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Alkalinizing effect of $NaHCO_3$ with and without glucose when administered orally to euhydrated neonatal dairy calves

W. Grünberg,*[1] H. Hartmann,† S. Arlt,‡ O. Burfeind,‡ and R. Staufenbiel§
*Department of Farm Animal Health, Universiteit Utrecht, Utrecht, the Netherlands
†Institut für Veterinär-Physiologie, and
‡Tierklinik für Fortpflanzung, and
§Klinik für Klauentiere, Freie Universität Berlin, 14163 Berlin, Germany

ABSTRACT

The use of oral rehydration solutions (ORS) is well established as an effective treatment to correct water-, electrolyte-, and acid-base balance in diarrheic calves. The main ingredients of a commercial ORS are Na, glucose, and alkalinizing agents, such as $NaHCO_3$. Particular importance is attributed to the combination of glucose and Na at a specific ratio to optimize intestinal sodium, and thereby water uptake, through the sodium-glucose co-transport. Enhancing intestinal Na absorption by combining glucose and Na in an ORS has the potential to improve the alkalinizing effect of an ORS according the strong ion theory. The objective of this study was to investigate the effect of glucose on the alkalinizing effect of $NaHCO_3$ when administered orally. Nine healthy neonatal Holstein-Friesian calves underwent 3 oral treatments with 2-L solutions of $NaHCO_3$ (150 mmol/L), glucose (300 mmol/L), and glucose + $NaHCO_3$ (300 mmol/L + 150 mmol/L, respectively) in randomized order. Arterial and venous blood was obtained before treatment and in 30-min intervals thereafter for blood gas analysis and determination of plasma protein and electrolyte concentrations. Urine was collected volumetrically to determine urine volume, osmolality, pH, net acid excretion, and renal Na excretion after treatment. Plasma volume changes were extrapolated from plasma protein concentration changes. Treatment and time effects were tested with repeated measures ANOVA. Only subtle differences between oral administration of $NaHCO_3$, with and without glucose, were observed for the change of the standard HCO_3 concentration relative to baseline. No differences in plasma Na, plasma volume expansion, renal Na, net base excretion, urine volume, or pH could be identified between animals treated orally with $NaHCO_3$ with and without glucose. Similarly, no differences in blood glucose concentration, plasma volume expansion, urine volume, or renal glucose excretion were observed in the 8 h after treatment when comparing oral glucose treatment with and without $NaHCO_3$. Our results indicate that combination of $NaHCO_3$ with glucose in a hypertonic ORS only had a minor effect on the alkalinizing effect of $NaHCO_3$, which is unlikely to be of clinical relevance. The combination of $NaHCO_3$ and glucose neither improved Na, glucose, nor water absorption in euhydrated neonatal dairy calves, questioning the relevance of a specific ratio between Na and glucose in ORS for calves.

Key words: oral electrolyte solution, calf, glucose, sodium bicarbonate

INTRODUCTION

Diarrhea is the main cause for morbidity in dairy calves, accounting for more than 50% of losses in unweaned dairy calves in the United States (USDA, 2007). Economic losses associated with diarrhea in calves are not only due to increased mortality rates, but also to labor, medication, and veterinary expenses. Besides resulting in dehydration, diarrhea is frequently associated with acidemia, metabolic acidosis, electrolyte imbalances, and hypoglycemia (Naylor, 1999). For mildly to moderately affected calves, oral rehydration therapy provides an easily applicable, efficient, and inexpensive treatment approach in farm animal practice. Oral rehydration solutions (**ORS**), when formulated correctly, can efficiently correct moderate dehydration, acidemia, hyperkalemia, and hypoglycemia. Effective ORS are required to provide (1) adequate amounts of Na to correct and maintain extracellular volume homeostasis; (2) sufficient organic compounds, such as glucose or glycine, to assist intestinal Na and thereby water absorption through sodium-glucose linked transport proteins (**SGLT**); (3) alkalinizing agents to correct acidemia or metabolic acidosis frequently encountered in diarrheic calves; and (4) to provide energy to reduce negative energy balance (Smith, 2009). Glucose is used as an ingredient in most commercial ORS to improve intestinal Na and water absorption and to provide read-

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[1]Corresponding author: waltergruenberg@yahoo.com

ily available energy for the organism. In contrast, oral glucose administration is not known to have any effect on acid-base homeostasis. The strong ion theory provides theoretical support for the hypothesis that orally administered glucose could indirectly affect acid-base homeostasis by facilitating intestinal Na absorption (Stewart, 1978). The strong ion theory is based on the concept that acid-base homeostasis of the extracellular space depends on the equilibrium between strong cations and strong anions, with cations, such as Na or potassium, having an alkalinizing effect and strong anions, such as chloride, having an acidifying effect (Stewart, 1978). Increasing the availability of Na in the extracellular space by enhancing Na absorption from the gut through the combination of glucose with Na in an ORS could potentiate the alkalinizing capacity of Na, according to the strong ion theory. Accordingly, we hypothesized that the combination of $NaHCO_3$ with glucose in an ORS would improve the alkalinizing effect of $NaHCO_3$ when compared with an ORS containing $NaHCO_3$ alone. The objective of the present study was to compare the alkalinizing effect of $NaHCO_3$ after oral administration with and without glucose in euhydrated neonatal calves.

MATERIALS AND METHODS

All methods were approved by the Animal Care and Use Committee, Berlin, Germany (Permit #0384/10).

Animal Housing and Feeding

Nine healthy male Holstein-Friesian calves were obtained from a commercial dairy farm between 7 and 14 d of age. Results of this study focusing on the effect of orally applied electrolyte solutions on plasma potassium concentration in neonatal dairy calves have been published previously (Grünberg et al., 2011b). Calves were kept unrestrained in groups of 2 in stalls bedded on straw in a climate-controlled environment. All animals were allowed a 6- to 8-d acclimatization period, during which their health status was monitored. A commercial CN-based milk replacer (Sprayfro Sprint, Sloten, Diepholz, Germany) with 22.5% CP, 16% crude fat, 0.1% crude fiber, and 7.0% crude ash was fed twice daily (150 g of milk replacer per liter of water; 60 mL of solution per kilogram of BW; pH = 6.5; temperature = 38°C) in a nipple bucket (equivalent to approximately 900 g of milk replacer per day). Calves had access to fresh water ad libitum, except for an 8-h period following each experimental treatment. All calves were completely physically examined 12 to 24 h before the start of the first treatment and were instrumented as follows. A 16 gauge, 83-mm catheter (Angiocath, Becton Dickinson, Franklin Lakes, NJ) was aseptically fitted in a jugular vein and an aortic catheter was aseptically placed in the abdominal aorta under ultarsonographic control as described by Offinger et al. (2011). A urine collection bag with a connection port to attach tubing for urine collection was glued onto the hair around the preputium of the calves. Catheters and urine collection bags remained in place from d 5 until the end of the study. Venous and aortic catheterization was performed after sedation with xylazine (0.2 mg/kg of BW i.m.), aseptic preparation of the skin, and injection of 1 mL of procaine 4% into and under the skin at the site of catheter placement. For venous catheterization, a small stab incision through the skin was made with a scalpel to facilitate catheter placement. The catheter was placed into the vein, connected to an extension set (Discofix C-3, 10 cm, Braun Melsungen AG, Melsungen, Germany), and secured in place with suture material. At the same time of venous catheterization, an aortic catheter was placed in the left paraveterebral area between the third and fourth lumbar transversal process. For aortic catheter placement, the skin was prepierced with a 12 gauge needle. A 10-cm, 12 gauge needle was then advanced through the prepierced skin and the lumbar musculature to penetrate through the transversal ligament between the third and the fourth lumbar vertebrae. Using a 7.5-MHz linear transducer placed in the left flank, the needle was forwarded under visual control into the aorta. Once blood gushed through the 12 gauge needle, sterile polyamide tubing (4 French, 1.37 mm outer diameter, 40 cm length; Walter Veterinärinstrumente e.K., Baruth, Germany) threaded over a Teflon-coated J-tipped guide wire (J-wire, Teflon coated, 0.81 mm, 150 cm length; Walter Veterinärinstrumente e.K.) was inserted into the aorta through the needle. The guide wire and the polyamide tubing were then advanced approximately 10 cm into the abdominal aorta in the caudal direction. The correct position of the polyamide tubing was confirmed ultrasonographically before removing the guide wire and the needle. The tubing was then secured in place with tape and suture material. Both catheters were flushed with heparinized 0.9% NaCl solution (40 U of heparin/mL) immediately before and after each blood collection and every 8 to 12 h while animals were not on study.

Experimental Protocol

Experimental treatments were administered between 15 and 24 d of age and at least 12 h after the last feeding. Calves on trial were restrained with a fence placed in the stall in such manner that they could lie and stand easily but could not turn. Treatment order was assigned randomly (by drawing cards) for each in-

dividual animal with a washout period of 48 h between treatments. On each trial day, calves were tube-fed between 0800 and 0815 h with one of the following test solutions at approximately 38°C: 25.2 g of $NaHCO_3$ in 2 L of tap water (**NaBic**; 150 mmol/L); 118 g of glucose monohydrate in 2 L of tap water (**Gluc**; 300 mmol/L); and 25.2 g of $NaHCO_3$ plus 118 g of glucose in 2 L of tap water (**Combi**). The solutions of group NaBic and Gluc were formulated to be isotonic (300 mOsmol/L); the test solution of group Combi was of double tonicity (600 mOsmol/L), but formulated to match the Na to glucose ratio of 1:2 on the molar basis recommended for ORS for calves (Smith, 2009). Tube feeding was chosen over voluntary intake to standardize the ingestion time of the test solutions, as different palatability of salt and glucose solution was likely to affect ingestion time.

Venous and arterial blood samples were obtained from the jugular and aortic catheters at 0 min (immediately before tube feeding) as well as 30, 60, 90, 120, 150, 180, 210, 240, 300, 360, 420, and 480 min after tube feeding. Blood for blood gas analysis was collected anaerobically into heparinized 1-mL plastic syringes that were immediately capped and kept at room temperature until analyzed. Blood gas analysis was performed within 10 min of collection. Blood for biochemical analysis was collected into 10-mL tubes containing Li-heparin as an anticoagulant and centrifuged within 10 min at 1,500 × *g* for 15 min at room temperature. Plasma was harvested and stored at −24°C until analyzed. Immediately after administration of the test solution, tubing connected to a 3-L collection vial was attached to the connecting port of the urine collection bag to allow volumetric urine collection for a period of 8 h after the start of treatment. The collection vial contained mineral oil to minimize air exposure of urine, which would alter urine pH. At the end of the 8-h study period, the volume of collected urine was determined and a urine sample was obtained anaerobically after thorough mixing. The sample was then transferred into two 5-mL vials that were completely filled and immediately capped to minimize exposure to air. One tube was placed in a water bath at 38°C and the pH was measured within 15 min. Tubes were then stored at −21°C for further analyzes.

Plasma samples were assayed for concentration of Na (flame atomic absorption spectrometry), K (flame atomic absorption spectrometry), chloride (indirect ion selective electrode system), glucose (hexokinase), and total protein (**TP**; biuret). An automated chemistry analyzer (Cobas Mira Plus, Roche, Basel, Switzerland) was used for the plasma biochemical analysis; flame atomic absorption spectrometry was conducted on a Solaar M6 spectrometer (Thermo Fisher Scientific, Schwerte, Germany). Blood gas analysis was performed on an automated blood gas analyzer (Radiometer AVL5, Brønshøj, Denmark). Measured values for blood pH, partial pressure of CO_2 (**P_{CO_2}**), and partial pressure of O_2 were corrected for rectal temperature and used to calculate the actual venous blood (**vABC**) and standard venous blood HCO_3 (**vSBC**; concentration of the bicarbonate ion in blood calculated for a standard P_{CO2} = 5.33 kPa) concentration using standard equations (Burnett et al., 1995). Urine was analyzed for urine Na and glucose as described for plasma. Total excretion of Na and glucose was calculated from the concentration of these compounds and the determined urine volume. Urine osmolality was determined by freezing-point depression (Micro Osmette, Precision Systems Inc., Natick, MA). Urinary net base excretion (**NBE**) and ammonium concentration were determined by titration as described elsewhere (Chan, 1972; Constable et al., 2009; Grünberg et al., 2011a). Briefly, previously frozen urine was thawed at room temperature, acidified by the addition of a fixed volume of 1 N of HCl and heated to a slow boil for at least 2 min to expel CO_2. Urine was then back-titrated with 0.1 N of NaOH to the pH of 7.4. Eight percent formaldehyde was then added and the volume of 0.1 NaOH needed to back-titrate the urine sample to a pH of 7.4 was determined.

To crudely estimate the volume changes of extracellular space that might have occurred after treatment, changes in plasma volume at each time point *i* relative to the beginning of the experiment (T_0) were extrapolated from the changes in [TP] as follows: $VolDiff_i$ (%) = $([TP_0] - [TP_i]) \times 100/[TP_i]$ (Nouri and Constable, 2006).

The strong ion difference (**SID**) was calculated from the plasma concentrations of Na, K, and Cl as follows: SID_3 (mEq/L) = $\{([Na] + [K]) - [Cl]\}$. Anion Gap (**AG**) in mEq/L was calculated from the calculated value for [vABC] (Constable, 1999) as AG = $([Na] + [K]) - ([Cl] + [vABC])$. Strong ion gap (**SIG**; in mEq/L) was calculated as SIG = $[TP] \times \{0.343/(1 + 10^{7.08-pH})\} - AG$, where [TP] was measured in g/L (Constable et al., 2005).

To determine the kinetics of glucose absorption, the maximal glucose concentration (**C_{max}**) and the time to maximal glucose concentration (**T_{max}**) were obtained from the plasma glucose concentration-time curves The increment of concentration of glucose relative to T_0 was determined for each time point *i* using the equation $GlucDiff_i = [glucose_i] - [glucose_0]$. Furthermore, the maximal increment of the glucose concentration ($C_{max\text{-}GlucDiff}$) and the time to maximal increment of the glucose concentration ($T_{max\text{-}GlucDiff}$) were determined for each treatment. In a similar manner, the changes in concentration for each time point relative to T_0 were determined for Na ($NaDiff_i$), vSBC ($vSBCDiff_i$), and SID (SID_3Diff_i). The change of the plasma [glucose]

and plasma [Na] were also corrected for plasma volume changes relative to T_0 using the equation

$$\text{GlucDiffVol}_i \text{ (mmol/L)} = \text{GlucDiff}_i + (\text{GlucDiff}_i \times \text{VolDiff}_i/100).$$

The area under curve (**AUC**) for plasma [glucose], [Na], and VolDiff increment − time for the first 4 h after treatment ($AUC_{GlucDiff\text{-}240}$, $AUC_{HCO3Diff\text{-}240}$, $AUC_{BEDiff\text{-}240}$), as well as the AUC of the change of plasma vSBC relative to T_0 for the entire study period ($AUC_{vSBCDiff\text{-}480}$), were calculated using the trapezoidal rule.

Statistical Analysis

Data are expressed as mean ± SD or as median and interquartile range. Values determined at $P < 0.05$ were considered to be significant. Values were log-transformed when necessary to achieve a normal distribution. Repeated measures ANOVA was used to detect differences in measured parameters between treatment groups and over time using PROC MIXED (SAS 9.2, SAS Institute Inc., Cary, NC). Bonferroni-adjusted P-values were used to assess differences over time whenever the F test was significant. A power analysis was conducted using PROC POWER to determine the smallest effect size on vSBC, vSBCDiff, [glucose], and GlucDiff detectable with $\alpha = 0.05$, Power = 0.8, and n = 9.

RESULTS

Acid-Base Homeostasis

Venous blood pH and the difference of vSBC relative to T_0 (vSBCDiff) over time and stratified by treatment group are presented in Figure 1. Actual venous HCO_3, vSBC, arterial blood pH, and arterial Pco_2 are presented in Table 1, stratified by treatment and sampling time. Treatment effects were identified for venous blood pH ($P < 0.0001$), vABC ($P = 0.001$), vSBC ($P = 0.005$), and arterial pH ($P = 0.0048$), with group Gluc differing significantly from groups NaBic and Combi. No differences were found between groups NaBic and Combi. Differences between the latter 2 groups were identified only for vSBCDiff_i (Figure 1). The $AUC_{VSBC480}$ was 1,203 ± 472 mmol/min per L, −195 ± 654 mmol/min per L, and 1,767 ± 862 mmol/minper L for groups NaBic, Gluc, and Combi, respectively. Values determined for group Gluc were significantly below those calculated for groups NaBic and Combi. No difference was identified between groups NaBic and Combi. A treatment effect was not determined on AG, SIG, or SID.

Plasma Na, Glucose, and Plasma Volume Changes

The plasma Na concentration-time curves stratified by treatments are presented in Figure 2. Treatment and time effects were identified on the plasma [Na], with group Gluc differing significantly from groups NaBic and Combi. Changes in plasma [Na] over time were not significant in any of the treatment groups when applying a Bonferroni correction. The $AUC_{DiffNa240}$ was 255.0 ± 411.2 mmol/min per L, −338.3 ± 548.4 mmol/min per L, and −8.0 ± 482.6 mmol/min per L for groups NaBic, Gluc, and Combi, respectively. No treatment effect on $AUC_{DiffNa240}$ was observed. Volume-corrected plasma [Na] in group NaBic were above concentrations calculated for group Gluc from 90 to 300 min posttreatment (Figure 3). Volume-corrected plasma [Na] in group Combi ranged between values calculated for group NaBic and Gluc. Differences between Combi and NaBic were significant at only 1 time point (Figure 3).

Plasma glucose concentration-time curves had similar slopes and amplitudes in groups Gluc and Combi, whereas, plasma [glucose] remained unchanged throughout the study period in group NaBic, as expected (Grünberg et al., 2011b; Figure 4). Treatment and time effects were identified on plasma [glucose], with group NaBic differing significantly from groups Gluc and Combi. A treatment effect was also determined on $C_{max\text{-}GlucDiff}$, $T_{max\text{-}GlucDiff}$, and $AUC_{GlucDiff\ 240}$, with group NaBic differing from groups Gluc and Combi. No differences between groups Gluc and Combi were found for any of those parameters. The C_{max} and T_{max} for plasma [glucose] were 5.2 ± 1.5 mmol/L and 83 ± 29 min, respectively, in group Gluc, and 5.4 ± 1.7 mmol/L and 64 ± 11 min, respectively, in group Combi. Differences between these 2 groups were not significant. The $AUC_{GlucDiff240}$ was −125.9 ± 110.0 mmol/min per L, 539.9 ± 254.6 mmol/min per L and 513.7 ± 220.1 mmol/min per L for NaBic, Gluc, and Combi, respectively. A treatment effect was identified, with values calculated for group NaBic being significantly lower than those calculated for groups Gluc and Combi. Volume-corrected changes for plasma [Glucose] in group NaBic were below values measured in groups Gluc and Combi from 30 to 240 min after treatment. No difference was determined between group Gluc and Combi at any sampling time.

Plasma volume, as estimated from the changes in plasma [TP], was significantly increased relative to T0 from 60 to 150 min after treatment,, but no treatment effect was determined (Grünberg et al. 2011b). The AUC of plasma volume expansion during the first 4 h after treatment ($AUC_{VolDiff240}$) was 920.4 ± 653.8% per min, 264.0 ± 389.7% per min, and 730.5 ± 802.3% per

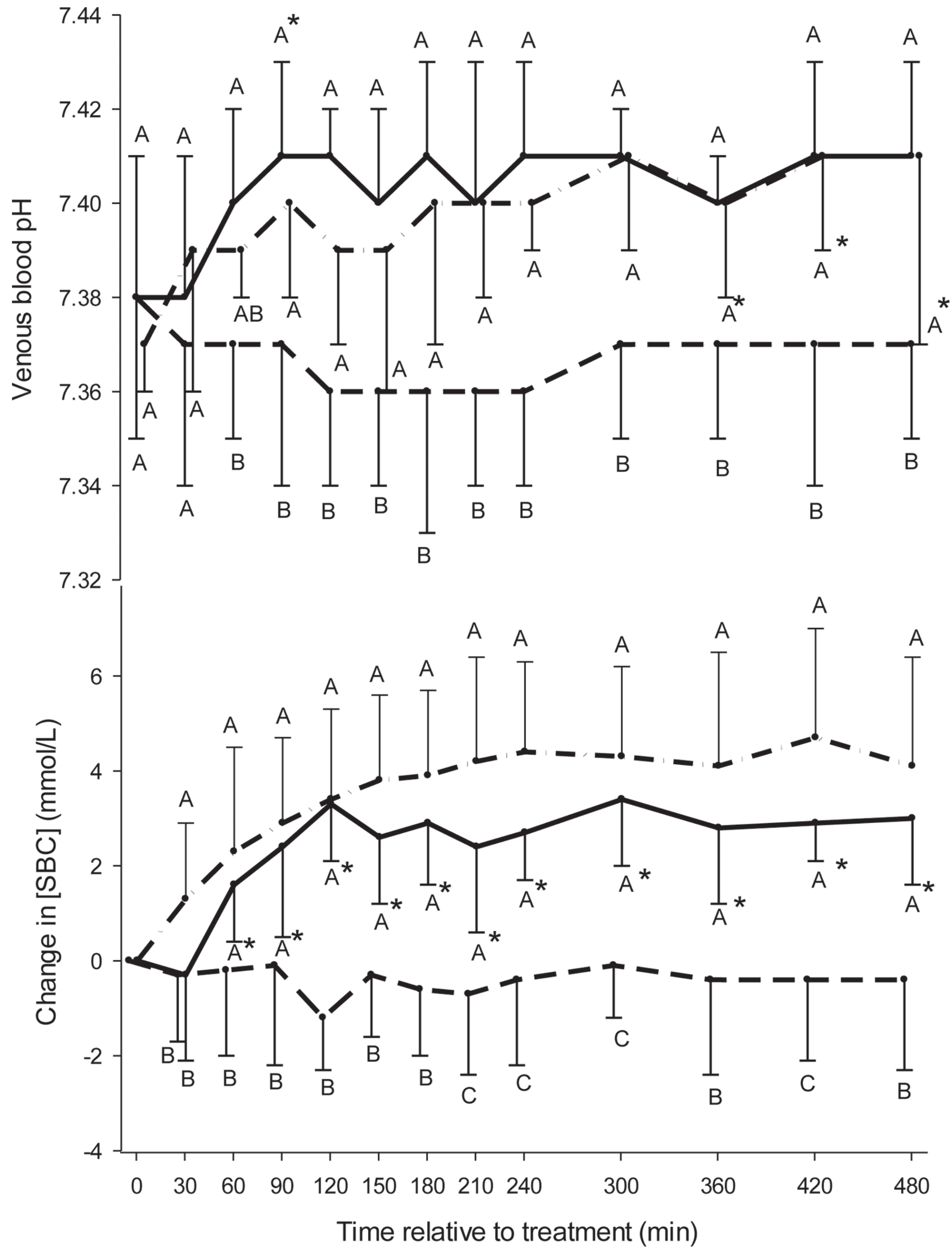

Figure 1. Mean ± SD of venous blood pH (upper panel) and change of venous standard bicarbonate concentration of blood [SBC] relative to the beginning of the experiment (T0) for treatment groups: 25.2 g of $NaHCO_3$ in 2 L of tap water (NaBic; solid line); 118 g of glucose monohydrate in 2 L of tap water (Gluc; dashed line); and 25.2 g of $NaHCO_3$ and 118 g of glucose monohydrate in 2 L of tap water (Combi; dash-dotted line). Treatment was administered at T0. Values with different capital letters differ significantly between groups ($P < 0.05$). Values marked with an asterisk differed significantly ($P < 0.05$, Bonferroni corrected) from T0 values.

Table 1. Mean ± SD of venous actual bicarbonate concentration (vABC), venous standard bicarbonate concentration (vSBC), arterial pH (apH), and arterial partial pressure of CO_2 (apCO_2) at different sampling times stratified by treatment groups

Time (min)	Group[1]	vABC (mmol/L)	vSBC (mmol/L)	apH	apCO_2 (kPa)
0	NaBic	30.8 ± 3.4[a]	28.2 ± 2.9[a]	7.42 ± 0.03[a]	5.9 ± 0.4[a]
	Gluc	29.3 ± 1.7[a]	27.7 ± 1.6[a]	7.42 ± 0.02[a]	6.2 ± 0.6[a]
	Combi	29.4 ± 2.2[a]	27.0 ± 1.6[a]	7.40 ± 0.02[a]	6.2 ± 0.5[a]
30	NaBic	30.2 ± 4.0[a]	27.9 ± 3.1[a]	7.42 ± 0.05[a]	6.3 ± 0.2[a]
	Gluc	29.6 ± 1.8[a]	27.3 ± 1.8[a]	7.41 ± 0.01[a]	6.3 ± 0.5[a]
	Combi	30.3 ± 1.9[a]	28.3 ± 1.6[a]*	7.41 ± 0.01[a]	6.2 ± 0.7[a]
60	NaBic	32.1 ± 4.0[a]	29.8 ± 3.3[a]*	7.42 ± 0.03[a]	6.4 ± 0.4[a]
	Gluc	29.6 ± 2.3[b]	27.4 ± 2.2[b]	7.42 ± 0.02[a]	6.0 ± 0.2[a]
	Combi	31.8 ± 2.6[ab]*	29.3 ± 2.2[ab]*	7.44 ± 0.04[a]*	6.2 ± 0.9[a]
90	NaBic	33.0 ± 3.8[a]*	30.7 ± 3.2[a]*	7.43 ± 0.03[ab]	6.5 ± 0.5[a]
	Gluc	29.8 ± 2.4[b]	27.6 ± 2.1[b]	7.41 ± 0.02[b]	6.2 ± 0.3[a]
	Combi	32.1 ± 2.8[a]*	29.9 ± 2.3[a]*	7.45 ± 0.04[a]	6.3 ± 0.9[a]
120	NaBic	34.3 ± 3.2[a]*	31.6 ± 2.7[a]*	7.44 ± 0.03[a]	6.6 ± 0.5[a]
	Gluc	28.8 ± 2.4[b]	26.4 ± 1.7[b]	7.41 ± 0.03[a]	6.2 ± 0.7[a]
	Combi	33.6 ± 2.7[a]*	30.4 ± 2.3[a]*	7.43 ± 0.02[a]	6.6 ± 0.4[a]
150	NaBic	33.9 ± 3.3[a]*	30.8 ± 2.6[a]*	7.44 ± 0.02[a]	6.3 ± 0.5[a]
	Gluc	29.8 ± 1.9[b]	27.3 ± 1.5[b]	7.40 ± 0.02[b]	6.3 ± 0.4[a]
	Combi	34.0 ± 3.0[a]*	30.8 ± 2.2[a]*	7.44 ± 0.03[a]	6.4 ± 0.8[a]
180	NaBic	33.9 ± 3.4[a]*	31.1 ± 2.6[a]*	7.44 ± 0.01[a]	6.5 ± 0.7[a]
	Gluc	29.8 ± 1.7[b]	27.1 ± 1.6[b]	7.41 ± 0.02[b]	6.2 ± 0.4[a]
	Combi	33.6 ± 3.0[a]*	30.9 ± 2.5[a]*	7.43 ± 0.01[ab]	6.5 ± 0.8[a]
210	NaBic	33.0 ± 3.3[a]	30.7 ± 2.8[a]*	7.44 ± 0.02[a]	6.6 ± 0.5[a]
	Gluc	29.4 ± 1.7[b]	27.0 ± 1.9[b]	7.43 ± 0.03[a]	5.7 ± 0.6[b]
	Combi	34.0 ± 2.9[a]*	31.2 ± 2.5[a]*	7.43 ± 0.02[a]	6.8 ± 0.6[a]
240	NaBic	33.7 ± 3.6[a]*	30.9 ± 2.6[a]*	7.44 ± 0.02[a]	6.5 ± 0.5[a]
	Gluc	29.4 ± 2.8[b]	27.2 ± 1.8[b]	7.40 ± 0.02[b]	6.2 ± 0.4[a]
	Combi	34.7 ± 2.7[a]*	31.4 ± 1.9[a]*	7.44 ± 0.01[a]	6.3 ± 0.6[a]
300	NaBic	34.6 ± 3.6[a]*	31.7 ± 2.5[a]*	7.45 ± 0.03[a]	6.4 ± 0.5[a]
	Gluc	30.1 ± 2.3[b]	27.6 ± 1.6[b]	7.41 ± 0.03[b]	6.2 ± 0.6[a]
	Combi	34.6 ± 2.7[a] *	31.3 ± 1.9[a]*	7.45 ± 0.02[a]	6.5 ± 0.6[a]
360	NaBic	33.8 ± 3.0[a]	31.0 ± 2.2[a]*	7.45 ± 0.02[a]	6.4 ± 0.5[a]
	Gluc	29.5 ± 2.6[b]	27.2 ± 1.7[b]	7.41 ± 0.02[b]	6.2 ± 0.5[a]
	Combi	34.2 ± 3.1[a]*	31.1 ± 2.4[a]*	7.44 ± 0.03[ab]	6.7 ± 0.4[a]
420	NaBic	34.3 ± 3.1[a*]	31.1 ± 2.6[a]*	7.44 ± 0.02[a]	6.4 ± 0.4[a]
	Gluc	29.9 ± 2.0[b]	27.2 ± 1.8[b]	7.41 ± 0.02[a]	6.1 ± 0.6[a]
	Combi	34.6 ± 3.1[a]*	31.7 ± 2.4[a]*	7.44 ± 0.02[a]	6.6 ± 0.6[a]
480	NaBic	33.9 ± 2.9[a]*	32.1 ± 2.0[a]*	7.43 ± 0.02[a]	6.6 ± 0.4[a]
	Gluc	29.3 ± 3.2[b]	27.2 ± 2.4[b]	7.42 ± 0.04[a]	5.8 ± 0.4[a]
	Combi	34.1 ± 2.3[a]*	31.1 ± 2.5[a]*	7.44 ± 0.01[a]	6.5 ± 0.4[a]

[a,b]Values from the same sampling time with different letters are significantly different ($P < 0.05$).

[1]NaBic = 25.2 g of $NaHCO_3$ in 2 L of tap water; Gluc = 118 g of glucose monohydrate in 2 L of tap water; Combi = 25.2 g of $NaHCO_3$ and 118 g of glucose monohydrate in 2 L of tap water.

*Values are significantly different from values obtained at the beginning of the experiment in the same group ($P < 0.05$, bonferroni corrected).

min for groups NaBic, Gluc, and Combi, respectively. The treatment effect was not significant.

Urine Volume, pH, Renal Sodium, and Net Base Excretion

Urine volume production over 8 h following experimental treatment was similar in all groups, but showed broad variability between animals (Table 2). Urine pH, NBE, total renal Na excretion, and urine osmolality were significantly higher in groups NaBic and Combi compared with Gluc (Table 2). Numerical differences between NaBic and Combi for NBE did not reach significance level (Table 2).

Sample Size and Statistical Power

The power analysis performed to determine the smallest detectable effect size on vSBC and SBCDiff as well as [glucose] and GlucDiff, with $\alpha = 0.05$, Power = 0.8, and n = 9, indicated that the sample size was sufficient to identify significant differences between groups of 1.6 mmol/L and 1.0 mmol/L for vSBC and vSBCDiff , respectively. Similarly, the smallest detectable effect size

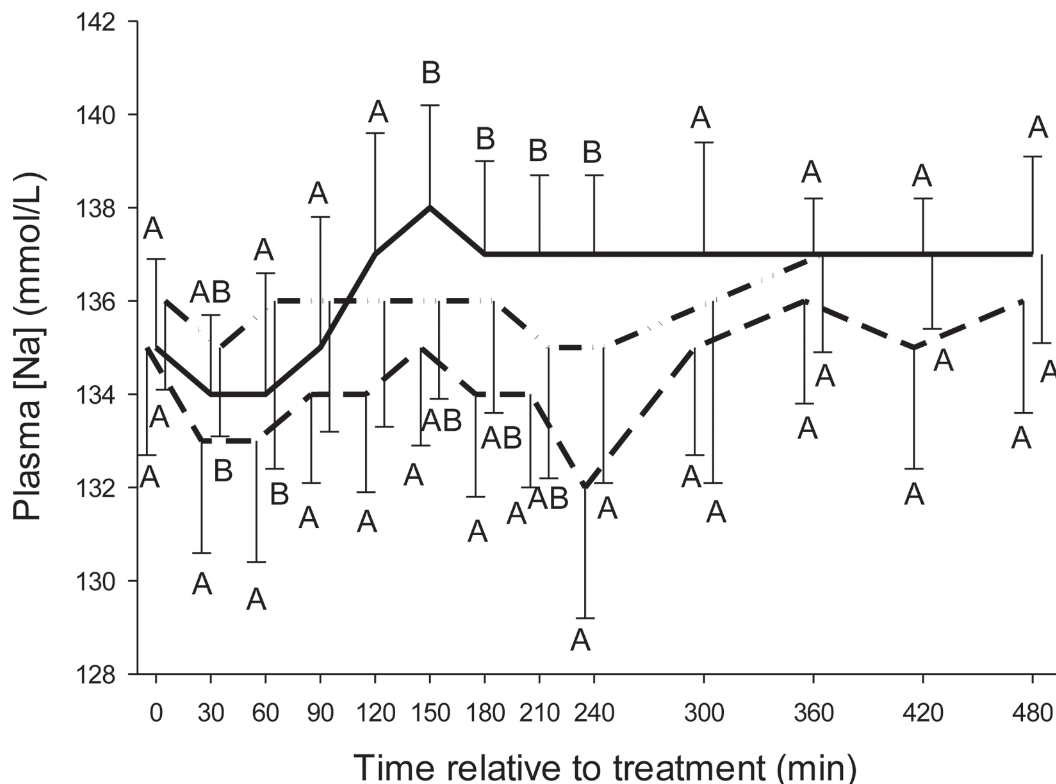

Figure 2. Mean ± SD plasma Na concentration for treatment groups: 25.2 g of $NaHCO_3$ in 2 L of tap water (NaBic; solid line); 118 g of glucose monohydrate in 2 L of tap water (Gluc; dashed line); and 25.2 g of $NaHCO_3$ and 118 g of glucose monohydrate in 2 L of tap water (Combi; dash-dotted line). Treatment was administered at the beginning of the experiment (T0). Values with different letters differ significantly between groups ($P < 0.05$).

for plasma [glucose] was 2.5 mmol/L and 2.0 mmol/L for [glucose] and GlucDiff, respectively.

DISCUSSION

The objective of the current study was to determine if the combination of $NaHCO_3$ and glucose, when administered orally to neonatal calves, potentiates the alkalinizing effect of $NaHCO_3$ by facilitating enteral Na uptake through SGLT. This hypothesis was based on the strong ion theory, suggesting that enhanced enteral Na absorption in the presence of glucose would result in higher cation content with an alkalinizing effect in the extracellular space (Stewart, 1978). In the current study, we were only able to identify very subtle effects of the combination of $NaHCO_3$ with glucose on acid-base homeostasis when compared with the oral administration of $NaHCO_3$ alone. The observed effect of less than 2 mmol/L in vSBCDiff between animals receiving oral $NaHCO_3$, with and without glucose, was clearly below what was expected from SGLT, which is considered a major route of intestinal Na and glucose absorption based on our hypothesis. The results of the power analysis indicate that the sample size provided sufficient power to identify group differences of at least 1 mmol/L for vSBCDiff, which is approximately equivalent to the precision of the results provided by standard blood gas analyzers. Interestingly, we not only failed in identifying any measurable effect of orally administered glucose on the intestinal uptake of Na or water, but also did not detect any effect of orally administered Na on the intestinal absorption kinetics of glucose.

Values for the threshold concentration for Na in the small intestinal lumen in different species above which net Na absorption from the gut can be expected to range from 50 to 120 mmol/L, as reported in the literature (Aperia et al., 1983; Elliott et al., 1989; Elliott et al., 1991; Gisolfi et al., 1992). Therefore, it appears reasonable to assume that intestinal net Na absorption occurred after oral administration of solutions with a [Na] of 150 mmol/L, as was the case in groups NaBic and Combi. A comparison of the concentration-time curves of actual and volume-corrected plasma [Na], renal Na, and NBE excretions during the first 8 h after treatment between animals having received $NaHCO_3$ with and without glucose, did not reveal any net effect of glucose on intestinal Na absorption after administration of $NaHCO_3$. Similar plasma volume expansion-

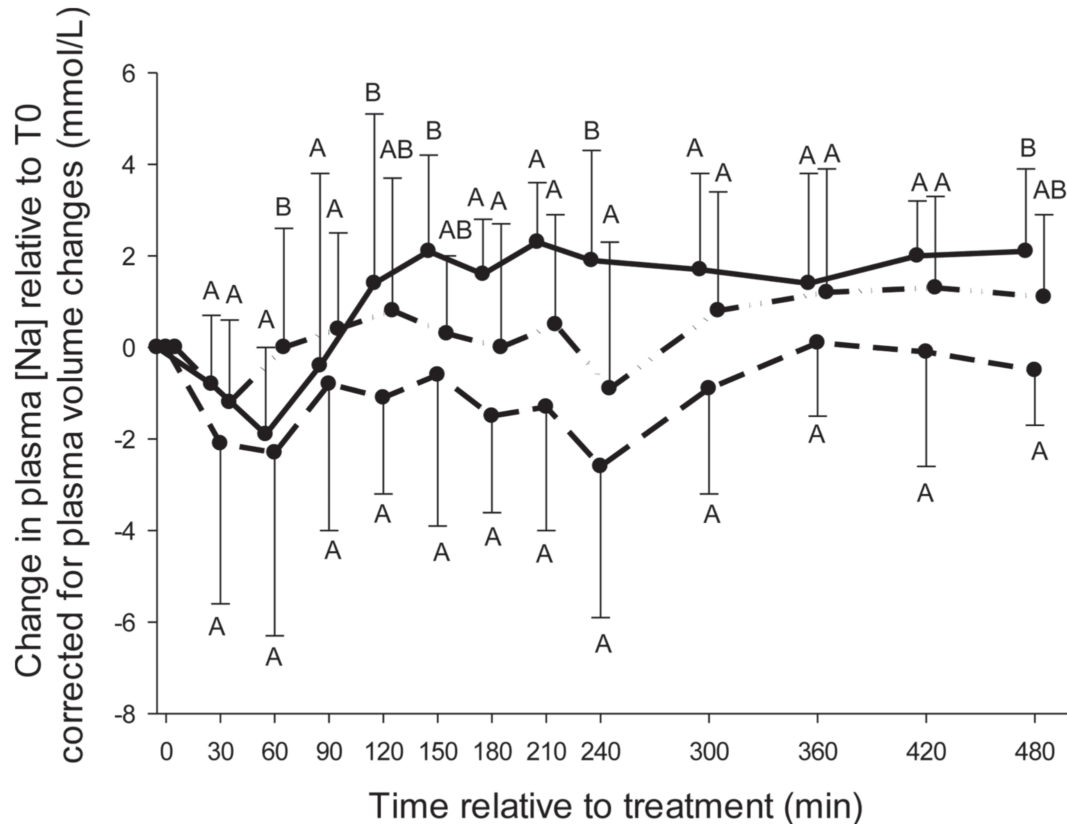

Figure 3. Mean ± SD change in plasma Na concentration relative to baseline concentration at the beginning of the experiment (T0) corrected for changes in plasma volume relative to T0 for treatment groups: 25.2 g of $NaHCO_3$ in 2 L of tap water (NaBic; solid line); 118 g of glucose monohydrate in 2 L of tap water (Gluc; dashed line); and 25.2 g of $NaHCO_3$ and 118 g of glucose monohydrate in 2 L of tap water (Combi; dash-dotted line). Treatment was administered at T0. Values with different capital letters differ significantly between groups ($P < 0.05$).

time curves and urine volumes in all groups further suggests that net water absorption was not measurably enhanced by the combination of $NaHCO_3$ with glucose.

The extent of intestinal Na and water absorption is dictated by the equilibrium between several mechanisms: electrogenic Na absorption, solvent drag moving Na along with water, the coupled transport of Na with glucose and other organic compounds, the coupled transport with Cl, and the Na-H-exchange mechanism. (Elliott et al., 1989; Gisolfi et al., 1992). Of those mechanisms, Na transport through SGLT and solvent drag are presumably affected by the combination of $NaHCO_3$ with glucose. Whereas the combination of $NaHCO_3$ with glucose is considered to increase enteral net Na absorption by providing both substrates for SGLT, solvent drag of water into the intestinal lumen after ingestion of a hypertonic solution containing $NaHCO_3$ and glucose likely hampers net Na and water absorption when compared with animals receiving $NaHCO_3$ alone (Phillips and Summersk, 1967; Aperia et al., 1983; Pfeiffer et al., 1998). The results of this study suggest that if intestinal Na absorption through SGLT was enhanced in animals receiving hypertonic ORS containing $NaHCO_3$ and glucose, this effect was most likely antagonized by the effect of hypertonicity dragging water from the intercellular space into the gut lumen.

Similar glucose concentration-time curves in animals having received oral glucose with and without $NaHCO_3$ indicate that the efficacy of intestinal glucose absorption in this study did not depend on oral Na supplementation. Intestinal glucose absorption through SGLT is currently perceived to be the predominant pathway of intestinal glucose uptake (Wood et al., 2000; Banks and Farthing, 2002). Sodium-glucose linked transport occurs at a fixed stochiometric ratio of 2 Na to 1 glucose molecule, and is therefore dependent on the availability of Na in the intestinal lumen in sufficient quantities (Turk et al., 2000; Wright et al., 2011). As mentioned previously, the direction and extent of the Na flux across the small intestinal mucosa, and therefore the availability of Na in the small intestinal lumen, strongly depends on the electrochemical gradient for Na between gut lumen and subepithelial space (Elliott

Table 2. Mean ± SD or median and interquartile range of urine variables stratified by treatment group[1]

Parameter	NaBic	Gluc	Combi
Urine volume (mL/8 h)	1,270 ± 762	1,361 ± 562	1,346 ± 698
Urine pH	7.54 ± 0.61[a]	6.69 ± 0.32[b]	7.42 ± 0.53[a]
Urine net base excretion(mmol/L)	61.2 ± 46.9	8.5 ± 6.2	38.6 ± 30.7
Total renal Na excretion (mmol/8 h)	102.2 ± 21.2[a]	26.6 ± 12.0[b]	108.6 ± 63.6[a]
Total renal glucose excretion (mmol/8 h)	0.0 [0.0–0.0]	0.0 [0.0–0.4]	0.1 [0.0–0.7]
Urine osmolarity (mOsmol/L)	281 ± 149[a]	115 ± 43[b]	253 ± 53[a]

[a,b]Values with different letters in one line are significantly different ($P < 0.05$)

[1]NaBic = 25.2 g of $NaHCO_3$ in 2 L of tap water; Gluc = 118 g of glucose monohydrate in 2 L of tap water; Combi = 25.2 g of $NaHCO_3$ and 118 g of glucose monohydrate in 2 L of tap water.

et al., 1989; Gisolfi et al., 1992). Administration of a test solution containing glucose but no Na is likely to trigger increased Na secretion into the small intestinal lumen along a steeper electrochemical gradient, thereby providing Na for SGLT (Spiller et al., 1987). The initial ratio between glucose and Na would not only be altered by the electrochemical gradient but also by the tonicity created in the gut lumen, which would determine direction and degree of the drag of water and Na across the small intestinal mucosa (Aperia et al., 1983; Pfeiffer et al., 1998). This effect potentially explains similar glucose concentration-time curves in animals having received glucose with and without $NaHCO_3$, but would also question the importance of formulating ORS with a specific ratio of glucose to Na to optimize enteral Na absorption. An earlier study conducted in humans found that net water absorption was not dependent on the ratio between Na and glucose in the ORS, a finding that was explained by rapid changes in luminal [Na] and [glucose] as ORS passed through the small intestinal tract (Gisolfi et al., 1992). Similar results were reported in horses, where the addition of glucose to

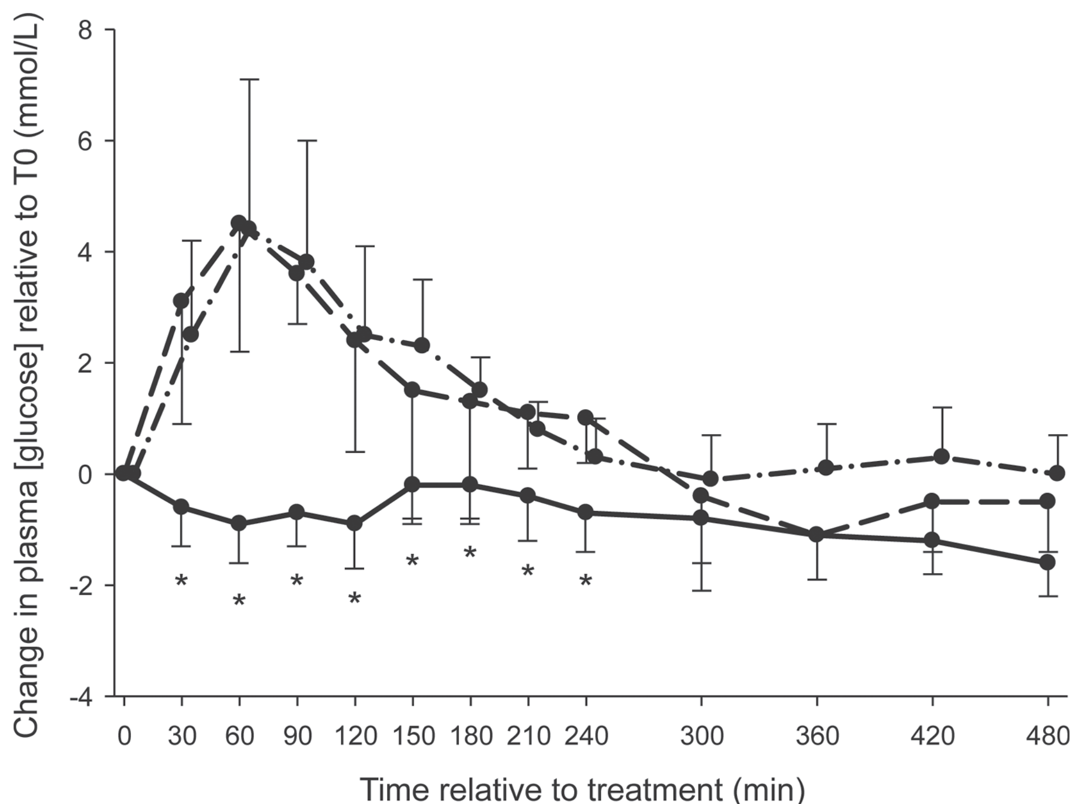

Figure 4. Mean ± SD of the change in plasma glucose concentration relative to baseline concentration at the beginning of the experiment (T0) for treatment groups: 25.2 g of $NaHCO_3$ in 2 L of tap water (NaBic; solid line); 118 g of glucose monohydrate in 2 L of tap water (Gluc; dashed line); and 25.2 g of $NaHCO_3$ and 118 g of glucose monohydrate in 2 L of tap water (Combi; dash-dotted line). Treatment was administered at T0. Values marked with an asterisk differ significantly from values obtained in all other groups at the same sampling time ($P < 0.05$).

ORS containing Na had no effect on the intestinal fluid uptake in experimentally dehydrated adult horses (Sosa León et al., 1995).

Although the importance of SGLT for intestinal glucose absorption is well established, evidence for another quantitatively relevant, Na-independent mechanism for enteral glucose absorption has been reported (Gisolfi et al., 1992). Rapid and quantitatively important translocation of GLUT2 transport proteins onto the jejunal brush border membrane as glucose content in the small intestinal lumen increased has been documented in several studies conducted in rats (Kellett and Helliwell, 2000). This exteriorization of GLUT2 was associated with an important increase in Na-independent glucose absorption from the jejunum that could be inhibited by the administration of phlorizine (Kellett and Helliwell, 2000). A similar GLUT2-dependent upregulation of glucose absorption has not yet been identified in ruminants, but would certainly explain the identical glucose concentration-time curves after oral administration of the same amount of glucose with and without Na.

In the present study, ORS with markedly different osmolarity were compared with each other. We opted not to equilibrate test solutions Gluc and NaBic to the same osmolarity as Combi to avoid the use of another osmotically active compound that would likely have confounded the results by either altering the SID of the test solution or the osmolarity of the intestinal content by presenting different absorption kinetics than glucose. Thus, the benefits of equilibrating all test solutions to the same osmolarity were considered to be limited. Osmolarities of the test solutions used in this study ranged between 300 and 600 mOsmol/L and, therefore, were in the range of osmolarities of common commercial ORS for calves (Smith, 2009).

Changes in body mass during the study period have been used in earlier studies with parenteral fluid administration to estimate water retention (Fielding et al., 2008). For the present study, this parameter was considered unsuitable because oral administration of solutions with markedly different osmolarities were administered orally. Differences in osmolarity not only have the potential to affect abomasal emptying time, and thereby the transit time of ingesta through the gastrointestinal tract, but also the fecal water content, and thereby the mass of the gastrointestinal content. Differences in body mass changes between groups in this study would not have allowed us to draw conclusions on differences in intestinal water absorption between groups.

The effect of tonicity on the efficacy of an ORS is an issue of great controversy in the human and veterinary literature (Rao, 2004; Michell, 2005). In human medicine, general consensus exists that hypotonic ORS are more suitable to treat dehydration than isotonic ORS, and that hypertonic ORS are contraindicated in dehydrated patients. Concerns about the use of iso- or hypertonic electrolyte solutions in humans are related to incidental reports of hypernatremia attributed to the use of isotonic oral electrolyte solutions, as well as to the potential risk for osmotic diarrhea (Farthing, 1994). Indeed, a number intestinal perfusion and several randomized controlled field studies conducted in humans and other species revealed that ORS with lower Na content and lower osmolarity improved intestinal net water and Na absorption and reduced morbidity time and number of treatment failures requiring parenteral fluid administration (Duggan et al., 2004; Atia and Buchman, 2009). Conversely, due to concerns with inadequate Na and energy supply in diarrheic calves the use of hypertonic ORS in calves has intensively been studied in the last decades and strongly encouraged (Levy et al., 1990; Brooks et al., 1996; Constable et al., 2001; Sen et al., 2006; Smith, 2009). In contrast to concerns raised in human medicine, several studies showed that hypertonic ORS administered to dehydrated diarrheic calves neither exacerbated dehydration nor caused osmotic diarrhea or hypernatremia, but provided more energy through higher glucose absorption (Levy et al., 1990; Brooks et al., 1996; Constable et al., 2001; Sen et al., 2006). However, similar to the findings reported here, studies comparing hypertonic and isotonic ORS containing Na and glucose administered to calves failed to identify a positive effect of hypertonic solutions on hydration status (Levy et al., 1990; Brooks et al., 1996; Constable et al., 2001). The absence of negative effects on hydration status or intestinal water absorption when using hypertonic ORS is consistent with results presented in this study and has been explained by a countercurrent mechanism hypothesized to function in the small intestinal mucosa. Similar to the mechanism described in the renal tubuli, this countercurrent mechanism is believed to allow absorption of hypertonic fluid with an osmolarity of up to 600 mOsmol/L from the gut lumen (Jodal and Lundgren, 1986; Smith, 2009).

When formulating the test solutions used in this study, care was taken not to exceed the expected absorptive capacity for glucose of the gastrointestinal tract to prevent osmotic diarrhea. The upper limit for glucose content in ORS for calves was estimated to be around 3.6 g/kg of BW, above which unabsorbed and osmotically active glucose may carry over into the large intestine (Sen et al., 2006). In the present study 118 g of glucose were administered per application in group Gluc and Combi, equivalent to approximately 2 g/kg of BW.

In earlier studies, the plasma glucose concentration-time curve was used to estimate abomasal emptying

rates in neonatal calves after administration of ORS with varying tonicity. In these studies, a decreased abomasal emptying rate in healthy neonatal calves was determined when feeding ORS with 600 mmol/L of glucose compared with solutions containing 300 mmol/L of glucose (Sen et al., 2006). This delay in abomasal emptying was associated with a delay in time to reach maximal blood glucose concentrations ($T_{maxGluc}$). The results presented here show identical glucose concentration time curves and thus identical times to reach maximal blood glucose concentrations after administration of solutions containing the same amount of glucose but markedly different osmolarity. This discrepancy suggests the delayed abomasal emptying observed by Sen et al. (2006) may not be due to increased osmolarity, but rather to the increased glucose load itself or the ensuing higher caloric content as it is the case in other species (Moran et al., 1999). Because the plasma glucose concentration measured after oral glucose administration is influenced in a nonlinear manner by a number or regulatory mechanisms, such as the release of insulin and renal glucose excretion, the plasma glucose concentration-time curve can only be considered a crude parameter to estimate the abomasal emptying rate in calves.

An indirect ion selective electrode (**ISE**) system was used to determine the plasma [Cl], which was then used to calculate SID and AG. Measurement of electrolyte concentrations with indirect ISE systems have been reported to be affected by the plasma protein concentration, with decreasing plasma protein concentrations, as observed in the present study, resulting in artificially increased plasma electrolyte concentrations (Dimeski and Barnett, 2005). Therefore, it is possible that a mild artificial decrease over time in the SID and AG calculated from plasma [Cl] may have occurred in our data set. The SID and AG calculated from artificially increased plasma [Cl] may have resulted in a mild artificial decrease of these parameters, thereby occulting a possibly developing strong ion alkalosis, as it would be expected after administration of sodium bicarbonate. For this reason in this and similar studies, chloride analysis with direct ISE systems would have been preferable over indirect ISE systems.

Although the treatment with ORS is relevant for dehydrated and acidemic diarrheic calves, we opted to conduct this study on clinically healthy and euhydrated calves. The efficacy of ORS to treat dehydration in calves and other species has largely been attributed to the function of SGLT, which in most cases is not or is only partially affected by enteral disease (Naylor, 1999). Results from this study can potentially contribute to our understanding of the function of ORS in sick animals, but need to be confirmed in dehydrated and acidotic calves. Models of mild acidemia, with or without dehydration, that have been used successfully in earlier studies would be suitable to determine whether observations of this studies in euhydrated calves can be reproduced in states of acidemia and dehydration (Iwabuchi et al., 2003; Leal et al., 2012).

CONCLUSIONS

The combination of $NaHCO_3$ with glucose in a hypertonic oral rehydration solution did not enhance the alkalinizing effect of $NaHCO_3$ when compared with ORS containing $NaHCO_3$ alone. The combination of $NaHCO_3$ and glucose did not improve Na, glucose, or water absorption in euhydrated neonatal dairy calves, bringing into question the relevance of a specific ratio between Na and glucose in oral rehydration solutions for calves.

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