. 2011; 21:238–246. [PubMed: 20561229]
31. Iwata O, Okamura H, Saito H, et al. Diurnal cortisol changes in newborn infants suggesting entrainment of peripheral circadian clock *in utero* and at birth. *J Clin Endocrinol Metab*. 2013; 98:E25–E32. [PubMed: 23150686]
32. Anderson BJ, Holford NHG. Mechanism-based concepts of size and maturity in pharmacokinetics. *Annu Rev Pharmacol Toxicol*. 2008; 48:303–332. [PubMed: 17914927]
33. Kleiber M. Body size and metabolism. *Hilgardia*. 1932; 6:315–353.
34. Holford N. A size standard for pharmacokinetics. *Clin Pharm*. 1996; 30:329–332.
35. Coolens JL, Van Baelen H, Heyns W. Clinical use of unbound plasma cortisol as calculated from total cortisol and corticosteroid-binding globulin. *J Steroid Biochem*. 1987; 26:197–202. [PubMed: 3560936]
36. Mueller UW, Potter JM. Binding of cortisol to human albumin and serum: the effect of protein concentration. *Biochem Pharmacol*. 1981; 30:727–733. [PubMed: 7247957]
37. Smith JB, Nolan G, Jubiz W. The relationship between unbound and total cortisol: its usefulness in detecting CBG abnormalities. *Clinica Chimica Acta*. 1980; 108:435–445.

38. Perogamvros I, Aarons L, Miller AG, et al. Corticosteroid-binding globulin regulates cortisol pharmacokinetics. *Clin Endocrinol*. 2011; 74:30–36.
39. Ginsberg G, Hattis D, Sonawane B, et al. Evaluation of child/adult pharmacokinetic differences from a database derived from the therapeutic drug literature. *Toxicol Sci*. 2002; 66:185–200. [PubMed: 11896285]
40. Beishuizen A, Thijs LG, Vermes I. Patterns of corticosteroid-binding globulin and free cortisol during septic shock and multitrauma. *Intensive Care Med*. 2001; 27:1584–1591. [PubMed: 11685298]
41. Rokicki W. Free cortisol of human plasma in the first 3 months of life. *Biol Neonate*. 1990; 57:21–29. [PubMed: 2302434]
42. Peterson RE, Wyngaarden JB, Guerra SL, et al. The physiological disposition and metabolic fate of hydrocortisone in man. *J Clin Invest*. 1955; 34:1779–1794. [PubMed: 13271563]

Figure 1.

Clinical protocol for the administration of intravenous (IV) hydrocortisone (HC) to neonates and infants with vasopressor-resistant hypotension.

*All patients deemed to have vasopressor-resistant hypotension were started on IV HC as soon as the baseline concentration was drawn. All patients thus received 8 stress doses of IV HC. Further treatment was guided by the initial baseline total cortisol concentration.

**The 12 hours allowed for a washout period after the last stress dose.

Figure 2.
Concentration-time profile for unbound hydrocortisone following intravenous hydrocortisone administration (n=62).

Figure 3. Plots of (a) observations versus model-predicted hydrocortisone concentrations and (b) observations versus model-predicted hydrocortisone concentrations based on individual parameter estimates. The solid line is the line of unity.

Table 1

Characteristics of the study population at treatment (n=62)

	Median	Range
Gestational age (weeks)	27	23 - 41
Postnatal age (weeks)	0.7	0.1 - 9.3
Postmenstrual age (weeks)	28	24 - 41
Weight (kg)	1.2	0.5 - 4.4
	Number	Percent
Sex n, %		
a. Male	33	53.2
b. Female	29	46.8
Serum creatinine * n, %		
a. 1.1 mg/dL	48	77.4
b. >1.1mg/dL	14	22.6

* Serum creatinine 1.1 mg/dL is considered normal in this patient population.

Table 2

Unbound hydrocortisone pharmacokinetic parameter estimates and bootstrap results

Parameter (units)	Final Estimate	RSE (%)	95% CI	Bootstrap Estimate (median)	Bootstrap 95% CI
CL (L/h)	20.2	10.8	15.9-24.5	20.4	16.1-25.6
PMA effect	0.11	17.6	0.075-0.145	0.11	0.076-0.154
V (L)	244	21.5	160-328	270	170-598
Baseline cortisol (ng/mL)	1.37	16.1	0.792-1.95	1.39	0.882-2.04
Between subject variance in CL (CV%)	0.293 (54.1)	22.6	0.163-0.423	0.293	0.157-0.484
Between subject variance in baseline cortisol (CV%)	2.41 (155%)	11.9	1.85-2.97	2.37	1.78-2.90
Variance for RV by proportional error model (CV%)	0.328 (57.3%)	13.2	0.243-0.413	0.326	0.246-0.413
RV by additive error model (SD)	0.049 (0.220)	15.8	0.034-0.064	0.048	0.033-0.065

RSE (%) = 100% x standard error/estimate; CI = confidence interval; CL (L/h) = clearance; PMA = postmenstrual age; V (L) = volume of distribution; RV = residual variability; CV (%) = coefficient of variation; SD = standard deviation.