D-Lactic Acidosis in Neonatal Ruminants

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KEYWORDS

• D-lactic acidosis • Ruminants • Neonates • Calf diarrhea • Ruminal drinking

KEY POINTS

- D-Lactic metabolic acidosis in neonatal ruminants is caused by absorption of D-lactic acid abnormally produced and accumulated in the rumen or the intestines as a result of fermentation of easily fermentable carbohydrates.
- D-Lactic metabolic acidosis can develop after ruminal drinking as a result of dysfunction of the esophageal groove reflex.
- D-Lactic metabolic acidosis is a common complication of neonatal calf diarrhea, and it is responsible for most of the clinical signs, such as depression and ataxia.
- Syndromes of D-lactic acidosis without dehydration and with no, or minimal, diarrhea occur in calves, goat kids, and lambs. The cause is so far unknown.
- Serum D-lactate concentrations regularly decrease after complete correction of metabolic acidosis, and when necessary, dehydration, in affected animals.

Videos of calves with metabolic acidosis/D-Lactatemia accompany this article at http://www.vetfood.theclinics.com/

Until the 1980s, D-lactic metabolic acidosis was known to occur only in adult ruminants caused by acute ruminal acidosis as a result of carbohydrate overload.[1] Metabolic acidosis in calves with neonatal diarrhea was believed to be mainly caused by the loss of bicarbonate via the intestines or the formation of L-lactate during anaerobic glycolysis after tissue hypoperfusion in dehydrated calves. Because D-lactate was not considered to be of interest in human or veterinary medicine, routine diagnostic methods targeted the detection of L-lactate only. The development of stereospecific assays for the measurement of D-lactate[2,3] facilitated research in the area, so that our knowledge on the subject has multiplied over the last decade. This article summarizes the available information on D-lactic metabolic acidosis in neonatal ruminants.

The authors have nothing to disclose.

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METABOLISM OF D-LACTATE

In mammals, D-lactatemia is mainly of gastrointestinal origin. The small quantity of D-lactate that is formed in eukaryotic cells through the methylglyoxal pathway seems to be negligible.[4]

Corresponding to the experience with acute ruminal acidosis in veterinary medicine,[1] when in 1979, D-lactic acidosis was first described in humans in a patient affected by short bowel syndrome who presented with neurologic manifestations and severe metabolic acidosis,[5] the accumulation of D-lactate was attributed to the absorption of D-lactate abnormally fermented in the colon and not adequately removed because of the lack of specific metabolic pathways. At that time, it was believed that mammals metabolize D-lactate slowly, because of the lack of the specific enzyme D-lactate dehydrogenase. D-α-hydroxy acid dehydrogenase, an intramitochondrial flavoprotein enzyme, was considered the only nonspecific enzyme that initiates the metabolism of D-lactate.[6,7]

In subsequent decades, evidence was provided by different studies that mammals are able to metabolize D-lactate more efficiently than originally suggested.

Oh and colleagues[8] showed that normal humans were able to metabolize D-lactate at a rate of 1.52 mmol/kg/h at a serum level of 5.2 mmol/L, when DL-lactate was infused intravenously (IV) at a rate of 1.92 mmol/kg/h for each stereoisomer. In this study, 75% to 90% of infused D-lactate was metabolized, depending on the infusion rate. The renal threshold of D-lactate is lower than that of L-lactate, and both stereoisomers compete with each other for renal tubular reabsorption, so that a considerable proportion of D-lactate escaped through the kidneys in this experiment. Giesecke and colleagues[9] found only an average 1.2% to 2.2% of oral DL-lactic acid loads from 50 to 200 mg/kg body weight (BW) in the urine. de Vrese and colleagues[10] established a half-life of 21 minutes for D-lactate in the blood of healthy humans given an oral load of 6.4 mmol/kg BW. When a higher dose of 12.8 mmol/kg BW was used, half-life increased to 40 minutes. Less than 2% of D-lactate was excreted via the kidneys in this study.

As further evidence that D-lactate is readily metabolized by mammals, Flick and Konieczny[11] identified D-lactate dehydrogenases in mammalian tissues, capable of converting D-lactate into pyruvate, and providing therefore a glycolysis bypass for pyruvate formation from dihydroxyacetone phosphate. More recently Ling and colleagues[12] have shown that D-lactate dehydrogenase activity is high in rat liver cells, whereas it is low in brain and heart tissue.

Both stereoisomers of lactic acid are produced in the gastrointestinal tract of ruminants under physiologic conditions, and considerable amounts of D-lactic and L-lactic acid can be ingested with fermented feeds. In their basic studies on lactic acidosis in cattle after engorgement with highly fermentable carbohydrates, Dunlop and Hammond[1] found concentrations of D-lactate of up to 10 mmol/L in the blood of affected animals.

After separate infusion of the sodium salts of the 2 stereoisomers, a slower decline in blood concentration followed the infusion of sodium D-lactate. Later, it was shown that the volume of distribution for D-lactate after a single IV injection of DL-lactate was 23.5% and 24% of BW in a cow and in sheep, respectively, and 31.5% in 4 goats.[13] The latter finding was most probably because the goats that were used in this experiment were younger. The half-life of D-lactate increased with increasing concentrations of D-lactate, and goats eliminated D-lactate twice as fast as sheep and the cow in this study.[14] The renal threshold concentrations of D-lactate show differences between species, but in general, they are about half as high as the values for L-lactate. In goats, a renal threshold for D-lactate of 1.9 mmol/L was found, whereas the value for sheep and cow was 4.3 mmol/L.[15]

Induction of high concentrations of D-lactate by injection of 100 mL of a 25% sodium-D-lactate solution (223.07 mmol) in healthy calves led to a higher plasma half-time of D-lactate (183 minutes) than that reported before. Nevertheless, it was shown in this study that young calves are able to eliminate considerable amounts of D-lactate from the blood. The mean value for renal clearance was lower than that given for glomerular filtration rate[16] and thus gives strong evidence of tubular reabsorption of D-lactate. The fact that total clearance and the clearance of the 2-compartment model were higher than renal clearance indicated metabolic utilization of D-lactate by the calves.[17]

ORIGIN OF D-LACTATE IN NEONATAL RUMINANTS

Regardless of the fact that D-lactate can be theoretically introduced through ingestion of fermented feed (spoiled milk or feeding of yogurt instead of milk), the origin of D-lactate in neonatal ruminants is for practical purposes caused by fermentative processes that occur in the reticuloruminal compartment or in the intestinal tract.

Production of D-Lactate in the Reticulorumen

The mechanisms of the production and absorption of D-lactate from the rumen of adult ruminants suffering from acute ruminal acidosis caused by carbohydrate overload have been known since the middle of the last century.[1] After the first reports of the clinical picture of ruminal drinking, it seemed reasonable to assume that lactic fermentation could also be the cause of ruminal acidosis in calves.

In repeated analyses of ruminal fluid of 37 ruminal drinkers, Dirr[18] found 2 different predominant types of fermentative acidification: lactic and butyric, or both in temporal sequence. However, lactic fermentation was the one found in most ruminal drinkers. On the day of hospitalization of the animal, the concentrations of these stereoisomers was 10 $\pm$ 10 mmol/L for D-lactic acid and 31 $\pm$ 13 mmol/L for L-lactic acid, respectively, in the 20 calves with lactic acid fermentation.

High concentrations of lactic acid (up to values of 60 mmol/L) in the rumen were also reached after experimental force-feeding of whole milk; however, the stereoisomers were not measured separately in this study.[19]

Force-feeding of different oral rehydration solutions led to ruminal acidosis in all cases; however, the extent of acidification and the distribution between D-lactate and L-lactate depended strongly on the composition of the administered solutions. The concentrations of total lactic acid in the ruminal fluids in this experiment reached up to 90 mmol/L, with L-lactate being the predominant stereoisomer.[20] Gentile and colleagues[21] repeated this experiment by force-feeding calves with milk replacers. The ruminal acidosis was accompanied by concentrations of total lactic acid up to around 155.8 mmol/L. The 2 lactate stereoisomers were equally represented. To complete the spectrum of substrate potentially responsible for ruminal acidosis, Gentile and colleagues[22] force-fed whole milk, which led to intraruminal concentrations of lactic acid up to 94 mmol/L, with the 2 lactate stereoisomers equally represented.

All these studies confirmed that similarly to adult cattle, both stereoisomers of lactic acid can be abundantly produced in the rumen when easily fermentable carbohydrates contained in milk, milk replacer, or oral rehydration solutions enter the reticulorumen and are fermented by the ruminal flora in calves.

Production of D-Lactate in Neonatal Calf Diarrhea

Carbohydrates that escape digestion and absorption in the small intestine because of enteritis represent a rich fermentative substrate for colonic bacteria growing in the

large intestine. The subsequent acidification of the intestinal milieu favors lactic acid producers, resulting in generation of larger amounts of L-lactic and D-lactic acids.

Several studies found increased D-lactate concentration in the feces of diarrheic calves when compared with healthy controls,[23–25] which suggests the intestines as a source of D-lactate. The fact that D-lactic metabolic acidosis was shown in diarrheic calves without increase of D-lactate concentrations in the rumen[24,26,27] further strengthens this hypothesis.

In calves with neonatal diarrhea, the risk of developing D-lactic metabolic acidosis is age dependent. In a study including 121 animals,[28] calves that suffered from diarrhea within their first 6 days of life had significantly higher base excess and significantly lower D-lactate concentrations than older calves (**Figs. 1** and **2**). Koch and Kaske[29] described that calves infected with enterotoxigenic *Escherichia coli* were younger and less acidemic than calves suffering from neonatal diarrhea caused by viral or *Cryptosporidium* infections. This finding is compatible with the hypothesis that an increase in production of D-lactate in diarrheic calves results from villous atrophy in the small intestine with maldigestion and malabsorption and subsequent microbial fermentation of substrates in the large intestine.[25]

In a study investigating D-lactate concentrations throughout the gastrointestinal tract of calves that have been euthanized for various medical reasons,[30] increased D-lactate concentrations were found throughout the gastrointestinal tract in some calves. In these calves, significantly more gram-positive rods could be found in the abomasum, the distal part of the jejunum, the cecum, and the colon when D-lactate was present (>3 mmol/L), compared with cases with negligible concentrations of D-lactate at the respective locations. It can only be speculated as to whether D-lactate is produced throughout the whole intestinal tract, or only in circumscribed areas and subsequently distributed by means of intestinal motility.

Production of D-Lactate in Acidosis Without Dehydration Syndromes

It is likely that D-lactic metabolic acidosis without dehydration and no or minimal diarrhea in the different ruminant species is also caused by overproduction of D-lactate in the intestines. Goat kids with D-lactic acidosis (floppy kid disease [FKD]) had

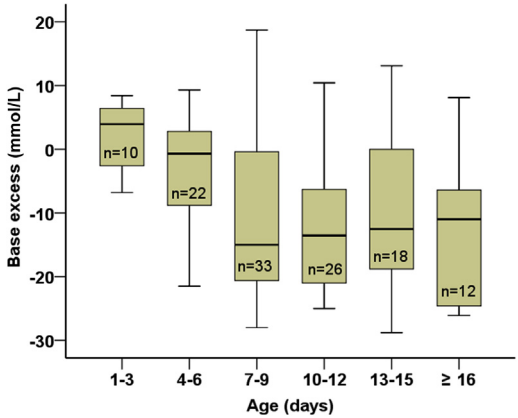

Fig. 1. Base excess concentrations in relation to age in 121 calves with neonatal diarrhea. (*From* Trefz F, Lorch A, Feist M, et al. Metabolic acidosis in neonatal calf diarrhea–clinical findings and theoretical assessment of a simple treatment protocol. J Vet Intern Med 2012;26:166; with permission.)

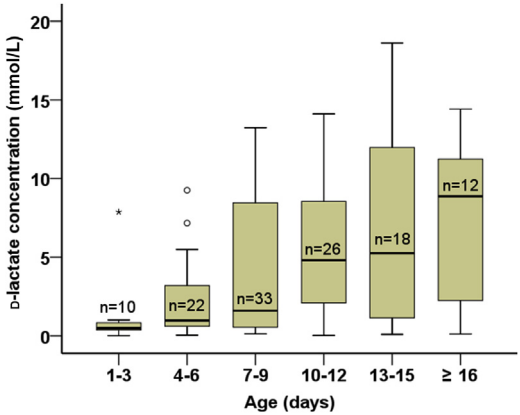

Fig. 2. D-Lactate concentrations in relation to age in 121 calves with neonatal diarrhea (○ indicates mild outliers; * indicates extreme outliers). (*From* Trefz F, Lorch A, Feist M, et al. Metabolic acidosis in neonatal calf diarrhea–clinical findings and theoretical assessment of a simple treatment protocol. J Vet Intern Med 2012;26:166; with permission.)

significantly greater colony-forming unit counts for enterococci, streptococci, staphylococci, and lactobacilli in their feces than healthy kids, which points to dysbacteria of unknown origin as the cause of the D-lactate accumulation in these animals.[31] However, the underlying pathophysiologic mechanisms leading to the suggested shift in the intestinal bacteria are not known.

CLINICAL SIGNS OF D-LACTATEMIA

Main clinical signs observed in humans with D-lactic metabolic acidosis are altered mental status, slurred speech, ataxia, disorientation, and weakness. In some cases, episodes of hostile behavior occurred.[32]

Ataxia and depression are also the most common clinical signs reported in studies investigating clinical indicators of metabolic acidosis in calves.[33–39]

However, a study on diarrheic calves with moderate to severe acidosis first suggested that D-lactate, rather than metabolic acidosis per se, was associated with impaired posture, behavior, and especially, impairment of the palpebral reflex (Video 1; available online at http://www.vetfood.theclinics.com/), whereas the sucking reflex appeared to be influenced by dehydration and metabolic acidosis.[40]

In the meantime, this hypothesis was confirmed by a series of experimental studies:

Experimentally induced severe D-lactatemia without acidosis resulted in profound changes in posture and behavior in 5 healthy calves, which could be clearly differentiated from a control group receiving 0.9% sodium chloride. All experimental calves showed impaired palpebral reflex (Video 1), with 3 calves somnolent and the remaining 2 appeared quiet and withdrawn. All calves had a staggering, drunken gait (Video 2; available online at http://www.vetfood.theclinics.com/), which was marked in 4 calves. In 4 calves, long periods of motionless or slightly wavering/tottering standing with lowered head and drooping ears were recorded (Video 3; available online at http://www.vetfood.theclinics.com/). Four calves lay down more often or for longer periods than control calves and needed help to rise. All but 1 calf assumed unphysiologic postures while standing (eg, sawhorse stance) or lying (eg, 1 foreleg extended backwards parallel to the body) for prolonged periods. No impairment of the sucking reflex could be

observed in any of the calves. In this blinded study,[17] calves received an injection of 100 mL of a 25% sodium-D-lactate solution (223.07 mmol).

Induction of hyperchloremic metabolic acidosis with a mean base deficit of up to 22.4 mmol/L with an IV infusion of 4000 mL of a solution containing 400 mmol HCl in 0.9% NaCl over a period of 80 minutes in healthy calves did not cause any central nervous system signs (Video 4; available online at http://www.vetfood.theclinics.com/).[41] However, in prolonged HCl-induced metabolic acidosis, a mild depression of neurologic function could be observed.[42] In this study, acidosis was produced by infusion of either isomolar DL-lactic acid, L-lactic acid, or HCl, respectively, over a period of 6 hours. Only DL-lactic acidosis was associated with severe disturbances in neurologic functions (ie, ataxia, and depressed menace, palpebral and tactile reflexes), whereas either form of acidosis triggered depression of the sucking reflex.[42]

The fact that the impairment of the palpebral reflex (Video 1) is highly specific for D-lactic metabolic acidosis was confirmed recently by Trefz and colleagues,[43] who described a clinical picture characterized by general weakness similar to D-lactic metabolic acidosis in diarrheic calves, which is caused by hyperkalemia. The impairment or promptness of the palpebral reflex was found to be a good clinical indicator that allows a distinction to be made between these 2 disorders. Potassium and D-lactate concentrations are negatively correlated in diarrheic calves, which makes the occurrence of D-lactic acidosis and hyperkalemia simultaneously unlikely.[44]

PATHOGENESIS OF NEUROLOGIC SIGNS IN D-LACTATEMIA

Abeysekara and colleagues[42] have shown that D-lactate values in cerebrospinal fluid of calves correlated to serum concentrations after infusion of DL-lactic acid, although cerebrospinal fluid concentrations were lower and also lagged behind changes in serum concentrations.

It was hypothesized that D-lactate interfered with pyruvate metabolism because of the similarities between inherited and acquired abnormalities in pyruvate metabolism and D-lactic metabolic acidosis.[45] Studies on mitochondria from different rat tissues have recently confirmed that D-lactate is not only a poor substrate for energy production in the brain when compared with pyruvate and L-lactate but its presence also impairs the energy production from pyruvate and L-lactate.[12] These findings, together with indications that it is L-lactate, and not glucose, that is preferentially metabolized by neurons in the brain of mammals,[46,47] strengthen the hypothesis that the neurologic signs of D-lactic metabolic acidosis are caused by impairment of the energy production in the neurons.

CLINICAL SYNDROMES CAUSED BY D-LACTIC METABOLIC ACIDOSIS IN NEONATAL RUMINANTS

D-Lactic Metabolic Acidosis in Ruminal Drinkers

Fermentative intraruminal disorders (ruminal acidosis) that occur when dysfunction of the esophageal groove reflex allows milk to spill into the reticulorumen (ruminal drinking) instead of being delivered directly into the abomasum can be a starting point for D-lactic metabolic acidosis in young calves.[22,48]

Although the first descriptions of ruminal drinking were in veal calves,[49] D-lactic metabolic acidosis in ruminal drinkers has since been found[18] to occur mainly when the dysfunction of the reticular groove reflex is a complication of various primary diseases (particularly neonatal diarrhea) in artificially fed dairy calves. The early studies on reticular groove dysfunction–induced ruminal acidosis were not accompanied by the determination of serum D-lactate, but the clinical descriptions reported at that time

might support that assumption. Ruminal drinking syndrome in veal calves was reported as a chronic disease characterized mainly by unthriftiness, poor appetite, retarded growth, a dull hair coat, and claylike feces.[49] On the contrary, ruminal drinking as a complication of various primary diseases in dairy calves was described as an acute process characterized by weakness, depression, prolonged recumbency, reluctance to move, inappetence, dehydration, cardiocirculatory collapse, and frequent lethal outcome.[18] This clinical picture is similar to the clinical picture that was later described as typical for D-lactic metabolic acidosis.[40]

Two forms of ruminal acidosis in calves have therefore been differentiated: an acute and a chronic form.[50] In acute ruminal acidosis, the dysfunction of the esophageal groove usually occurs secondary to diseases with systemic effects, such as neonatal diarrhea,[51] primary anorexia, and force-feeding,[52,53] or painful situations (eg, painful cough, otitis, or phlebitis of the jugular vein).[50] In chronic ruminal acidosis, the failure of the reticular groove reflex occurs in initially healthy calves and is caused by stress factors (such as prolonged transportation to assembly centers and onwards to fattening units or new groupings) or suboptimal feeding practices (eg, irregular feeding times, poor quality milk replacer, cold temperature of the milk, drinking from an open bucket).[54]

The first evidence for esophageal groove dysfunction as a severe complication of neonatal diarrhea was provided by Dirksen and Dirr in 1989.[51] In their study, 28 (11.2%) of 249 calves affected by neonatal diarrhea were confirmed as in addition suffering from ruminal acidosis. Although the clinical findings were not reported, the severity of the condition can be deduced by the fact that 11 (39.3%) of the 28 ruminal drinkers died or had to be euthanized during the hospitalization, as opposed to less than 20% in uncomplicated diarrhea.

Acute ruminal acidosis can also be induced by force-feeding of calves that are anorexic because of underlying diseases, in which case the prognosis deteriorates even further.[55,56]

A series of experiments aimed to investigate the clinical repercussions of ruminal acidosis caused by ruminal drinking indicated that the composition of the liquid entering the reticulorumen is likely to be one of the factors influencing the severity of the clinical signs.[19–22] The most distinct clinical signs (marked depression, severe dehydration, absence of sucking reflex, lack of appetite, prolonged recumbency) were observed after intraruminal administration of whole milk.[19,22] After force-feeding of milk replacer, clinical findings were limited to transitory dullness and reduced growth rate when compared with control calves,[21] and also the intraruminal administration of oral rehydration solutions provoked less severe clinical signs than that of whole milk.[20]

In a retrospective study on 293 calves younger than 4 weeks, in which ruminal acidosis (pH<6) was diagnosed on hospitalization, Gentile and colleagues[48] found a high anion gap metabolic acidosis, with the highest values in the group of calves with ruminal pH less than 5. Metabolic acidosis was not only present in animals with diarrhea or with a history of diarrhea but also in the group of calves admitted without any history of diarrhea. In this group, 46 of 91 calves (50.5%) showed metabolic acidosis, with the highest prevalence in the subgroup with ruminal pH less than 5 (39/54 = 72.2%). Because the measured L-lactate values were within the physiologic range, D-lactate was suspected as the cause of the increase of the anion gap; however, serum D-lactate concentrations were not available. A similar conclusion was drawn by Stocker and colleagues,[57] who found a high anion gap metabolic acidosis in 50 calves with chronic indigestion caused by ruminal drinking. Neither of the lactate stereoisomers was determined in this study. A mild metabolic acidosis was also

observed after prolonged intraruminal administration of milk replacers.[21] Only L-lactate was measured in this study, which constantly remained within the physiologic range.

Gentile and colleagues[22] were able to provoke severe D-lactic metabolic acidosis in 8 of 9 experimental calves after intraruminal administration of whole milk. The most severe metabolic aberrations were reached after the first 10 days of the study, during which the pH of the ruminal fluid was constantly less than 4.5. At this point, mean calculated base excess was −10.0 mmol/L (±7.89), anion gap 22.5 mmol/L (±3.31), and serum D-lactate level 8.5 mmol/L (±2.1). D-Lactatemia reached peak values of 6.75 to 11.5 mmol/L in individual calves. Force-feeding was discontinued in 7 of 9 calves because of profound clinical or metabolic alterations (severe depression, estimated degree of dehydration >10%, absence of sucking reflex, lack of appetite for 2 consecutive feedings, severe metabolic acidosis with calculated actual base excess less than −15 mmol/L). Despite increased D-lactate concentrations, 2 calves developed no distinct clinical signs up to the end of the study at day 17. L-lactate constantly remained within the physiologic ranges in all calves.

It is obvious that D-lactic metabolic acidosis in calves can be caused by ruminal acidosis as a result of fermentation of carbohydrate rich solutions in the reticulorumen. However, because ruminal acidosis most often occurs as a complication of other disorders, it is in many cases difficult to distinguish the contribution of the lactate production in the rumen to the clinical and metabolic alterations in individual cases.

Metabolic Acidosis Without Dehydration Syndrome in Suckler Calves

Schelcher and colleagues[58] confirmed D-lactic acid as the cause of a syndrome of high anion gap metabolic acidosis in suckler calves with no dehydration and no or minimal diarrhea. Mean values of up to approximately 13 mmol/L were found in affected calves, with values of 1.27 ± 1.14 and 2.31 ± 1.61 mmol/L, respectively, for healthy controls in 2 consecutive years. The acidosis without dehydration syndrome was first described in 1984 by Kasari and Naylor,[33] who identified unconsciousness or depression, weakness, and ataxia as the main clinical signs. These investigators identified an increased anion gap; however, they were unable to determine the causative organic acid, because the concentrations of L-lactate, acetate, and acetoacetate were normal, and the concentration of D-lactate was not measured.

D-Lactic Metabolic Acidosis in Neonatal Calf Diarrhea

An investigation[26] into the metabolic consequences of ruminal drinking first showed that D-lactic acidosis existed in neonatal diarrheic calves in the absence of ruminal acidosis. Several studies[25,27,59] have since shown that D-lactic metabolic acidosis is a common occurrence in hospitalized diarrheic calves and that D-lactate concentrations together with occasionally increased L-lactate concentrations largely explain the significantly increased anion gap found in those calves. A study[27] including 300 otherwise unselected calves with neonatal diarrhea admitted to a university hospital found more than half of the calves to have serum D-lactate concentrations higher than 3 mmol/L (**Fig. 3**). In the same study, the subgroup of calves with ruminal acidosis in addition to diarrhea showed significantly higher serum D-lactate concentrations than the calves without ruminal acidosis. However, it was speculated that the ruminal acidosis was not necessarily responsible for the higher D-lactate concentrations. Instead, it was suggested that the ruminal acidosis found in many diarrheic calves was a complication caused by the clinical manifestations of D-lactic acidosis, insofar as the weakness and incoordination caused by increased blood concentrations of

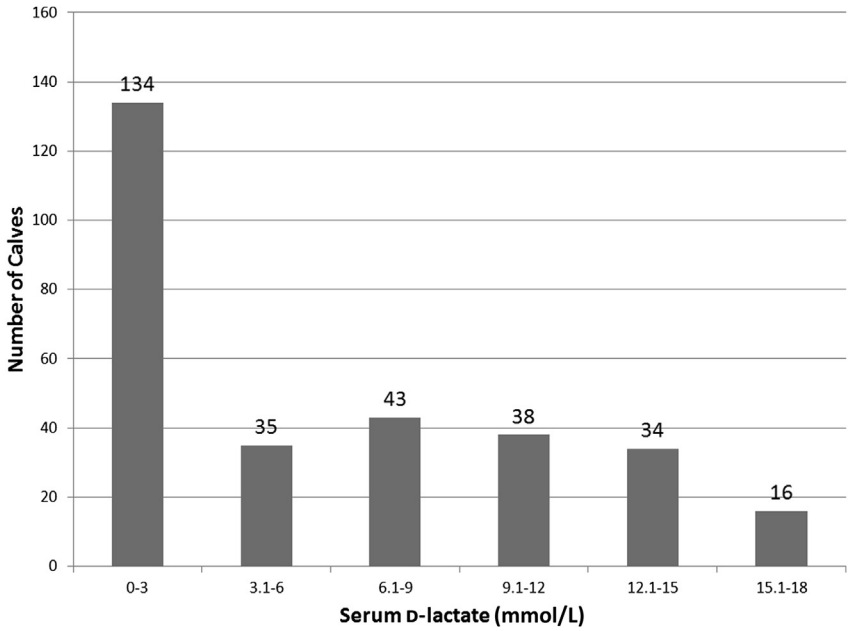

Fig. 3. Serum D-lactate concentrations of 300 calves with neonatal diarrhea. (*From* Lorenz I. Influence of D-lactate on metabolic acidosis and on prognosis in neonatal calves with diarrhoea. J Vet Med A Physiol Pathol Clin Med 2004;51:426; with permission.)

D-lactic acid could interfere with the esophageal groove reflex and thus lead to ruminal drinking.

D-Lactic Metabolic Acidosis in Neonatal Small Ruminants

A syndrome similar to the acidosis without dehydration syndrome in suckler calves was first described in 7 goat kids in 1991.[60] As in calves, this syndrome, now usually referred to as FKD, is characterized by depression and weakness, high anion gap metabolic acidosis, and can be successfully treated with oral or IV therapy with sodium bicarbonate.[60,61] Bleul and colleagues[70] confirmed in 2006 that this syndrome is caused by D-lactic metabolic acidosis. Affected kids do usually not show diarrhea, and the cause of the accumulation of D-lactate remains unclear. Recent reports suggest that the disease can be avoided by hand-rearing kids on cow's milk, milk replacer, or heat-treated milk.[62,63] However, because both studies included only 1 farm each, it is questionable if the results can be generalized.

D-Lactic metabolic acidosis in lambs causing a clinical picture comparable with FKD was first described in 2009.[64] Two neonatal lambs representing a flock problem characterized by somnolence, ataxia or recumbency, and anorexia showed high anion gap acidosis, with base deficit and D-lactate values of 31.9/18.5 mmol/L and 20.1/10.8 mmol/L, respectively. One lamb was in a comatose state at time of admission and was euthanized. The postmortem examination, which included histopathologic examination of the liver, kidneys, spleen, heart, and brain, as well as bacteriologic and parasitologic examinations, showed no abnormalities, with the exception of some oxalate crystals in the renal tubules, which were detected on histopathologic examination. The second lamb recovered after treatment with sodium

bicarbonate. Recently, postmortem results of 10 lambs affected by the same syndrome showed different degrees of nephrosis on renal histopathology in all cases.[65] Nephrosis has not been found in any cases of FKD or acidosis without dehydration syndrome. However, not many postmortem results are described in the literature in kids or calves with these disorders, because in all studies, treatment was performed, and in most cases, it was successful. It has also been confirmed in more cases that D-lactic metabolic acidosis in lambs can be treated successfully by application of sodium bicarbonate.[66]

In lambs with mild to moderate diarrhea, serum D-lactate concentrations were increased, but stayed lower than clinically significant concentrations.[67]

TREATMENT OF D-LACTIC METABOLIC ACIDOSIS

Wherever the site of D-lactate production is throughout the gastrointestinal tract, it is obvious that production and absorption of D-lactate can overcome the capacity of metabolism and excretion in calves, goat kids, and lambs to cause these clinical syndromes. This observation implies that successful treatment can either target decrease of D-lactate production and absorption or increase in metabolism and excretion. D-Lactate concentrations decrease regularly within 24 to 48 hours of initiation of therapy that includes correction of acidosis as 1 component.[66,68–70]

Ewaschuk and colleagues[24] considered low kidney perfusion and increased tubular reabsorption of D-lactate in dehydrated calves as the cause of accumulation. Accordingly, enhancement of renal perfusion by rehydration would trigger D-lactate excretion. On first sight, this argument seems to be valid only for diarrheic calves and not the syndromes described that are not accompanied by diarrhea or clinical signs of dehydration. However, because clinical signs of dehydration lag behind the fluid loss, renal perfusion can be impaired in animals without clinically detectable dehydration. Most studies in which urea and creatinine values were reported showed increased urea concentrations in the absence of clinical dehydration either as a mean within the affected group[35,58,70] or individually in most affected animals.[64,65] In 10 calves with diarrhea and dehydration, urine volume and D-lactate clearance increased significantly within the first 6 hours after initiation of IV fluid therapy,[71] which indicates renal excretion as an important factor in the decline of D-lactate concentrations in dehydrated animals.

In addition to rehydration, correction of metabolic acidosis is the other obvious change that may initiate the decline of D-lactate concentration in acidotic diarrheic calves. It can be speculated that production of D-lactate can be influenced by the correction of metabolic acidosis. It seems possible that a vicious cycle with the following elements may develop: lactic acid is formed in the intestine in higher than normal rates, most probably because of malabsorption of carbohydrates in diarrheic calves or dysbacteria of unknown reason, creating an acidic environment in the intestines (intestinal acidosis with a pathogenesis similar to ruminal acidosis). After absorption of lactic acid, the bicarbonate pool is depleted by buffering, and therefore, less bicarbonate is secreted into the intestines; the intestinal environment remains acidic, and lactic acid–forming bacteria are further favored in their multiplication and activity. The cycle could be broken by therapeutic infusion of bicarbonate, and thus, enhancement of bicarbonate secretion into the gut. This theory is supported in a study[71] involving 10 neonatal calves with diarrhea and D-lactic metabolic acidosis in which fecal D-lactate concentrations and fecal pH were measured in quantitatively collected fecal samples in 3-hourly intervals. After correction of the metabolic acidosis within the first 3 hours of the study period, the median of the fecal pH increased from 6.3 to 6.9 in the feces collected over the next 3-hour period. At the same time, the D-lactate

concentration and the total mass of excreted D-lactate remained unchanged, but decreased considerable in all samples thereafter.

In humans suffering from short bowel syndrome, different treatment strategies have been tried, but nonspecific therapy for metabolic acidosis with bicarbonate has only seldom been reported in this context. Instead, modification of the abnormal intestinal flora by oral application of antibiotics is the most commonly used therapy.[32] Ewaschuk and colleagues[69] discussed the routine use of antibiotics as 1 possible reason for the decline not only in serum D-lactate but also in fecal D-lactate concentration in diarrheic calves observed after therapy was started. However, the same decline in serum and fecal D-lactate concentration was found in 10 calves after IV fluid therapy and correction of acidosis, whereby only 1 of these calves received antibiotic treatment.[71] A recent study,[72] in which only about half of the involved calves with diarrhea were treated with antibiotics, implied that the complete correction of metabolic acidosis and dehydration are likely to be more important for the treatment success than antibiotic therapy. Because rehydration and correction of acidosis are obviously sufficient for successful treatment of D-lactic metabolic acidosis, and use of antibiotics promotes the selection, and subsequent proliferation, of antibiotic-resistant strains of bacteria, the attempt to reduce D-lactate production by oral antibiotic treatment cannot be recommended for this purpose in neonatal ruminants.

Another common therapeutic strategy in the short bowel syndrome aims at reduction of the quantity of substrate for intestinal fermentation by oral fasting with IV alimentation or change of diet.[32] In newer studies[68,71,72] investigating treatment options for diarrheic calves, milk is usually offered throughout the course of treatment, concurrent with best available scientific evidence, which has shown that withholding milk in calf diarrhea can rapidly lead to malnutrition and emaciation.[73,74] However, because calves are generally severely ill when admitted to university hospitals, most probably, most of the animals involved in these studies experience or will have experienced a period of decreased milk intake when therapy is started, which could also contribute to the declining serum and fecal D-lactate concentrations.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.cvfa.2014.03.004.

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