

Evaluation of plasma catecholamine and serum cortisol concentrations in horses with colic

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Objective—To evaluate plasma epinephrine and norepinephrine concentrations and serum cortisol concentration in horses with colic and assess the relationship of these variables with clinical signs, routinely measured clinicopathologic variables, and outcome in affected horses.

Design—Prospective observational study.

Animals—35 horses with colic.

Procedure—Blood samples were collected within 30 minutes of arrival at the veterinary hospital from horses referred because of colic. Plasma and serum samples were analyzed for cortisol, epinephrine, norepinephrine, lactate, and electrolyte concentrations and acid-base variables. Heart rate at admission and outcome (survival or nonsurvival) were recorded. Univariate logistic regression was used to calculate crude (unadjusted) odds ratios and 95% confidence intervals.

Results—Of the 35 horses with colic, 26 survived. Higher plasma epinephrine, plasma lactate, and serum cortisol concentrations were significantly associated with increased risk of nonsurvival, but plasma norepinephrine concentration was not associated with outcome. Plasma epinephrine concentration was significantly correlated with heart rate ($r = 0.68$), plasma lactate concentration ($r = 0.87$), blood pH ($r = -0.83$), anion gap ($r = 0.74$), and base excess ($r = -0.81$).

Conclusions and Clinical Relevance—The risk of death appears to be greater in colic-affected horses with high circulating concentrations of epinephrine and cortisol. The correlation of epinephrine with other biochemical markers of illness severity and with heart rate indicates that the degree of sympathetic activation in horses with colic can be inferred from routinely measured variables. (*J Am Vet Med Assoc* 2005;227:276–280)

Serum biochemical and hematologic abnormalities in horses with colic include hemoconcentration, metabolic acidosis, abnormally high anion gap and blood lactate concentration, and azotemia.¹⁻⁶ These clinicopathologic abnormalities likely result from a complex interaction between the inciting disease and

the host and are consistent with sepsis, endotoxin toxicosis, or hypovolemic shock.⁷ In humans and laboratory animals, shock, sepsis, or administration of endotoxin is associated with marked increases in plasma concentrations of catecholamines.⁸⁻¹² Although the cardiovascular and metabolic responses of horses to experimentally induced endotoxemia are described^{3,13,14} and it is well recognized that some horses with colic have endotoxemia,¹⁵ we are not aware of reports of plasma catecholamine concentrations in horses with colic. Furthermore, to our knowledge, the association between plasma epinephrine and norepinephrine concentrations and risk of death in horses with colic has not been reported. We speculated that plasma epinephrine and norepinephrine concentrations would be increased in some horses with colic and that the plasma concentrations of these substances would be highest in horses that died or were euthanatized as a result of colic.

High serum concentrations of cortisol are associated with an increased risk of death in human patients with septic shock, and horses with colic have higher serum cortisol concentrations than clinically normal horses.¹⁶⁻¹⁸ To our knowledge, there are no reports of the relationship between serum cortisol concentration and risk of death in horses with colic. We speculated that, compared with horses with colic that survived, horses with colic that did not survive would have higher serum concentrations of cortisol at the time of initial examination in a referral center.

Measurement of plasma catecholamine concentrations and, to a lesser extent, serum cortisol concentration is demanding in terms of time and equipment and is unlikely to become a routine procedure in assessments of horses with colic. Therefore, knowledge of any association between plasma catecholamine concentrations and more readily measured clinicopathologic or physical variables may provide a more convenient means of assessing the degree of sympathetic stimulation in horses with colic.

The purposes of the study reported here were to determine plasma concentrations of epinephrine and norepinephrine and serum concentration of cortisol in horses with colic and to investigate associations between these variables and survival of affected horses. Furthermore, we sought to determine the relationships among easily or routinely measured variables (including heart rate, serum glucose concentration, base excess, and plasma lactate concentration) and indicators of sympathetic (ie, plasma epinephrine and norepinephrine concentrations) and adrenal gland cortical activity (ie, serum cortisol concentration) in horses with colic.

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Materials and Methods

In a prospective observational study, plasma lactate, epinephrine, and norepinephrine concentrations; serum cortisol concentration; and outcome were evaluated in horses with colic. All horses with colic examined at the Veterinary Teaching Hospital of The Ohio State University between June 24 and August 8, 1992, were eligible for inclusion in the study. To be included in the study, a blood sample for measurement of selected variables had to have been collected from the affected horse within 30 minutes of its arrival at the hospital. For eligible horses, age, sex, breed, heart rate at initial evaluation, selected results of routine clinicopathologic analyses, measurements of venous blood pH and gas tensions, and outcome (ie, survived [discharged from hospital alive] or did not survive to discharge) were recorded. Horses that did not survive either died or were euthanatized because of a hopeless prognosis (as determined by the attending veterinarian).

Blood samples were collected via jugular venipuncture into evacuated glass tubes^a containing potassium oxalate and K₃EDTA for measurement of plasma lactate concentration; 7-mL glass tubes containing K₃EDTA and 160 μ L of reduced glutathione (6.0 g/100 mL; pH, 7.4) for measurement of plasma epinephrine and norepinephrine concentrations; and an evacuated glass tube containing no anticoagulants for measurement of serum cortisol concentration. Blood samples were collected into evacuated glass tubes^a containing no anticoagulant for measurement of serum electrolyte (sodium, potassium, and chloride) and creatinine concentrations and into evacuated glass tubes containing K₃EDTA for measurement of Hct and plasma total protein concentration. For measurements of blood pH and partial pressures of carbon dioxide (PvCO₂) and oxygen (PvO₂) and calculation of base excess, a venous blood sample from each horse was also collected anaerobically into a 3-mL plastic syringe, the dead space of which was filled with sodium heparin (1,000 U/mL).

Each blood sample for measurement of plasma lactate concentration was centrifuged at 1,500 \times g for 10 minutes, and an aliquot of the plasma was stored at -80°C until analyzed.^b Each blood sample for measurement of serum cortisol concentration was allowed to clot before centrifugation (1,500 \times g for 10 minutes), and an aliquot of the serum was stored at -80°C until analyzed by use of a validated radioimmunoassay.¹⁹ Each blood sample for measurement of plasma epinephrine and norepinephrine concentrations was centrifuged immediately after collection, and plasma aliquots were stored at -80°C until analyzed via high-performance liquid chromatography.¹⁹ The assay had intra-assay coefficients of variation of 4.3% and 6.8% for norepinephrine and epinephrine, respectively, and interassay coefficients of variation of 4.4% and 8.3% for norepinephrine and epinephrine, respectively. Plasma concentrations of catecholamines and lactate and serum concentration of cortisol were determined within 6 months of sample collection. Serum electrolyte, glucose, and creatinine concentrations were measured by use of a commercial analyzer,^c and Hct and plasma total protein concentration were determined via automated analysis.^d Within 15 minutes of blood collection, blood pH, PvCO₂, and PvO₂ were measured and base excess and bicarbonate concentration was calculated by use of an automated blood gas analyzer.^e Blood gas tensions and pH were not corrected for divergence of the temperature of the analyzer (37°C) from that of the horse.

Statistical analyses—Data regarding continuous variables were examined for normality of distribution before testing of specific statistical hypotheses. Raw data for plasma lactate, epinephrine, and norepinephrine concentrations and serum cortisol concentration were transformed as the natural logarithm of the value before univariate analysis.

Univariate logistic regression was used to determine associations between outcome (survival and nonsurvival) and plasma epinephrine, norepinephrine, and lactate concentrations and serum cortisol concentration. Because of the low number of animals and to prevent inflation of the type I error rate, formal statistical comparisons were not performed for routinely measured clinicopathologic variables. Correlations among plasma lactate, epinephrine, and norepinephrine concentrations; serum cortisol and glucose concentrations; base excess; and heart rate were assessed by use of a Pearson product moment correlation of data from all horses with colic. Data are expressed as means and 95% confidence intervals (CIs), except for data that were transformed, in which case summary data are geometric means and 95% CIs. Data were analyzed by use of commercial statistical programs.^{f,g} Values of $P < 0.05$ were considered significant.

Results

During the study period, 37 horses were examined because of colic. Of these, 2 horses died before blood samples were collected, and these horses were not included in the study. Blood samples for measurement of plasma epinephrine, norepinephrine, and lactate concentrations; serum cortisol concentrations; and routine serum biochemical analyses were collected from 35 horses. Venous blood samples for measurement of blood pH, PvCO₂, PvO₂, and HCO₃ and calculation of base excess were collected from 34 horses (a sample was not collected from 1 horse that died) and measurement of serum electrolyte and creatinine concentration from 33 horses (samples were not collected from 2 horses that survived).

Horses included in the study were 1 to 23 years old; the mean \pm SD ages of survivors and nonsurvivors were 6.0 \pm 5.0 years and 7.2 \pm 4.0 years, respectively. Among the 35 horses, there were 15 females, 10 castrated males, and 10 sexually intact males. The breeds in the study group included Quarter Horse (n = 10), Standardbred (9), Thoroughbred (5), Paso Fino (3), Arabian (2), Trakehner (2), Haflinger (1), Tennessee Walking Horse (1), Belgian (1), and 1 pony. All horses had signs of abdominal pain on initial examination, and none of the horses had extra-abdominal disease as the cause of their signs.

Twenty-seven horses were discharged alive from the hospital, and 8 horses did not survive to be discharged from hospital (1 horse died and 7 horses were euthanatized). One horse was discharged alive to be euthanatized at its home; for data analyses, this horse was considered a nonsurvivor. Therefore, 26 horses survived and 9 horses did not survive. Of the 26 horses that survived, 5 were discharged without a definite diagnosis for the cause of the colic; the diagnoses made in the remaining horses included impaction of the large colon (n = 5), large colon displacement (7), strangulating lesions of the gastrointestinal tract (3), intussusceptions (2), anterior enteritis (3), and ileal impaction. Six of the 9 horses that did not survive had strangulating lesions, 1 had enteritis, 1 had right dorsal displacement of the colon, and a diagnosis was not recorded for 1 horse. None of these horses had impaction colic.

Compared with horses that survived to be discharged from hospital, horses that did not survive had

Table 1—Mean (95% confidence interval [CI]) plasma epinephrine, norepinephrine, and lactate concentrations and serum cortisol concentration in 35 horses with colic that did or did not survive treatment.

Variable	Reference range	Survivors (n = 26)	Nonsurvivors (9)	Crude odds ratio* (95% CI)	P value
Cortisol ($\mu\text{g/dL}$)	0.5–2.0	7.1 (6.1–8.5)	15.4 (9.1–25.7)†	1.28 (1.03–1.61)	0.037
Epinephrine (pg/mL)	NK	14.8 (9.1–24.1)	60.8 (15.0–247)†	1.01 (1.00–1.02)	0.035
Norepinephrine (pg/mL)	NK	197 (163–239)	275 (159–473)	1.01 (1.00–1.01)	0.091
Lactate (mmol/L)	0.5–2.0	1.3 (1.1–3.6)	5.6 (2.5–12.2)†	3.7 (1.1–13)	0.039

*Crude odds ratio for an increase from 1 quartile to the next. †Value significantly ($P < 0.05$) different from that of the group of horses that survived.
NK = Not known (reference range not established).

Table 2—Mean (95% CI) blood gas values, clinicopathologic variables, and heart rate in 35 horses with colic that did or did not survive treatment.

Variable	Survivors (n = 26)	Nonsurvivors (9)	Reference range
Serum glucose concentration (mg/dL)	116 (108–124)	164 (108–220)	83–114
Blood pH*	7.40 (7.39–7.41)	7.31 (7.23–7.39)	7.32–7.45
PvO ₂ (mm Hg)*	36.9 (35.0–38.8)	32.0 (26.5–35.5)	24–39
PvcO ₂ (mm Hg)*	45.6 (43.4–47.6)	48.1 (44.3–52.0)	34–53
HCO ₃ (mmol/L)*	28.8 (27.6–29.9)	25.1 (20.1–30.1)	23–31
Base excess (mEq/L)*	3.78 (2.72–4.84)	–1.15 (6.85–4.55)	–1.0–5.0
Serum sodium concentration (mmol/L)†	141 (139–143)	142 (138–46)	132–142
Serum potassium concentration (mmol/L)†	3.7 (3.5–3.9)	3.7 (3.2–4.1)	2.4–4.6
Serum chloride concentration (mmol/L)†	98.0 (95.7–100.3)	93.3 (88.6–97.8)	97–105
Anion gap (mEq/L)	17.7 (10.4–20.0)	27.5 (20.1–34.8)	7–15
Serum creatinine concentration (mg/dL)†	1.7 (1.4–2.0)	3.9 (1.4–6.4)	0.8–1.7
Hct (%)	38 (35–41)	52 (45–59)	27–44
Plasma total protein concentration (g/dL)	6.9 (6.6–7.0)	6.6 (5.8–7.2)	6.4–7.9
Heart rate (beats/min)	50 (45–55)	75 (51–98)	24–44

*Data not available from 1 horse that died. †Data not available from 2 horses that survived.
PvO₂ = Partial pressure of oxygen in venous blood. PvcO₂ = Partial pressure of carbon dioxide in venous blood.

significantly higher plasma epinephrine and serum cortisol concentrations; however, plasma norepinephrine concentration was not significantly different between the 2 groups (Table 1). With regard to plasma epinephrine concentrations, there were wide ranges of values among horses in both groups; some horses that did not survive had very low plasma concentrations of epinephrine (eg, < 4 pg/mL) at the initial examination, whereas some horses that survived had high concentrations (eg, 222 pg/mL). Plasma lactate concentrations were higher in horses that did not survive. Univariate logistic regression revealed that outcome was significantly associated with plasma epinephrine, plasma lactate, and serum cortisol concentrations but not with plasma norepinephrine concentration.

There were significant linear correlations between plasma epinephrine concentration and each of the following variables: plasma lactate concentration ($r = 0.87$; $P < 0.001$), serum cortisol concentration ($r = 0.70$; $P < 0.001$), plasma norepinephrine concentration ($r = 0.77$; $P < 0.001$), base excess ($r = -0.82$; $P < 0.001$), blood pH ($r = -0.83$; $P < 0.001$), anion gap ($r = 0.64$; $P < 0.001$), Hct ($r = 0.62$; $P < 0.001$), and heart rate ($r = 0.68$; $P < 0.001$). There was no significant linear correlation between plasma epinephrine concentration and serum glucose concentration ($r = 0.23$; $P = 0.19$). Formal statistical comparisons were not performed for values of routinely measured clinical

variables and blood gas analysis in surviving and nonsurviving horses (Table 2).

Discussion

At the initial examination in the present study, horses that subsequently did not survive treatment for colic had significantly higher plasma epinephrine and serum cortisol concentrations than did horses that survived to be discharged from hospital. However, plasma norepinephrine concentrations were not significantly different between the 2 groups. Similar to findings of another study,[†] we detected an association between plasma lactate concentration and outcome in horses with colic. Furthermore, significant linear correlations between plasma epinephrine concentrations and several variables (including plasma lactate concentration, blood pH, base excess, anion gap, serum cortisol concentration, and heart rate) were detected in horses with colic in our study.

Circulating concentrations of epinephrine and norepinephrine in humans, pigs, and rats with experimentally induced or naturally occurring septic shock or endotoxemia are increased, compared with values in unaffected individuals, and those increases are greater in animals or humans with more severe disease.^{8,10,11,20,21} In pigs, increases in plasma epinephrine concentration are strongly associated with increasing severity of septic shock, as indicated by the extent of lactic acidosis and

deterioration in hemodynamic status.⁸ This direct association between the severity of shock (as determined by increases in plasma lactate concentration and heart rate and decreases in blood pH and base excess) and plasma concentration of epinephrine was also evident in the horses in our study. Higher circulating concentrations of epinephrine and norepinephrine are associated with lower survival rates in humans and laboratory animals with septic or endotoxemic shock.^{8,21} In the present study, a similar association was identified in horses with colic, in that higher plasma concentration of epinephrine was associated with increased risk of death.

Although high plasma concentration of epinephrine was associated with more severe disease and greater risk of death in horses with colic, there were wide ranges of values among horses in both groups; some horses that did not survive had very low plasma concentrations of epinephrine (< 4 pg/mL) at initial examination, whereas some horses that survived had high concentrations (222 pg/mL). Although no definitive explanation for these variations in plasma epinephrine concentration can be determined from our data, it is plausible that plasma epinephrine concentration in horses is affected by medications administered prior to the initial examination and by the cause of the colic. For example, detomidine decreases the plasma concentration of epinephrine in clinically normal horses and butorphanol attenuates the increase in serum concentration of cortisol in horses with colic.^{22,23} It is also possible that horses with severe disease and low serum concentrations of epinephrine had sympathetic system exhaustion. The highest plasma epinephrine concentration (516 pg/mL) was measured in a horse that died as a result of small intestinal volvulus and perforation of the ileum, whereas the lowest concentrations of epinephrine (< 4 pg/mL) were measured in horses for which a definitive diagnosis was not made or with impaction of the large colon that survived. The high plasma concentrations of epinephrine in horses with colic likely represent a homeostatic response to tissue hypoxia and decreased mean arterial pressure, although pain may have resulted in increased plasma epinephrine concentrations as it does in other species.²⁴ As indicated by the relationship between plasma epinephrine concentration and risk of death in the present study, higher plasma concentrations of catecholamines are probably a reflection of more severe disease.

Results of a previous study¹⁸ indicated that horses with colic may have serum cortisol concentrations higher than those of clinically normal horses. Further to that finding, the present study in horses has revealed an association between serum cortisol concentration and risk of death from colic. In humans admitted to intensive care units and those with septic shock, high plasma or blood cortisol concentrations are associated with increased risk of death.^{16,25-27} In horses, changes in serum cortisol concentration in response to sepsis, septic shock, or endotoxemia have been minimally investigated. However, in humans and laboratory animal species, sepsis and shock are associated with increased serum or plasma concentrations of cortisol^{9,10} (secondary to increased adrenal gland secretion²⁶), compared with concentrations in unaffected individuals.

Presumably, a similar mechanism underlies the high serum cortisol concentration detected in horses with colic in the present study, although this remains to be determined. In contrast, acutely ill humans frequently have circulating concentrations of cortisol that are less than the lower reference limit²⁷; this apparent hypoadrenocorticism may adversely affect their outcome. Furthermore, it is likely that pain associated with colic resulted in an increase in serum cortisol concentration in the horses of our study.^{23,28}

The significant correlations between plasma epinephrine concentration and other clinicopathologic markers of disease severity indicate that measurement of these variables is sufficient to infer the degree of sympathetic activation in horses with colic. Rather than representing a cause-and-effect relationship, these correlations likely reflect the effect of a common stimulus or stimuli in horses with colic on multiple organ and endocrine systems.

Our data indicate that death as a result of colic in horses is associated with marked increases in plasma epinephrine, plasma lactate, and serum cortisol concentrations, compared with values in horses with colic that survive. High plasma concentrations of epinephrine may be inferred when heart rate is high, blood lactate concentration or anion gap is high, or pH or base excess is low, compared with reference ranges. However, horses with colic that have high plasma concentrations of epinephrine may nevertheless survive.

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- a. Vacutainer, Becton-Dickinson, Parsipany, NJ.
 - b. Lactate analyzer 1500S, Yellow Springs Instruments, Yellow Springs, Ohio.
 - c. DACO-Dart reagent system, Coulter Diagnostics, Hialeah, Fla.
 - d. Coulter counter, Coulter Diagnostics, Hialeah, Fla.
 - e. IL1307, Instrumentation Laboratories, Lexington, Mass.
 - f. Systat, version 9, SPSS, Chicago, Ill.
 - g. Sigmapstat 2.03, SPSS, Chicago, Ill.
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