INVITED REVIEW

General overview to treatment of strong ion (metabolic) acidosis in neonatal calves with diarrhea

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Özet

Sen I, Constable PD. İshalli neonatal buzağılarda strong (metabolik) ion asidozisin tedavisine genel bakış. **Eurasian J Vet Sci, 2013, 29, 3, 114-120**

Neonatal buzağı ishallerine bir veya birden daha fazla etken neden olabilir. İshalli buzağılarda strong ion (metabolic) asidozis yaygın olarak gözükür. Strong ion asidozisle ilişkili klinik semptomlar spesifik olmayıp belirsizdir. Fakat strong ion asidozisin şiddetinin tahmininde buzağının yaşı göz önünde bulundurulabilir. Çünkü aynı klinik bulgulara sahip buzağılardan yaşamının ilk haftasındaki buzağılar, bir haftalıktan büyük buzağılara kıyasla daha az asidemiktir. Ayrıca emme refleksi ile baz açığı değeri arasında yakın ilişki bulunmaktadır. Buzağılarda ishalle ilişkili ölümün azaltılmasında en önemli faktörlerden biri uygun oral veya intravenöz sıvıların kullanılmasıdır. Sistemik metabolik asidozisisi düzeltmek için uygun alkalize ajanların kullanılması gerekmektedir. Bikarbonat kandaki H^+ iyonu ile direk reaksiyona girdiğinden dolayı, bikarbonat içeren intravenöz sıvılar şiddetli asideminin düzeltilmesinde oldukça etkilidir. Laktatlı ringer veya asetatlı ringer solüsyonlar ise hafif-orta derecede metabolik asidozisi düzeltmede tercih edilir.

Anahtar kelimeler: Buzağı, ishal, strong (metabolik asidozis) ion, dehidrasyon

Abstract

Sen I, Constable PD. General overview to treatment of strong ion (metabolic) acidosis in neonatal calves with diarrhea. **Eurasian J Vet Sci, 2013, 29, 3, 114-120**

Diarrhea in neonatal calves is due to one or more causes. Strong ion (metabolic) acidosis is common in diarrheic calves. Clinical signs associated with metabolic acidosis are vague and non-specific. However, the calf's age can be used to predict the severity of metabolic acidosis, because one weak old diarrheic calves are less acidemic than older calves despite they have similar clinical signs. Moreover, the suckling reflex is closely associated with base excess parameters. One of the most important factors for decreasing mortality rates associated with diarrhea in calves is parenteral and oral administration of appropriately formulated electrolyte solutions. Inclusion of an alkalinizing agent is required to correct systemic metabolic acidosis. Bicarbonate-containing fluids are more effective at rapidly correcting severe acidemia, since bicarbonate reacts directly with H^+ ions. Lactated Ringers solution or Acetated Ringers solutions can be used to correct mild to moderate acidosis.

Keywords: Calf, diarrhea, strong (metabolic) ion acidosis, dehydration

Introduction

Diarrhea in calves is due to one or more the "big six" causes (Enterotoxigenic *E. coli*; rotavirus; coronavirus; *Cryptosporidium parvum*; *Salmonella enterica*; nutritional) and results in an increased loss of electrolytes and water in the stool, decreased milk intake, and changes in the small intestinal bacterial flora. The net result of these changes is: 1) dehydration (free water loss); 2) strong ion (metabolic) acidosis; 3) electrolyte abnormalities; 4) negative energy balance; and 5) overgrowth of the small intestine with gram negative bacteria. It is important to realize that 30% of calves with diarrhea that are sick (as indicated by decreased suckle, presence of a fever, or weakness) develop *E. coli* bacteremia. Treatment needs to be aggressively directed against each of these 5 factors. Hypothermia may complicate the clinical management whenever calves are raised in cold climates. Calves with diarrhea die because of: 1) septicemia, 2) acidemia, 3) hyperkalemia, 4) prolonged malnutrition and hypoglycemia, and 5) hypothermia. Calves do not die of dehydration; instead they die of the consequences of dehydration. Normalization of hydration status therefore remains an important component of treatment. One of the most important factors in decreasing mortality associated with diarrhea in calves is the proper use of oral and intravenous (IV) fluid therapy (Argenzio 1985, Basoglu et al 2004, Radostits et al 2007, Berchtold 2009, Ok et al 2009, Sen et al 2013).

Dehydration

Dehydration in calves that have diarrhea is accompanied by large decreases in the extracellular fluid volume along with small increases in intracellular fluid volume (Naylor 1987, Constable et al 1998, Smith 2009). The intestinal loss of electrolytes in these calves causes to hypoosmotic extracellular fluids. Hence free water moves from the extracellular fluid (ECF) to the intracellular fluid (ICF) space, thereby increasing the ICF volume. The veterinary practitioner must therefore attempt to clinically estimate the degree of ECF loss in dehydrated calves during physical examination. Attempts to estimate dehydration based on physical examination findings have been around for more than 40 years. In 1965, Watt (1965) evaluated hydration status by assessing the attitude of the calf, eyeball position, skin elasticity, mucous membrane appearance, capillary refill time, and urine production and classified dehydration as mild, moderate, or severe. It was later recognized; however, that these guidelines were subject to error (Buntain and Selman 1980). One of the more accurate predictors of acute dehydration is monitoring change in body weight. Using this principle, Bywater (1983) took the three established categories of severity and assigned weight losses of 1% to 5% for mild dehydration, 6% to 8% for moderate dehydration, and 9% to 11% for severe dehydration. These categories were likely developed based on data that indicated most calf deaths occurred when weight loss was between 12.7% and 13.4% of body weight (Lewis and Phillips 1972, Groutides and Michell 1990, Naylor 2006, Smith 2009, Sen et al 2013). The most accurate methods for assessing dehydration are the extent of eyeball recession into the orbit and skin tent duration in the neck region (Constable et al 1998). Eye recession is measured by rolling the lower eyelid out to its normal position and measuring the distance between the cornea and lower eyelid. The recommended formula to estimate hydration status is: % dehydration = 1.7 x (eyeball recession in mm).

Urea nitrogen and creatinine are metabolic breakdown constituents that can be used to assess the degree of dehydration and to distinguish between prerenal, renal and postrenal uremia. Plasma concentrations of urea nitrogen and creatinine in neonatal calf diarrhea will be elevated depending on severity of the dehydration (Guzelbektas et al 2007, Lorenz and Klee 2007). Following appropriate treatment of diarrheic calves with prerenal uremia, plasma urea nitrogen and creatinine concentrations decline (Radostits et al 2007). In other words, treatment efficacy can be evaluated by serial monitoring of plasma urea nitrogen and creatinine concentrations.

Strong ion (metabolic) acidosis

Strong ion (metabolic) acidosis is commonly occured in diarrheic calves. Calves dying with diarrhea tend to have venous blood pH's between 6.50 and 7.05 (Naylor 2006). Strong ion (metabolic) acidosis is due mainly to hyponatremia, forestomach/intestinal fermentation of lactose and glucose to D-lactate and volatile fatty acids, and intestinal bicarbonate loss. There are minor contributions from lactic acid production in tissues secondary to tissue hypoxia, and decreased acid secretion by poorly perfused kidneys in calves with dehydration (Kasari 1999, Constable 2000). However, serum L-lactate levels are similar in healthy and diarrheic calves, and severe dehydration produces slightly L-lactic acidosis in calves (Kasari and Naylor 1985, Walker et al 1998, Lorenz 2009). The result of strong ion acidosis is progressive central nervous system depression, decreased suckle reflex, ataxia, recumbency, coma, and then death, particularly when plasma D-lactate concentrations are elevated (Radostits et al 2007). The degree of strong ion acidosis can not be predicted with sufficient exactly based on clinical signs of dehydration. A weak correlation between base excess and degree of dehydration is determined (Grove-White and White 1993, Guzelbektes et al 2007, Trefz et al 2011, Bellino et al 2012). Therefore, dehydration and strong ion acidosis should be evaluated, particularly in calves with different clinical signs attributable to D-lactic acidosis (impairment of the palpebral reflex). Clinical signs associated with metabolic acidosis are vague and non-specific. However, the calf age may be used to predict the severity of strong ion acidosis, because diarrheic calves are less acidemic during their first seven days of life than older calves with similar clinical symptoms. Furthermore, the suckling reflex is strictly correlated with base excess (BE) parameters. Furthermore, the suckling reflex is closely correlated with base excess values (Naylor 1989, Nay-

lor 2006). Trefz et al (2011) showed that analysis of correlation between clinical and laboratory values revealed that the degree of strong ion acidosis could be predicted on the basis of alterations in posture and behavior whereas the degree of loss of the palpebral reflex offers a reliable tool for the estimate of increased D-lactate levels. The gold standard method for detecting and quantifying strong ion acidosis is blood gas analysis (pH, base deficit). Venous blood should be used for blood gas analysis unless concurrent respiratory disease is suspected. If a blood gas analyzer is not available, the base deficit can estimated from the total CO_2 content (tCO_2) of the serum or plasma. Many automated serum biochemical analyzers will measure tCO_2. If access to laboratory equipment is not available, then the degree of strong ion acidosis can be estimated on the basis of clinical signs and age (this is often wrong). Base Deficit = 15 to 20 mEq/L for calves >1 week old requiring IV fluids; 10 to 15 mEq/L for calves <1 week old requiring IV fluids (Constable et al 1998, Constable 1999b, Constable 2000).

Electrolytic imbalances

Intestinal electrolyte loss and decreased milk intake results in a total body deficit of Na^+, Cl-, and K^+ in calves with diarrhea. Plasma Na^+ is almost always decreased in calves with diarrhea. In contrast, plasma K^+ concentration is variable in diarrheic calves and does not reflect body stores, because K^+ is primarily an intracellular ion. The plasma K^+ concentration is also influenced by the degree of acidemia: for $\Delta[K]/\Delta pH$ of -0.3 to -0.5 mEq/L per 0.1 pH unit (Fisher 1967, Constable 2003, Lorenz and Klee 2007, Constable and Grünberg 2013). Plasma K^+ concentrations exceeding 8 mmol/L can be associated with signs of arrhythmia, muscular weakness, and excitability (Basoglu et al 1996, Basoglu et al 2012); however, tachycardia is the most commonly observed abnormality. Bradycardia (≤90 beats per minute) can be suggestive of hyperkalaemia, but is common in hypothermic calves in that heart rate decreases by about 10 beats per minute for every 1oC decrease in rectal temperature. In summary, the cardiac rate and rhythm do not provide reliable signs of hyperkalaemia (Fisher 1967, Constable 1999, Lorenz and Klee 2007, Constable and Grünberg 2013).

Hyperkalaemia has a more profound effect on atrial conduction than the sino-atrial node or ventricular conduction. Consequently, hyperkalemia is most often associated with diminished P wave amplitude to non-detectable P waves (Weldon et al 1992); the latter finding has been incorrectly called atrial standstill. The term atrial standstill is not recommended because the electrocardiogram reflects the electrical and not the mechanical activity of the heart, and because standstill is a mechanical term. Additional increases in plasma K+ concentrations result in delayed ventricular depolarization (manifest as increased QRS duration), symmetric T waves (often called peaked T waves) and bradyarrhythmias. As an example (Basoglu and Aydogdu 2012), clinical examination of a 7-day-old Holstein dairy calf weighing 35 kg and suffering from diarrhea identified poor pulse quality, occasional pulse deficits, normal heart rate (heart rate=92 beats/min), acidaemia and metabolic acidosis (pH=7.06, HCO_3=10.4 mEq/L, BE=-19 mEq/L, L-Lactate=7.9 mmol/L, pCO_2=40 mmHg), and severe hyperkalemia (K^+=9.5 mEq/L). Electrocardiographic analysis supported a presumptive diagnosis of hyperkalemia (Basoglu and Aydogdu 2012).

Fluid therapy

Fluids and electrolytes usually are administrated orally or parenterally to ruminants. The method used for fluid administration in calves with diarrhea should be based on the presence or absence of a suckle reflex and degree of dehydration. Calves that are able to suckle and are less than 6% dehydrated (eye recessed < 3 mm into the orbit) should be administered an oral electrolyte solution; some of the fluid can be intubated using oro-esophageal intubation if needed. Calves that are not able to suckle or that are 8% or more dehydrated (eye recessed 4 or more mm into the orbit) should receive intravenous fluids. These can be administered by placement of a jugular venous catheter or auricular vein catheter (Roussel and Kasari 1990, Constable 2003, Naylor 2006, Smith 2009).

Oral electrolyte fluid therapy

The oral route for fluid administration should be used whenever possible, because oral solutions are cheaper and faster to administer than intravenous fluids and do not need to be sterile or pyrogen-free. The ideal oral electrolyte solution should (1) supply adequate sodium to facilitate normalization of extracellular fluid deficits; (2) provide two or more agents (such as acetate, propionate, glucose or glycine) that facilitate intestinal absorption of water and sodium; (3) provide an alkalinizing agent (such as propionate, citrate, acetate, or bicarbonate) to treat the metabolic acidosis often present in dehydrated diarrheic calves; (4) not interfere with the clotting of milk; (5) provide sufficient energy, because these electrolyte solutions can be administered instead of milk or milk replacer for short periods; and (6) facilitate repair of damaged intestinal epithelium (Fayet 1971, Naylor et al 1990, Constable et al 2001, Constable 2003). Calves that are not depressed but have profuse diarrhea or are depressed and still have a good suck reflex should be treated with oral electrolyte solutions (Roussel 1983, Naylor 2006, Smith 2009).

Commercially available oral electrolyte products can range from isotonic (280–300 mOsm/L) to extremely hypertonic (700–800 mOsm/L). The primary difference in most of these products is the amount of glucose that is added (Constable et al 2001, Constable 2003). Because of a countercurrent exchange mechanism in the small intestine, the effective osmolality at the tip of the intestinal villus is about 600 mOsm/L (Jodal and Lundgren 1986, Sen et al 2006). Although markedly hypertonic fluids should be avoided in animals having severe villous damage, it is impossible to predict which ani-

mals have severe villous damage on the basis of the physical examination findings and measurement of fecal pH or other body parameter (Constable et al 2001). Hypertonic oral electrolyte solutions have also been shown to slow abomasal emptying rates as compared with isotonic products (Sen et al 2006, Nouri et al 2006). Calves fed an oral electrolyte solution with a total osmolality of 360 mOsm/L had a significantly faster abomasal emptying rate as compared with calves fed a solution with an osmolality of 717 mOsm/L (Nouri and Constable 2006). This finding suggests that electrolyte products with a high osmolality (or high glucose concentrations) would be likely to induce abomasal hypomotility, thus increasing the risk for bloat or abomasitis. Low osmolality fluids (300 mOsm/kg) have inadequate energy content because they have insufficient glucose. For this reason, if milk is withheld, then hypertonic oral electrolyte solutions (~600 mOsm/kg) should be administered. If milk is fed, then isotonic oral electrolyte solutions (300 mOsm/kg) should be administered (Constable 2003).

The sodium concentration should be between 90 and 130 mM/L. Adequate sodium absorption is the principle determinant of successful expansion of the extracellular space. Sodium concentrations <90 mM/L provide an inadequate sodium load, whereas sodium concentrations >130 mM/L can lead to hypernatremia and additional free water loss (Constable 2003, Naylor 2006, Smith 2009). The oral electrolyte solution should also contain glucose and either acetate, propionate, or glycine to facilitate Na^+ absorption and provide energy (Smith 2009, Sen et al 2009). There are cotransport mechanisms for Na^+ and glucose, Na^+ and volatile fatty acids such as acetate and propionate, and Na^+ and amino acids in the luminal membrane of villus epithelial cells. Administration of glucose, acetate, propionate, and glycine facilitates Na^+ absorption. These transport mechanisms are unimpaired in enterotoxigenic *E.coli* and are at least partially functional in malabsorptive/maldigestive diarrheas (Constable 2003, Smith 2009).

The ideal alkalinizing agent should be acetate or propionate at a concentration range of 40 to 80 mM/L. Acetate-containing fluids are as effective as bicarbonate-containing solutions at correcting mild to moderate acidosis [acetate- = CH_3COO-] + H+ + $2O_2 \Rightarrow 2CO_2 + 2H_2O$ (Constable 2003). Acetate must be metabolized to be effective, and metabolism may be impaired in severely dehydrated or acidemic animals (Sen et al 2009). Acetate-containing fluids can be fed with milk as acetate does not raise abomasal pH or inhibit milk clotting (Marshal et al 2005).

Bicarbonate-containing fluids are more effective at rapidly correcting severe acidemia, since bicarbonate reacts directly with H+ ions (HCO_3- + H+ $\Leftrightarrow$ $H2CO_3 \Leftrightarrow$ H2O + CO_2). The main disadvantage of bicarbonate-containing oral fluids are that the pH of the abomasum (a natural defense mechanism) is increased (Sen et al 2006). Although bicarbonate and high concentrations of citrate interfere with milk clotting when tested in vitro (Naylor 1992), a recent in vivo study indicated that low bicarbonate containing fluids (25 mmol/L) do not inhibit clotting (Constable et al 2009). Propionate is the weak anion chosen because it is a source of energy, appears to enhance sodium absorption in the small intestine, does not interfere with abomasal pH, and may even inhibit overgrowth of *Salmonella* species (Smith 2009). Stämpfli et al (2012) suggested sodium propionate is a valid substitute for commonly used sodium base equivalents in oral electrolyte solutions. Gluconate is not metabolizable in calves and probably not in other large animals (Radostits et al 2007). Glutamine-containing oral electrolyte solutions have been investigated as an adjunct therapy; however, studies indicate that glutamine does not improve gut morphology in diarrheic calves (Naylor 1999).

The ideal rate of oral fluid administration has not been determined. In general, the maximum amount of oral fluid are given 8 L/daily (divided into at least 4 feeds of 2 L or less) to diarrheic calf (Naylor 2006, Sen et al 2009). In diarrheic calves fed milk and oral electrolyte solutions, ongoing fecal water losses are generally between 1 and 4 L of a day (Heath et al 1989).

Intravenous fluid therapy

Strong ion (metabolic) acidosis in which the BEecf is more negative than–10 mmol/L is considered severe. In general, sodium bicarbonate solutions are indicated for use in the treatment of severe metabolic acidosis (BEecf more negative than –10 mmol/L), whereas acetated Ringer's solution or lactated Ringer's solution should be used in the correction of less severe metabolic acidosis (Garcia 1999, Kasari 1999, Sen et al 2009). Lactated Ringers solution (LRS), or Acetated Ringers solutions can be used to correct mild to moderate acidosis (venous pH >7.20, base deficit >-10 mEq/L). Lactate and acetate must be metabolized before they have an alkalinizing effect (Iwabuchi et al 2003).

Bicarbonate should be used to correct severe acidemia (pH <7.20, base excess <-10 mEq/L) (Coskun et al 2010, Abeysekara et al 2012). Bicarbonate should not be added to solutions containing calcium as a calcium carbonate precipitate forms. Isotonic sodium bicarbonate (1.3-1.4 % solution = 13-14 g of $NaHCO_3$/L) is used to correct severe acidemia. The amount of $NaHCO_3$ required is calculated from the base deficit: base deficit x 0.6 x (body weight in kg) = mEq of HCO_3- required. 1 gram of $NaHCO_3$ contains 12 mEq of bicarbonate, so the (mEq of HCO_3- required)/12 = grams $NaHCO_3$ required. This means that the total grams $NaHCO_3$ required = (base deficit x 0.6 x body weight in kg)/12. This calculation method assumes that HCO_3- distributes in the extracellular fluid space that is equal to 60% of the body weight in the suckling calf. Sodium bicarbonate is the alkalinizing agent of choice and is often recommended as a 1.3% isotonic solution (13 g $NaHCO_3$/L) (Roussel et al 1998, Constable 1999, Suziki et al 2002a, Suziki et al 2002b, Koch and Kaske 2008, Coskun et al

2010, Sen et al 2013). Isotonic sodium bicarbonate has an effective strong ion difference of 155 mEq/L and is alkalinizing because it buffers hydrogen ions and increases the strong ion difference in blood. Müller et al (2012) confirmed that 1.3 % sodium bicarbonate is much more effective in alkalinizing diarrheic calves with strong ion acidosis than a solution with sodium gluconate. Available hypertonic preparations of sodium bicarbonate include 4.2%, 5%, and 8.4% solutions with a theoretic osmolality of 1000 mOsm/L, 1190 mOsm/L, and 2000 mOsm/L, respectively (Constable 2003). Hypertonic formulations of sodium bicarbonate are ideal for adding to larger quantities of isotonic saline to create a mildly hypertonic solution containing volume-expanding fluid and buffer (Bertchold 1999, Bertchold 2009). Coskun et al (2010) showed that IV administrations of 1.3% and 8.4% sodium bicarbonate solutions were similarly effective in treating acid-base abnormalities in calves with marked strong ion acidosis. Administration of 8.4% $NaHCO_3$ led to a more rapid improvement of venous acid base abnormalities than did administration of 1.3% $NaHCO_3$. However, 8.4% $NaHCO_3$ should not be used to treat severe respiratory acidosis because the additional carbon dioxide (CO_2) generated may worsen the respiratory acidosis and potentially further decrease blood pH. The speed of intravenous administration of 8.4% $NaHCO_3$ should not exceed 1 mL/kg/min (Constable 2003). 5% sodium bicarbonate is 1190 mOsm/L (approximately four times normal osmolarity). This solution also is used for rapid alkalinization in the presence of severe acidemia (pH < 7.20). The speed of intravenous administration of 5.0% $NaHCO_3$ should not exceed 2 mL/kg/min.

The intravenous administration of hypertonic saline must be combined with oral administration of an isotonic alkalinizing electrolyte solution. Hypertonic saline alone does not correct acidemia due to metabolic acidosis; alkalinizing activity must therefore come from concurrent administration of an oral electrolyte solution (Constable 1999a). Alternatively, intravenous administration of hypertonic sodium bicarbonate solution (8.4%, 2000 mOsm/L; 4-5 ml/kg over 4-5 minutes) can be used instead of hypertonic saline to increase blood pH in calves with metabolic acidosis (Constable 2003, Bertchold 2009).

Conclusions

One of the most important factors for decreasing mortality rates associated with diarrhea in calves is parenteral and oral administration of appropriately formulated electrolyte solutions, which can correct the dehydration, acidemia, strong ion (metabolic) acidosis, and electrolyte imbalances, particularly hyperkalemia and hyponatremia. Inclusion of an alkalinizing agent is required to correct systemic metabolic acidosis. Oral electrolyte solutions containing acetate or propionate are preferred over solutions containing bicarbonate. Oral electrolyte solutions are indicated in any diarrheic calf that has at least a partially functional gastrointestinal tract (especially suckle reflex). Sodium bicarbonate solutions are indicated for use in the treatment of severe acidosis (Beecf more negative than –10 mmol/L). However, Lactated Ringers solution, or Acetated Ringers solutions can be used to correct mild to moderate acidosis (venous pH >7.20; base deficit >-10 mEq/L). Isotonic sodium bicarbonate (1.3% 13 g of $NaHCO_3$/L) at a dose of 1 to 4 L is the recommended solution for IV treatment of calves with diarrhea. When a calf's suckle reflex is re-established, further treatment can be given orally. Undiluted 8.4% hypertonic sodium bicarbonate solutions should be used with caution in severely dehydrated calves with diarrhea.

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