

Review of the Clinical Use of Lactate

Robert Paul Franklin, DVM, Diplomate ACVIM; and
John G. Peloso, DVM, MS, Diplomate ACVS

Lactate, a simple laboratory blood test, has been shown to be an extremely useful indicator of survival in human and equine intensive care patients. Rejuvenation in the clinical use of lactate analysis has occurred in recent years. Despite this renaissance, practitioners often struggle with integrating lactate measurement into the clinical setting. This review shows the etiology of lactate, how to measure it, interpretation of results, and implication to critical patients. Authors' address: Equine Medical Center of Ocala, 7107 West Highway 326, Ocala, FL 34482; e-mail: rfranklin@emcOcala.com (Franklin). © 2006 AAEP.

1. Introduction

Recent advancements in equine therapeutics over the past 20 years underscore the importance of a similar timely advance in the practitioner's ability to evaluate, prognosticate, and monitor a patient's response to therapy. Lactate, the ionized form of lactic acid, has been measured in the equine critical care setting since the mid-1970s.^{1,2} However, its interest was relatively short lived, and by the mid-1990s, there became relative lactate ignorance among veterinarians. The use of lactate as a marker of severe disease, a prognostic indicator, and a trigger point for therapy has stood the test of time in human critical care.³⁻⁵ A recent veterinary resurgence in lactate interest has occurred in the horse, primarily stemming from equine practitioner involvement with the colleges of veterinary emergency and critical care and veterinary internal medicine. This wave of interest suggests a review of the use of lactate in clinical practice is warranted.

2. Origin of Lactate

Lactate exists in two forms: the L isomer, L-lactate, commonly found in mammalian species and a

D isomer, D-lactate, which is generated by eukaryotic organisms. Lactate is generated by skeletal muscle, erythrocytes, the brain, and the gut. In a normal setting, aerobic metabolism converts pyruvate through the citric acid cycle to generate 38 molecules of ATP. This process is facilitated by the enzyme pyruvate dehydrogenase, an ample supply of oxygen and substrate (glucose), and functioning mitochondria. In relative oxygen-deficient states, anaerobic metabolism fails to convert pyruvate to acetyl-CoA through the citric acid cycle. Instead, two molecules of ATP and two molecules of lactate are generated by the conversion of pyruvate to lactate using the enzyme lactate dehydrogenase.

Lactate is constantly produced during normal metabolic and athletic events. However, lactate levels do not rise until production begins to exceed clearance. Lactate may be used by many organ systems (heart, liver, kidneys) as fuel. Additionally, erythrocytes, devoid of mitochondria, are able to generate small amounts of energy by converting glucose to pyruvate and subsequently two ATP and two lactate molecules. The excess lactate is ex-

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pelled to allow the other organs to recycle its energy resource. Myocytes, hepatocytes, and renal cells, as mentioned above, can immediately recycle generated lactate. Recycling occurs by the process of oxidation whereby lactate is reconverted to pyruvate, which re-enters the citric acid cycle to produce ATP.

Lactate that is not oxidized can be regulated by the liver by use of the Cori cycle. The Cori cycle allows lactate to be converted to glucose through gluconeogenesis; in so doing, lactate's energy is preserved for future use.⁶ Similarly, and notable here, the use of lactated Ringer solution does not in itself contribute to hyperlactatemia. The lactate in this resuscitation fluid is quickly converted to glucose by the liver,⁷ as long as this organ is functioning properly.

It is imperative that we understand how lactate can be generated to comprehend and manage cases of hyperlactatemia. Although widely heralded as the principle source of hyperlactatemia, anaerobic metabolism is only one of several common mechanisms attributable to increased lactate levels. Any mechanism that results in tissue hypoxia may result in hyperlactatemia, such as pulmonary dysfunction, circulatory failure, or the lack of ample oxygen delivery secondary to anemia.

Endotoxemia may also lead to rises in lactate because of blunting of gluconeogenesis, increases in oxygen consumption, and marked elevations of pyruvate production. Through these actions, additional pyruvate is diverted to lactate, resulting in hyperlactatemia. Endotoxin does not actually alter the activity of pyruvate dehydrogenase or dull oxygen uptake as previously perceived.⁸

Hepatic failure will ultimately lead to hyperlactatemia. This may occur in primary liver disease or in those conditions, such as sepsis, hypoxia, hypovolemia, hypothermia, or a combination of these, that limit the cellular capacity of the liver to regulate lactate levels by using the Cori cycle.

Hyperglycemia commonly affects neonates and septic patients. Unexplained, persistent hyperlactatemia is often remedied by correcting elevations in blood glucose with intensive insulin therapy. The mechanism of this form of hyperlactatemia is increased lactate production by adipocytes.⁹

Although D-lactic acidosis is not a common problem in the horse, translocation of D-lactate produced by fermentative bacteria in the hindgut may be detected in clinical monitoring of the blood pH.¹⁰ D-lactate will not register on most conventional lactate analyzers.

Intense exercise leads to the generation of enormous amounts of lactate. This level of production greatly outweighs the ability of the liver to clear lactate. Interestingly, the production of lactate is beneficial because it allows energy creation and continuation of exercise. The production of lactate with exercise does not directly lead to acidosis, nor does the accumulation of lactate in muscle lead to myositis. It is actually the rapid generation of

ATP, and hydrogen ions liberated when it is hydrolyzed, that lead to an acid content greater than that of the body's buffering capacity.¹¹

3. Normal Lactate Levels

The normal concentration of lactate in the resting horse is 1–2 mmol/l. Hyperlactatemia is identified as a moderate rise of lactate to levels of 2–5 mmol/l without acidosis. Lactic acidosis occurs at lactate levels >5 mmol/l and results in metabolic acidosis. Elevations in lactate have been broken down to two categories by Cohen and Woods. Type A hyperlactatemia results from decreased perfusion, and Type B covers all other reasons for elevations in lactate where oxygen and perfusion levels are normal.¹² This method of categorizing elevated lactate levels is not widely used in equine medicine.

4. Measuring Lactate

Indirect measurements have been found to misrepresent hyperlactatemia in a large number of cases.¹³ For this reason it is suggested that the practitioner rely on direct assessments of lactate. Direct measurements are readily available, inexpensive, and accurate. A handheld lactate analyzer^a has been evaluated and found to be accurate in the horse between 0.8 and 20 mmol/l. Results were underestimated when lactate concentrations were >10 mmol/l or packed cell volume (PCV) was >53% in heavily exercised horses.¹⁴ The handheld analyzer was also found to be accurate when compared to a benchmark enzymatic kit and portable blood gas analyzer^b in horses with colic.¹⁵ Limitations were also identified in this study when lactate levels were >10 mmol/l. The portable blood gas analyzer^b was evaluated in exercising horses and compared with in-house analyzers with excellent results.¹⁶

5. Using Lactate in Practice

Lactate is a good indicator of severity of disease. Regardless of the cause (diarrhea, colic, neonatal sepsis, anesthetic, etc.), a patient with hyperlactatemia should be viewed with suspicion for having a possibly more severe problem than initially assessed. The initial lactate values are very helpful in guiding clients' choices for therapy. For example, some cases are presented with strict budgets that must be adhered to. When a patient is found to have extremely high lactate values (>8 mmol/l), a different opinion may be given to the owner to protect them from "throwing good money after bad." Not to say that every horse with lactate levels >8 mmol/l will necessarily die, but every horse with lactate levels >8 mmol/l will require expensive intensive care.

For several years, colic scores were developed and rehashed. The first of these occurred in the mid-1970s.^{1,2} Their findings indicated blood lactate should be used as a matter of determining severity or as a prognostic aid and not in establishing an accurate diagnosis. Dr. Svendsen further com-

mented on 42 horses with colic and concluded lactate, in addition to packed cell volume, was the most interesting data collected when determining a prognosis.¹⁷ Dr. Parry followed this study with a prognostic paper indicating that lactate, when combined with systolic pressure, blood urea nitrogen (BUN), and packed cell volume, accurately classified survival for 93% of the horses studied.¹⁸ The same authors published again in 1983 and found that many variables contribute to colic case assessment, but those assessing cardiovascular function (including lactate) were the best prognostic guides.¹⁹ Dr. Orsini assessed 29 horses with colic and retrospectively analyzed 17 variables to determine that serum lactate and packed cell volume had a combined predictive value of 94%. Packed cell volumes of $\leq 43\%$ and lactate levels of ≤ 3.1 mmol/l compared with packed cell volumes of $\geq 50\%$ and lactate level ≥ 5.7 mmol/l, respectively, differentiated survival from death.²⁰ A paper from Germany further studied lactate in 271 horses with colic. Highly significant prognostic values were found when capillary refill time, pulse rate, heart rate, respiratory rate, hematocrit, hemoglobin, blood lactate, base excess, and anion gap were considered.²¹ Finally, Dr. Furr and others reported on the colic severity score after studying 165 horses. Their model used four variables (heart rate, peritoneal fluid protein levels, blood lactate, and abnormal mucous membrane color) to calculate the scoring chart with very accurate results.²²

Additionally, lactate can be measured in other bodily fluids. Abdominal fluid levels are measured to determine severity of colic. Normal peritoneal fluid contains a lactate level less than that found in the blood.²³ The value of peritoneal lactate has been evaluated in three studies.²³⁻²⁵ In short, horses with strangulating diseases of the intestinal tract will have greatly elevated peritoneal lactate levels. However, severe medical diseases such as anterior enteritis, colitis, and peritonitis may also have elevated lactate levels making this measurement a useful tool, but not an absolute criterion for surgery. The findings of Latson were perhaps the most notable. Although an accurate complicated formula was presented for calculating the likelihood of ischemic bowel, it has not been tried in a population of horses where severe non-surgical intestinal disease is prevalent. The determination of a peritoneal:peripheral lactate ratio, however, is very exciting. This group determined that if peritoneal:peripheral lactate ratios are >1 , there is a very high probability of a severe, abdominally originated disease present. This information has assisted the decision-making in many subsequent colic patients in our hospital. By identifying ratios >1 , we have been much more critical of the surgical decision and have also been able to guide our clients decision-making process more effectively than previously. Ratios >1 will ultimately require at least expensive

medical intensive care or surgery and are unlikely to ever resolve with laxatives and analgesics alone.

Brumbaugh and Benson²⁶ measured lactate from pleural fluid in horses with non-septic pleural disease and those with pleuropneumonia. There were no differences in venous blood lactate and pleural lactate levels in non-septic pleural diseases, but septic pleuropneumonia did reveal that pleural lactate levels were higher than that of venous blood. These findings are again similar to the determination of Latson of a peritoneal:peripheral lactate ratio.

Synovial fluid was evaluated for lactate concentrations in a model of infectious arthritis. Cellular changes preceded biochemical changes as the white blood cell count rose quickly within 24 h, but varied significantly at other time-points. Synovial lactate was found to be diagnostic in the acute phases more so than in chronic stages.²⁷ Lactate measurement to determine septic versus non-septic inflammatory synovitis has been used in the human medical field for >25 yr. Two such papers suggested that lactate levels >7.2 mmol/l are consistent with bacterial infection.^{28,29}

Lactate levels are also very helpful as trigger or end points for therapy. Take a hypovolemic patient for example. When determining whether or not fluid therapy is indicated, one might consider the lactate values as a trigger point. If the patient is hyperlactemic and a fluid bolus is given, endpoint lactate levels can be reassessed to determine if the treatment has been effective in restoring effective circulatory volume. Similarly, anemic, hypoxemic, and endotoxemic patients may have specific therapies instituted based on elevated lactate levels and clinical acumen. Response to treatment may be gauged on clinical and biochemical improvement. This type of trigger and endpoint therapy is constantly used in our intensive care unit. Some critical patients may be reassessed every 30 min to gauge response to treatment, whereas other intermediate care patients may have their values monitored daily to ensure their conditions have not deteriorated.

Veterinarians are constantly asked to give their clients an accurate prognosis. Lactate is helpful as an objective measurement in developing this prognosis in combination with a good physical exam, other laboratory work, and diagnostics as noted in previous citations. As mentioned earlier, initial lactate levels offer some indication of severity of disease. To form an accurate prognosis, human intensivists have found the most rewarding information to come from the information gained with initial and 24-h lactate levels or lactate clearance.^{30,31} Recently, a group from New Bolton Center reported on the survival of foals admitted to the neonatal intensive care unit. From their preliminary data, foals with early lactate clearance (elevated lactate on admission with normal values obtained within 24-48 h) had increased survival compared with

foals with delayed clearance.³² Dr. Corley also reported on neonatal lactate levels in the intensive care unit and discovered that lactate levels on admission were associated with short-term survival, the presence of bacteremia, and evidence of systemic inflammatory response syndrome (SIRS). Lactate clearance was also statistically important because foals with improved lactate levels within 18–36 h were at decreased risk of death or development of SIRS.¹³ Often, a situation is presented where a veterinarian is given a set time or money limit to establish how a case will respond to treatment. This is especially common when dealing with neonates. In this sense, we have relied heavily on lactate levels to guide decision making at that 24-h mark. During this time period, the practitioner has had the opportunity to determine the foal's problems, address them specifically, and look for a response. If the lactate level was initially quite high, say >12 mmol/l, and at 24 h, the lactate level has dropped to <4 mmol/l, I would be very encouraging to the client to continue to invest in the foal's care. If the lactate levels had partially responded, to a level of 8 from 12 mmol/l, I would be less supportive of the foal's favorable prognosis. Unless the client was prepared to invest a substantial amount of money and still take a loss, I would advise against continuing treatment unless physical findings were obscenely favorable. To further this point, if the lactate levels failed to respond, remained around 12 mmol/l or actually increased, I would give a grave prognosis to the client. To reiterate, lactate has become a valuable objective indicator of survival when baseline and 24-h levels (lactate clearance) are assessed in light of physical findings.

In summary, lactate is generated from several identifiable sources. It can be easily measured through direct tests that are inexpensive and portable. Lactate levels can be measured on almost any body fluid, and the information gained can be useful in indicating severity, establishing trigger and end-points in therapy, and establishing a prognosis.

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^aAccutrend lactate analyzer, Sports Resource Group.

^bI-Stat, Abbott Point of Care, East Windsor, NJ 08520.