REVIEW - NARRATIVE

Treatment of Lactic Acidosis: Appropriate Confusion

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BACKGROUND: Lactic acidosis (LA) is common in hospitalized patients and is associated with poor clinical outcomes. There have been major recent advances in our understanding of lactate generation and physiology. However, treatment of LA is an area of controversy and uncertainty, and the use of agents to raise pH is not clearly beneficial.

AIM AND METHODS: We reviewed animal and human studies on the pathogenesis, impact, and treatment of LA, published in the English language and available through the PubMed/MEDLINE database. Our aim was to clarify the physiology of the generation of LA, its impact on outcomes, and the different treatment modalities available. We also examined relevant data regarding LA induced by medications commonly prescribed by hospitalists: biguanides, nucleoside analog reverse-transcriptase inhibitors (NRTIs), linezolid, and lorazepam.

RESULTS/CONCLUSIONS: Lactic acid is a marker of tissue ischemia but it also may accumulate without tissue hypoperfusion. In the latter circumstance, lactic acid accumulation may be an adaptive mechanism—a novel possibility quite in contrast to the traditional view of lactic acid as only a marker of tissue ischemia. Studies on the treatment of LA with sodium bicarbonate or other buffers fail to show consistent clinical benefit. Severe acidemia in the setting of LA is a particularly poorly studied area. In the settings of medication-induced LA, optimal treatment, apart from prompt cessation of the offending agent, is still unclear. *Journal of Hospital Medicine* 2010;5:E1–E7. © 2010 Society of Hospital Medicine.

KEYWORDS: lactic acidosis, sodium bicarbonate, treatment.

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Lactic acidosis (LA) is common in hospitalized patients and is associated with a high mortality.[1,2] Commonly, it is defined as a lactic acid concentration greater than 5 mmol/L with a pH less than 7.35.[3] There are no evidence-based guidelines for the treatment of LA despite progress in our understanding of its pathophysiology.[3–6] This is not surprising, given the uncertainty regarding the impact of LA itself on clinical outcomes. In this regard, it is interesting to note that, despite its well-recognized role as a marker of tissue hypoxia, lactate accumulation appears to have beneficial effects and may function as an adaptive mechanism. This raises the possibility that therapy directed at altering this adaptation may be detrimental. Pursuing "correction" of the pH in LA has been shown to have untoward physiologic effects. These and other ambiguities in the pathophysiology and treatment of LA are the focus of this review.

Lactate Metabolism

The body produces approximately 1400 mmol of lactate daily.[7] Lactate is derived from the metabolism of pyruvate through an anaerobic reaction that occurs in all tissues (Figure 1). The liver is the primary site of lactate clearance and can metabolize up to 100 mmol per hour under normal conditions.[8] There, lactate is converted to glucose to serve as an energy source during periods of hypoxia (Figure 2).[9]

Approximately 20% to 30% of the daily lactate load is metabolized by the kidneys.[10,11] Renal clearance is increased in acidosis[12] and is maintained even in the presence of low renal perfusion.[10,12,13] Renal lactate clearance is primarily through metabolism and not excretion.[10,14]

LA Subtypes

Generally, lactic acid accumulation results from excess lactic acid production and not from reduced clearance.[15] In cases of fulminant liver failure, it is due to a combination of decreased clearance and tissue hypoxia.[16] In the setting of tissue hypoxia, an impairment of mitochondrial oxidative capacity results in the accumulation of pyruvate and generation of lactate. Lactic acid accumulation through this mechanism has historically been described as Type A LA.[7] Hence, in critically ill patients lactate has traditionally been viewed as a marker of tissue hypoxia.[15,17–21] Hyperlactatemia without tissue hypoxia has been referred to as type B LA. This is seen in a variety of circumstances. In sepsis, for example, several studies have shown lactic acid accumulation, despite adequate oxygen delivery.[22–24]

Hyperlactatemia may also occur in cases of "pure" mitochondrial dysfunction, which can be induced by commonly prescribed medications such as the biguanides, nucleoside analog reverse-transcriptase inhibitors (NRTIs), and linezolid.[25–27] Alternatively, lactate generation from metabolism of agents such as propylene glycol is possible. Finally, excessive lactate generation may occur following stress due to altered carbohydrate metabolism, or with respiratory alkalosis.[28–31]
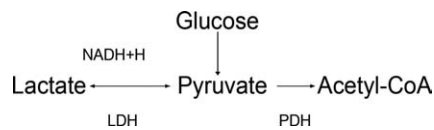
FIGURE 1. Normal generation of lactate.

Lactate: A Metabolic Adaptation

Lactate was traditionally considered only as a marker of tissue hypoxia and anaerobic metabolism.[17] This is certainly the case in situations of poor perfusion such as cardiogenic,[15,18] vasopressor-resistant,[19] or hypovolemic shock.[20,21]

Alternative explanations for lactic acid accumulation, without tissue hypoperfusion, include catecholamine-induced alterations in glycolysis,[32,33] mitochondrial disturbances,[34-36] and increased pyruvate production combined with increased glucose entry into cells.[24,37] In addition, the activity of an enzyme regulating lactate metabolism, pyruvate dehydrogenase kinase, increases in sepsis.[38] This enzyme inactivates the pyruvate dehydrogenase (PDH) complex, which metabolizes pyruvate. Pyruvate and lactate may accumulate as a result. These changes partly explain the generation of LA in sepsis, independent of any effect of diminished tissue perfusion.

Recognizing the body's tendency toward homeostasis, it is appealing to speculate that lactate accumulation is adaptive.[9] A number of findings support this. For example, lactate may act to "shuttle" energy between organs, or between cell types in the same organ. The astrocyte–neuron lactate shuttle and the spermatogenic lactate shuttle are 2 examples of lactate's valuable effects on cellular metabolism.[39] In the astrocyte–neuron lactate shuttle, astrocytes support the increased metabolic demands of neurons through lactic acid production.[40] Specifically, the neurotransmitter glutamate is released by the neurons and taken up by the astrocytes. Astrocytes produce lactate, which then moves back to the neuron to be used as an energy source. Glutamine, also released by the astrocytes, leads to the regeneration of glutamate and the potential to restart the cycle.[39]

Animal and human studies have suggested that, in periods of stress, lactate is the preferential energy substrate in the brain.[41-44] The usefulness of increased lactate production routinely seen in sepsis may thus represent multiple adaptive processes aimed primarily at improving the delivery of energy substrates. Thus, therapeutic strategies aimed specifically at lowering lactic acid levels may prove to have deleterious effects on cellular metabolism.

Impact of LA on Morbidity and Mortality

The poor prognosis in patients with LA is well recognized.[2,45-48] For example, in a study of 126 patients with various causes of LA, the median survival was 38.5 hours and 30-day survival was 17%.[2]

Studies have revealed that LA with low pH is associated with adverse effects on the cardiovascular system, particularly a decrease in cardiac contractility.[49,50] This effect is
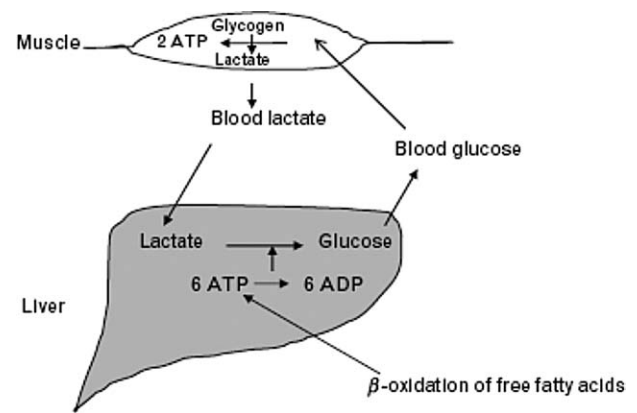

FIGURE 2. Cori cycle (used with permission from Ref. 9).

particularly prominent with a pH below 7.20. In contrast, acidosis in animal models has been shown to limit myocardial infarct size after reperfusion.[51,52] Variable effects of LA on cell death have been found. A worsening of apoptosis in myocytes has been noted;[53] alternatively, protection from hypoxic injury in hepatocytes and myocardium has been observed.[52,54] Thus, although LA is associated with poor outcomes in human studies,[2,45-47] it is still unclear to what extent lactic acid accumulation is a marker of severe illness, an independent effector of pathology, or a mechanism with the potential to serve a protective role.

Available data indicate that lactate itself is not harmful. Studies on infusion of lactate solutions to postoperative patients was shown to be safe.[55] Also, the fact that lactate generation in states of respiratory alkalosis, stress, or altered carbohydrate metabolism without sepsis is not associated with worse outcomes supports the fact that lactic acid alone may not be maladaptive.[28-31]

Similarly, low pH is not necessarily maladaptive. In the postictal state,[56] diabetic ketoacidosis,[57] spontaneous respiratory acidosis,[58] or permissive hypercapnia,[59] low blood pH is not deleterious.

In summary, LA is associated with poor outcomes, and indirect evidence suggests that it is the underlying causative condition rather than the low pH or the lactate that is responsible for the dire outcomes.

Treatment of LA with Sodium Bicarbonate

Since excessive lactic acid generation is accompanied by consumption of plasma bicarbonate and a fall in plasma pH, sodium bicarbonate has been long proposed as a treatment for LA. While theoretically appealing, this strategy has not been validated by studies in animals or humans. Indeed, bicarbonate administration in LA often has been shown to be detrimental.[60,61] The adverse effects of bicarbonate administration in LA, while initially paradoxical, have a number of possible explanations.

First, bicarbonate administration can induce a reduction in intracellular pH.[60,62,63] The mechanism involves bicarbonate's effect to increase carbon dioxide (CO_2) generation

through mass action effect. Because the cell membrane is more permeable to CO_2 than to bicarbonate, intracellular pH falls.[64,65] In sepsis, this intracellular/extracellular pH discrepancy may be more pronounced due to alterations in blood flow.[66] Other reports on outcomes of intracellular pH with bicarbonate therapy show variable effects.[67-72]

Second, to the extent that bicarbonate administration raises extracellular pH, it is associated with a reduction in ionized calcium concentration, since the binding of calcium to albumin is pH dependent.[73] A sodium bicarbonate load administered to patients with LA was associated with a significant fall in ionized calcium concentration, whereas a sodium chloride load was not.[1] This can affect cardiac function, as the latter varies proportionally with calcium levels.[74]

Third, bicarbonate administration may reduce tissue oxygen delivery since the affinity of hemoglobin for oxygen increases as pH rises (Bohr effect).[75] The administration of bicarbonate worsened systemic oxygen consumption in one study[76] and decreased oxygen delivery in another.[75]

Fourth, bicarbonate administration may indirectly increase intracellular calcium concentration. Low intracellular pH (see above) stimulates proton efflux by way of proton transporters and exchangers, increasing intracellular sodium content.[77] A high cell sodium content then may increase intracellular calcium, through the Na/Ca exchanger, impairing cellular function.[77-79] Compounding this, the reduced function of the Na/H ATPase as a regulator of intracellular sodium in sepsis may not be adequate to limit cell swelling.[77]

Against this background of mechanistic concerns with the use of bicarbonate treatment, it is not surprising that clinical outcomes have been inconsistent at best. In animal models of LA, the use of sodium bicarbonate has either negative effects on cardiac output[60,72] or no significant hemodynamic effect when compared to sodium chloride infusion.[67,80,81] One animal study did show some benefit with sodium bicarbonate compared to saline, though all animals subsequently died.[50]

In humans, sodium bicarbonate was studied in 2 randomized trials of sepsis-induced LA.[1,82] In a study by Cooper et al.,[1] 14 critically-ill patients received sequential infusions of sodium bicarbonate or sodium chloride. Neither solution was superior to the other in terms of hemodynamic improvement. No benefit was noted even when analysis was limited to those with very low pH (<7.2). Mathieu et al.[82] randomized 10 critically-ill patients to sequential infusion of either sodium bicarbonate or sodium chloride. Similarly, no significant difference in hemodynamic variables was noted.

When taken together, these studies evaluating sodium bicarbonate in LA fail to show convincing benefit and raise serious questions about its detrimental effects. Extracellular pH may be a misleading marker of success in the treatment of LA, given its direct influence by sodium bicarbonate administration.

Treatment of LA and Use of Other Buffers

Other buffers (Carbicarb, dichloroacetate, and tromethamine [THAM]) have been studied for treatment of LA.

Human studies have not shown superiority of any of the buffers as far as improving pH,[83,84] hemodynamics, or survival.[85]

Treatment of LA by Renal Replacement Therapy

Renal replacement therapy (RRT; dialysis and its variants) has been studied for the treatment of severe acidosis. RRT has a number of theoretical advantages over purely medical therapies in the treatment of LA: it can deliver large quantities of base without contributing to volume overload; it can directly remove lactate from the plasma; and it can mitigate the effect of alkalinization on ionized calcium concentration by delivering calcium.

In critically ill patients with intact liver function, continuous venovenous hemofiltration (CVVH) appears to contribute very little (less then 3%) to overall lactate clearance.[86] While outcome studies are limited, continuous dialysis modalities consistently show improved resolution of acidosis of various types when compared to intermittent modalities.[87,88] As described above, this is related to base administration and is not a surprising finding. There are no studies comparing RRT and medical therapy with respect to clinical outcomes in patients with LA.

Special Situations
Biguanides

Biguanide-induced LA can be due to impairment of hepatic neoglucogenesis, in the case of metformin, or increasing hepatic oxidative phosphorylation, in the case of phenformin.[89] This infrequent complication[90,91] is associated with a high mortality.[92] Proposed therapy has included the use of sodium bicarbonate infusion.[93] In this setting, it is unclear if the use of bicarbonate alone improves clinical outcomes.[94]

Renal replacement therapy in a wide variety of formats has been used to treat this condition.[93,95-101] Metformin has a high clearance during dialysis due to its low molecular weight and lack of protein binding.[97,98,102] Nonetheless, its high volume of distribution suggests a longer dialysis time would be more beneficial if the main goal is reducing metformin levels.[97,103] The limited prospective literature and lack of conclusive evidence about what levels of metformin induce LA makes generalized recommendations about duration of hemodialysis purely speculative.[104]

NRTIs

The use of NRTIs is associated with LA due to impairment of mitochondrial oxidative phosphorylation.[105-108] This uncommon complication, if not recognized early, is associated with a high mortality.[101,109] Investigations are ongoing into agents directed at improving mitochondrial function such as riboflavin, thiamine, and L-carnitine.[110-112] As with biguanide-associated LA, RRT decisions should be individualized based on metabolic circumstances.

Lorazepam

Many intravenous medications are formulated in the alcohol solvent, propylene glycol. Injectable lorazepam has the highest proportional amount of propylene glycol compared with other commonly used agents.[113,114] The kidney normally eliminates 12% to 50% of administered propylene glycol via proximal tubule secretion.[115] The remainder is metabolized by the liver to form pyruvate and lactate.[114,116,117]

When propylene glycol accumulates, as in cases of reduced renal function, it results in hyperosmolarity, LA, and can even induce additional kidney injury (probably through proximal tubular cell necrosis).[118]

LA due to propylene glycol has been reported by many authors and its incidence with high dose intravenous (IV) lorazepam has been estimated to be as high as 19%.[114,116,119,120] This disorder can frequently go unrecognized, as many other factors that induce LA often coincide in such patients. But when identified and promptly addressed, its prognosis seems to be favorable.[114]

The best treatment is prevention, by avoiding the use of IV lorazepam in patients with impaired renal function. Once it is recognized, the drug should be promptly withdrawn. In addition, removal by hemodialysis can quickly lower propylene glycol levels since it is a small, highly water soluble, non-protein-bound molecule.[121] As no rebound in the level is expected, intermittent dialysis should be an acceptable modality.[117]

Linezolid

Recently, Gram-positive bacteria in general and methicillin-resistant *Staphylococcus aureus* in particular have emerged as major causes of nosocomial and community-acquired infections. Linezolid, an oxazolidinone, is increasingly used to treat such infections. Several cases of LA have been associated with linezolid.[27,122,123] and a survey of the Infectious Diseases Society of America (IDSA) Emerging Infections Network members revealed that this complication was commonly encountered.[124] Linezolid causes LA by mitochondrial toxicity[125,126] and risk factors include prolonged exposure and older age. Once the disorder is recognized, the clinician should stop the drug immediately. Chemistries should be monitored frequently in patients on long-term therapy.

Conclusions

Many studies note the association between LA and adverse outcomes.[2,45–47] Though metabolic acidosis from elevated lactate levels may negatively affect organ function, the evidence supporting therapy specifically aimed at increasing pH in these settings is consistently poor.[3,127] Limitations have included small numbers of subjects,[1,82] variable outcomes studied, and the inability to assess intracellular metabolic stability.[1,61] When taking these factors into account it is hard to justify aggressive treatment of LA with mecha-

nisms aimed at raising pH. Literature on the treatment of patients with LA and very low pH (below 7.2) is even more limited.

Moreover, lactate elevations may not represent tissue hypoperfusion. Lactate may have an important role in improving energy metabolism. This represents 1 additional reason to be hesitant when attempting to "normalize" pH in LA; we may be disrupting the body's physiologic response to sepsis. A conflict for clinicians emerges, however, as lactate is often used to define tissue ischemia. Obviously, more specific markers of tissue hypoperfusion would be ideal.

Bicarbonate therapy is an understandably attractive means to "improve" the acidemia, but there are serious mechanistic concerns with it use. Moreover, neither animal nor human studies, limited as they may be, show a convincing benefit. LA in the setting of acute kidney injury may be best treated with renal replacement therapy with bicarbonate-based buffers, but controlled trials are lacking.

A number of commonly used drugs can cause LA. A heightened awareness on the part of clinicians will lead to prompt recognition of these cases, and timely treatment.

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