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Importance of the Effective Strong Ion Difference of an Intravenous Solution in the Treatment of Diarrheic Calves with Naturally Acquired Acidemia and Strong Ion (Metabolic) Acidosis

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Background: The effect of sodium bicarbonate on acid-base balance in metabolic acidosis is interpreted differently by Henderson-Hasselbalch and strong ion acid-base approaches. Application of the traditional bicarbonate-centric approach indicates that bicarbonate administration corrects the metabolic acidosis by buffering hydrogen ions, whereas strong ion difference theory indicates that the co-administration of the strong cation sodium with a volatile buffer (bicarbonate) corrects the strong ion acidosis by increasing the strong ion difference (SID) in plasma.

Objective: To investigate the relative importance of the effective SID of IV solutions in correcting acidemia in calves with diarrhea.

Animals: Twenty-two Holstein-Friesian calves (4–21 days old) with naturally acquired diarrhea and strong ion (metabolic) acidosis.

Methods: Calves were randomly assigned to IV treatment with a solution of sodium bicarbonate (1.4%) or sodium gluconate (3.26%). Fluids were administered over 4 hours and the effect on acid-base balance was determined.

Results: Calves suffered from acidemia owing to moderate to strong ion acidosis arising from hyponatremia and hyper-D-lactatemia. Sodium bicarbonate infusion was effective in correcting the strong ion acidosis. In contrast, sodium gluconate infusion did not change blood pH, presumably because the strong anion gluconate was minimally metabolized.

Conclusions: A solution containing a high effective SID (sodium bicarbonate) is much more effective in alkalinizing diarrheic calves with strong ion acidosis than a solution with a low effective SID (sodium gluconate). Sodium gluconate is ineffective in correcting acidemia, which can be explained using traditional acid-base theory but requires a new parameter, effective SID, to be understood using the strong ion approach.

Key words: Calf diarrhea; Sodium bicarbonate; Sodium gluconate; Strong ion difference.

The Henderson-Hasselbalch equation[1,2] has been used for almost 100 years to characterize the acid-base status of critically ill humans and animals. Application of the Henderson-Hasselbalch equation uses pH as an overall index of acid-base status, the partial pressure of carbon dioxide (pCO_2) as an index of the respiratory component of acid-base balance, and either the bicarbonate concentration ($cHCO_3^-$) or extracellular base excess ($BE_{(ecf)}$) as an index of the metabolic or nonrespiratory component of acid-base balance.[3,4] The Henderson-Hasselbalch approach quantifies the unmeasured anion concentration by calculating the anion gap (AG) from the measured values for the concentrations of sodium, potassium, and chloride in plasma or serum and the calculated value for $cHCO_3^-$.[3–7]

Peter Stewart developed a quantitative physicochemical approach to the clinical assessment of acid-base balance from 1978 to 1983,[8–10] and his physicochemical approach was simplified by Constable in 1997.[11]

Abbreviations:

AG	anion gap
Alb	albumin
A_{tot}	total plasma concentration of nonvolatile weak acids
BE	base excess
mEq	milliequivalent
pCO_2	partial carbon dioxide pressure
P	*P*-value
SID	strong ion difference
SIG	strong ion gap
TP	total protein

Stewart criticized the traditional Henderson-Hasselbalch model as being too simple and incomplete, especially with regard to metabolic acid-base disturbances.[8–10] With respect to dissociation equilibria, electroneutrality, and conservation of mass, Stewart's strong ion and Constable's simplified strong ion approaches state that 3 independent variables, pCO_2, strong ion difference (SID), and total weak acid concentration (A_{tot}), directly determine the dependent variables pH and $cHCO_3^-$.[10,11] Strong ions dissociate completely at physiologic pH and can be subdivided into strong cations (Na^+, K^+, Ca^{2+}, Mg^{2+}) or strong anions (principally Cl^-, L-lactate, D-lactate, uremic anions, and ketoacids in cattle).[11] The strong ion charge difference (Σ strong cation charge – Σ strong anion charge) generates a positive value for SID, which is counterbalanced by the negative charges residing on bicarbonate, albumin, globulin, and phosphate.[10,11] The simplified strong ion approach quantifies the unmeasured strong ion equation by calculating

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the strong ion gap (SIG) from measured values for the plasma or serum concentrations of strong cations and strong anions, the total protein or albumin concentration, and experimentally determined values for A_{tot} and p*K*a in calf plasma.[5,7,12]

Some authors state that in fact the Stewart concept is not completely separate from traditional acid-base concepts, but can rather be seen as an advancement of them. Descriptive indices (BE, Henderson-Hasselbalch equation) are useful for describing and classifying acid-base disorders, whereas quantitative indices (SID, A_{tot}) are more useful for quantifying and explaining these disorders.[13]

Although, the strong ion and simplified strong ion approaches have been criticized,[14,15] several research groups have investigated quantitative acid-base analysis in domestic animals and concluded that the strong ion approach provided a more comprehensive evaluation of acid-base balance than application of the traditional Henderson-Hasselbalch equation.[7,16–21] A key question remains to be answered: does application of strong ion theory improve our ability to understand the mechanisms of acid-base equilibrium in vivo and treat acid-base disturbances?

Acid-base disturbances occur commonly in diarrheic calves. The majority of calves have a metabolic acidosis that was traditionally attributed to excessive losses of electrolytes, bicarbonate, and free water in diarrheic feces and decreased renal blood flow that minimized homeostatic adjustments.[22] As early as 1990 it was recognized that the causes of acidemia in diarrheic calves were incompletely understood.[23] Nappert, Naylor, and colleagues speculated in 1997 that increased production of organic acids in the gut contributed to the metabolic acidosis and acidemia[24] and the first reports of hyper-D-lactatemia in sick calves were published the same year in France[25] and in 1998.[26] Studies by Naylor and colleagues in Canada[27–30] and related studies by Lorenz, Gentile, Klee, and colleagues in Europe[31–34] showed that metabolic acidosis in diarrheic calves frequently resulted from hyper-D-lactatemia because of decreased absorption of substrate with subsequent formation of D-lactate in the gastrointestinal tract. A 2005 study that applied SID theory identified hyponatremia to be an important contributing factor to metabolic acidosis in diarrheic calves, with hyponatremia and hyper-D-lactatemia decreasing SID and thereby inducing a strong ion acidosis.[7] The same study identified that free water loss and dehydration contributed to the acidemia by increasing serum total protein concentration and consequently the value for A_{tot}.[7]

Intravenous administration of sodium bicarbonate (1.3% or 1.4% solution) has long been regarded as the therapy of choice in the treatment of diarrheic calves with metabolic acidosis.[22,35–37] It is of clinical interest that the mechanism of the effect of sodium bicarbonate administration on acid-base balance is interpreted differently by the 2 acid-base models. According to the traditional Henderson-Hasselbalch approach, the administered bicarbonate corrects the metabolic acidosis by buffering hydrogen ions in the extracellular and intracellular compartments,[38,39] whereas the SID approach indicates that the high effective SID of sodium bicarbonate corrects the strong ion acidosis by increasing the independent variable SID.[40–44] The effective SID (SID_e) of a solution is the difference in charge between the sum of strong (non-metabolizable or fixed) cations such as Na^+, K^+, Ca^{2+}, and Mg^{2+}, and the sum of strong (nonmetabolizable or fixed) anions such as chloride and gluconate.[37] For example, 0.9% NaCl, 7.2% NaCl, Ringers solution, and 5% dextrose solution have an effective SID of 0 mEq/L and therefore have a net acidifying effect when large volumes are rapidly administered IV.[40–42] In contrast, 1.4% $NaHCO_3$ and 8.4% $NaHCO_3$ have effective SID values of 167 and 1,000 mEq/L, respectively. The importance of effective SID in the alkalinizing ability of an orally administered electrolyte solution was first identified by Staempfli et al in 1996[45] and the concept was extended to characterize the alkalinizing ability of IV fluids in 2003.[37] The effective SID is not equivalent to bicarbonate because sodium formate is alkalinizing.[32] The strong ion formate is metabolized primarily to CO_2 (thereby increasing SID), but formate does not appear to be metabolized to HCO_3^-.[46–48]

Another clinically important issue is whether effective volume expansion by administering an isotonic solution with sodium as the only cation is sufficient to correct the metabolic acidosis in diarrheic calves. Only a few studies have been conducted previously in dehydrated diarrheic calves comparing the alkalinizing effect of different sodium containing salts.[35,49,50] As a result of those studies, the importance of a high effective SID of the infused solution has been identified as central to successful alkalinization.

The primary aim of this clinical study therefore was to clarify the role of increased bicarbonate load to increased sodium load in the treatment of calves with naturally acquired strong ion (metabolic) acidosis because of diarrhea. We achieved our aim by administering approximately isotonic solutions containing similar sodium loads (sodium bicarbonate, sodium gluconate) but markedly different effective SID values. Sodium gluconate was selected for investigation because gluconate is minimally metabolized in calves,[36] dogs[51], and rats.[52] Experimental studies in rats indicate that <15% of gluconate is metabolized to CO_2 within 24 hours, with 60–85% of the administered gluconate being eliminated in the urine.[52] The effective SID of an isotonic sodium gluconate solution therefore approximates 0 mEq/L, whereas the effective SID of a 1.4% sodium bicarbonate solution approximates 167 mEq/L. Sodium gluconate therefore provides an excellent solution to compare the specific effects of bicarbonate administration or sodium administration, and effective SID, on acid-base balance.

Materials and Methods

The study was carried out in collaboration with the Faculty of Veterinary Medicine – University of Bologna, under the supervision of the local Centralized Veterinary Service for Welfare of

Experimental Animals and with the approval of the Ethical Review Committee of Animal Experimentation of the University of Bologna.

Animals

The study was performed using a convenience sample of calves from a collaborating farm in Madonna dell'Oppio, Modena, Italy. Calves were housed in open front shelters with individual pens on straw bedding. Twenty-two Holstein-Friesian calves (14 male, 8 female) were enrolled in the study based on the following criteria: age $\leq$21 days, neonatal diarrhea (defined as loose or watery feces), strong ion (metabolic) acidosis characterized by an extracellular base excess ($BE_{(ecf)}$) of ≤ -7 mmol/L, and the absence of clinical signs of pneumonia or ruminal acidosis.

Clinical Examination and Collection of Samples

Calves meeting selection criteria were weighed[a] and examined using a standardized protocol. Clinical assessments were carried out by the same person who was not blinded to treatment assignment. The general condition and state of hydration of the calf was assessed using a complex composite-scoring system (general condition: posture, behavior, suckling reflex, palpebral reflex): 4–5 = lively, physiologic; 6–9 = slight lethargy; 10–13 = moderate lethargy; 14–18 = severe lethargy; state of hydration: (degree of enophthalmus, degree of skin tenting): 2 = physiologic; 3–4 = slight dehydration; 5–6 = moderate dehydration; 7–8 = severe dehydration.

Heparinized blood samples were drawn anaerobically from the jugular vein into polypropylene syringes[b] for analysis of blood gas partial pressures, pH, and serum biochemical variables. The syringes were placed in iced water and acid-base parameters were determined within 10 minutes of collection whereas blood for serum analysis was centrifuged (5,000 × *g*, 10 minutes) and the serum stored at −20°C until analyzed at the Clinic for Ruminants, Oberschleissheim, Germany. An IV catheter[c] was placed in an auricular vein.

Treatment

Calves were randomly assigned (by drawing lots) to be treated with either isotonic sodium bicarbonate solution or sodium gluconate solution. Calves were treated by warmed infusion of a slightly hypertonic solution of sodium bicarbonate (1.4%, 167 mM) or an isotonic solution of sodium gluconate (3.26%, 149 mM) over 4 hours.

The volume administered was calculated according to the following equation: volume in L = (body weight in kg) × (0.6 L/kg) × ($BE_{(ecf)}$ mmol/L) × (L/mmol of bicarbonate or gluconate) where the factor (0.6 × body weight) was considered to represent the apparent distribution space for bicarbonate in neonatal calves with dehydration and strong ion acidosis. Intravenous solutions were produced by mixing sodium bicarbonate[d] or sodium gluconate[e] powder with distilled water[f] and warmed to approximately 38°C.

Jugular venous blood samples were obtained immediately before the beginning of infusion (T0), after 2 hours (T120), and after 4 hours, which corresponded to the end of infusion (T240). Clinical variables examined at the end of infusion (T240) included assessment of general condition and state of hydration. Calves were not permitted access to water, milk, or mineral supplements during the 4-hour treatment phase. After the end of infusion, calves were given additional treatments as deemed necessary by the attending veterinarian, based on the results of blood gas and acid-base analysis.

Laboratory Analyses

Venous blood pH, partial pressure of carbon dioxide (pCO_2), serum concentrations of sodium (cNa^+), chloride (cCl^-), potassium (cK^+), and calcium (cCa^{2+}) were determined with a point of care instrument[g] on the farm and expressed in mEq/L. Serum concentrations of magnesium (cMg^{2+}), total protein (*c*TP), and albumin (*c*Alb) as well as concentrations of D- and L-lactate were determined using an automatic analyzing system[h] at the Clinic for Ruminants, Oberschleissheim, Germany.

Calculations

Henderson-Hasselbalch Equation and Anion Gap. The Henderson-Hasselbalch equation was used to calculate $cHCO_3^-$ from the measured values for venous pH and pCO_2 and assigned values for *S* and pK_1' at 37°C of 0.0307 mmol × L^{-1} × $mmHg^{-1}$ and 6.095, respectively,[53] whereby

$$cHCO_3^- = S \times pCO_2 \times 10^{(pH - pK1')} \quad (1)$$

Base excess of extracellular fluid ($BE_{(ecf)}$, in mmol/L) was calculated from the measured pH and pCO_2, and assigned values for *S* and pK_1'[53] such that:

$$BE_{(ecf)} = S \times pCO_2 \times 10^{(pH - pK1')} - 24.8 + 16.2 \times (pH - 7.40) \quad (2)$$

The unmeasured anion concentration was estimated by calculating the anion gap (AG) as follows[3–6]:

$$AG = (cNa^+ + cK^+) - (cCl^- + cHCO_3^-) \quad (3)$$

Strong Ion Difference, A_{tot}, and Strong Ion Gap. Measured strong ion difference ($SIDm_7$) in mEq/L was calculated as follows based on the number of strong ions measured (SIDm, n = 7) in plasma:

$$SIDm_7 = ([cNa^+] + [cK^+] + [cCa^{2+}] + [cMg^{2+}]) - ([cCl^-] + [c\text{D-lactate}^-] + [c\text{L-lactate}^-])$$

The value for A_{tot} was calculated from the total protein concentration in serum (*c*TP) in g/L using experimentally determined values for calf plasma,[7] whereby:

$$A_{tot} = 0.343 \times cTP \quad (5)$$

The SIG was calculated from the measured value for cTP in g/L and temperature corrected blood pCO_2 and pH value using the SIG equation for calf plasma as follows[7]:

$$SIG = A_{tot}/(1 + 10^{(pKa - pH)}) - AG = cTP \times [0.343/(1 + 10^{(7.08 - pH)})] - AG \quad (6)$$

The unmeasured strong ion concentration (*c*USI) was calculated as follows:

$$\mathrm{USI} = \mathrm{SIG} + ([c\text{D-lactate}^-] + [c\text{L-lactate}^-]) \quad (7)$$

The effective SID (SID_e) was calculated as follows:

$$\mathrm{SIDm}_7 + c\mathrm{USI} \quad (8)$$

Change in Plasma Volume. The change in plasma volume at time i was calculated from the serum cTP at time = 0 minutes ($c\mathrm{TP}_0$) and the serum cTP at time i ($c\mathrm{TP}_i$),[54] whereby:

$$\text{Percent change in plasma volume} = (c\mathrm{TP}_0 - c\mathrm{TP}_i) \times 100/c\mathrm{TP}_i \quad (9)$$

Statistical Analysis

Statistical analyses were performed using SPSS for Windows version 16. For the 3 sampling times (T0, T120, and T240), a Mann-Whitney-*U*-test was used to compare variables in both groups. Owing to the small number of animals, results are depicted as medians with 25th and 75th percentiles. Because of the large number of potentially correlated variables, differences were classified as significant if $P < .01$.

Results

All calves survived the study. Calves in the sodium bicarbonate group received mean volumes of 1.72 ± 0.39 L of isotonic sodium bicarbonate (1.4%) solution whereas calves in the sodium gluconate group received mean volumes of 1.67 ± 0.51 L of isotonic sodium gluconate (3.26%) solution. The variability in volume administered was attributable to the study design whereby calves were given individual volumes of 1 of the solutions. Infusion of sodium gluconate induced moderate inspiratory stertor in 4 calves. The stertor disappeared after T240.

Clinical Appearance, Hydration Status, and Change in Plasma Volume

Rectal temperature was unchanged during treatment and was similar for both groups (least squares grand mean, 38.7°C). The general condition of the calves improved in both groups within 4 hours of infusion (Fig 1). Initially, calves had a median clinical score of 8.0 (sodium bicarbonate) and 7.0 (sodium gluconate), respectively, indicating slight lethargy. After the study, calves showed almost normal behavior with median clinical scores of 6.0 in both groups.

The hydration status improved similarly in both groups within 4 hours, decreasing from a median score of 5.0 (sodium bicarbonate) and 6.0 (sodium gluconate), respectively (moderate dehydration), to a score of 3.0 (sodium bicarbonate) and 4.0 (sodium gluconate) (mild dehydration) (Fig 2). Serum creatinine concentration decreased numerically but not significantly in both groups by T240 (Table 1).

Plasma volume increased significantly in both groups within 2 hours (Table 1); surprisingly, the magnitude of the increase was significantly greater for sodium bicarbonate than sodium gluconate at T240.

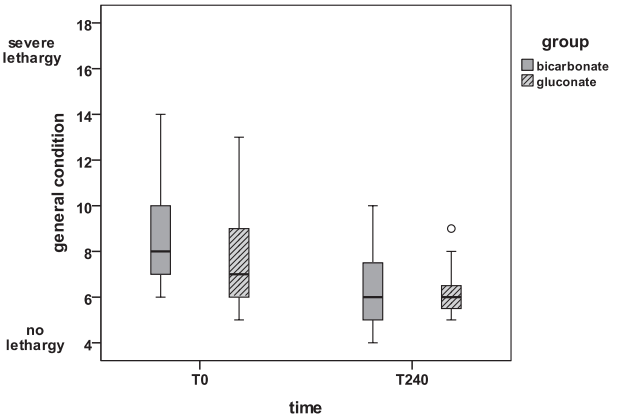

Fig 1. General condition score before (T0) and after (T240) infusion.

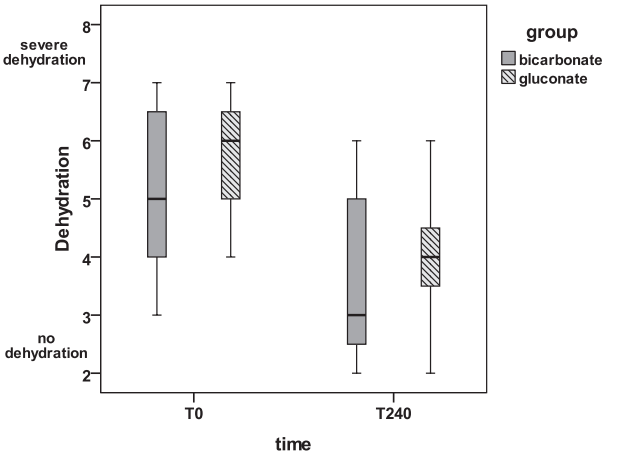

Fig 2. Dehydration score before (T0) and after (T240) infusion.

Serum Electrolyte Concentrations

Initially, all calves showed moderate hyponatremia (median preprandial sodium concentration: 126–128 mEq/L) and although sodium concentrations tended to increase by T240 concentrations remained below the reference interval (Table 1). Serum chloride concentrations were in the reference range at the start of infusion (104 mEq/L in the sodium bicarbonate group; 97 mEq/L in the sodium gluconate group) and decreased slightly in both groups during the study (Table 1).

Henderson-Hasselbalch Assessment of Acid-Base Balance

Calves suffered from acidemia because of a moderate metabolic acidosis with partial respiratory compensation, as indicated by median values for $BE_{(ecf)}$ of −11.3 mmol/L (sodium bicarbonate) and

Table 1. Measured blood gas and pH values, serum electrolyte, total protein, and albumin concentrations, and calculated acid-base parameters before (T0), during (T120) and after (T240) infusion of individual volumes of either sodium bicarbonate (Na-Bic) or sodium gluconate (Na-Gluc). $SIDm_7$ is strong ion difference calculated from 7 strong cations and strong anions. Reference values in square brackets.

		T0		T120		T240	
Blood variable		$\tilde{x}$	Q_{25}/Q_{75}	$\tilde{x}$	Q_{25}/Q_{75}	$\tilde{x}$	Q_{25}/Q_{75}
Henderson-Hasselbalch							
pH	Na-Bic	7.172	7.157/7.216	7.306[a]	7.291/7.321	7.371[a]	7.359/7.405
[7.35–7.50][59]	Na-Gluc	7.199	7.155/7.238	7.201[b]	7.166/7.270	7.217[b]	7.189/7.287
pCO_2 (mmHg)	Na-Bic	42.6	38.9/48.1	46.9	44.3/50.1	48.3[a]	45.6/53.3
[34–45][59]	Na-Gluc	45.1	44.0/51.4	44.2	43.6/48.5	46.6	43.8/51.7
HCO_3^- (mmol/L)	Na-Bic	15.4	14.1/16.8	22.7[a]	20.8/24.5	28.0[a]	26.2/30.5
[20–30][59]	Na-Gluc	17.2	16.6/18.4	17.9[b]	16.0/18.7	19.4[b]	17.3/20.0
$BE_{(ecf)}$ (mmol/L)	Na-Bic	−11.3	−13.3/−10.6	−3.3[a]	−4.2/−1.4	3.7[a]	1.4/4.9
[−2.5–2.5][59]	Na-Gluc	−10.4	−11.5/−7.8	−9.6[b]	−11.3/−7.2	−7.8[b]	−10.6/−5.8
Anion gap (mEq/L)	Na-Bic	19.9	16.3/23.0	20.5	14.2/21.5	17.2	14.6/19.8
[14–26][59]	Na-Gluc	17.1	16.3/19.8	21.0	19.8/28.9	23.2[b]	21.7/27.6
Strong ion difference model							
$SIDm_7$ (mEq/L)	Na-Bic	33.9	30.4/35.2	38.4[a]	36.5/40.3	44.6[a]	41.4/44.9
[40±2][7]	Na-Gluc	35.3	34.1/37.1	42.6[a]	40.1/43.7	43.3[a]	42.0/46.2
SID_e (mEq/l)	Na-Bic	30.8	29.3/33.1	35.5[a]	35.5/38.8	44.1[a]	41.5/45.6
[40±2][7]	Na-Gluc	31.0	30.2/34.2	33.0	29.4/34.6	32.8[b]	31.0/34.7
A_{tot} (mmol/L)	Na-Bic	20.6	16.1/23.8	18.7[a]	15.0/21.1	18.4[a]	14.6/20.4
[19.2±6.1][7]	Na-Gluc	18.5	17.4/20.0	17.2[a]	16.4/18.2	17.9	16.8/18.9
Strong ion gap (mEq/L)	Na-Bic	−8.7	−14.3/−4.9	−7.6	−11.7/−2.4	−6.0[a]	−7.9/−3.1
[−3–3][7]	Na-Gluc	−6.2	−11.4/−5.2	−11.2[a]	−20,6/−9.6	−12.1[ab]	−20.7/−11.5
Unmeasured strong ions (mEq/L)	Na-Bic	−1.8	−5.1/−0.4	−2.4	−3.3/+1.4	0.5[a]	−1.5/+2.3
	Na-Gluc	-4.7	−5.3/−2.1	−10.4[ab]	−13.5/−4.0	−11.1[ab]	−13.9/−8.3
Serum biochemical analysis							
Strong cations							
Na^+ (mEq/L)	Na-Bic	126	122/134	131	124/133	130	126/135
[132–152][59]	Na-Gluc	128	120/132	129	119/132	130	121/134
K^+ (mEq/L)	Na-Bic	4.6	4.1/5.2	4.5	3.6/4.8	3.9	3.2/4.2
[3.9–5.8][59]	Na-Gluc	3.8	3.4/4.5	3.7	3.6/4.0	3.6	3.5/4.0
Ca^{2+} (mEq/L)	Na-Bic	2.18	1.92/2.44	2.06	1.80/2.24	1.94	1.65/2.06
[1.2–1.6][59]	Na-Gluc	2.10	1.96/2.36	2.18	1.95/2.24	1.98	1.91/2.24
Mg^{2+} (mEq/L)	Na-Bic	1.74	1.57/2.26	1.52	1.45/1.87	1.54	1.40/1.89
[0.74–1.10][59]	Na-Gluc	1.80	1.63/2.00	1.70	1.62/1.90	1.64	1.59/1.82
Strong anions							
Cl^- (mmol/l)	Na-Bic	104	91/101	90[a]	86/96	86[a]	83/92
[95–110][59]	Na-Gluc	97	87/101	88[a]	80/94	90[a]	79/94
D-$Lactate^-$ (mmol/l)	Na-Bic	3.06	1.59/7.00	3.75	1.81/7.27	3.65	1.82/6.73
[0.6–2.2][59]	Na-Gluc	2.87	0.27/5.34	2.76	0.14/5.26	2.66	0.19/5.27
L-$Lactate^-$ (mmol/l)	Na-Bic	0.67	0.54/0.77	0.79	0.56/0.98	0.87	0.65/1.46
[0.6–2.2][59]	Na-Gluc	0.84	0.52/1.27	0.63	0.47/0.77	0.55	0.46/0.74
Nonvolatile buffer ions							
Total protein (g/l)	Na-Bic	60.1	46.9/69.5	54.6[a]	43.8/62.7	53.6[a]	42.6/59.6
[57–81][59]	Na-Gluc	54.0	50.7/58.3	50.0[a]	47.8/53.2	52.2	49.1/55.2
Albumin (g/l)	Na-Bic	27.1	24.0/28.5	24.6	22.6/25.9	23.8	21.6/25.1
[21–36][59]	Na-Gluc	27.6	26.8/30.5	26.1	25.0/27.5	26.0	25.1/27.4
Phosphorus (mmol/L)	Na-Bic	2.6	2.3/3.6	2.4	2.1/2.9	2.2	2.1/2.8
[1.08–2.76][59]	Na-Gluc	2.6	2.5/3.0	2.6	2.5/2.7	2.6	2.5/2.7
Creatinine (umol/L)	Na-Bic	107.8	67.0/171.1	93.2	61.8/150.7	92.6	57.1/136.9
[67–175][59]	Na-Gluc	116.4	90.5/144.4	104.7	88.5/125.5	96.9	87.7/118.1
Percent change in plasma volume	Na-Bic	0.0	0.0/0.0	+11.4[a]	8.9/19.0	+14.6[a]	11.5/20.1
	Na-Gluc	0.0	0.0/0.0	+9.0[a]	4.0/14.7	+7.5[a,b]	4.4/11.2

$\tilde{x}$ = median.
Q_{25}/Q_{75} = 25-/75-quartiles
[a]Significantly different from time = 0 value within a group.
[b]Significantly different between the 2 groups at the same time ($P \leq 0.0023$).

−10.4 mmol/L (sodium gluconate), and pCO_2 of 43 mmHg (sodium bicarbonate) and 45 mmHg (sodium gluconate) immediately before treatment. Blood pH, $cHCO_3^-$, and $BE_{(ecf)}$ were increased at T120 and T240, and pCO_2 was increased at T240 after sodium bicarbonate infusion, at which time the values reached the reference range (Table 1; Fig 3). In marked contrast, infusion of sodium gluconate did not change blood pH, pCO_2, $cHCO_3^-$, and $BE_{(ecf)}$ values. Consequently, blood pH, $cHCO_3^-$, and $BE_{(ecf)}$ (Fig 3) were significantly different ($P \leq .01$) at T120 and T240 between the 2 groups. The AG remained constant in calves treated with sodium bicarbonate but was significantly increased in calves treated with sodium gluconate. Collectively, these results indicate that sodium bicarbonate was an effective alkalinizing agent, sodium gluconate was an ineffective alkalizing agent, and the increase in AG indicated that much of the infused gluconate was not metabolized or failed to be eliminated by urinary clearance.

Strong Ion Difference Theory Assessment of Acid-Base Balance

Calves suffered from acidemia immediately before treatment that was primarily because of strong ion acidosis (decreased median values for $SIDm_7$, SID_e, and negative values for SIG) and to a lesser extent because of nonvolatile buffer ion acidosis (increased values for A_{tot}; Table 1). The decreases in $SIDm_7$ and SID_e primarily were because of hyponatremia and increased concentration of the strong ion D-lactate. Blood pH, $SIDm_7$ (Fig 4), and SID_e were increased, SIG was more positive (Fig 5), and A_{tot} was decreased at T120 and T240 after sodium bicarbonate infusion at which time the values reached the reference range (Table 1; Fig 6). In marked contrast, infusion of sodium gluconate did not change blood pH and effective SID, despite an increase in $SIDm_7$ and decrease in A_{tot} after treatment (Fig 6). The SIG was significantly more negative after sodium gluconate administration. Also in this model, sodium bicarbonate was an effective alkalinizing agent, sodium gluconate was an ineffective alkalinizing agent, and the increase in SIG indicated that much of the infused gluconate was not metabolized or failed to be eliminated by urinary clearance.

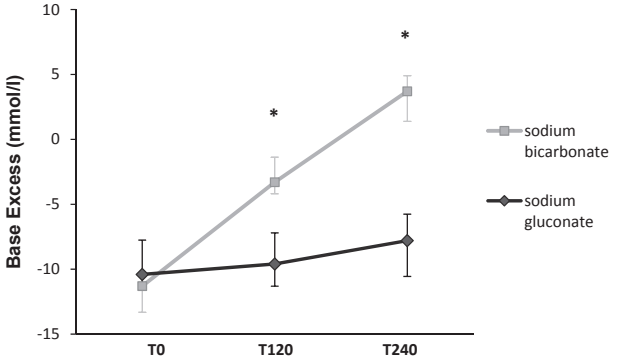

Fig 3. Medians and 25th and 75th quartiles of base excess values before (T0), during (T120), and after (T240) infusion. * = significant difference between the 2 groups at the same time ($P \leq .0023$).

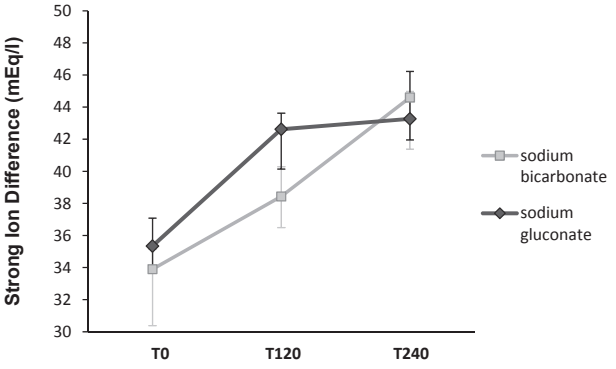

Fig 4. Medians and 25th and 75th quartiles of strong ion difference ($SIDm_7$) values before (T0), during (T120) and, after (T240) infusion.

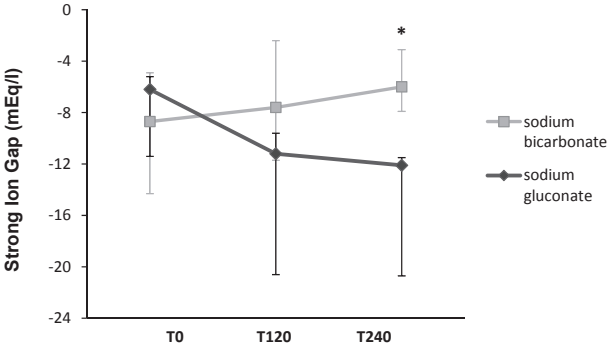

Fig 5. Medians and 25th and 75th quartiles of strong ion gap values before (T0), during (T120), and after (T240) infusion. * = significant difference between the 2 groups at the same time ($P \leq .0023$).

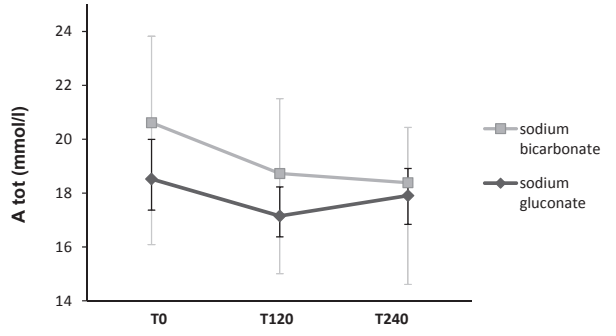

Fig 6. Medians and 25th and 75th quartiles of A_{tot} values before (T0), during (T120), and after (T240) infusion.

Discussion

The results of this study provide clear evidence of the central role that the effective SID of the infused solution exerts on acid base status. Specifically, infusion of an isotonic solution with an effective SID of approximately 0 mEq/L (such as 3.26% sodium gluconate, this study) or 0.9% NaCl[23] has minimal effect on blood pH, whereas infusion of a slightly hypertonic solution with a high effective SID of 167 mEq/L (1.4% sodium bicarbonate) is an effective alkalinizing agent. This finding confirms the previous finding by Naylor and Forsyth in 1986[36] that sodium gluconate is not an effective alkalinizing agent in neonatal calves and emphasizes the important role that the effective SID of the infused solution has on altering acid-base status.[7,37,40–42]

Moderate to severe hyponatremia (127 mmol/L) was observed in diarrheic calves, presumably owing to excessive sodium loss in the small intestine and decreased milk intake.[22,55] The important role that hyponatremia plays in producing acidemia and strong ion (metabolic) acidosis in diarrheic calves was first identified by application of strong ion difference theory.[7] The clinical importance of hyponatremia was overlooked before publication of the 2005 study because the Henderson-Hasselbalch approach to acid-base equilibria is more descriptive than mechanistic,[11] and may fail to identify the mechanism for an acid-base disturbance.[3,4,7,11] The clinical importance of hyponatremia in driving the strong ion acidosis in calves with diarrhea has provided strong support for the administration of hypertonic solutions of sodium bicarbonate[56,57] as part of the initial treatment of diarrheic calves. Moreover, the common occurrence of hyponatremia in untreated calves strongly suggests that 1.4% sodium bicarbonate solutions are more appropriate for the routine treatment of affected calves than 1.3% sodium bicarbonate solutions.

Changes in total protein concentration of plasma were minor in the calves of this study and consequently had minimal effects on acid-base balance. This observation is in contrast to a previous study in diarrheic calves in which affected animals were more dehydrated and consequently had increased concentrations of total protein and albumin in serum.[7] Nevertheless, the small decrease in serum *c*TP that occurs after IV infusion of 1.4% sodium bicarbonate or 3.26% sodium gluconate would be expected to exert a mild alkalinizing effect that probably offsets the acidifying effect of infusing sodium gluconate, which has an effective SID of approximately 0 mEq/L.[37,40–42]

A clinically important weakness of strong ion difference theory is the difficulty in obtaining an accurate estimate off SID.[3,4,7,11] When SID is calculated from measured strong cation and anion concentrations, it is preferable to call the factor measured SID (SIDm) to emphasize that it is measured and therefore an estimated value for SID and not necessarily an accurate value. Moreover, it is helpful to indicate the number of strong cations and strong anions used to provide the estimate for SID,[7,11,12] hence, the use of the term $SIDm_7$ in the study reported here. $SIDm_7$ was low initially in both groups (34–35 mEq/L), compared to an estimated SID value of 44 mEq/L (Table 1) in healthy calves.[7] Infusion of sodium bicarbonate and sodium gluconate increased $SIDm_7$ to approximately 43–45 mEq/L, but, the calculated value for $SIDm_7$ in calves treated with sodium gluconate failed to include the quantitatively important effect of gluconate on the true value for SID. This highlights the importance of calculating SIG when applying strong ion difference theory. This is because the SIG quantifies the net strong ion charge in plasma and alerts the clinician to the presence of unmeasured strong anions (such as gluconate), or much less commonly, strong cations. Indeed, calculation of the effective SID showed that infusion of sodium gluconate did not alter effective SID values, whereas sodium bicarbonate produced an increase in SID_e to 44 mEq/L.

Both AG and SIG were able to identify the presence of increased concentrations of an unmeasured anion (AG) or strong ion (SIG) after infusion of 3.26% sodium gluconate (Fig 5). Although not verified in the study reported here, it is believed that SIG provides a more accurate estimate of the unmeasured strong anion concentration than AG because SIG accounts for concurrent changes in serum total protein concentration; the latter changes markedly in critically ill patients treated with IV fluids.[3–5] Moreover, changes in SIG over time provide a quantitative measure of the rate of metabolism of an unmeasured strong anion such as gluconate. Other investigators reported high concentrations of unmeasured strong anions after infusion of a commercially available solution containing acetate and gluconate in patients with cardiopulmonary bypass,[58] presumably because of the presence of unmetabolized gluconate. Because gluconate is an important component of commercially available solutions such as 23% calcium gluconate and acetated Ringer's solution, the slow metabolism of gluconate is clinically important because the sustained presence of a strong anion will result in hypochloremia, and in some cases, strong ion acidosis.

The SID approach to acid-base equilibria posits that the high effective SID of a 1.4% sodium bicarbonate solution corrects the strong ion acidosis by increasing the independent variable SID.[37,40–43] In the SID context, sodium gluconate failed to correct the strong ion acidosis because the effective SID of the infused solution was approximately 0 mEq/L, which will tend to have a mild acidifying effect. The traditional Henderson-Hasselbalch approach also provides an explanation for the observed results in that 1.4% sodium bicarbonate solution corrects the metabolic acidosis by buffering protons in the extracellular and intracellular compartments, producing water and CO_2,[38,39] such that $HCO_3^- + H^+ \leftrightarrow CO_2 + H_2O$. In this study, pCO_2 was significantly increased at T240 after sodium bicarbonate infusion whereas infusion of sodium gluconate produced little change in pCO_2 (Table 1). The Henderson-Hasselbalch approach to acid-base equilibria

posits that sodium gluconate failed to correct the metabolic acidosis because it was not metabolized to bicarbonate and therefore was unable to buffer protons in the extracellular and intracellular compartments. Previous studies demonstrated that gluconate is poorly metabolized in healthy and acidotic calves.[36,38] Infusion of sodium gluconate produced little change in pH or base excess with time and blood gluconate concentrations increased to high concentrations as the gluconate accumulated in blood. Other metabolizable bases such as acetate or L-lactate were rapidly metabolized and the alkalinizing effect had a similar time course to that seen with bicarbonate.[36]

The general condition and degree of hydration of the calves were assessed by a clinical score. Our finding that the general condition of the calves entering the study was only slightly abnormal was attributed to the close observation and daily care by a veterinarian. Owing to this close monitoring, calves entered the study immediately after fulfilling the selection criteria and responded well to treatment during the 4 hours of the study and immediately after calves were infused with 3.26% sodium gluconate. A 1.4% sodium bicarbonate solution expanded the plasma volume to a greater extent than did 3.26% sodium gluconate solution. This was most likely owing to the higher sodium load and tonicity of the infused solution in calves treated with 1.4% sodium bicarbonate (sodium concentration = 167 mmol/L) versus 3.26% sodium gluconate (sodium concentration = 149 mmol/L).

Infusion of sodium gluconate induced moderate inspiratory stertor in 4 calves, which probably occurred owing to slight swelling of mucous membranes in the upper airways. The cause for this sign is unknown. Because the infused solutions were prepared individually with intervals of days or weeks, and other calves receiving the sodium gluconate solution did not show stertor, contamination of the infused solutions seems unlikely. The stertor disappeared shortly after infusion (after approximately 30 minutes).

In other studies, the plasma D-lactate concentration decreased exponentially with time[30,32] whereas in this study *c*D-lactate did not decrease significantly in both groups within 4 hours of infusion. Possibly, a mean volume of 1.7 L of infused solution was not enough to reestablish urine production and therefore excretion of D-lactate or perhaps exogenous production of D-lactate continued in the gastrointestinal tract of the diarrheic calves during the study, with intestinal absorption rates approximating the clearance rate from plasma.

In conclusion, results of this study support the application of strong ion difference theory to acid-base disorders. The results confirm from the previous findings[7] that hyponatremia and hyper-D-lactatemia play important and primary roles in the development of acidemia and strong ion (metabolic) acidosis in diarrheic calves. Moreover, application of strong ion theory provides an easily understood explanation for the important role that the effective SID of administered fluids plays in altering acid-base balance.

Footnotes

[a] Analog weigh scales, not specified
[b] BD Discardit™ II, 2 mL, Becton, Dickinson and Company, Franklin Lakes, NJ
[c] Vasuflo T, G20, Dispomed Witt oHG, Gelnhausen, Germany
[d] Sodio Bicarbonato E500 Polvere, Polichimica S.R.L., Bologna, Italy
[e] Natrium-D-Gluconat, 1000 g, Firma Sigma-Aldrich Chemie GmbH, Steinheim, Germany
[f] Acqua per Preparazioni iniettabili sterile apirogena, 2000 mL, Firma ACME S.R.L., Cavriago, Italy
[g] ABL 700, Radiometer, Copenhagen, Denmark
[h] Hitachi Automatic Analyzer 912 E, Roche Diagnostics, Mannheim, Germany

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