Daily endogenous cortisol production and hydrocortisone pharmacokinetics in adult horses and neonatal foals

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Objective—To compare daily endogenous cortisol production rate and the pharmacokinetics of an IV bolus of hydrocortisone between neonatal foals and adult horses.

Animals—10 healthy full-term 2- to 4-day-old foals and 7 healthy adult horses.

Procedures—Blood samples were collected from each horse every 15 to 20 minutes for 24 hours for determination of 24-hour mean cortisol concentration. Afterward, dexamethasone (0.08 mg/kg) was administered IV to suppress endogenous cortisol production. Twelve hours afterward, hydrocortisone sodium succinate (1.0 mg/kg) was administered as a rapid IV bolus and serial blood samples were collected to determine hydrocortisone pharmacokinetics. Cortisol concentrations, daily cortisol production rate, and hydrocortisone pharmacokinetics were determined, and results were compared between adult horses and foals.

Results—The mean ± SD 24-hour cortisol concentration was significantly lower in foals (20 ± 4 ng/mL) than in horses (26 ± 6 ng/mL), but the daily cortisol production rate was significantly greater in foals (6,710 ± 320 ng/kg/d) than in horses (2,140 ± 400 ng/kg/d). For hydrocortisone, foals had a significantly greater volume of distribution at steady state (1.92 ± 1.11 L/kg) and total body clearance (1.39 ± 0.108 L/kg/h) and significantly lower peak plasma concentration (1,051 ± 343 ng/mL) than did horses (0.58 ± 0.15 L/kg, 0.349 ± 0.065 L/kg/h, and 8,934 ± 3,843 ng/mL, respectively).

Conclusions and Clinical Relevance—Important differences were detected in cortisol production and metabolism between neonatal foals and adult horses consistent with lower plasma protein binding of cortisol in foals. This decrease may contribute to cortisol insufficiency during prolonged critical illness in neonatal foals. (Am J Vet Res 2012;73:68–75)
thalamus or pituitary gland, adrenocortical dysfunction resulting in limited cortisol synthetic capacity, or decreased glucocorticoid sensitivity or activity in the peripheral tissues.\textsuperscript{1,2} The condition has also been reported in veterinary medicine\textsuperscript{3-10} and has been observed in approximately 50% of septic people\textsuperscript{2,11-13} and septic foals.\textsuperscript{13} In addition, CIRCI is associated with an increased incidence of shock, multiple organ dysfunction syndrome, and death in critically ill people, dogs, and foals.\textsuperscript{1,3-7,9,13}

Several human studies,\textsuperscript{14-17} including 3 meta-analyses,\textsuperscript{18-20} have demonstrated an improvement in outcome for septic patients with CIRCI when they are provided with glucocorticoid supplementation in the form of low-dose hydrocortisone replacement. The general premise for hydrocortisone replacement during critical illness is to provide synthetic cortisol in the form of hydrocortisone in an amount comparable to an appropriate cortisol response in a patient with intact HPA-axis function.\textsuperscript{2,21-23} However, it is difficult to predict the specific cortisol response to critical illness that would be ideal for individual patients. Hydrocortisone dosage recommendations used in human intensive care units thus differ widely, although current recommendations for hydrocortisone replacement regimens for septic adults consist of a 50-mg IV bolus every 6 hours (approx 2.5 to 3 mg/kg/d) or a 100-mg loading dose followed by a continuous rate infusion of 10 mg/h, IV (approx 4 to 6 mg/kg/d).\textsuperscript{15,23} Hydrocortisone replacement protocols for use in situations of neonatal and pediatric septic shock are less well-defined; current recommendations range from 2 to 50 mg/kg/d as a continuous rate infusion or intermittent bolus dosing.\textsuperscript{24} Such dosing strategies evolved on the basis of the maximal cortisol secretory rate in healthy people in response to exogenous HPA-axis stimulation with cosyntropin\textsuperscript{25} or by multiplying the daily endogenous cortisol production rate in healthy, unstressed individuals by a variable illness factor to take into account appropriate increases in cortisol in response to the stress of severe illness.\textsuperscript{26}

Although septic neonatal foals with CIRCI may also potentially benefit from hydrocortisone replacement, such treatment has not been critically evaluated in foals. Given the marked differences in HPA-axis function and cortisol dynamics in foals, compared with those in adult humans and human neonates,\textsuperscript{27,32} hydrocortisone replacement regimens used in people may not be directly applicable to foals. In addition, to the authors’ knowledge, daily endogenous cortisol production rate and hydrocortisone pharmacokinetics have not been evaluated in foals.

The purpose of the study reported here was to determine daily endogenous cortisol production and hydrocortisone pharmacokinetics and compare these parameters between adult horses and foals, with the ultimate aim of determining an appropriate hydrocortisone replacement regimen for future study in septic foals with CIRCI. We hypothesized that parameter values would differ significantly between adult horses and foals.

**Materials and Methods**

**Animals**—Ten healthy 2- to 5-day-old Quarter Horse foals (4 males and 6 females) from research herds maintained at the University of Georgia and Clemson University equine breeding facilities were used in the study. All foals had been carried full term (gestation time, \( \geq 330 \) days) and were born via unassisted vaginal delivery. Foaling was observed and accurate age was known for 3 foals. The remaining 7 foals were born during the night to mares kept on pasture, so their age was estimated on the basis that birth would have occurred during the 12 hours prior to first detection. Foals were determined healthy prior to and during inclusion in the study by lack of abnormalities identified on physical examination. Adequate transfer of passive immunity was confirmed through measurement of serum immunoglobulin concentration at 12 to 24 hours of age in all foals. An immunoglobulin concentration \( \geq 800 \) mg/dL was deemed sufficient.

In addition, 7 healthy adult horses from the University of Georgia equine research herd were included to allow comparisons between foals and adult horses. Four horses aged 5 to 12 years were used for the determination of 24-hour cortisol production and included a warmblood gelding, Paint gelding, Quarter Horse stallion, and Paint stallion. Three of these horses were not available for immediate subsequent determination of hydrocortisone pharmacokinetics as was performed in foals, so 3 additional Quarter Horse geldings (5 to 15 years of age) and the Paint gelding were used to determine hydrocortisone pharmacokinetics at a later date.

Mare-foal pairs were stabilized in a free box stall for at least 24 hours before sample collection was initiated and during the entire study period. Adult horses were similarly housed in a stall during the study period but were acclimatized to the stall for at least 48 hours before sample collection began. Foals were permitted to suckle freely, and adult horses had free access to grass hay and water during the entire study period. Study methods were approved by the University of Georgia and Clemson University Institutional Animal Care and Use Committees. All adult horses and mare-foal pairs were cared for in accordance with the principles and guidelines of an animal use protocol determined and approved by the universities’ departments of animal resources.

**Sample collection for serum cortisol assessment**—At least 12 hours before sample collection began, a jugular catheter was placed in each horse and foal to facilitate blood collection. Catheters were placed in standing foals during brief restraint by experienced foal handlers, with the mare in the same stall. Sedation was not necessary for catheter placement in any foal or adult.

At 8 AM on the day after catheter placement, blood sample collection was initiated in four 2-day-old foals (3 females and 1 male) and 4 adult horses for determination of 24-hour endogenous cortisol concentration. Two milliliters of blood was collected via the jugular catheter every 15 minutes (foals) or every 20 minutes (horses) for 24 hours. Blood samples were transferred to glass serum separator tubes and allowed to clot at room temperature (23°C). Samples were centrifuged and serum removed within 30 to 90 minutes after collection. Serum samples were stored at –80°C until analysis (within 30 days after collection).
Serum cortisol assay—Serum total cortisol concentrations (ie, cortisol concentrations) were determined by use of an automated analyzer by means of a chemiluminescent enzyme immunoassay validated for use in horses. The lower limit of detection for this assay was 2 ng/mL. Each animal’s 24-hour mean cortisol concentration was determined as the mean of all the cortisol concentrations measured over the 24-hour period in each horse. The arithmetic means of the individual mean cortisol concentrations were then calculated for the 4 adult horses and the 4 foals to determine a mean 24-hour cortisol concentration for each group.

Dexamethasone suppression protocol development in foals—Because the efficacy of the dexamethasone suppression protocol is known in adult horses but has not been evaluated in foals, a preliminary trial in foals was conducted. Six Quarter Horse foals (3 males and 3 females) other than those used for serum cortisol measurements were used to determine an appropriate dexamethasone suppression protocol for use in the study. In these 6 foals, 2 mL of blood was collected via the jugular catheter prior to and every 2 hours after dexamethasone administration for 48 hours. The first foal received 0.04 mg of dexamethasone sodium phosphate/kg IV at 6 AM. Suppression of endogenous cortisol production to a concentration less than the assay’s lower limit of detection (2 ng/mL) was evident by 6 hours after dexamethasone administration and was maintained until 20 hours afterward. Because suppression of endogenous cortisol production for at least 24 hours was necessary for determination of hydrocortisone pharmacokinetics, 3 foals received a second 0.04 mg/kg dose of dexamethasone IV 16 hours after the first dose in an attempt to maintain suppression for this 48-hour period. However, adequate cortisol suppression was obtained with this protocol in just 1 of the 3 foals. Therefore, the dexamethasone dose was doubled to 0.08 mg/kg, IV, and 2 doses 16 hours apart were administered to 2 additional foals. Suppression of endogenous cortisol production to a concentration at or less than the assay’s lower limit of detection was obtained in both these foals by 6 to 8 hours after dexamethasone administration and was maintained for 48 hours afterward. This last protocol was used for the hydrocortisone pharmacokinetic testing in foals and in adult horses.

Sample collection for hydrocortisone pharmacokinetic measurements—The pharmacokinetic properties of hydrocortisone were then determined in the same 4 foals used for serum cortisol measurements, beginning 12 hours after the 24-hour cortisol measurement period concluded. The adult horses used in pharmacokinetic assessments (n = 4) were different from those included in the serum cortisol measurements and were evaluated separately, with the exception of 1 adult horse that was used at different time points for both portions of the study.

Dexamethasone (0.08 mg/kg) was administered to all foals and adult horses in accordance with the pre-established protocol described above. Suppression of the circulating endogenous cortisol concentration to ≤ 2 ng/mL was confirmed in each. Twelve hours after dexamethasone administration, hydrocortisone sodium succinate (1.0 mg/kg) was administered as a rapid IV bolus via the noncatheterized jugular vein. Two milliliters of blood was collected from the IV catheter immediately prior to and at 6, 9, 12, 15, 30, 45, 60, 75, and 90 minutes and 2, 4, 6, 8, 10, 12, and 24 hours after hydrocortisone administration. A second dose of dexamethasone was administered 16 hours after the first dose was given. Samples were processed and serum collected and stored as previously described. Serum hydrocortisone concentrations were determined by use of the same cortisol assay that was used for cortisol measurement, which has 100% cross-reactivity with hydrocortisone and 0% cross-reactivity with dexamethasone.

Pharmacokinetic analysis—Pharmacokinetic analyses were performed by use of a nonlinear regression program. The goodness of the fit was evaluated by use of the Akaike information criterion, residual plots, and visual inspection. The data were weighted as 1/(y_\text{end})^2, in which y_\text{end} is the model-predicted concentration at the actual time. Area under the curve following IV hydrocortisone administration was measured by use of a linear trapezoidal approximation with extrapolation to infinity and the log-linear of the serum drug concentration versus time curve was determined by means of least squares regression.

Pharmacokinetic parameters of hydrocortisone were explained by use of a 2-compartmental open-body model with a first-order elimination process. The compartmental model used for the determination of the pharmacokinetic parameters of hydrocortisone can be represented by a general equation:

\[ C_p = (A \times e^{\alpha t}) + (B \times e^{\beta t}) \]

in which \( C_p \) is plasma concentration of compound at any time (t); A and B are the y-intercepts associated with distribution and elimination phases, respectively; and \( \alpha \) and \( \beta \) represent the rate constants of distribution and terminal elimination phases, respectively. The rate constant of distribution (\( \alpha \)) and distribution half-life (\( t_{1/2\alpha} \)) were determined by use of the method of residuals. The terminal half-life (\( t_{1/2\beta} \)) was calculated according to the following equation:

\[ t_{1/2\beta} = \ln(2)/\beta \]

Total body clearance was calculated by use of the following equation:

\[ Cl = IV \text{dose/AUC}_{\infty} \]

The Vd_s, Vd_{ss}, and Vd_{cl} were calculated according to the following equations:

\[ Vd_s = IV \text{dose}/(A + B) \]
\[ Vd_{ss} = IV \text{dose}/(AUC_{0\rightarrow\infty} \times \beta) \]
\[ Vd_{cl} = IV \text{dose}/(AUMC_{0\rightarrow\infty} \times (AUC_{0\rightarrow\infty})^2) \]

in which AUMC is area under the first-moment curve and is calculated by use of the trapezoidal method and extrapolated to infinity; \( K_{in} \) is first-order elimination.
rate constant, which describes elimination of drug from the central compartment; and $K_{12}$ and $K_{21}$ are distribution rate constants from central to peripheral and from peripheral to central compartments, respectively. $K_{10}$, $K_{12}$, and $K_{21}$ were calculated according to the following equations:

$$K_{10} = \frac{\alpha \times \beta}{K_{21}}$$
$$K_{12} = \alpha + \beta - K_{21} - K_{10}$$
$$K_{21} = (B \times \alpha) + \frac{(A \times \beta)}{(A + B)}$$

Determination of daily endogenous cortisol production rate—Cortisol production rate (ng/kg/h) was calculated by use of the mean endogenous cortisol concentration for the 24-hour period and Cl following an IV bolus dose of hydrocortisone (1 mg/kg) according to the following equation:

$$\text{Production rate} = \text{Cl} \times (\text{mean endogenous cortisol concentration})$$

Each foal’s 24-hour cortisol concentration and hydrocortisone Cl were used to determine a cortisol production rate specific to that foal. Because the same adult horses were not used to determine 24-hour cortisol concentrations and hydrocortisone pharmacokinetics, the mean 24-hour cortisol concentration for the group of 4 adult horses in the first portion of the study was multiplied by the hydrocortisone Cl achieved in each individual horse in the second portion of the study to determine a cortisol production rate for each horse.

Statistical analysis—Mean 24-hour cortisol concentration, pharmacokinetic parameters, and daily endogenous cortisol production rate were compared between adult horses and foals with Mann-Whitney $U$ tests by use of commercial statistical software. A non-parametric test was selected because the small sample size ($n = 4$) in each group precluded accurate assessment of the distribution of the data. Hypothesis tests were 2-tailed, and values of $P < 0.05$ were considered significant for all analyses. Data are expressed as mean ± SD.

Results

24-hour cortisol concentrations—Values suggestive of pulsatile cortisol secretion were apparent in adult horses and foals, but a circadian rhythm to cortisol secretion with lower concentrations in the afternoon and evening was apparent only in adult horses (Figure 1). The mean 24-hour cortisol concentration was significantly ($P < 0.001$) lower in foals ($20 ± 4$ ng/mL) than in adult horses ($26 ± 6$ ng/mL).

Hydrocortisone pharmacokinetics—Cortisol concentrations in 2 foals in which the dexamethasone suppression protocol was developed prior to hydrocortisone measurements were graphically displayed (Figure 2). Hydrocortisone was detectable in the serum of all foals and adult horses at the first measurement point after IV administration (6 minutes). Calculated hydrocortisone parameters for adult horses and foals were summarized (Tables 1 and 2). In foals and adult horses, hydrocortisone was not detectable at 10 and 24 hours, respectively, following hydrocortisone administration (Figure 3). The extrapolated area under the curve for each horse and foal was 15%. Peak serum hydrocortisone concentration was significantly ($P = 0.029$) lower in foals than in adult horses, and $V_{dss}$ and hydrocortisone systemic clearance were significantly ($P = 0.029$ for both comparisons) greater in foals than in adult horses (Table 3). Serum half-life was not significantly ($P = 0.886$) different between adult horses and foals, but foals had substantially more variability in half-life duration than did adult horses.

Daily endogenous cortisol production rate—The daily endogenous cortisol production rate was significantly ($P = 0.029$) higher in foals than in adult horses (Table 3).
The objective of the present study was to determine and compare daily endogenous cortisol production rates and hydrocortisone pharmacokinetics between adult horses and foals. The results suggested substantial differences in cortisol homeostasis between foals and adult horses and thus supported our initial hypothesis that daily endogenous cortisol production rate and hydrocortisone pharmacokinetic parameters differ significantly between adult horses and foals.

Daily endogenous cortisol production rate and hydrocortisone pharmacokinetic parameters in adult horses determined in the present study are consistent with those of previous reports. A method similar to ours was used in 1 study, revealing a clearance rate of 0.609 L/kg/h following an IV bolus of hydrocortisone (1 mg/kg) and daily cortisol production rate of 7,080 ng/kg/d in adult horses at rest. However, the pharmacokinetic parameters in foals were found to be significantly different from those in adults.

### Table 1—Calculated pharmacokinetic parameters in 4 adult horses after IV administration of a bolus of hydrocortisone (1 mg/kg).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Horse 1</th>
<th>Horse 2</th>
<th>Horse 3</th>
<th>Horse 4</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight (kg)</td>
<td>604</td>
<td>606</td>
<td>528</td>
<td>594</td>
<td>583 ± 37</td>
</tr>
<tr>
<td>A (ng/mL)</td>
<td>13,349</td>
<td>7,073</td>
<td>4,378</td>
<td>9,088</td>
<td>8,467 ± 3,780</td>
</tr>
<tr>
<td>B (ng/mL)</td>
<td>542</td>
<td>674</td>
<td>303</td>
<td>347</td>
<td>467 ± 173</td>
</tr>
<tr>
<td>t1/2 (h)</td>
<td>0.984</td>
<td>0.993</td>
<td>0.988</td>
<td>0.989</td>
<td>0.989 ± 0.004</td>
</tr>
<tr>
<td>t1/2 α (h)</td>
<td>0.170</td>
<td>0.256</td>
<td>0.318</td>
<td>0.234</td>
<td>0.245 ± 0.061</td>
</tr>
<tr>
<td>t1/2 β (h)</td>
<td>2.08</td>
<td>2.01</td>
<td>2.24</td>
<td>2.43</td>
<td>2.19 ± 0.19</td>
</tr>
<tr>
<td>Cl (L/kg/h)</td>
<td>0.290</td>
<td>0.348</td>
<td>0.440</td>
<td>0.318</td>
<td>0.349 ± 0.065</td>
</tr>
<tr>
<td>Vd (L/kg)</td>
<td>0.072</td>
<td>0.128</td>
<td>0.202</td>
<td>0.107</td>
<td>0.127 ± 0.055</td>
</tr>
<tr>
<td>Vd, (L/kg)</td>
<td>0.364</td>
<td>0.580</td>
<td>0.511</td>
<td>0.361</td>
<td>0.454 ± 0.109</td>
</tr>
<tr>
<td>Vd, (L/kg)</td>
<td>0.435</td>
<td>0.708</td>
<td>0.713</td>
<td>0.468</td>
<td>0.581 ± 0.150</td>
</tr>
<tr>
<td>AUC (ng × h/mL)</td>
<td>3,422</td>
<td>2,349</td>
<td>2,150</td>
<td>3,178</td>
<td>2,900 ± 552</td>
</tr>
<tr>
<td>MRT (h)</td>
<td>1.50</td>
<td>2.04</td>
<td>1.62</td>
<td>1.47</td>
<td>1.658 ± 0.263</td>
</tr>
</tbody>
</table>

A = Y-intercept associated with the distribution phase. B = Y-intercept associated with the elimination phase. K10 = First-order elimination constant. MRT = Mean residence time.

### Table 2—Calculated pharmacokinetic parameters in four 3-day-old foals after IV administration of a bolus of hydrocortisone (1 mg/kg).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Foal 1</th>
<th>Foal 2</th>
<th>Foal 3</th>
<th>Foal 4</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight (kg)</td>
<td>50.9</td>
<td>46.8</td>
<td>50.5</td>
<td>42.3</td>
<td>47.83 ± 4</td>
</tr>
<tr>
<td>A (ng/mL)</td>
<td>1,303</td>
<td>847</td>
<td>741</td>
<td>977</td>
<td>855 ± 172</td>
</tr>
<tr>
<td>B (ng/mL)</td>
<td>236</td>
<td>49</td>
<td>11</td>
<td>38</td>
<td>84 ± 103</td>
</tr>
<tr>
<td>t1/2 (h)</td>
<td>0.998</td>
<td>0.998</td>
<td>0.999</td>
<td>0.994</td>
<td>0.997 ± 0.002</td>
</tr>
<tr>
<td>t1/2 α (h)</td>
<td>0.430</td>
<td>0.565</td>
<td>0.595</td>
<td>0.505</td>
<td>0.524 ± 0.073</td>
</tr>
<tr>
<td>t1/2 β (h)</td>
<td>1.03</td>
<td>2.13</td>
<td>7.1</td>
<td>2.02</td>
<td>3.07 ± 2.73</td>
</tr>
<tr>
<td>Cl, (L/kg/h)</td>
<td>1.305</td>
<td>1.370</td>
<td>1.55</td>
<td>1.35</td>
<td>1.394 ± 0.108</td>
</tr>
<tr>
<td>Vd, (L/kg)</td>
<td>0.808</td>
<td>1.12</td>
<td>1.33</td>
<td>0.986</td>
<td>0.897 ± 0.126</td>
</tr>
<tr>
<td>Vd, (L/kg)</td>
<td>1.94</td>
<td>4.22</td>
<td>15.82</td>
<td>3.95</td>
<td>6.48 ± 6.31</td>
</tr>
<tr>
<td>Vd, (L/kg)</td>
<td>1.18</td>
<td>1.61</td>
<td>3.96</td>
<td>1.33</td>
<td>1.92 ± 1.108</td>
</tr>
<tr>
<td>AUC (ng × h/mL)</td>
<td>767</td>
<td>730</td>
<td>645</td>
<td>739</td>
<td>720 ± 53</td>
</tr>
<tr>
<td>MRT (h)</td>
<td>0.91</td>
<td>1.18</td>
<td>2.40</td>
<td>0.98</td>
<td>1.37 ± 0.70</td>
</tr>
</tbody>
</table>

See Table 1 for key.

### Discussion

The objective of the present study was to determine and compare daily endogenous cortisol production rates and hydrocortisone pharmacokinetics between adult horses and foals. The results suggested substantial differences in cortisol homeostasis between foals and adult horses and thus supported our initial hypothesis that daily endogenous cortisol production rate and hydrocortisone pharmacokinetic parameters differ significantly between adult horses and foals.

Daily endogenous cortisol production rate and hydrocortisone pharmacokinetic parameters in adult horses determined in the present study are consistent with those of previous reports. A method similar to ours was used in 1 study, revealing a clearance rate of 0.609 L/kg/h following an IV bolus of hydrocortisone (1 mg/kg) and daily cortisol production rate of 7,080 ng/kg/d in adult horses at rest. However, future studies are needed to further investigate the differences in cortisol homeostasis between adult horses and foals.
in that study, endogenous cortisol production was not suppressed prior to bolus administration of hydrocortisone. In a later portion of that study,14 dexamethasone was used to suppress endogenous cortisol production prior to administration of an IV infusion of hydrocortisone at 0.03 mg/kg/h, and cortisol systemic clearance and a daily cortisol production rate were closer to values found in the present study, at 0.404 L/kg/h and 4,590 μg/kg/d, respectively. A different study34 revealed a similar systemic clearance rate of 0.338 L/kg/h in 6 healthy adult horses at rest following administration of radiolabeled cortisol and a daily cortisol production rate of 1.060 ng/kg/d. The daily cortisol production rate in adult horses in the present study (2,140 ± 400 ng/ kg/d) was also similar to the daily cortisol production rate reported for healthy people (6.1 ± 0.4 mg/m²/d) at approximate 1,630 ng/kg/d).45

Daily cortisol production and hydrocortisone pharmacokinetics have not been reported for neonatal foals. Results of the present study indicated that the daily endogenous cortisol production rate is significantly higher in healthy full-term foals than in adult horses. It is possible that this increased production rate in neonatal foals reflects an increase in HPA-axis stimulation in response to environmental or physiologic stress during the neonatal period as foals transition from the intrauterine to the extraterine environment. However, daily endogenous cortisol production rates in full-term infants are comparable with rates in older children and adults.46 In addition, although an increase in plasma ACTH and cortisol concentrations is consistently observed in neonatal foals immediately after parturition, concentrations of these hormones decrease to resting concentrations or lower by 6 to 12 hours of age in healthy foals,30,31,47 suggesting that healthy 2- to 3-day-old foals do not undergo considerable HPA-axis stimulation, compared with adult horses at rest. Finally, if ongoing stress-related HPA-axis activation during the neonatal period were the sole explanation for the higher daily cortisol production rate in foals versus adult horses, then one would expect the mean 24-hour cortisol concentration to also be higher in foals than in adult horses at rest. However, in the present study, the mean 24-hour cortisol concentration was actually significantly lower in foals than in adult horses. Thus, the higher daily cortisol production rate observed in foals in this study is not likely a simple reflection of increased HPA-axis stimulation in response to stress in the neonatal period, but rather is presumably related to the 4-fold increase in cortisol clearance in foals, compared with clearance in adult horses. Specifically, the higher cortisol production rate in foals most likely reflects an attempt of the HPA axis to maintain appropriate circulating basal cortisol concentrations in foals in the presence of this dramatic increase in systemic clearance rate.

The significantly increased systemic clearance rate and increased volume of distribution for hydrocortisone found in foals versus adult horses are best explained by the significantly lower cortisol-binding capacity reported for foals.32 Hydrocortisone and other steroid hormones are lipophilic and are transported in the plasma on specific binding proteins, including cortisol-binding globulin and albumin. In most species and in adult horses, approximately 90% to 95% of circulating cortisol is protein bound, with just 5% to 10% remaining unbound.46–51 However, it is this small free fraction that is biologically available to enter target cells and bind cytoplasmic glucocorticoid receptors to exert cortisol-specific tissue effects.49

In neonatal foals during the first week after birth, a substantially larger amount of circulating cortisol (30% to 60%) is unbound to proteins.32 This larger free fraction permits cortisol to more rapidly and extensively enter tissues, resulting in the larger hydrocortisone volume of distribution observed in foals in the present study. Given that protein-bound cortisol essentially provides a reservoir of circulating cortisol that is protected from metabolism and renal excretion,34 this decreased plasma cortisol-binding capacity in foals most likely results in the more rapid clearance and larger volume of distribution for hydrocortisone observed in the present study, compared with values in adult horses. It is possible that hepatic metabolism and renal excretion of cortisol differ greatly between adult horses and foals and thus may also contribute to the more rapid clearance in foals, but the larger volume of distribution in foals is best explained by decreased cortisol-binding capacity in foals. In addition, a similar increase in cortisol clearance and volume of distribution associated with transient exercise-induced increases in free cortisol concentration has been reported for adult horses.33

The physiologic and clinical consequences of the aforementioned differences in cortisol and hydrocortisone distribution and metabolism in foals may be substantial. Cortisol is synthesized and secreted immediately in response to changes in systemic ACTH concentrations with HPA-axis stimulation and is not stored in the adrenal cortices or peripheral tissues. Although the increase in daily cortisol production rate in foals in the present study suggests that adrenal cortices in foals

### Table 3—Mean ± SD (range) values of selected pharmacokinetic parameters in 4 healthy adult horses and 4 healthy 2- to 4-day-old foals after IV administration of a bolus dose of hydrocortisone (1 mg/kg).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Adult horses</th>
<th>Foals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortisol concentration (ng/mL)</td>
<td>8.334 ± 3.843 (4.681–13.891)</td>
<td>1.051 ± 343* (752–1,015)</td>
</tr>
<tr>
<td>t½ (h)</td>
<td>2.19 ± 0.117 (2.01–2.43)</td>
<td>3.07 ± 2.73 (1.03–7.10)</td>
</tr>
<tr>
<td>CL (L/kg/h)</td>
<td>0.349 ± 0.095 (0.290–0.440)</td>
<td>1.394 ± 0.128* (1.305–1.550)</td>
</tr>
<tr>
<td>Vd (L/kg)</td>
<td>0.127 ± 0.055 (0.072–0.202)</td>
<td>0.897 ± 0.126* (0.808–1.3300)</td>
</tr>
<tr>
<td>Vdss (L/kg)</td>
<td>0.45 ± 0.11 (0.36–0.58)</td>
<td>6.48 ± 6.31* (3.95–15.82)</td>
</tr>
<tr>
<td>Vdss (L/kg)</td>
<td>0.58 ± 0.15 (0.44–0.71)</td>
<td>1.92 ± 1.11* (1.18–3.56)</td>
</tr>
<tr>
<td>Daily cortisol production rate (ng/kg/d)</td>
<td>2,140 ± 400 (1,780–2,710)</td>
<td>6,710 ± 320* (6,510–7,180)</td>
</tr>
</tbody>
</table>

*Value differs significantly (P < 0.05) between adult horses and foals.
can increase cortisol production appropriately during health states, the capacity of neonatal foals to maintain such high cortisol production during critical illness is unknown.

Cortisol and other steroid hormones are synthesized from cholesterol via a multistep process requiring several specific enzymes; however, in contrast to other species, some of the critical enzymes necessary for cortisol production are not present until the immediate periparturient period in foals. Consequently, foals may be unable to sustain such high cortisol production for a prolonged period. In fact, several studies have demonstrated decreased cortisol responses to endogenous and exogenous ACTH in healthy full-term neonatal foals, compared with responses in adult horses, as well as higher ACTH-to-cortisol ratios in nonsurviving septic foals, compared with ratios in survivors. These findings may reflect decreased sensitivity to ACTH, limited glucocorticoid synthetic capacity, or both in neonatal foals versus adult horses. Coupled with the increased cortisol clearance rate in foals in the present study, these factors may put foals at increased risk for the development of cortisol synthetic failure and CIRCI during periods of prolonged, intense HPA-axis stimulation such as in critical illness.

In addition, the differences in hydrocortisone clearance and distribution that were evident in the present study must be considered when glucocorticoids are used in foals in a clinical setting. Foals may require higher hydrocortisone doses and more frequent dosing than adult horses to achieve similar plasma concentrations. However, given that substantially more cortisol is biologically available in foals versus adult horses because of a higher free fraction in foals, may be able to compensate somewhat for this rapid clearance and lower plasma concentrations. For this reason, an appropriate hydrocortisone replacement dose for use in septic foals with CIRCI might be in the range of 1.0 to 3.0 mg/kg/d, which is 1.5 to 4.5 times the mean daily endogenous cortisol production rate of 6,710 ± 320 ng/kg/d (0.671 ± 0.032 mg/kg/d) in healthy foals in the present study. Calculation of this proposed dose was performed as described for humans by use of a so-called illness factor, by which concentrations in healthy individuals are multiplied in light of an expected 1.5- to 4.5-fold increase in basal cortisol concentrations as observed in response to physiologic and supraphysiologic cosyntropin stimulation in healthy foals. The high end of this hydrocortisone dose range is slightly lower than dosages most often used in septic people and infants (approx 2 to 4 mg/kg/d), but a lower dose may be suitable for use in foals because of their high amount of circulating cortisol remaining unbound to protein. However, any such proposed hydrocortisone replacement regimen must be evaluated further before clinical application in sick and septic foals.

One important limitation of the present study is that it was conducted only in healthy foals and adult horses; consequently, the effects of illness on daily endogenous cortisol production rate and hydrocortisone pharmacokinetics in foals are not known. In addition, given the well-described negative consequences of high-dose corticosteroid treatment in septic people, any hydrocortisone replacement regimen for use in septic foals should be evaluated to ensure it does not induce undesirable consequences. Although our findings highlight important differences in cortisol production and metabolism among foals, adult horses, and humans and provide initial data for use in determining a potential hydrocortisone replacement regimen for use in foals, additional research is necessary before such a regimen can be recommended for critically ill foals in a clinical setting.

References


