L-lactate and D-lactate - clinical significance of the difference

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Modern blood gas analyzers often have incorporated sensor technology that allows measurement of plasma lactate concentration. In nature lactate exists in two isoforms: L-lactate and D-lactate.

In all vertebrates, including humans, the L-lactate form is by far the most abundant and pathophysiologically significant, and it is this form that is specifically measured by the lactate sensors in blood gas analyzers and indeed all routine methods used to measure lactate in the clinical laboratory.

The main focus of this brief review is physiological and pathological aspects that distinguish L-lactate and D-lactate. Consideration will be given to the very rare instance when measurement of blood D-lactate is clinically useful and just why the lactate sensor in blood gas analyzers is not useful in such rare circumstance.

Introduction

Lactate, the anion that results from dissociation of lactic acid, is an intracellular metabolite of glucose; specifically it is the end product of anaerobic glycolysis, the final step of which is conversion of pyruvate to lactate by the enzyme lactate dehydrogenase.

In health around 1500 mmol of lactate is produced daily and so long as normal rate of metabolic disposal - principally by the liver and kidneys - is maintained, blood plasma concentration remains within the approximate reference range of 0.5-1.5 mmol/L [1]. Abnormal increase in plasma lactate (called hyperlactatemia) occurs if the rate of production exceeds the rate of disposal.

If hyperlactatemia is sufficiently severe (plasma lactate >5.0 mmol/L), it is associated with acidosis (blood pH <7.35). The condition is then called lactic acidosis. There are many causes of hyperlactatemia and the resulting lactic acidosis but the most common is increased production of lactate from anaerobic glycolysis due to reduced oxygen delivery to tissue cells (tissue hypoxia).

Tissue hypoxia, which is the result of inadequate perfusion of tissues and/or reduced blood oxygen (hypoxemia), is a common feature of many kinds of critical illness so that lactate measurement is most frequently used to monitor tissue oxygenation in the critically ill.

Plasma lactate within the reference range is considered reliable evidence that tissues are adequately oxygenated. Detail of normal lactate production and disposal, along with the pathophysiology of hyperlactatemia and lactic acidosis (the most common cause of metabolic acidosis) is contained in a recent review article [2].

Lactate exists in two isomeric forms

In common with many biologically active molecules (e.g. amino acids, glucose) lactate exists in nature in two stereoisomeric forms due to the presence of an asymmetric carbon atom. Molecules like lactate that exhibit stereoisomerism are optically active, meaning that the two isomers rotate plane-polarized light in opposite directions.

The two lactate isomers are known as L-lactate and D-lactate; L-lactate rotates light clockwise (+) and D-lactate rotates light counterclockwise (-). This is reflected in the sometimes used nomenclature: D(-) lactate and L(+) lactate.

Both forms (stereoisomers) of lactate are produced from and metabolized to pyruvate by the action of the enzyme lactate dehydrogenase (LDH). However, the enzyme is isomer-specific so that production and metabolism of D-lactate requires D-LDH and L-lactate requires L-LDH.

Mammalian cells only contain L-LDH so that in humans the lactate produced is almost exclusively L-lactate. Carbohydrate-fermenting bacterial species (e.g. lactobacillus spp) have by contrast both enzymes and therefore the capacity to produce both D-lactate and L-lactate. Some species produce only D-lactate, some only L-lactate and others both forms.

It was once supposed that the relatively very small amount of D-lactate normally present in the blood of humans (concentration 5-20 μmol/L in healthy adults [3] compared to 1000 μmol/L, i.e. 1.0 mmol/L for L-lactate) is solely derived from exogenous sources (diet and the carbohydrate-fermenting bacteria normally present in the gastrointestinal tract).

However, it is now clear that despite the absence of D-LDH, D-lactate is both produced and metabolized within human cells, albeit in tiny amounts compared to that of L-lactate. Metabolic production of D-lactate in human cells is the result of the methylgloxal pathway, a minor off-shoot pathway of glycolysis that results in nanomolar production of methylgloxal, a toxic product that is converted to D-lactate [4, 5].

In the absence of D-LDH, human cells can metabolize D-lactate to pyruvate by the action of the mitochondrial enzyme D-2-hydroxyacid-dehydroganse [4, 5].

In summary, the small amount of D-lactate normally present in blood is derived from three sources:

- cellular production by the methylgloxal pathway
- diet (foods containing D-lactate, e.g. yoghurts, soured cream, cheese)
- lactate-producing bacterial species normally resident in the large intestine (colon).

Overgrowth of bacteria in the colon is a feature of short-bowel syndrome, the only pathology associated with increase in plasma D-lactate concentration of sufficient severity to cause acidosis (D-lactic acidosis).

Short-bowel syndrome and D-lactic acidosis

Prior to 1979 it was presumed that all cases of hyperlactatemia and lactic acidosis were the result of increase in the predominant L-lactate isoform. In that year the first identified case of lactic acidosis resulting solely from increase in D-lactate rather than L-lactate was reported in a patient who 3 years previously had required life-saving surgery to remove a diseased section of his small intestine [6]. This case provided the first evidence of the now established link between short-bowel syndrome and D-lactic acidosis.

Short-bowel syndrome is a not inevitable complication following surgical resection of more than half the length of the small intestine. Such radical surgery is employed to treat intestinal disease (e.g. Crohn's disease, intestinal cancer, intestinal ischemia), traumatic injury to the intestine, and congenital intestinal defects (e.g. midgut volvulus) evident at birth.

Short-bowel syndrome may also occur in patients who have received surgery (jejunoileal bypass) for severe obesity. This particular kind of surgical treatment is no longer recommended for the morbidly obese, partly because of the risk of short-bowel syndrome.

D-lactic acidosis, defined as plasma D-lactate >3.0 mmol/L in association with metabolic acidosis (blood pH <7.35) [5], is just one of many metabolic derangements that can occur in patients with short-bowel syndrome.

The central defect that explains the development of D-lactic acidosis in those with short-bowel syndrome is carbohydrate malabsorption. Surgical resection reduces the capacity for digestion and absorption of dietary carbohydrate that normally takes place within the small intestine. An increased load of carbohydrate is consequently delivered to the colon where carbohydrate-fermenting bacteria reside.

Within the colon, bacteria convert the increased carbohydrate load to lactate (both D and L isomers), which is then absorbed. The body has ample metabolic capacity, in the form of L-LDH, to deal with the abnormally high influx of L-lactate that results from this increased bacterial production of lactate, but only limited capacity to deal with the increased D-lactate load. Once that capacity is overwhelmed, D-lactate accumulates in blood and eventually acidosis develops.

A massive (hundred-fold) increase in plasma D-lactic concentration to >2.5-3.0 mmol/L is required for development of D-lactic acidosis and symptomatic effect. Symptoms of D-lactic acidosis reflect the neurotoxicity of D-lactate and are evident as recurrent episodes of encephalopathy [4].

During these episodes all patients have reduced mental state, which may range from mild drowsiness or lethargy to coma. Other symptoms vary between patients but may include slurred speech, confusion, inability to concentrate, unsteady gait and headache.

Blood gas analysis reveals a metabolic acidosis with increased anion gap, but crucially plasma lactate is normal. The paradox of normal lactate concentration in patients with D-lactic acidosis is explained by consideration of the routine methods used to measure lactate.

Measurement of plasma lactate

Routine methods used to measure plasma lactate are based on measuring the product of enzymic action on lactate. One of two enzymes is commonly used for these analyses: lactate dehydrogenase, derived from animal tissue, and lactate oxidase derived from bacteria.

The lactate sensors incorporated in blood gas analyzers employ lactate oxidase, which is immobilized on a membrane. On contact with this immobilized enzyme, lactate in the sample is oxidized to pyruvate and hydrogen peroxide. The hydrogen peroxide generated is measured amperometrically by an electrode assembly contained within the sensor.

Crucially for this discussion the enzymes employed in these analyses are L-lactate-specific, they are L-lactate dehydrogenase and L-lactate oxidase. This means of course that only L-lactate is measured. Despite massive increase in plasma D-lactate concentration that may be well in excess of 10.0 mmol/L in some cases of D-lactic acidosis, measured plasma lactate remains within the normal range.

Methods for specific measurement of plasma D-lactate have been developed [7.8]. These assays, which necessarily have to be much more sensitive than plasma L-lactate assays if they are to distinguish normal from abnormal, are mostly based on D-lactate dehydrogenase and are not widely available.

Although some clinical laboratories have the means to measure plasma D-lactate, obviously a necessary step for the diagnosis D-lactic acidosis, there is currently no point-of-care means of measuring D-lactate.

The current relative lack of availability of D-lactate assays might change now that there is growing research interest in the clinical significance of subclinical elevation of plasma D-lactate concentration [8], i.e. plasma D-lactate concentration in the approximate range (50 µmol/L - 2.0 mmol/L).

Summary

- Lactate exists in nature in two stereoisoforms: L-lactate and D-lactate
- The predominant form in humans is L-lactate - blood contains approximately 100 times more L-lactate than D-lactate
- D-lactate is the predominant form of lactate produced by some bacterial species

- Pathological significance of lactate is almost entirely confined to the L-lactate isoform and it is specifically this isoform that is routinely measured at the point of care and in the laboratory
- Short-bowel syndrome is the only condition to be associated with increase in D-lactate of sufficient severity to cause symptoms and acidosis (D-lactic acidosis)
- Blood L-lactate is typically normal in those with D-lactic acidosis
- Measurement of D-lactate should be considered in all patients with unexplained metabolic acidosis (i.e. normal lactate) presenting with symptoms of encephalopathy. In such patients a past history of bowel surgery is highly suggestive of D-lactic acidosis.
- It must be emphasized that short-bowel syndrome is a rare condition and that D-lactic acidosis does not necessarily occur in all those with the condition so that the clinical demand for measurement of D-lactic acid is extremely low. In practically all cases of lactic acidosis it is only the L-lactic acid isomer (i.e. the isomer measured in blood gas machines) that is clinically significant.

A note on the effect of IV solutions containing lactate on plasma D-lactate concentration

The only IV solution routinely used in clinical practice that contains lactate is "lactated" Ringer's solution (alternative name Hartmann's solution) [9]. This fluid, which is isotonic with blood, is used as a resuscitative fluid in those who have suffered significant hemorrhage due to trauma or surgery. The lactate in these solutions is slowly metabolized to glucose and bicarbonate.

The principal value of lactate in Ringer's solution is that the bicarbonate produced prevents or mitigates metabolic acidosis by its buffering action. The lactate is present at a standard concentration of 28 mmol/L. In some preparations the lactate is solely the L-lactate isomer but more commonly it is a racemic mixture of equal amounts of L-lactate (14 mmol/L) and D-lactate (14 mmol/L) [10].

A question arises about the effect that the use of these solutions has on plasma D-lactate measurement. Clearly plasma D-lactate concentration is unaffected if the IV fluid contains only L-lactate.

If the IV solution contains a racemic mixture, best evidence gleaned from limited animal and human studies [10,11] suggests that there is a maximum 13-fold increase in plasma D-lactate concentration and 2-fold increase in plasma L-lactate concentration. Return to preinfusion D- and L-lactate concentration occurs within a few hours of stopping the treatment.

A 13-fold increase is not as significant as might be supposed because, as demonstrated above, at least a hundred-fold increase in plasma D-lactate concentration is required for D-lactic acidosis and symptomatic effect.

In any case, given the rarity of short-bowel syndrome and the limited clinical application of infusing "lactated" Ringer's solution, it is highly unlikely that plasma D-lactate measurement would ever be clinically indicated in a patient receiving "lactated" Ringer's solution.

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