Pharmacokinetics of intra-articular, intravenous, and intramuscular administration of triamcinolone acetonide and its effect on endogenous plasma hydrocortisone and cortisone concentrations in horses

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Objective—To compare pharmacokinetics of triamcinolone acetonide (TA) following IV, intra-articular (IA), and IM administration and determine its effect on plasma concentrations of hydrocortisone and cortisone.

Animals—6 Thoroughbreds.

Procedures—TA (0.04 mg/kg) was administered IV, IM, or IA, and plasma TA, hydrocortisone, and cortisone concentrations were determined.

Results—IV administration of TA was fitted to a 2-compartment model. Median distribution half-life was 0.50 hours (range, 0.24 to 0.67 hours); elimination half-life was 6.1 hours (range, 5.0 to 6.4 hours). Transfer half-life of TA from joint to plasma was 5.2 hours (range, 0.49 to 7.3 hours); elimination half-life was 23.8 hours (range, 18.9 to 32.2 hours). Maximum plasma concentration following IA administration was 2.0 ng/mL (range, 0.94 to 2.5 ng/mL), and was attained at 10 hours (range, 8 to 12 hours). Maximum plasma concentration following IM administration was 0.34 ng/mL (range, 0.20 to 0.48 ng/mL) and was attained at 13.0 hours (range, 12 to 16 hours); concentration was still quantifiable at 360 hours. Hydrocortisone plasma concentrations were significantly different from baseline within 0.75, 2, and 1 hours after IV, IA, and IM administration, respectively, and remained significantly different from baseline at 96 and 264 hours for IV and IA administration. Following IM administration of TA, plasma concentrations of hydrocortisone did not recover to baseline concentrations by 360 hours.

Conclusions and Clinical Relevance—Pharmacokinetics of TA and related changes in hydrocortisone were described following IV, IA, and IM administration. A single administration of TA has profound effects on secretion of endogenous hydrocortisone. (Am J Vet Res 2011;72:1234–1242)

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humans following IA, topical, or local administration of glucocorticoids. Decreased plasma concentrations of endogenous glucocorticoids following IA administration of methylprednisolone have been detected for up to 1 week in humans,3 to 10 days in horses,16,17 and 12 weeks in cows. In horses, endogenous hydrocortisone does not reach pretreatment concentrations until 14 days after IM administration of TA. Topical and ophthalmic applications of TA or dexamethasone suppress endogenous cortisol concentrations in horses and dogs. Limited information is available on the pharmacokinetics of TA in horses.

The purpose of the study reported here was to compare the pharmacokinetics of TA in horses following IV, IA, or IM administration and to determine the pharmacodynamics of TA on the basis of changes in endogenous corticosteroid and glucose concentrations.

Materials and Methods

Horses—The study protocol was approved by the University of Pennsylvania Institutional Animal Care and Use Committee. Six Thoroughbreds (3 male and 3 female), ranging in age from 5 to 7 years with a mean ± SD body weight of 502.7 ± 17.8 kg, were used in the study. The horses were no longer actively racing. However, on the basis of results of direct physical examination, routine clinical biochemical analyses, and lameness examination, all horses were considered healthy and had nondiseased carpal joints. The 6 horses were assigned to 2 groups of 3; 1 group was studied at a time. Each horse in the group was administered TA IV, IM, or IA in a Latin square–assigned sequence. Grouping was based on housing, which prevented separation of groups of horses from each other for long periods and perturbations in the horses’ accustomed environment that might disrupt hydrocortisone circadian rhythm. A washout period of 4 weeks was allowed before the next drug administration.

To establish endogenous glucocorticoid circadian rhythm and daily variation in glucose plasma concentrations over a 24-hour period, each group of horses was brought into stalls 2 days before sample collection. On the third day, samples were collected each hour for 24 hours, starting at 6 AM. The 3 horses were returned to the same stalls 1 week later for the first TA administration. All horses were fed 1 quart of grain in the morning and late in the afternoon; grass hay and water were provided ad libitum.

Dose and administration—Prior to IA injection of TA into the left carpal joint or placement of a 14F catheter into the jugular vein for collection of blood samples, both areas were clipped of hair, washed with sterile water and surgical soap, and rinsed with a bactericidal solution with 2 mM ammonium formate-methanol (40:60 [vol/vol]; pH, 3.4) and stored at 4°C. Prepared calibrators had concentrations of 100, 50, 10, 5, 1, 0.5, and 0.1 ng/mL; quality-control samples had concentrations of 0.5, 5, and 50 ng/mL; and fluoxymesterone was the internal standard.

Analyst separation was performed by use of a C8 high-performance liquid chromatography column. Analyses were performed by use of a liquid chromatography–mass spectrometry system consisting of a liquid chromatography pump with an online degasser, an autosampler, and a mass spectrometer equipped with an electrospray ionization probe. Standard operating procedures for the quantification of analytes by our laboratory meet requirements for accreditation by the American Association for Laboratory Accreditation and ISO 17025 International Guidelines. The limit of quantification was 0.1 ng/mL for all analytes. The intraday precision and accuracy for a concentration range of 0.1 to 50 ng/mL were < 5% and 103%, respectively. The interday precision and accuracy were < 6.0% and 105%, respectively.

Plasma glucose was assayed by use of an automated lactate analyzer. Baseline samples were obtained at 7 AM prior to each drug administration.

Pharmacokinetic analysis—Plasma concentration versus time curves of TA and hydrocortisone following IV, IA, or IM administration were analyzed by use of standard nonlinear compartmental analysis. Two- and 3-compartment models were fitted to the IV plasma concentration-time curve from each horse. Models that described the best fit for IV, IA, or IM administration were based on the appearance of observed
and predicted concentrations, reduction in the sums of squares, and reduction in the fractional SD of each estimated parameter (Figure 1).

The fractional rate constants for the IV compartment model were estimated with elimination ($k_{10}$) from the central compartment ($C_1$) and distribution ($[k_{1,2} \text{ and } k_{2,1}]$ and $[k_{1,3} \text{ and } k_{3,1}]$) to peripheral compartments ($C_2$ and $C_3$). Microconstants ($k_{1,2}$ and $k_{2,1}$) were converted to macroconstant exponents ($\alpha$ and $\beta$) as described.32,33 A 2-compartment model with injection into the joint or muscle ($C_1$) with transfer from joint ($k_t$) or absorption ($k_a$) from muscle and elimination ($k_{el}$) from the central compartment ($C_2$) was fitted to IA and IM administration data for each horse (Figure 1).

Indirect response models have been used in a number of studies to describe the effects of exogenous hormones on endogenous processes.34,35 A hydrocortisone suppression model was used in horses in the present study to describe the inhibition of the secretion of endogenous hormone hydrocortisone on the basis of the changing concentrations of TA administered IV, IA, or IM. This was designated as compartment 3 (Figure 1).

Transfer of TA (g/h) out of the joint or muscle from compartment 1 ($C_1$) into compartment 2 ($C_2$) was described by the following equation:

$$\frac{dM_1(t)}{dt} = -k_t \cdot M_1(t)$$

where $M_1(0) = M_{10}$.

The rate of change of the concentration of TA (g/L/h) in $C_2$ was described by the following equation:

$$\frac{d(TA_2)}{dt} = \left(kt \cdot M_1 - kel \cdot M_2\right)/V_2$$

where $M_{10}$ is the quantity (µg) of TA injected into the joint or muscle ($C_1$), $k_t$ is the fractional transfer rate constant (h$^{-1}$) from $C_1$ to $C_2$, $V_2$ is the volume (L) of compartment 2 ($C_2$), $M_1(t)$ and $M_2(t)$ are functions describing the quantities (µg) of TA in $C_1$ and $C_2$ at time $t$, and $k_{el}$ is the elimination rate constant (h$^{-1}$) from $C_2$. The concentration of TA in $C_2$ controls the pattern of change in the concentration of hydrocortisone in compartment 3 ($C_3$).

Suppression of hydrocortisone production attributable to plasma TA was calculated from the following equation:

$$k_{in} = \left([k_{out} \cdot HYD_0]/\left[1 + TA_2/\phi\right]\right) \cdot HYD_V$$

where $k_{in}$ (µg/L/h) is the rate of production of hydrocortisone, $HYD_0$ (µg/L) is the baseline hydrocortisone concentration, $k_{out}$ (h$^{-1}$) is the natural hormone degradation rate, $TA_2$ (µg/L) is the concentration of TA in $C_2$, and $\phi$ (µg/L) is a parameter that influences the persistence of inhibition of hormone secretion by TA. Hydrocortisone values were converted to micrograms by use of published volume of distribution values of hydrocortisone ($HYDV$).36 Fixing other model parameters but allowing bioavailability to increase allowed modeling of an increase in the persistence of the inhibition of hormone secretion or extension of the duration of drug effect.37,38 The rate of increase or decrease of plasma hydrocortisone concentration (µg/h) was calculated from the following equation:

$$\text{Plasma hydrocortisone concentration} = \left(k_{in} - k_{out} \cdot HYD_0\right) \cdot HYD_V$$

The baseline production rate (µg/h) of hydrocortisone was calculated from the following equation setting the net rate of increase of hydrocortisone to zero:

$$k_{in} = (k_{out} \cdot HYD_0) \cdot HYD_V$$

The pharmacokinetic and pharmacodynamic data were fitted simultaneously. The IV data were modeled
identically, with the concentration of TA in C1 controlling the pattern of changes in the concentration of hydrocortisone in C2.

A number of weighting schemes (W[K]) were used for IV, IM, and IA data during the fitting process. Fractional SD was in the form of W(K) = 1/(C*K(QO[K]))², where QO(K) is the kth observed datum and C is the fractional SD. The SD weighting scheme was W(K) = 1/C². The fractional SD weighting process favors the terminal phase of the decay curve, where SD favors the larger and intermediate data points. The fitting process (iterations) ceased when improvement in the sums of squares of the last iteration was < 1%.31

The A and B coefficients (ng/mL) for IV administration were calculated from the dose, Vc, and relevant compartmental rate constants.39 Half-lives of the apparent distribution (alpha) and elimination (beta) phases were calculated as Ln2 divided by the alpha and beta exponents. Plasma concentration at 0 time (C₀) was the sum of the coefficients A and B. The total AUC from 0 to infinity was calculated by the trapezoid method plus end area correction, which was the last plasma concentration (Cp[t∗]) to infinity and is estimated by Cp[t∗]/kel, where kel is the relevant terminal elimination rate constant for IV, IA, or IM administration.40 Fractional drug quantity absorbed from muscle or transferred from the joint to plasma was calculated as follows:

\[ \text{AUC}_{IA}/\text{AUC}_{IV} \quad \text{and} \quad \text{AUC}_{IM}/\text{AUC}_{IV} \]

Volume of the central compartment following IV administration was calculated as follows:

\[ V_c = \frac{D_{IV}}{C_0} \]

where DIV is the dose administered IV and C₀ is the plasma concentration at time zero. Ratios of the intercompartmental fractional rate constants k₁,₂/k₂,₁ multiplied by Vc were used to calculate the volume of C2, and the Vd, following IV administration was calculated as the sum of all compartments41:

\[ V_d = (k_{1,2} + k_{2,1})/V_c \]

Table 1—Pharmacokinetic parameter estimates following a single IV administration of TA at a dose of 0.04 mg/kg in 6 horses.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Median (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cp (ng/mL)</td>
<td>28.1 (19.4–33.2)</td>
</tr>
<tr>
<td>A (ng/mL)</td>
<td>19.5 (12.5–24.7)</td>
</tr>
<tr>
<td>α (h)</td>
<td>1.4 (1.0–2.8)</td>
</tr>
<tr>
<td>T½α (h)</td>
<td>0.50 (0.24–0.67)</td>
</tr>
<tr>
<td>B (ng/mL)</td>
<td>8.3 (6.5–12.2)</td>
</tr>
<tr>
<td>β (h)</td>
<td>0.11 (0.10–0.14)</td>
</tr>
<tr>
<td>T½β (h)</td>
<td>6.1 (5.0–6.4)</td>
</tr>
<tr>
<td>AUC₀ (ng/h/mL)</td>
<td>89.3 (63.8–103.9)</td>
</tr>
<tr>
<td>Cl (mL/h/kg)</td>
<td>447.8 (384.8–629.9)</td>
</tr>
<tr>
<td>V₀ (L/kg)</td>
<td>1.4 (1.2–2.1)</td>
</tr>
<tr>
<td>V₁ (L/kg)</td>
<td>2.0 (1.1–3.0)</td>
</tr>
<tr>
<td>V² (L/kg)</td>
<td>3.2 (2.7–3.5)</td>
</tr>
</tbody>
</table>

\[ \text{AUC}_{IV} = \text{Area under the plasma concentration-time curve from 0 to infinity}. \quad \text{Cp} = \text{Concentration at time 0}. \quad \text{A} \quad \text{and} \quad \text{B} = \text{Coefficients}. \quad \alpha \quad \text{and} \quad \beta = \text{Exponents}. \quad \text{Cl} = \text{Total body clearance}. \quad V_c = \text{Volume of compartment 2} \]

Clearance was calculated as follows:

\[ \text{D}_{IV}/\text{AUC}_{IV} \]

**Statistical analysis**—Pharmacokinetic parameter estimates of TA, hydrocortisone, and cortisol were expressed as median and range, and nonparametric Wilcoxon and Kruskal-Wallis rank-sum tests were used for statistical comparisons.42,43 An ANOVA was used for parametric analysis of plasma hydrocortisone and glucose concentrations over time and AUC comparisons. Plasma concentrations of TA were expressed as mean ± SD. Values of P < 0.05 were considered significant.

**Results**

**IV administration of TA**—The plasma concentration-time curve of TA administered IV was best described by a 2-compartment model, and the concurrent changes in hydrocortisone were described by a 3-compartment model (Figures 1 and 2). Pharmacokinetic parameters were estimated (Table 1). Triamcinolone acetate was quantifiable in all horses at 36 hours. Plasma concentrations were 36.13 ± 8.62 ng/mL, 0.54 ± 0.15 ng/mL, and 0.14 ± 0.50 ng/mL at 2 minutes, 24 hours, and 36 hours, respectively. Median alpha and beta T½ were 0.50 and 6.1 hours, respectively. Fractional SD for compartmental parameter estimates used in defining the IV model and concurrent changes in hydrocortisone was 0.03 ± 0.02.

**IA administration of TA**—Transfer of TA from the joint (C1) to and elimination from the central compartment (C2) and concurrent changes in hydrocortisone were described by a 3-compartment model (Figures 1 and 2). Pharmacokinetic parameters were estimated (Table 2). Triamcinolone was quantifiable in plasma within 5 minutes following administration of TA in 3 of the 6 horses and in all horses at 0.25 hours at plasma concentrations of 0.17 ± 0.11 ng/mL and 0.30 ± 0.39 ng/mL, respectively. Triamcinolone was quantifiable in all horses at 90 hours at a plasma concentration of 0.16 ± 0.04 ng/mL. The median transfer and elimination T½ were 5.2 and 23.8 hours, respectively. Fractional SD for all compartmental parameter estimates was 0.02 ± 0.01. Fractional quantity transferred from joint to plasma was 1.0 ± 0.2% of the administered dose.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>IA</th>
<th>IM</th>
</tr>
</thead>
<tbody>
<tr>
<td>k₁₂ (h)</td>
<td>0.14 (0.09–1.34)</td>
<td>1.32 (0.003–3.81)</td>
</tr>
<tr>
<td>Transfer T₁₀ (h)</td>
<td>5.2 (0.49–7.3)</td>
<td>0.52 (0.18–2.35)</td>
</tr>
<tr>
<td>k₂₃ (h)</td>
<td>0.03 (0.002–0.04)</td>
<td>0.005 (0.002–0.007)</td>
</tr>
<tr>
<td>Elimination T½ (h)</td>
<td>23.8 (18.5–32.2)</td>
<td>150.2 (104.2–290.9)</td>
</tr>
<tr>
<td>AUC₀ (ng/h/mL)</td>
<td>82.2 (73.8–102.6)</td>
<td>78.6 (29.8–107.4)</td>
</tr>
<tr>
<td>Cmax (ng/mL)</td>
<td>2.0 (0.94–2.5)</td>
<td>0.34 (0.20–0.48)</td>
</tr>
</tbody>
</table>

Values reported as median (range). Cmax = Maximum concentration. k₁₂ = Transfer rate constant. k₂₃ = Elimination rate constant. Tmax = Time to maximum concentration. See Table 1 for remainder of key.
IM administration of TA—Absorption of TA from muscle (C₁) and elimination from the central compartment (C₂) and concurrent changes in hydrocortisone were described by a 3-compartment model (Figures 1 and 2). Pharmacokinetic parameters were estimated (Table 2). The maximum concentration following IM administration was only 0.34 ng/mL with a mean concentration of 0.19 ± 0.09 ng/mL over 360 hours (15 days). Median absorption and elimination T₁/₂ were 0.52 and 150.2 hours, respectively. Fractional SD for all adjustable compartmental parameter estimates used in defining the IM model was 0.03 ± 0.02. Fractional quantity absorbed was 0.83 ± 0.42% of the total TA administered.

Hydrocortisone—The study was conducted over a 9-month period (May through January). Baseline plasma concentrations of hydrocortisone and cortisone were 93.4 ± 19.4 ng/mL and 2.9 ± 0.63 ng/mL, respectively. Significant differences in baseline concentrations of hydrocortisone (P = 0.02) and cortisone (P = 0.02) were observed among the 6 horses, but no significant differences were observed over the study period or between sexes. The 24-hour hydrocortisone plasma concentrations of the 6 study horses had a nadir at 11 PM at 18.3 ± 8.1 ng/mL. Spikes at 7 AM and 4 PM coincided with feeding of grain. The AUC for the 24-hour hydrocortisone control period was 1,559.8 ± 335.0 ng/h/mL for the 6 horses. The equivalent AUC for hydrocortisone during the first 24-hour period following IV, IA, or IM administration of TA was 361.6 ± 136.7 ng/h/mL, which represented a 76.4 ± 8.1% reduction in the hydrocortisone AUC for the first 24-hour period. No significant differences were observed in the hydrocortisone AUC for the 360 hours after injection following IM administration of TA.

Following IV, IA, or IM administration of TA, the decline in hydrocortisone plasma concentrations was significantly different from baseline within 0.75, 2, and 1 hours following IV (P < 0.03), IA (P < 0.005), and IM (P < 0.001) administration, respectively. Hydrocortisone plasma concentrations were still significantly different from baseline at 96 (P < 0.001) and 26+ hours (P = 0.006) for IV and IA administration, respectively. Following IM administration of TA, hydrocortisone plasma concentrations had not recovered to baseline concentrations by 360 hours (15 days).
taining the lowest plasma concentration (2.7 ± 0.94 ng/mL) at 25.2 ± 7.5 hours (Figure 3). The route of administration had no effect on the hydrocortisone nadir plasma concentration and at what time it was achieved. The route of administration did have an effect on the time at which the endogenous hydrocortisone concentration recovered to baseline (Figure 2). The mean estimated baseline hydrocortisone production rate was 2.19 ± 0.56 µg/kg/h with no significant differences in production rate among routes of administration, but as in baseline hydrocortisone concentrations, a significant (P = 0.01) difference was observed among horses. There was a rapid decrease in the estimated hydrocortisone production rate unrelated to the route of administration with a slow recovery to baseline that was determined by the route of administration of TA (Figure 4).

**Glucose**—Following IV administration (Figure 5), there was a significant (P = 0.01) increase in glucose concentration at 10 hours, which was still significantly (P = 0.02) different from baseline at 48 hours after administration. Following IA administration, the increase was significantly (P = 0.02) different from baseline at 8 hours and remained so until 96 hours (P = 0.003). Following IM administration, the increase was significantly (P < 0.001) different from baseline at 12 hours and remained so until 48 hours (P = 0.005). The increases in glucose plasma concentrations peaked at 24 hours regardless of the route of administration.

**Discussion**

In this study, the pharmacokinetics of TA and changes in hydrocortisone were described following IV, IA, or IM administration of 0.04 mg of TA/kg. In a previous study in horses, the plasma pharmacokinetics of TA following IV administration of 0.2 mg/kg were described by a 3-compartment model with a terminal T1/2 of 3 to 52 hours and detection until approximately 48 hours. The limit of quantification was 1 ng/mL for that study, which used a higher than clinically recommended dose. In contrast, a lower dose (0.04 mg/kg) was administered in the present study and a 2-compartment model was fitted to the data with a terminal T1/2 range of 5 to 6.4 hours. Triamcinolone acetate was administered in the same horses as in Figure 2 for the whole study period (A). The rate of decline within the first hour for the 3 administrations is given (B).

Figure 4—Suppression from baseline and recovery in the estimated production rate of hydrocortisone following IV (dotted line), IA (dotted and dashed line), and IM (dashed line) administration of TA (0.04 mg/kg) in the same horses as in Figure 2 for the whole study period (A). The rate of decline within the first hour for the 3 administrations is given (B).

Figure 5—Mean ± SD plasma concentrations of glucose following administration (A = IV; B = IA; C = IM) of 0.04 mg of TA/kg in the same horses as in Figure 2. Following IV administration (A), there was a significant increase in plasma glucose concentrations at 10 hours, which was significantly different from baseline at 48 hours after injection. Following IA administration (B), the increase was significantly different from baseline at 8 hours and remained so until 96 hours after injection. Following IM administration (C), the increase was significantly different from baseline at 12 hours and remained so until 48 hours after injection.
quantifiable for up to 36 hours in all horses following IV administration.

Peak plasma concentrations and elimination profiles similar to the results of the present study were reported following IA administration of 30 mg of TA. Triamcinolone serum concentration peaked at 12 hours and was quantified in serum for 78 to 102 hours in 4 horses by use of high-performance liquid chromatography.43 Synovial samples were not collected in the present study because intermittent sample collection from an injected joint may have disrupted the transfer of TA from the joint to plasma. The fractional quantity transferred from joint to plasma was calculated as approximately 1.0.

In a previous study,19 plasma concentration following IM administration of 0.2 mg/kg was incompletely described because of poor absorption of TA from muscle and lack of adequate sensitivity of the method used for quantification. In the present study, the fractional quantity absorbed in 15 days was approximately 0.83% based on plasma AUC for IM administration; for IV administration, plasma AUC was based on a 36-hour plasma concentration-time curve. Plasma concentration following the IM administration peaked at 13 hours with a maximum concentration of 0.34 ng/mL, and triamcinolone was still quantifiable in plasma at 15 days after administration. This finding following IA or IM administration is explained by a so-called flip-flop phenomenon, where drug absorption is the rate-limiting step of overall drug disposition and elimination. On the basis of the marked suppression and delayed recovery of the endogenous hydrocortisone, some investigators have suggested that suppression of hydrocortisone can be taken as an indication of exogenous administration of glucocorticoid.19

Steroid receptors are asymmetric proteins, and those for glucocorticoids are found in most mammalian tissues, reflecting their ubiquitous presence and regulatory importance.44 The administration of exogenous glucocorticoids is followed by suppression of endogenous hydrocortisone production by a feedback mechanism that inhibits the hypothalamic-pituitary-adrenal axis.45,46 Three major time frames of corticosteroid action have been described: fast, intermediate, and slow. The last time frame describes a rapid effect of corticosteroids at the cell membrane inhibiting the release of corticotropin-releasing factors and stress-induced ACTH secretion. The mechanism of the intermediate time frame feedback requires the presence of a protein synthesis which is corticosteroid dependent, and the slow time frame feedback apparently involves reduction in pituitary ACTH content by decreasing concentrations of mRNA encoding the ACTH precursor molecule.47 The immediate and prolonged suppression found in horses may be the consequence of 3 mechanisms of corticosteroid action on sensitive feedback sites.

The initial step in the development of a biological response to the administration of corticosteroids is rapid diffusion from plasma into cells for interaction with cytosolic receptors.48 Most of these endogenous and synthetic corticosteroids are lipid soluble; they enter the target cell organs and bind to intracellular receptors. Receptors have high affinity for these compounds, and low concentrations induce an effect.49

The rapid reduction in the estimated production rate of hydrocortisone in the present study (Figure 4) indicated that the hypothalamic-pituitary-adrenal axis was rapidly suppressed, thereby shutting off production of hydrocortisone and initiating a decrease in hydrocortisone concentration. Changes in hydrocortisone production rate have also been reported in humans following dexamethasone administration.50 The initial value is somewhat comparable to reported production rates in horses.36 The change in production rate was based on measurement of the initial value and assumed a steady-state production. This production rate was determined by use of a single value obtained at the start of the present study and not by use of a mean concentration measured over a period of time that would take into account natural fluctuations in hydrocortisone production and concentrations. It is possible that the use of a mean concentration may be a more appropriate approach. The rate of change in hydrocortisone production and its response to the changing concentrations of TA are the important comparative aspects of the estimated production rate. A decrease in estimated production rates was attained in < 1 hour regardless of the route of administration.

The decrease in plasma hydrocortisone concentrations following exogenous administration of glucocorticoids was not instantaneous but occurred on the basis of the natural elimination rate of hydrocortisone following suppression of the hypothalamic-pituitary-adrenal axis. In the present study, T1/2 for hydrocortisone was 2.1 hours, which was similar to the elimination T1/2 of hydrocortisone reported in horses following administration of dexamethasone (approx 1.9 hours) and methylprednisolone (approx 1.2 hours).17,31 Following IV administration of [3H] cortisol to horses, the T1/2 was approximately 1.5 hours,36 and following administration of hydrocortisone to humans, an approximately 1.5-hour T1/2 has also been reported.52

Other investigators have described circadian rhythm in horses that were accustomed to a management routine comprising stabling, feeding, and exercise, which may establish a circadian pattern.26 Prior to drug administration, horses in the present study had a 24-hour pattern with the nadir at 11 AM at 18.3 ± 8 ng/mL. All of our studies started at 7 AM; daily samplings were also performed at 7 AM, and all changes were referenced to the morning baseline concentrations. The rapid suppression of endogenous glucocorticoids may also be related to the time of TA administration because a chronobiological sensitivity has been described in humans, with greater degree of hydrocortisone suppression detected in human patients following administration at 8 AM.53

A plasma hydrocortisone concentration of approximately 0.15 ng/mL was measured within 5 minutes following IM administration of TA, indicating suppression of the hypothalamic-pituitary-adrenal axis and the production of hydrocortisone. The suppression of hydrocortisone was sustained for > 15 days; the mean plasma concentration of TA during this period was 0.19 ± 0.09 ng/mL. Results of the present study and other stud-
suggested that horses are sensitive to the effects of endogenously administered glucocorticoids. For example, dose-dependent suppression of endogenous hydrocortisone secretion had been detected in humans and a threshold concentration for maximum suppression was also suggested. Systemic administration of 1 to 2 ng of TA/mL orally, IV, or by inhalation causes significant suppression of hydrocortisone. Alternatively, a 50% inhibitory concentration of 1 ng of methylprednisolone/mL has also been reported in humans, which suggests there may be a corticosteroid-sparing dose that optimizes endogenous corticosteroid efficacy as adrenal suppression is minimized. In the present study in horses, no such effect was detected. Concentrations of cortisol from a single IV dose of dexamethasone recovered to baseline at 24 hours in humans, compared with 96 hours in horses.

Recovery of hydrocortisone began at approximately 19 to 36 hours following IV or IA administration, and at 15 days following IM administration, hydrocortisone suppression was still present. Slow recovery from suppression of endogenous corticosteroids may be caused by a sustained free non–protein-bound relevant tissue concentration of TA.

Oxidation of hydrocortisone, which occurs in the liver and kidneys, produces the inactive biomarker cortisone. Cortisone can be transformed to hydrocortisone (eg, orally administered cortisone must be metabolized to the bioactive hydrocortisone by hydroxylation of the oxygen on carbon 11 to a hydroxyl group). This conversion is an important mechanism for clearance of hydrocortisone by the kidney. Cortisone concentration was measured in this study but was not modeled. Cortisone suppression and recovery to baseline were parallel and were directly related to the changes in hydrocortisone plasma concentrations following TA administration.

Triamcinolone acetonide administered IV, IM, or IA, as with other glucocorticoids, induces a prolonged period of hyperglycemia, hyperinsulinemia, and hypertriglyceridemia. The mechanism suggested is reduced glucose use and increased gluconeogenesis. In the present study, increases in glucose concentration occurred within 8 to 12 hours following administration and peaked at 24 hours regardless of the route of administration. For IA and IM administrations, albeit not significant, glucose concentrations were greater than baseline for the duration of the study period (Figure 5).

Results of the present study in horses indicated that a single IV, IA, or IM administration of TA had profound effects on the production of endogenous corticosteroids. This resulted in suppression to values less than baseline plasma concentrations of hydrocortisone up to 96 and 264 hours for IV and IA administration, respectively. At 360 hours following IM administration, concentrations of hydrocortisone had not recovered to baseline.

This suppression of production and concentrations of endogenous glucocorticoids lasted well beyond the analytic capabilities of current liquid chromatography–mass spectrometry methods to detect TA and other corticosteroids. The long duration of suppression may have important consequences when attempting to establish withdrawal times following administration of synthetic glucocorticoids in racehorses if the criteria are based on concentrations that reflect the absence of measurable physiologic effects. The pharmacokinetic-pharmacodynamic model in this study describes the pharmacokinetics of TA and associated changes in plasma concentrations of endogenous corticosteroids after IV, IA, or IM administration of TA in horses.

References


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