TITLE: Retrospective evaluation of the association between admission blood glucose and l-lactate concentrations in ponies and horses with gastrointestinal disease (2008-2016): 545 cases

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Association between admission blood glucose and L-lactate concentrations in ponies and horses with gastrointestinal disease

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Running title: Blood glucose and L-lactate concentrations in horses and ponies with colic

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Abstract:

Objectives: A recent study described increased L-lactate concentrations in ponies with gastrointestinal disease compared to horses, but blood glucose (BG) concentrations were not considered. The study tested the hypothesis that BG and L-lactate concentrations are correlated in horses and ponies with gastrointestinal disease and that BG concentrations, not equid type (pony vs horse), are an independent predictor of L-lactate concentrations. It was further hypothesized that equid type was an independent predictor of BG concentrations.

Design: Retrospective study 2008-2016

Setting: University teaching hospital

Animals: Admission data from 545 animals (384 horses and 161 ponies) with gastrointestinal disease.

Interventions: Data collected included signalment, clinicopathological findings on admission and nature and location of the gastrointestinal lesion (strangulating vs non-strangulating and large vs small intestinal lesion). The association between admission blood L-lactate concentrations, equid type (pony or horse) and BG concentrations was investigated in a multivariable model.

Measurements and Main Results: Admission L-lactate and BG concentrations were strongly correlated (n=522; r=0.63; p<0.001). Ponies had significantly higher L-lactate (2.7mmol/L (0.5-18.0mmol/L) versus 1.4mmol/L (0.3-19mmol/L); p<0.001) and BG concentrations than horses (8.4mmol/L (4.2-24.4mmol/L); 151mg/dL (76-439mg/dL) versus 6.9mmol/L (3.4-26.8mmol/L); 124mg/dL (61-482mg/dL); p<0.001). In the multivariable analysis, L-lactate concentrations were significantly and positively associated with admission BG concentrations in all animals and also with equid type. For each mmol/L (18mg/dL) increase in BG, L-lactate concentrations increased by 7.9% (5.9, 9.9); p<0.001. In comparison to ponies, L-lactate concentrations were decreased by 27.7% (37.4, 16.5); p<0.001 in horses. Admission BG concentrations were significantly and positively associated with L-lactate concentrations in all

animals. For each mmol/L increase in L-lactate concentration, BG concentration increased by 6.2% (4.7, 7.6; $p<0.001$). Admission BG concentrations were not associated with equid type. *Conclusion:* Admission BG concentrations and equid type are independent predictors of blood L-lactate concentrations in equids with gastrointestinal disease but their relationship requires further investigation.

Introduction:

Hyperglycemia and hyperlactatemia are common findings in human patients admitted to emergency departments[1]. Initial studies indicated that BG concentrations are an independent risk factor for morbidity and mortality[2-4]. However, the direct relationship between BG and mortality has been questioned, particularly as L-lactate concentrations were not taken into consideration in the aforementioned studies[5, 6]. Indeed, two subsequent investigations found that hyperlactatemia significantly influenced the relationship between BG and mortality[7, 8]. Both studies demonstrated that an independent relationship between hyperglycemia and mortality no longer existed once L-lactate concentrations were considered[7, 8]. The authors concluded that L-lactate concentrations are directly associated with BG concentrations and mortality, and that a direct association between BG concentrations and mortality did not exist. In earlier studies in people, it is likely that a direct association was wrongly assumed due to the omission of L-lactate from statistical analyses. These findings highlight the importance of including both parameters, BG and L-lactate concentrations, in clinical investigations as alterations in one will affect the other. Omission of one parameter could lead to erroneous

conclusions, as demonstrated in the investigations into the association between BG concentrations and outcome in people[7, 8].

A recent study in equids documented higher L-lactate concentrations in ponies with gastrointestinal disease when compared to large breed horses with a similar disease severity[9]. Reasons for the differences in L-lactate concentrations were not immediately apparent but BG concentrations were not included in the analysis. Differences in insulin sensitivity and BG concentrations between ponies and horses have long been identified. Normal ponies respond with higher BG and insulin concentrations to an oral glucose tolerance test compared to large breed horses, suggesting a degree of insulin resistance in ponies. These differences are exacerbated in obese and laminitic ponies[10]. It is conceivable that the previously identified differences in L-lactate concentrations between horses and ponies were indeed secondary to differences in BG concentrations and not equid type (horse versus pony). As BG concentrations were not included, this relationship may not have been uncovered and a direct association between L-lactate and equid type was assumed.

The current study tested the hypothesis that admission BG and L-lactate concentrations are correlated in horses and ponies with gastrointestinal disease and that BG concentrations, not equid type (pony vs horse), are an independent predictor of L-lactate concentrations. It was further hypothesized that equid type was an independent predictor of admission BG concentrations.

Materials and Methods:

Medical records from September 2008 to April 2016 were reviewed retrospectively for any horse or pony presenting to The Royal Veterinary College Equine Referral Hospital with a primary complaint of gastrointestinal disease in which BG and/or L-lactate had been measured on admission. Some of the animals had been included in an earlier study[9]. Data extracted from the medical records included duration of clinical signs, clinicopathological findings on admission and location (small vs large intestine) and nature (strangulating vs non-strangulating) of the intestinal lesion. Equids were classified as pony type by breed and/or height. In animals with absent or ambiguous breed recordings (for example "pony", "Cob", "pony cross", "crossbreed") only animals ≤14 hands (classified as pony type) and ≥15 hands (classified as horse type) were included to avoid misclassification.

Jugular venous blood samples were collected on admission in 2.5ml heparinised syringes (Arterial Blood Sampler)[a] and in-house blood gas analysis and L-lactate, electrolyte, blood glucose and creatinine measurements were carried out on whole blood immediately following collection using a commercial analyser (Stat Profile® Critical Care Xpress)[b]. Other clinicopathological data collected included packed cell volume (PCV), total plasma solid concentration (TS) and results of peritoneal fluid analysis (protein concentration and nucleated cell count). Protein concentrations in plasma and peritoneal fluid were measured using a hand-held refractometer while nucleated cell counts on blood and peritoneal fluid were performed using an automated analyser[c].

Cases were excluded if disease was found to be other than gastrointestinal in origin. Animals <1 year of age and donkeys were also excluded.

Statistical analysis

Data were analyzed using a commercially available software programme[d]. Continuous data are expressed as mean ± standard deviation (if normally distributed) or median and range (minimum to maximum) and categorical data are presented as numbers and percentages. Normality of the data was assessed using the Shapiro-Wilk test and comparisons between ponies and horses were made using a Mann Whitney U test (all continuous data were not normally distributed). Chi-squared test was used to compare categorical measurements between the two groups.

The relationship between admission BG and L-lactate concentrations was evaluated using bivariate Spearman's correlation (*r*).

To achieve a normal distribution for the association analysis, admission blood L-lactate and BG concentrations were $\log_{10}$ transformed (logLact and logBG). Since BG and L-lactate concentrations are interconnected metabolites in the carbohydrate metabolism and each can lead to the generation of the other, two separated linear models were used to investigate their association where logLact or logBG was each in turn used as response variable and the other as a predictor. Equid type (pony vs horse) and other confounding variables were also assessed in both models. All confounding variables with a p-value <0.1 in the univariable analysis were assessed in the multivariable analysis, and manual backward elimination procedure was adopted to obtain the final multivariable model.

Results of the final linear models were displayed as regression coefficient ± standard error. Since the response was $\log_{10}$ transformed, its expected change in the original scale and 95% confidence interval were also presented.

Statistical significance was set at $p \leq 0.05$ for all analyses.

Results:

Five hundred and forty five animals (384 horses and 161 ponies) were included in the study, comprised of 224 mares, 302 geldings and 19 stallions with a median age of 12 years (range 1-33 years). Horse types consisted of Thoroughbreds and Thoroughbred crosses (n=94), Warmbloods and Warmblood crosses (n=86), Irish Sport and Irish Draft horses (n=62), Cobs (n=42), Arabians and Arabian crosses (n=17), other Draft breeds (n=15), Andalusians (n=5), Frisians (n=5) and a number of horses from other breeds (n=57). Pony types were comprised of Welsh ponies (n=45), native pony breeds (n=39), Shetland ponies (n=24), Connemaras (n=9) miniature breeds (n=5) and a number of ponies from other breeds (n=39). Table 1 summarizes clinicopathological findings and details of intestinal lesions divided by horse and pony types; differences in height were pre-determined by definition of "horse" and "pony".

Inspection of scatterplots and Spearman's correlation indicated a strong positive relationship between BG and L-lactate concentrations in all animals (Figure 1; n=522; r=0.63; $p<0.001$) and in ponies (n=154; r=0.52; $p<0.001$) and horses (n=368; r=0.66; $p<0.001$) when analysed separately.

LogLact was significantly associated with equid type in a univariable model ($p<0.001$). Factors included in the multivariable model ($p<0.1$) were equid type, HR, RR, T, PCV, TS, peritoneal protein, creatinine and BG concentrations, reflux volume and location (small or large intestine) and nature (strangulating or non-strangulating) of the intestinal lesion. Sex, age, duration of clinical signs prior to admission and peritoneal WBC were not included ($p>0.1$). In the final multivariable analysis, equid type, admission BG concentration, HR, PCV, T and nature of the

lesion were all significantly associated with logLact (Table 2). For each mmol/L (18mg/dL) increase in BG, L-lactate concentration increased by 7.9%; $p<0.001$.

LogBG was significantly different between equid types in the univariable model ($p<0.001$). Factors assessed in the multivariable model ($p<0.1$) were equid type, age, HR, RR, PCV, peritoneal protein and nucleated cell count and creatinine concentration, reflux volume and location (small or large intestine) and nature (strangulating/non-strangulating) of the intestinal lesion. Sex, duration of clinical signs prior to admission, temperature and TS were not included ($p>0.1$). In the final multivariable model, only blood L-lactate, peritoneal protein concentration, HR and lesion location (small versus large intestine) were significantly associated with logBG (Table 3); equid type was not significantly associated ($p=0.065$). For each mmol/L increase in L-lactate concentration, BG concentration increased by 6.2%.

Discussion:

As demonstrated in investigations in people, a strong positive correlation between blood L-lactate and glucose concentrations was also detected in horses and ponies with gastrointestinal disease. This finding confirms the importance of analysing both parameters together as alterations in one may strongly influence the other. Against the proposed hypothesis, results of this study concurred with those of a previous study that equid type did significantly influence blood L-lactate concentrations. This association was independent of BG concentrations, although BG concentrations were also significantly associated with L-lactate concentrations. As the close correlation between the two parameters highlights, BG and L-lactate concentrations are interconnected metabolites in the carbohydrate metabolism and each can lead to the generation of the other[11, 12]. Anaerobic glycolysis of glucose generates L-lactate as

an end product while L-lactate, via generation of pyruvate, can initiate gluconeogenesis or glycogen formation[13]. In septic human patients, 45% of L-lactate is converted into glucose either by gluconeogenesis or glycogen production[14]. It is therefore conceivable that increased L-lactate concentrations, at least partially, contribute to the increased BG observed in critically ill equids. In equids with gastrointestinal disease and human patients with sepsis or septic shock, increased blood L-lactate concentrations are commonly viewed as markers of tissue hypoxia, presumed to be secondary to hypoperfusion[15, 16]. At least in critically ill people, this view is currently changing and some investigators have suggested that increased aerobic glycolysis secondary to adrenergic stimulation plays a large, if not the largest, role in the development of hyperlactatemia[15, 17]. It is assumed that the underlying mechanism involves stimulation of muscle glycogenolysis through ß-adrenergic activation of glycogen phosphorylase activity to provide quickly available energy substrates[18]. Interestingly, a strong positive association between plasma adrenalin and L-lactate concentrations has also been identified in horses with colic[19]. Other reasons for increased L-lactate concentrations include decreased clearance due to organ dysfunction, the nature of an underlying disease process, presence of drugs or toxins that alter the metabolism or inborn errors of metabolism[20]. The exact source of increased L-lactate concentrations in critically ill equids therefore requires further investigations to confirm or refute the use of L-lactate largely as a marker of tissue hypoxia.

The underlying reason for higher L-lactate concentrations in ponies compared to horses is still unknown. In people, increases in L-lactate concentrations are closely associated with fasting glucose and insulin concentrations, insulin resistance and type 2 diabetes[21-24]. Increases in L-lactate concentration are predictive of development of insulin resistance and might be an independent risk factor for the development of type 2 diabetes[25, 26]. In a mouse model, increased

L-lactate production by adipose and muscle tissue was thought to be at least partially responsible for insulin resistance and diabetes[25]. The origin of the increased L-lactate concentrations in people is still unknown but a decreased aerobic capacity has been suggested[27]. A low oxidative capacity due to impaired mitochondrial phosphorylation has been associated with subclinical or clinical insulin resistance[23]. Although it is currently unknown whether the low oxidative capacity is a consequence or cause of insulin resistance, recent studies have suggested that a low oxidative capacity may precede insulin resistance and diabetes[28, 29]. It is possible that an underlying lower oxidative capacity could contribute to the observed differences in L-lactate, glucose and insulin metabolism between ponies and horses[9, 10]. Another possibility are differences in the metabolic response under sympathetic stimulation. In people, adrenalin directly increases lipolysis and L-lactate release from leg tissue[18] and a similar lipolytic effect after adrenergic stimulation has been observed in horses and ponies[30]. However, in contrast to horse adipocytes, pony adipocytes release free fatty acid in an accelerated linear fashion in response to norepinephrine, which is thought to contribute to the predisposition of hyperlipemia in ponies[31]. It is possible that similar differences in the sympathetic regulation of glucose and L-lactate metabolism exist between horses and ponies, causing tissues in ponies to release L-lactate more rapidly or in larger quantities. Further studies are necessary to investigate these possibilities.

Blood L-lactate concentrations were also significantly associated with lesion nature (strangulating vs non-strangulating), as previously reported in other studies[32]. Concentrations were lower in animals with non-strangulating lesions, supporting the assumption that high L-lactate concentrations in animals admitted for colic are often associated with the presence of a strangulating lesion.

Surprisingly, and against the study hypothesis, equid type had no significant influence on BG concentrations. This was an unexpected finding as previous investigations have suggested differences in insulin sensitivity and BG concentrations between ponies and horses with ponies showing a degree of insulin resistance[10, 33, 34]. Altered insulin sensitivity has also been documented in certain horse breeds, particularly Andalusians, who (like ponies) exhibit insulin resistance, and it is possible that further differences exist, with some horse and pony breeds being more, or less, insulin sensitive than others[33, 34]. Whether these differences are the result of an early disease process or simply represent metabolic differences is currently unknown. Inspection of horse breeds included in this study identified 5 Andalusians but exclusion of these did not alter the results significantly. It is possible that inclusion of more animals would have identified a significant association as the p-value was bordering on significance ($p=0.064$). On the other hand, differences in glucose metabolism associated with equid type may be no longer be apparent once the animal is exposed to the stresses of gastrointestinal disease. The association with other parameters closely linked to disease severity such as heart rate and peritoneal protein concentration suggests this might be the case. Blood L-lactate concentrations were also an important predictor of blood glucose concentrations, as one would expect based on the close correlation.

Admission BG concentrations were also correlated with lesion location, being higher in animals with small intestinal lesions compared to those with large intestinal lesions. It is possible that small intestinal lesions were associated with more intense pain and cardiovascular disturbances, contributing to higher admission BG concentrations in this group.

In summary, admission BG concentrations and equid type were significantly correlated with admission blood L-lactate concentrations in animals with gastrointestinal disease. However,

equid type, even though an independent predictor of L-lactate, was not significantly associated with blood glucose concentrations in equids in this study. The relationship between BG and L-lactate concentrations and the influence of equid type on L-lactate concentrations requires further investigation.

Footnotes:

a: Radiometer Medical ApS, 2700 Brønshøj, Denmark

b: Nova Biomedical U.K., Runcorn, Cheshire, WA7 3FY, UK

c: Scil animal care company GmbH, Viernheim, Germany

d: SPSS version 19 SPSS Inc., Chicago, IL 60606, USA

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Legends:

Figure 1: Scatter plot showing correlation between admission blood L-lactate (x-axis) and glucose (y-axis) concentrations from 522 horses and ponies with gastro-intestinal disease.

Table 1: Comparison between clinicopathological findings and intestinal lesion location and nature between horses and ponies. Data are displayed as median (range) [§]: based on χ^2 test; all other comparisons were carried out using a Mann-Whitney U test. A p-value of ≤ 0.05 was considered significant.

Table 2: Results of a general linear model investigating the association between log-transformed blood L-lactate concentrations (dependent variable), equid type (pony vs horse) and confounding variables. Lesion nature refers to strangulating or non-strangulating intestinal lesions. SE: standard error; a p-value of ≤ 0.05 was considered significant.

Table 3: Results of a general linear model investigating the association between log-transformed blood glucose concentrations (dependent variable), equid type (pony vs horse) and confounding variables. Lesion location refers to small or large intestinal lesions. SE: standard error; a p-value of ≤ 0.05 was considered significant.

Table 1:

	Horse	Pony	p-value
Age	12 (1-31) n=382	13 (1-33) n=160	0.4
Height (cm)	165 (152-188) n=340	135 (71-147) n=139	<0.001
Weight (kg)	553 (334-879) n=365	350 (57-580) n=154	<0.001
Duration of signs (h)	7 (1-240) n=326	8 (1-332) n=139	0.06
Heart rate (bpm)	48 (28-130) n=375	58 (30-120) n=160	<0.001
Respiratory rate (bpm)	20 (6-92) n=366	20 (8-88) n=158	0.002
Rectal temperature (°C)	37.7 (34-39.6) n=336	37.8 (35-39.9) n=146	0.12
Packed cell volume (%)	39 (23-80) n=377	39 (24-70) n=158	0. 95
Total plasma solids concentration (g/L and g/dL)	66 (36-108) n=374 6.6 (3.6-10.8)	68 (37-110) n=155 6.8 (3.7-11)	0.12
L-lactate concentration (mmol/L)	1.4 (0.3-19) n=367	2.7 (0.5-18.0) n=155	<0.001
Creatinine concentration (µmol/L and mg/dL)	121 (73-1445) n=307 1.4 (0.8-16.3)	111 (50-633) n=120 111 (0.6-7.2)	0.35
Blood glucose concentration (mmol/L)	6.9 (3.4-26.8) n=313 124 (61-482)	8.4 (4.2-24.4) n=130 151 (76-439)	<0.001
Peritoneal protein concentration (g/L and g/dL)	15 (0.4-99) n=257 1.5 (0-9.9)	22 (2-58) n=104 2.2 (0.2-5.8)	0.023
Reflux (L)	0 (0-22) n=335	0 (0-12) n=149	0.85
Small intestinal lesion	129	81	0.003[§]
Large intestinal lesion	244	77	
Non-strangulating lesion	269	107	0.52[§]
Strangulating lesion	115	54	

Table 2:

Variable	Regression Coefficient ± SE (log scale)	% change in L-lactate concentration	p-value
Equid type (pony reference)	-0.141±0.032	-27.7 (-37.4, -16.5)	<0.001
Lesion nature (strangulating lesion reference)	-0.116±0.033	-23.4 (-34.1, -11.1)	0.001
Heart rate	0.005±0.001	1.2 (0.7, 1.6)	<0.001
Temperature	0.042±0.02	10.2 (0.6, 20.6)	0.036
Packed cell volume	0.007±0.002	1.6 (0.7, 2.5)	<0.001
Blood glucose concentration	0.033±0.004	7.9 (5.9, 9.9)	<0.001

Table 3:

Variable	Regression Coefficient ± SE	% change in glucose concentration	p-value
Lesion location (large intestine reference)	0.045±0.018	10.9 (2.3, 20.3)	0.014
Heart rate	0.001±0.0001	0.2 (0.1, 0.7)	0.045
L-Lactate concentration	0.026±0.003	6.2 (4.7, 7.6)	<0.001
Peritoneal protein	0.003±0.001	0.7 (0.2, 1.1)	<0.001