The monitoring of blood lactate concentrations has become an established component of critical care in equine practice, especially with the validation of point-of-care devices for horses. Blood lactate measurements now are frequently used to assess tissue perfusion, guide initial fluid resuscitation, and help formulate prognoses in horses. Several studies have shown that blood lactate concentration is associated with outcome in adult horses and foals.

Dexamethasone is a corticosteroid often used in equine practice to treat a variety of diseases such as recurrent airway obstruction, inflammatory airway disease, or hemolytic anemia, with suggested dosages ranging from 0.05 to 0.1 mg/kg q24h. A previous study in dogs showed that administration of prednisone caused a statistically significant increase in lactate concentrations, whereby increased rates of glucose production and utilization lead to increased production of pyruvate and lactate.

Given that blood lactate concentrations often are monitored in sick horses and given the common use of corticosteroids in the treatment of various diseases, it is important to know whether the administration of dexamethasone has an impact on blood lactate concentration in horses. The treatments of type A and type B hyperlactatemia differ, and overly aggressive fluid therapy to correct lactate concentrations in cases of unrecognized type B hyperlactatemia is likely to be successful and could be dangerous. Additionally, failure to recognize type B hyperlactatemia could lead to perceived treatment failure or attribution of a worse prognosis than is warranted.

Effect of Dexamethasone on Resting Blood Lactate Concentrations in Horses

K. Mizen, J. Woodman, S.R. Boysen, C. Wagg, P. Greco-Otto, R. Léguillette, and M.-F. Roy

Background: Blood lactate concentration is a marker of tissue perfusion and helps guide therapeutic interventions in critically ill horses. In both humans and dogs, administration of corticosteroids can increase blood lactate concentration, leading to type B hyperlactatemia. This effect could be a consequence of the impact of corticosteroids on glucose metabolism.

Objectives: To investigate the effects of daily IM dexamethasone administration on blood lactate and glucose concentrations in horses.

Animals: Nine healthy adult horses.

Methods: A randomized, blinded, controlled, cross-over study design was used. Horses were randomly assigned to 1 of 2 groups, either receiving 0.05 mg/kg of dexamethasone IM or an equivalent volume of saline, daily for 7 days. Blood was collected to determine lactate and glucose concentrations at baseline, 2 hours after the daily injections and 24 hours after the last injection.

Results: Dexamethasone treatment had a statistically significant effect on lactate (P = .000) and glucose (P = .033) concentrations. The least squares mean lactate concentration was 0.93 mmol/L (95% CI: 0.87-0.99) in the dexamethasone group compared to 0.71 mmol/L (95% CI: 0.70-0.73) for the saline group. A positive relationship between blood lactate and glucose concentrations was identified, with a 0.07 mmol/L (95% CI: 0.05-0.09) increase in lactate concentration per unit increase in glucose (P < .0001) concentration.

Conclusions and Clinical Importance: Dexamethasone induces statistically significant increases in blood lactate and glucose concentrations in healthy horses. Awareness of the potential for corticosteroids to induce type B hyperlactatemia might be important in the management of critically ill horses receiving dexamethasone.

Key words: Corticosteroids; Equine; Glucose; Hyperlactatemia.

Abbreviation:

95% CI 95% confidence interval

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Given that blood lactate concentrations often are monitored in sick horses and given the common use of corticosteroids in the treatment of various diseases, it is important to know whether the administration of dexamethasone has an impact on blood lactate concentration in horses. The treatments of type A and type B hyperlactatemia differ, and overly aggressive fluid therapy to correct lactate concentrations in cases of unrecognized type B hyperlactatemia is unlikely to be successful and could be dangerous. Additionally, failure to recognize type B hyperlactatemia could lead to perceived treatment failure or attribution of a worse prognosis than is warranted.

To our knowledge, the effect of glucocorticoid administration on blood lactate concentrations has not been examined in horses. The objective of our study therefore was to examine the impact of a low dose of...
dexamethasone on resting blood lactate concentrations in healthy horses. Given the possible link between glucose metabolism and hyperlactatemia, we also concurrently measured blood glucose concentrations. We hypothesized that the administration of dexamethasone would result in a statistically significant increase in blood lactate concentrations compared to the injection of saline and that the changes in blood lactate concentration would be associated with changes in blood glucose concentration.

Materials and Methods

Experimental Design

We used a randomized controlled blinded cross-over design. The horses were randomly assigned a number and then randomly distributed into the dexamethasone treatment or saline control group, with 5 horses in each. The investigators were blinded to the treatment that each horse received (dexamethasone or saline).

Animals

Ten adult horses (3 geldings and 7 mares) ranging from 8 to 22 years of age were used. The horses were members of the teaching herd of our institution and were deemed healthy based on physical examination, history, and behavior. The horses were housed in pens as pairs according to temperament to decrease the stress associated with mixing. Horses were fed mixed grass hay twice daily and had ad libitum access to water. By the time of blood sampling, the horses had received their morning feeding. Three days were allotted for acclimation before any handling, injections, or blood collection. A physical examination was performed on each horse daily. Body condition scores for all horses were 5 or 6 on a 9-point scale. All procedures were approved by the Animal Care Committee of our institution. The study started on lactate and glucose concentrations on days 0–8 were compared between the treatment groups using a 2-way repeated-measure ANOVA with Sidak’s multiple comparisons test. The mean difference for each comparison is shown graphically with 95% CI and associated P value. Linear mixed-effects models were used to examine the effects of treatment and time (as fixed effects) on lactate and glucose concentrations (as outcomes), adjusting for the baseline glucose concentration at day 0 in the case of glucose, after accounting for the nested data structure from horses and phases of the cross-over experiment (as random effects). In addition, a similar model was used to study the relationship between lactate and glucose concentrations, adjusting for treatment and time. The assumptions of normality and equal variance were assessed for using the models. The 2-way repeated-measure ANOVA and all the of graphs were performed using Prism version 6.24. The linear mixed-effects model analyses were performed using R version 3.3.0 and the “nlme” package version 3.1. A P value of <.05 was considered to indicate statistical significance.

Results

Blood Lactate

The average time from injection (dexamethasone or saline) to blood collection was 2 hours and 2 minutes with a range of 1 hour 58 minutes to 2 hours and 14 minutes. Blood lactate concentrations at baseline (day 0) were below the detection limit of the lactate reader (<0.8 mmol/L) for all horses (Fig 1A). The daily administration of dexamethasone led to a statistically significant increase in blood lactate concentrations compared to the administration of saline, starting on day 2 and persisting until day 7, before returning to baseline values on day 8, 24 hours after the last dose of dexamethasone (Fig 1A). The daily mean lactate differences between the treated and control group, 95% CI, and associated P values are shown in Figure 1B. Mixed linear model analysis showed that dexamethasone treatment (but not time) had a statistically significant effect on lactate concentration (P = .006). The least squares mean lactate concentration over time (day 1 to day 8) was 0.93 mmol/L (95% CI: 0.87–0.99) in the dexamethasone-treated group compared to 0.71 mmol/L (95% CI: 0.70–0.73) for the saline group.

Blood Glucose

Similar to the changes observed for resting blood lactate concentrations, the daily administration of dexamethasone led to a statistically significant increase in blood glucose concentrations compared to the administration of saline, starting on day 2 and persisting until the end of the study on day 8, 24 hours after the last injection of dexamethasone (Fig 2A). The mean glucose concentration difference between the treated and control

Data Analysis

The individual daily blood lactate and blood glucose concentrations are shown for each horse as scatter plots, with the mean and 95% confidence interval (95% CI; Figs 1 and 2). The mean blood lactate and blood glucose concentrations on days 0–8 were compared between the treatment groups using a 2-way repeated-measure ANOVA with Sidak’s multiple comparisons test. The mean difference for each comparison is shown graphically with 95% CI and associated P value. Linear mixed-effects models were used to examine the effects of treatment and time (as fixed effects) on lactate and glucose concentrations (as outcomes), adjusting for the baseline glucose concentration at day 0 in the case of glucose, after accounting for the nested data structure from horses and phases of the cross-over experiment (as random effects). In addition, a similar model was used to study the relationship between lactate and glucose concentrations, adjusting for treatment and time. The assumptions of normality and equal variance were assessed for using the models. The 2-way repeated-measure ANOVA and all the of graphs were performed using Prism version 6.24. The linear mixed-effects model analyses were performed using R version 3.3.0 and the “nlme” package version 3.1. A P value of <.05 was considered to indicate statistical significance.

Blood Processing

Lactate measurements on whole blood samples were performed within 5 minutes of blood collection using the Lactate Pro blood lactate test metera and test strips. This device has been validated for measuring blood lactate concentration in horses.24 Lactate concentrations ≤0.8 mmol/L read as “low” and were assigned a value of 0.7 mmol/L for statistical analysis. Blood glucose concentration was measured on whole blood within 5 minutes of blood collection using a handheld blood glucose monitoring system that has been validated in horses.24 All lactate and glucose concentrations were determined in duplicate and averaged for statistical analysis.

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group, 95% CI, and associated $P$ value are shown in Figure 2B. Both treatment and time, as well as their interaction, had statistically significant effects on blood glucose concentration, with $P$ values of .033, .003, and .011, respectively. The baseline (day 0) glucose concentration of each horse did not have an effect on subsequent glucose measurements. The least squares mean glucose concentration over time (day 1 to day 8) was 8.01 mmol/L (95% CI: 7.12–8.89) in the dexamethasone-treated group compared to 5.62 mmol/L (95% CI: 4.80–6.44) in saline group.

**Lactate–Glucose Correlation**

Throughout the study, blood lactate concentrations appeared to vary according to changes in blood glucose concentrations (Fig 3). Mixed linear model analysis showed that there was a positive relationship between lactate and glucose concentrations, with a 0.07 mmol/L (95% CI: 0.05–0.09) increase in lactate concentration per unit increase in glucose concentration ($P < .0001$).

**Discussion**

We demonstrated that administration of a low dose of dexamethasone to healthy horses induced a statistically significant increase in resting blood lactate concentrations. These results may be important given the widespread monitoring of blood lactate concentrations in critically ill horses and the common use of dexamethasone in the treatment of various diseases of horses.

Despite the potential important clinical implications of glucocorticosteroid-induced type B hyperlactatemia, only a few studies have documented this phenomenon. In healthy dogs, daily administration of a low (1 mg/kg) or high (4 mg/kg) dosage of prednisone led to a statistically significant increase in blood lactate concentrations up to 4.3 mmol/L for the high prednisone dosage, well above what would be considered normal. These results were similar to an earlier study, also showing an increase in blood lactate concentrations in healthy dogs after administration of methylprednisolone. This phenomenon also is observed in human medicine, where cardiac surgery patients receiving a single perioperative high dose of dexamethasone had increased blood lactate concentration (2.1 mmol/L versus 0.7 mmol/L) and blood glucose concentrations (10.0 mmol/L versus 8.0 mmol/L) after surgery compared to the placebo group. Similarly, an increase in blood lactate concentrations also was observed in humans with Cushing’s disease or after corticosteroid administration. The mechanism by which corticosteroids induce hyperlactatemia is not fully understood. Given the
diverse effects of corticosteroids and the complexity of lactate metabolism. Several factors probably contribute to corticosteroid-induced hyperlactatemia. One potential explanation for dexamethasone-induced type B hyperlactatemia is the hyperglycemic effect of glucocorticoids. Glucocorticoids are stress hormones that are essential to mammalian glucose homeostasis. By stimulating hepatic gluconeogenesis and inhibiting glucose uptake and utilization in muscle and adipose tissue, they allow plasma glucose concentrations to increase, an adaptation that might be important in maintaining optimal brain function in times of stress. Blood glucose and lactate concentrations appear to be closely related, and an increase in blood glucose concentrations in human cardiac surgery patients appears to precede an increase in blood lactate concentrations. In patients with septic or hemorrhagic shock, hyperlactatemia may occur secondary to marked increases in
glucose turnover. Finally, increased gluconeogenesis arising from increased protein metabolism after glucocorticoid administration, and subsequently increased glucose utilization, might also contribute to increased blood lactate concentrations in healthy dogs receiving methylprednisolone. Although a causal relationship cannot be ascertained from our study, a statistically significant positive relationship between blood glucose and lactate concentrations was identified in healthy horses receiving dexamethasone.

Whereas dexamethasone administration was associated with a statistically significant increase in blood lactate concentration in our study, the increase (up to 1.6 mmol/L) was not considered to be clinically relevant. However, administration of higher doses of dexamethasone in horses with steroid-responsive conditions potentially associated with type A hyperlactatemia (eg, purpura hemorrhagica or immune-mediated hemolytic anemia) or in horses with decreased lactate clearance could confound interpretation of blood lactate concentrations, particularly if lactate concentrations were to exceed the value of 5 mmol/L. The time frame of the effect of dexamethasone on blood lactate concentration in horses is not known. The 2-hour postinjection time chosen in our study was based on the known effects of steroid administration on glucose metabolism in horses. The effect of a single low dose of dexamethasone (similar to the dose used in our study) on glucose metabolism in healthy horses can be observed as early as 2 hours postdexamethasone injection with maximal effect at 24 hours postinjection. Furthermore, although the IM route of steroid administration was chosen in our study, we hypothesize that similar results would have been observed if the IV route of steroid administration had been used given that the pharmacokinetics of dexamethasone have been shown to be similar for IV and IM injections.

Our study has a few limitations. First, the method of lactate measurement used had a lower limit of detection of 0.8 mmol/L. In healthy horses, blood lactate concentrations often fall below this level, and thus, in our study, we had several samples that read as “low” on our handheld device. Although we attributed a value of 0.7 mmol/L to these readings, it is quite likely that several of these were lower than 0.7 mmol/L. Therefore, we might have underestimated the difference between the treatment and control groups. Although not affecting the conclusions of our study, the use of more sensitive techniques for measuring blood lactate concentration might identify an even more pronounced effect of dexamethasone on resting blood lactate concentrations in horses. Second, our study used a relatively low dosage of dexamethasone (0.05 mg/kg) despite the fact that many horses with corticosteroid-responsive illnesses often receive, at least initially, a higher dosage of dexamethasone (0.1 mg/kg). Using a higher dosage of dexamethasone in our study might have identified higher increases in blood lactate concentrations that could have been more clinically relevant. Third, daily lactate concentrations can vary slightly throughout the day, and this variation could have affected the results of our study. The inclusion of a control group and our efforts to inject the horses and collect blood at approximately the same time each day should have minimized this potential confounding factor. Fourth, although the handheld meter used in this study has been validated in horses, the use of whole blood samples to measure lactate concentrations can lead to clinically relevant inaccuracies with some lactate meters. These inaccuracies were noted to be greatest when the lactate concentration is >5 mmol/L. Given that all of the lactate concentrations in our study were <5 mmol/L, and that the meter we used is more accurate (in cats and dogs) than the lactate meter used in the abovementioned study, it is unlikely that our results would change if a different methodology was used to measure blood lactate concentration. Finally, we did not continue our blood glucose measurements beyond day 8, even though the blood glucose concentrations were still increased in the dexamethasone-treated group, and future studies should document the time required for the blood glucose concentration to return to control concentrations.

In conclusion, we demonstrated that IM injection of a low dose of dexamethasone increases resting blood lactate concentrations in horses, similar to what has been documented in humans and dogs. The pathophysiology of the increase in blood lactate concentration likely is multifactorial, although glucocorticoid-induced hyperglycemia likely plays a role. Clinicians monitoring blood lactate concentrations should take these findings into account when making decisions regarding diagnosis, care, and prognosis of horses receiving dexamethasone.

Footnotes

a Dexamethasone 5, Vétoquinol, Lavaltrie, QC
b BD Vacutainer, BD Canada, Mississauga, ON
c Lactate Pro, Arkay, Kyoto, JA
d AlphaTRAK 2®, Abbott, Chicago, IL
e Prism 6 for Mac OS X, GraphPad software Inc., La Jolla, CA

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Conflict of Interest Declaration: Authors declare no conflict of interest.

Off-label Antimicrobial Declaration: Authors declare no off-label use of antimicrobials.

References

1. Evans DL, Golland LC. Accuracy of Accusport for measurement of lactate concentrations in equine blood and plasma. Equine Vet J 1996;28:398–402.
2. Kobayashi M. Simple lactate measurement in horses using a portable lactate analyzer with lancet skin punctures under field conditions. J Equine Sci 2007;18:5–11.
6. Tennent-Brown BS, Wilkins PA, Lindborg S, et al. Sequential plasma lactate concentrations as prognostic indicators in adult horses to a referral hospital. J Vet Intern Med 2007;21:1090–1098.

7. Tennent-Brown B, Blood lactate measurement and interpretation in critically ill equine adults and neonates. Vet Clin North Am Equine Pract 2014;30:399–413.

8. Radcliffe RM, Divers TJ, Fletcher DJ, et al. Evaluation of L-lactate and cardiac troponin I in horses undergoing emergency abdominal surgery. J Vet Emerg Crit Care 2012;22:313–319.

9. Tennent-Brown BS, Wilkins PA, Lindborg S, et al. Sequential plasma lactate concentrations as prognostic indicators in adult equine emergencies. J Vet Intern Med 2010;24:198–205.

10. Wotman K, Wilkins PA, Palmer JE, Boston RC. Association of blood lactate concentration and outcome in foals. J Vet Intern Med 2009;23:598–605.

11. Johnston K, Holcombe SJ, Hauptman JG. Plasma lactate as a predictor of colonic viability and survival after 360 degrees volvulus of the ascending colon in horses. Vet Surg 2007;36:563–567.

12. Corley KT, Donaldson LL, Furr MO. Arterial lactate concentration, hospital survival, sepsis and SIRS in critically ill neonatal foals. Equine Vet J 2005;37:53–59.

13. Furr MO, Lessard P, White NA. Development of a colic severity score for predicting the outcome of equine colic. Vet Surg 1995;24:97–101.

14. Parry BW, Anderson GA, Gay CC. Prognosis in equine colic: a comparative study of variables used to assess individual cases. Equine Vet J 1983;15:211–215.

15. Moore JN, Owen RR, Lumsden JH. Clinical evaluation of blood lactate levels in equine colic. Equine Vet J 1976;8:49–54.

16. Wilson ME, Robinson NE. Recurrent airway obstruction and inflammatory airway disease. In: Sprayberry KA, Robinson NE, eds. Robinson’s Current Therapy in Equine Medicine, 7th ed. St. Louis, Missouri: Elsevier-Saunders, 2015:257–267.

17. Boysen SR, Bozetti M, Rose L, et al. Effects of prednisone on blood lactate concentrations in healthy dogs. J Vet Intern Med 2009;23:1123–1125.

18. Ottens TH, Nijsten MW, Hofland J, et al. Effect of high-dose dexamethasone on perioperative lactate levels and glucose control: A randomized controlled trial. Crit Care 2015;19:41.

19. McMahon M, Gerich J, Rizza R. Effects of glucocorticoids on carbohydrate metabolism. Diabetes Metab Rev 1988;4:17–30.

20. Forbath N, Hall JD, Hetenyi G. The effect of methyl-prednisolone on the turnover of lactate and the conversion of lactate to glucose in dogs. Horm Metab Res 1969;1:178–182.

21. Henneman DH, Bunker JP. The pattern of intermediary carbohydrate metabolism in Cushing’s syndrome. Am J Med 1957;23:34–45.

22. Henderson ISF. Diagnostic and prognostic use of L-lactate measurement in equine practice. Equine Vet Educ 2013;25:468–475.

23. Fall PJ, Szerlip HM. Lactic acidosis: From sour milk to septic shock. J Intensive Care Med 2005;20:255–271.

24. Hackett ES, McCue PM. Evaluation of a veterinary glucometer for use in horses. J Vet Intern Med 2010;24:617–621.

25. Kuo T, McQueen A, Chen TC, Wang JC. Regulation of glucose homeostasis by glucocorticoids. Adv Exp Med Biol 2015;872:99–126.

26. Adeva-Andany M, López-Qén M, Fucasta-Calderón R, et al. Comprehensive review on lactate metabolism in human health. Mitochondrion 2014;17:76–100.

27. Revelly JP, Tappy L, Martinez A, et al. Lactate and glucose metabolism in severe sepsis and cardiogenic shock. Crit Care Med 2005;33:2235–2240.

28. Haffner JC, Eiler H, Hoffman RM, et al. Effect of a single dose of dexamethasone on glucose homeostasis in healthy horses by using the combined intravenous glucose and insulin test. J Anim Sci 2009;87:131–135.

29. Soma LR, Uboh CE, Liu Y, et al. Pharmacokinetics of dexamethasone following intra-articular, intravenous, intramuscular, and oral administration in horses and its effects on endogenous hydrocortisone. J Vet Pharmacol Ther 2013;36:181–191.

30. Acierno MJ, Johnson ME, Eddleman LA, Mitchell MA. Measuring statistical agreement between four point of care (POC) lactate meters and a laboratory blood analyzer in cats. J Feline Med Surg 2008;10:110–114.

31. Acierno MJ, Mitchell MA. Evaluation of four point-of-care meters for rapid determination of blood lactate concentrations in dogs. J Am Vet Med Assoc 2007;230:1315–1318.