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Effects of Alkalinization and Rehydration on Plasma Potassium Concentrations in Neonatal Calves with Diarrhea

F.M. Trefz, A. Lorch, J. Zitzl, A. Kutschke, G. Knubben-Schweizer, and I. Lorenz

Background: Increased plasma potassium concentrations (K^+) in neonatal calves with diarrhea are associated with acidemia and severe clinical dehydration and are therefore usually corrected by intravenous administration of fluids containing sodium bicarbonate.

Objectives: To identify clinical and laboratory variables that are associated with changes of plasma K^+ during the course of treatment and to document the plasma potassium-lowering effect of hypertonic (8.4%) sodium bicarbonate solutions.

Animals: Seventy-one neonatal diarrheic calves.

Methods: Prospective cohort study. Calves were treated according to a clinical protocol using an oral electrolyte solution and commercially available packages of 8.4% sodium bicarbonate (250–750 mmol), 0.9% saline (5–10 L), and 40% dextrose (0.5 L) infusion solutions.

Results: Infusions with 8.4% sodium bicarbonate solutions in an amount of 250–750 mmol had an immediate and sustained plasma potassium-lowering effect. One hour after the end of such infusions or the start of a sodium bicarbonate containing constant drip infusion, changes of plasma K^+ were most closely correlated to changes of venous blood pH, plasma sodium concentrations and plasma volume ($r = -0.73, -0.57, -0.53; P < .001$). Changes of plasma K^+ during the subsequent 23 hours were associated with changes of venous blood pH, clinical hydration status (enophthalmos) and serum creatinine concentrations ($r = -0.71, 0.63, 0.62; P < .001$).

Conclusions and Clinical Importance: This study emphasizes the importance of alkalinization and the correction of dehydration in the treatment of hyperkalemia in neonatal calves with diarrhea.

Key words: Fluid therapy; Hyperkalemia; Hypertonic sodium bicarbonate; Strong ion metabolic acidosis.

Metabolic disorders are common in severely ill neonatal calves with diarrhea and are typically characterized by strong ion (metabolic) acidosis, D-lactatemia, azotemia and electrolyte imbalances. Hyperkalemia occurs frequently in such calves and is associated with cardiac arrhythmias and electrocardiographic findings of atrial standstill and increased QRS-duration,[1–3] thus representing a potential life-threatening condition requiring immediate therapeutic intervention. The clinical picture of this electrolyte imbalance is also characterized by marked clinical dehydration, lethargy, cyanosis, and most importantly impairments of the ability to stand which is likely the result of skeletal muscle weakness.[4]

Increased plasma potassium concentrations (K^+) in neonatal calves with diarrhea were traditionally attributed to impaired intracellular translocation of potassium ions in an acidemic state.[5,6] However, the presence of hyperkalemia depends on the nature of an existing acidosis, but more importantly on the degree of dehydration and concomitant impairment of renal function.[7]

Abbreviations:

AG	anion gap
A_{tot}	concentration of nonvolatile weak acids
CDI	constant drip infusion
HBS	hypertonic (8.4%) sodium bicarbonate solution
ORS	oral rehydration solution
SID_6	measured strong ion difference calculated from plasma concentrations of 6 strong ions
SIG	strong ion gap

The correction of hyperkalemia in diarrheic calves occurs in response to the correction of concomitant acidemia and dehydration which is usually achieved by intravenous administration of sodium bicarbonate, saline and glucose solutions.[8–10] Hypertonic sodium bicarbonate solutions (HBS) are proposed to have a sound physiological basis in the treatment of dehydrated calves with hyperkalemia because the high osmolarity causes an immediate and sustained plasma volume expansion and therefore exerts a dilutional effect on plasma K^+.[11] Additionally the high alkalinizing activity of HBS corrects acidemia and is believed to enhance the redistribution of potassium ions between the extra- and intracellular spaces.[11] However, the latter remains controversial on the basis of studies in human patients[12] and the underlying mechanisms that are involved in the restoration of potassium homeostasis in dehydrated and acidemic calves are not well documented. In healthy calves, there is a comparable plasma potassium-lowering effect of orally administered solutions of glucose, sodium bicarbonate, and a combination thereof and plasma volume expansion is the most important underlying mechanism.[13] Based on these results and that dehydration seems to represent the key mechanism in

the pathogenesis of hyperkalemia in diarrheic calves, we therefore hypothesize that a sustained plasma volume expansion is also required for the restoration of potassium homeostasis in such animals.

Consequently the aim of this study was to document the potassium-lowering effect of hypertonic sodium bicarbonate solutions and to identify clinical and laboratory variables that are associated with the change of plasma K^+ during intravenous fluid therapy.

Materials and Methods

This study was performed in agreement with the Animal Welfare and Ethics Committee of the government of Upper Bavaria (# 55.2-1-54-2532.2-31-12).

Calves

Between November 2012 and September 2013 a prospective study was conducted involving 71 neonatal calves that were admitted to the Clinic for Ruminants with Ambulatory and Herd Health Services, LMU Munich, with a clinical diagnosis of diarrhea. Calves were excluded from the study if they fulfilled the criteria to exclusively receive oral rehydration treatment, which were unimpaired ability to stand, no enophthalmos, and intake of 1 L of oral rehydration solution after admission. Further exclusion criteria were concurrent health problems requiring specific therapeutic interventions, euthanasia or death during the first 48 hours of hospitalization on grounds of severe concurrent disease, failure to receive the entire determined infusion volume, or marked hypernatremia (>170 mmol/L).

Clinical Examinations

All physical examinations followed a standardized protocol and included the clinical assessment of posture/ability to stand, behavior, suckling and palpebral reflex, extent of enophthalmos (in mm) and duration of skin tenting (in seconds) as described previously.[14]

Treatment

Calves were treated for a study period of 24 hours using clinical guidelines for the dosage of sodium bicarbonate relying on the assessment of posture/ability to stand, the presence of an existing enophthalmos (visible gap between the eyeball and caruncula lacrimalis as sign of marked clinical dehydration) and the degree of reduction of the palpebral reflex as described before.[10] Commercially available packages of 250 mL bottles of hypertonic 8.4% sodium bicarbonate solution (HBS) were used for the performed procedures. Based on the performed treatment procedures calves were assigned to 3 treatment groups without regarding individual body mass.

CDI Group. Calves of this group were treated with a constant drip infusion (CDI) consisting of 5 or 10 L of 0.9% saline that was spiked with 250 mL of an 8.4% sodium bicarbonate solution. Calves were assigned to this treatment group if they were able to stand securely but had enophthalmos or refused to drink 1 L of the oral rehydration solution completely after the initial examination. A volume of 10 L of 0.9% saline was chosen if the extent of enophthalmos was ≥7 mm; otherwise a volume of 5 L was used. In cases of hypothermia (<37°C), no milk intake for more than 24 hours before admission or suspected septicemia (in cases of marked hyperemia of the mucous membranes and severe congestion of episcleral vessels) a volume of 0.5 L of a 40% dextrose was additionally added to the saline solution.

HBS Group. Calves of this treatment group were rapidly infused with hypertonic (8.4%) sodium bicarbonate solutions (HBS) in a total amount of 500 or 750 mL. The calves were assigned to this treatment group if they showed signs of moderate to severe metabolic acidosis (standing insecurely or unable to stand), but no enophthalmos and did not require glucose-containing infusions based on the listed criteria above. A volume of 750 mL of 8.4% sodium bicarbonate was chosen if calves were barely able to stand (unable to correct position if pushed) and exhibited a delayed or missing palpebral reflex or were unable to stand; otherwise a volume of 500 mL was used.

HBS+CDI Group. Calves of this treatment group were rapidly infused with 250 or 500 mL of an 8.4% sodium bicarbonate solution followed by a CDI consisting of 5 or 10 L of isotonic saline spiked with 250 mL of an 8.4% sodium bicarbonate solution and dextrose if necessary. The calves were assigned to this treatment group if they showed signs of moderate to severe metabolic acidosis as calves of the HBS group but were presented with enophthalmos or required glucose-containing infusions based on the criteria listed above. The treatment decisions concerning the total amount of sodium bicarbonate were based on the same criteria as in calves of the HBS group, and the chosen volume of administered 0.9% saline and addition of a 40% dextrose solution as in calves of the CDI group, respectively. The CDI was started 10 minutes after the end of rapid infusions with undiluted 8.4% sodium bicarbonate.

An overview of the performed treatment procedures during the study period of 24 hours is provided in Table S1. Infusion solutions were administered through an IV catheter[a] that was placed in an auricular vein. The undiluted 8.4% sodium bicarbonate solution was administered at the maximal infusion rate possible, without administering a 250 mL unit of the solution faster than within a 5 minute period. The resulting durations of those infusions were determined and documented.

Irrespective of the treatment groups a standardized oral rehydration solution was offered 3-times a day (10:00 AM, 3:00 PM, and 11:00 PM) in a total volume of 4 L per day. The oral rehydration solution contained 4 g sodium chloride, 20 g dextrose, 3 g potassium bicarbonate, and 3 g sodium propionate per liter. The calculated effective strong ion difference and measured osmolality of this homemade solution is 61 mEq/L and 380 mOsm/kg, respectively. Calves had access to fresh water throughout the study period.

Additionally, calves received meloxicam at a dosage of 0.5 mg/kg IV immediately after the admission examination. At that point of time, antimicrobial treatment with amoxicillin was initiated at a dosage of 15 mg/kg in a total of 33 calves because predefined criteria were fulfilled.[10]

Feeding

Depending on the initially determined body mass of calves, 1.5 L (≤40 kg) or 2 L (>40 kg) of whole milk were offered 3-times a day (7:00 AM, 12:00 PM, and 7:00 PM).

Sampling Conditions

Blood samples were taken from the jugular vein at times shown in Table 1. All calves were sampled during the initial examination after admission to the hospital ($T_{initial}$) and 24 hours after the initiation of treatment. The time interval between $T_{initial}$ and the onset of infusion was used for catheterization and preparation of infusion solutions and was not exactly determined. Calves that were initially assigned to groups HBS and HBS+CDI were sampled 0 and 10 minutes (T_{0min} and T_{10min}) after the end of the 8.4% sodium bicarbonate infusion. Additional blood samples in those

Table 1. Blood sampling times during the study period based on the initially performed treatment procedures.

Initial Treatment	$T_{initial}$	T_{0min}	T_{10min}	T_{60min}	T_{180min}	T_{24h}
CDI	X			X	X	X
HBS	X	X	X	X	X	X
HBS+CDI	X	X	X	X	X	X

CDI, calves that were treated with a constant drip infusion; HBS, calves which received IV administered fluids as 8.4% sodium bicarbonate solutions; HBS+CDI, calves that were treated by intravenous administration of 8.4% sodium bicarbonate followed by a constant drip infusion.

groups were taken 60 and 180 minutes (T_{60min} and T_{180min}) after the end of the 8.4% sodium bicarbonate infusion (HBS group) or onset of CDI at T_{10min} (HBS+CDI group). In calves of the CDI group T_{60min} and T_{180min} were defined as the time interval after the start of the CDI. At T_{60min} and T_{180min} infusions were stopped for 10 minutes before sampling in the CDI- and HBS+CDI group and the administered amount of the CDI determined (by weighing).

Laboratory Analysis

Lithium-heparinized blood samples were anaerobically collected using a 2 mL polypropylene syringe and blood pH, partial pressure of carbon dioxide (pCO_2), sodium, chloride, potassium, and ionized calcium concentrations were determined using a blood pH, gas and electrolyte analyzer with ion-selective electrodes.[b] Blood pH and pCO_2 were corrected for rectal temperature using standard algorithms.[15]

An automatic analyzing system was used for the biochemical analysis.[c] Concentrations of D-lactate, L-lactate, and glucose were determined from heparinized blood samples containing potassium fluoride to inhibit glycolysis. Serum samples (plain tubes) were assayed for concentrations of urea (urease), creatinine (picric acid), total protein (biuret), and inorganic phosphorus (molybdenum). D- and L-lactate concentrations were determined by means of enzymatic methods using D- and L-lactate dehydrogenase.[16,17] Normokalemia was defined as plasma potassium concentrations of 3.9–5.8 mmol/L.[18]

Calculations

Actual bicarbonate concentration ($cHCO_3^-$) was automatically calculated by the blood gas unit using the Henderson-Hasselbalch equation with measured blood pH and pCO_2 at 37°C:

$$cHCO_3^- = S \times pCO_2 \times 10^{(pH - pK_1')} \qquad (1)$$

Values for the negative logarithm of the dissociation constant of carbonic acid (pK_1') and solubility of carbon dioxide (S) for plasma were 6.105 and 0.0307 mmol/L per mmHg, respectively. After measuring the hemoglobin concentration (Hb in g/dL) photometrically, blood base excess (in vitro base excess) was automatically calculated in units of mmol/L using the van Slyke equation[19] with measured blood pH at 37°C and the determined actual bicarbonate concentration:

$$\text{Base excess} = (1 - 0.014 \times cHb) \times [(cHCO_3^- - 24.8) + (1.43 \times cHb + 7.7) \times (pH - 7.4)]$$
$$(2)$$

An estimate of the unmeasured anion concentration was obtained by calculating the anion gap (AG) in mEq/L, whereby:

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

Measured strong ion difference was obtained from 6 strong ions (SID_6; mEq/L) using the measured value for cCa^{2+} determined by ion-selective potentiometry and assigning a charge of -1 to D-lactate and L-lactate such that:

$$SID_6 = cNa^+ + cK^+ + cCa^{2+} - cCl^- - cD\text{-lactate}^- - cL\text{-lactate}^-$$
$$(4)$$

The concentration of non-volatile weak acids (A_{tot}) in mmol/L was calculated from serum concentrations of total protein[20]:

$$A_{tot} = 0.343 \times c\text{total protein} \qquad (5)$$

The strong ion gap (SIG) was calculated in order to obtain an estimate of the unmeasured strong anion concentration by using the experimentally determined value for A_{tot}, the experimentally determined value for the negative logarithm of dissociation constant of plasma nonvolatile weak acids ($pK_a = 7.08$), and the following equation[20]:

$$SIG = \{A_{tot}/(1 + 10^{(7.08 - pH)})\} - AG \qquad (6)$$

The percent changes in plasma volume at each time point x relative to a previous time point y were extrapolated from the changes in serum total protein concentrations[21] such that:

$$\Delta\text{Plasma volume}_x = (c\text{total protein}_y - c\text{total protein}_x) \times 100/c\text{total protein}_x \qquad (7)$$

The changes (differences) of several variables of hydration status and clinical biochemistry between a time point y and x were determined using the following equation[13]:

$$\Delta\text{Variable}_x = c\text{Variable}_x - c\text{Variable}_y \qquad (8)$$

Statistical Analysis

The software package SPSS 18.0[d] was used for the statistical analysis of the results. A level of significance of 0.05 was chosen. Data are presented as medians and interquartile ranges (Q_{25}/Q_{75}) because most of the data were not normally distributed based on the Shapiro-Wilks W-test and visual examination of QQ-plots. A Mann-Whitney U-test was used to determine statistically significant differences of continuous variables between groups. Within group differences of investigated variables during the investigation period were assessed by Friedman's test. The Wilcoxon signed rank test was used for the subsequent pairwise comparisons between initial and consecutive values. In this case, the level of significance was adjusted using the Bonferroni method. Spearman's coefficients of correlation (r_s) were used to characterize associations between variables. Stepwise forward multivariable linear regression models for the change of the plasma K^+ between defined time intervals were constructed, including the respective changes of variables of hydration status and clinical biochemistry significantly correlated to the dependent variable. The relative

importance of the included variables was assessed by the order of entry as well as by the change of the model R^2 value after the inclusion of the specific variable. The residuals of each model were graphically examined to confirm an approximately normal distribution. If 2 variables were closely correlated to each other ($r_s > 0.70$ or < -0.70), only that variable was entered into the multivariable model which had the highest coefficient of correlation in order to minimize the effects of collinearity.

Results

Because of regional preferences, 91.5% (n = 65) of the 71 calves were Simmental (German Fleckvieh), the most common dairy breed in Bavaria. The median value and interquartile range for age was 10.0 (7.0–15.0) days.

Fifteen calves were assigned to the HBS group, 34 calves to the HBS+CDI group, and 22 calves to the CDI group. The median values and interquartile ranges for body mass (kg) of calves of groups HBS, HBS+CDI, and CDI were 49.0 (44.0–53.0), 40.5 (36.4–46.9), and 42.3 (38.5–47.0), respectively.

On admission to the hospital, the range of plasma potassium concentrations in those 71 calves was 3.33–8.91 mmol/L. Hyperkalemia was present in 20 calves (28.2%), normokalemia in 45 calves (63.3%), and hypokalemia in 6 calves (8.5%).

All hyperkalemic calves of this study population presented with marked clinical dehydration as indicated by the presence of enophthalmos (visible gap between the eyeball and caruncula lacrimalis) and were therefore not assigned to the HBS group. A total of 5 of 20 hyperkalemic calves stood securely and were therefore assigned to the CDI group. The remaining 15 calves stood insecurely (13 calves) or were unable to stand (two calves) and were therefore assigned to the HBS+CDI group. Those 15 hyperkalemic calves had significantly ($P = .002$) lower plasma D-lactate concentrations (median: 3.8 mmol/L) than the 19 non-hyperkalemic calves (median: 10.1 mmol/L) that were also assigned to the HBS+CDI group.

The median duration (and interquartile ranges) of infusions with 8.4% sodium bicarbonate in groups HBS (500 or 750 mmol) and HBS+CDI (250 or 500 mmol) was 22.5 minutes (17.2–30.5 minutes) and 15.8 minutes (8.5–21.2 minutes), respectively ($P = .002$).

The determined median weight (and interquartile range) in kg of the administered mass of the CDI in groups CDI and HBS+CDI at T_{60min} was 1.1 (0.6–1.3) and 0.9 (0.8–1.2) as well as 2.2 (1.5–2.8) and 2.1 (1.7–2.4) at T_{180min}, respectively. Those differences were not statistically different ($P = .88$ and $P = .46$).

Changes of plasma potassium concentrations of individual calves in the 3 treatment groups during the time intervals $T_{initial}$ to T_{60min} and T_{60min} to T_{24h} are depicted in Fig S1. Dynamics of the plasma potassium and glucose concentration, of venous blood pH and change of plasma volume of calves in the 3 treatment groups between $T_{initial}$ and T_{24h} are shown in Table 2. Infusions with undiluted 8.4% sodium bicarbonate solutions in groups HBS and HBS+CDI resulted in an immediate expansion of plasma volume, alkalinization

and a decrease of plasma K^+ in nearly all cases. In 2 hyperkalemic calves (6.30 and 8.91 mmol/L) of group HBS+CDI, an increase of plasma K^+ was observed at T_{10min} (6.49 and 9.38 mmol/L) after infusion of 250 mL of 8.4% sodium bicarbonate. In 1 of those 2 calves, plasma K^+ was in the reference range at T_{180min} (5.44 mmol/L) but remained high in the other calf (7.89 mmol/L). The latter calf had increased sodium concentrations (165.8 mmol/L) which further increased until T_{10min} (171.3 mmol/L) and only slightly decreased until T_{180min} (170.6 mmol/L).

After 3 hours of treatment (T_{180min}), a hyperkalemic state was still evident in 4 calves (3 calves of the CDI- and 1 calf of the HBS+CDI group). Administration of dextrose in 11 calves of the HBS+CDI group resulted in a more pronounced decrease of plasma K^+ until T_{180min} (median: −1.61 mmol/L) compared to 23 calves of the same group that received no glucose in the CDI (median: −1.18 mmol/L), but the difference was not statistically significant ($P = .26$).

The coefficients of correlation between the changes in plasma K^+ and the concomitant changes in laboratory values or clinical findings for the intervals $T_{initial}$ to T_{60min} and T_{60min} to T_{24h} were determined for all calves (Table 3).

Results of a subsequent multivariable stepwise linear regression analysis which aimed to predict the changes of plasma K^+ between $T_{initial}$ and T_{60min} as well as between T_{60min} and T_{24h} by means of concomitant changes of variables of clinical biochemistry and clinical hydration status are summarized in Table 4. Changes of venous blood pH had the highest explanatory power and accounted for 48.5% of the variation of the change of plasma K^+ until T_{60min}. The change in creatinine concentration was identified as the most important predictor during the subsequent 23 hours which explained 40.5% of the variation of the change of plasma K^+.

Discussion

This study demonstrates that intravenous administration of hypertonic sodium bicarbonate solutions to neonatal calves with diarrhea and strong ion (metabolic) acidosis induces an immediate and sustained plasma potassium-lowering effect that appears to be caused by its efficient and rapid alkalinizing ability. The marked plasma potassium-lowering effect of alkalinization in the present study was not the expected finding, because dehydration and concomitant impairment of renal function was previously identified to play a key role in the pathogenesis of hyperkalemia in diarrheic calves.[4,7] Additionally, the potassium-lowering effect of orally administered sodium bicarbonate solutions in healthy calves was recently reported to be particularly based on the hemodilutive effect and expansion of plasma volume.[13] However, several mechanisms should be considered which might have contributed to the close association between changes of K^+ and venous blood pH as observed during the first hour of treatment. First, our findings strongly suggest the presence of a compartmental shift of potassium ions in response to

Table 2. Dynamics of the plasma potassium concentration, venous blood pH values, plasma glucose concentrations and changes of plasma volume during the first 24 hours of treatment in 71 neonatal calves with diarrhea based on the performed treatment procedures.

Variable	Median (Q_{25}/Q_{75})						P-Value
	$T_{initial}$	T_{0min}	T_{10min}	T_{60min}	T_{180min}	T_{24h}	
K^+ (mmol/L)							
CDI	5.18 (4.73/5.79)	ND	ND	4.91 (4.43/5.83)	4.76 (4.44/5.32)*	4.52 (4.22/4.82)*	.010
HBS	4.43 (3.97/4.76)	3.63 (3.18/3.78)*	3.35 (3.16/3.90)*	3.29 (3.10/3.85)*	3.43 (3.16/3.99)*	4.35 (3.98/4.84)	<.001
HBS+CDI	5.55 (4.42/6.31)	4.39 (3.54/5.25)*	4.34 (3.70/5.42)*	4.02 (3.33/4.87)*	3.99 (3.23/4.64)*	4.07 (3.57/4.36)*	<.001
ΔK^+ (mmol/L)							
CDI	N/A	ND	ND	−0.18 (−0.50/0.32)	−0.43 (−0.66/0.28)*	−0.70 (−1.33/0.07)*	.010
HBS	N/A	−0.84 (−1.03/−0.69)*	−0.90 (−0.99/−0.64)*	−0.85 (−1.05/−0.67)*	−0.87 (−1.13/−0.65)*	−0.03 (−0.45/0.41)	<.001
HBS+CDI	N/A	−1.05 (−1.41/−0.45)*	−0.87 (−1.48/−0.35)*	−1.10 (−1.81/−0.50)*	−1.2 (−1.85/−0.82)*	−1.53 (−2.38/−0.37)*	<.001
Venous blood pH							
CDI	7.25 (7.07/7.37)	ND	ND	7.29 (7.19/7.38)*	7.34 (7.23/7.37)*	7.36 (7.30/7.39)*	<.001
HBS	7.01 (6.96/7.13)	7.53 (7.49/7.59)*	7.47 (7.41/7.52)*	7.36 (7.32/7.42)*	7.32 (7.26/7.40)*	7.34 (7.27/7.36)*	<.001
HBS+CDI	6.95 (6.87/7.07)	7.46 (7.41/7.51)*	7.36 (7.31/7.41)*	7.28 (7.21/7.34)*	7.28 (7.23/7.34)*	7.31 (7.28/7.40)*	<.001
Glucose (mmol/L)							
CDI	4.9 (4.2/5.4)	ND	ND	4.2 (3.6/4.9)	3.9 (3.4/4.9)*	3.9 (3.6/4.5)*	<.001
HBS	5.0 (4.0/5.8)	ND	4.4 (3.5/5.0)	4.3 (4.0/5.3)	4.8 (4.1/5.8)	4.3 (4.2/4.9)	.217
HBS+CDI	4.8 (4.1/5.9)	ND	4.2 (3.7/5.3)*	5.1 (4.1/10.1)	5.4 (4.1/7.6)	4.2 (3.8/4.8)	<.001
Total protein (g/L)							
CDI	55.0 (49.1/65.1)	ND	ND	48.8 (43.9/54.2)*	45.0 (40.0/51.3)*	46.2 (43.7/50.2)*	<.001
HBS	47.0 (45.6/51.6)	ND	39.1 (36.7/43.0)*	42.0 (38.6/47.3)*	44.5 (41.4/47.7)*	41.8 (38.8/48.4)*	<.001
HBS+CDI	57.1 (50.2/63.3)	ND	43.5 (38.9/49.6)*	41.5 (37.8/49.4)*	43.1 (39.1/48.6)*	41.2 (39.5/45.7)*	<.001
ΔPlasma volume (%)							
CDI	N/A	ND	ND	12.9 (7.8/17.6)*	20.6 (15.0/27.9)*	17.1 (10.0/30.5)*	<.001
HBS	N/A	ND	19.5 (15.5/26.4)*	15.7 (7.2/20.0)*	9.6 (3.6/14.0)*	13.4 (7.7/19.6)*	<.001
HBS+CDI	N/A	ND	25.5 (16.2/40.6)*	31.2 (23.4/42.8)*	31.2 (22.4/40.0)*	33.3 (24.7/40.0)*	<.001

CDI, calves that were treated with a constant drip infusion (n = 22); HBS, calves which received intravenous fluids as 8.4% sodium bicarbonate solutions (n = 15); HBS+CDI, calves that were treated with intravenous 8.4% sodium bicarbonate followed by a constant drip infusion (n = 34); ND, not determined; N/A, not applicable; ΔPlasma volume, Change of plasma volume extrapolated from changes of total protein concentration relative to $T_{initial}$. ΔK^+, Change of plasma K^+ relative to $T_{initial}$.

P-values indicate a statistically significant change over time. Values within the same row that differ significantly from $T_{initial}$ (or from zero in case of Δplasma volume and ΔK^+) are indicated by asterisks.

Table 3. Coefficients of correlation between the change of the plasma potassium concentration and concomitant changes of selected clinical and laboratory variables during the first and subsequent 23 hours after the end of a hypertonic (8.4%) sodium bicarbonate infusion or the start of a sodium bicarbonate containing constant drip infusion in 71 neonatal calves with diarrhea.

	Period between $T_{initial}$ and T_{60min}	Period between T_{60min} and T_{24h}
H–H acid-base model		
ΔVenous blood pH	−0.73**	−0.71**
ΔpCO_2	−0.26*	0.16[NS]
ΔHCO_3^-	−0.47**	−0.50**
ΔBase excess	−0.59**	−0.59**
ΔAG	0.01[NS]	0.34**
SID acid-base model		
ΔSID_6	−0.45**	−0.20[NS]
ΔA_{tot}	0.47**	0.44**
ΔSIG	−0.17[NS]	−0.35**
Clinical biochemistry		
ΔD-lactate	−0.27*	−0.36**
ΔL-lactate	−0.50**	0.47**
ΔPhosphorus	0.39**	0.58**
ΔGlucose	−0.18[NS]	0.04[NS]
ΔUrea	0.25*	0.44**
ΔCreatinine	0.24*	0.62**
Electrolytes		
ΔNa^+	−0.57**	−0.30*
ΔCl^-	0.43**	−0.10[NS]
Hydration status		
ΔPlasma volume	−0.53**	−0.42**
ΔEnophthalmos[a]	0.06[NS]	0.63**
ΔSkin tent duration[a]	0.02[NS]	0.60**

[NS]not significant; SID_6, strong ion difference calculated from 6 strong ions; A_{tot}, concentration of nonvolatile weak acids; SIG, strong ion gap; H–H acid-base model, Henderson–Hasselbalch acid-base model; SID acid-base model, strong ion difference acid-base model.

[a]Information at T_{24h} was missing in 1 calf.

*$P < .05$.

**$P < .005$.

intravenous administration of hypertonic sodium bicarbonate. Based on the current understanding of cellular transport processes involved in extrarenal K^+ balance, increases in extracellular HCO_3^- concentration enhance cellular Na^+ uptake by a Na^+-HCO_3^- cotransport and Na^+-H^+ exchange which consequently stimulates Na^+, K^+-ATPase activity and consequently net cellular K^+ uptake.[22] Secondly, administration of undiluted 8.4% sodium bicarbonate solution resulted in a profound osmotically driven plasma volume expansion as indicated by marked decreases of total protein concentrations. Expansion of plasma volume did not only exert a dilutional effect on plasma K^+ but also resulted in a hypo-proteinemic state in a high proportion of calves (Table 2) and consequently in a decreased concentration of non-volatile weak acids[23] which might have slightly contributed to the association between changes of blood pH and plasma K^+. Volume dilution might also have an effect on other unmeasured anions such as uremic

Table 4. Results of a multivariable stepwise linear regression analysis for predicting the changes of the plasma potassium concentration in calves of the study population during the first and subsequent 23 hours after the end of a hypertonic (8.4%) sodium bicarbonate infusion or the start of a sodium bicarbonate containing constant drip infusion.

Order of Entry	Variable	Coefficient	±SE	P-Value	ΔR^2	Model R^2
Period between $T_{initial}$ and T_{60min}[a]						
	Constant	0.115	0.115	.320		
1	Δblood pH	−3.383	0.396	<.001	0.485	0.485
2	ΔCreatinine	0.013	0.003	<.001	0.103	0.589
Period between T_{60min} and T_{24h}[b]						
	Constant	0.104	0.155	.505		
1	ΔCreatinine	0.004	0.001	<.001	0.405	0.405
2	Δblood pH	−3.174	0.889	.001	0.160	0.564
3	ΔD-lactate	−0.080	0.026	.003	0.051	0.615
4	ΔA_{tot}	0.135	0.064	.038	0.025	0.641

[a]The variables Δblood pH, ΔpCO_2, ΔD-lactate, ΔL-lactate, ΔPhosphorus, ΔUrea, ΔCreatinine, and Δplasma volume were included in the model.

[b]The variables Δblood pH, ΔStrong ion gap, ΔA_{tot}, ΔD-lactate, ΔL-lactate, ΔCreatinine, ΔNa^+, ΔEnophthalmos, and ΔSkin tent duration were included in the model.

anions as determined by the decrease of strong ion gap until T_{60min} (in spite of slightly increased D- and L-lactate concentrations; Table S2).

Although, the potassium-lowering effect of isotonic and hypertonic sodium bicarbonate in neonatal calves with diarrhea has been documented in previous studies[8,9] there are generally discrepant results concerning the treatment efficacy of sodium bicarbonate in cases of acute hyperkalemia. This is particularly based on the results of studies in dogs with experimentally induced hyperkalemia[24] and human patients with end-stage renal disease[25,26] where alkalinization after intravenous administration of sodium bicarbonate was reported to be ineffective in lowering blood K^+ concentrations. However, it was discussed that the plasma potassium-lowering effect of sodium bicarbonate depends on the presence of a metabolic acidosis and more importantly on the degree of intracellular acidosis.[22] This could also explain the finding of a study,[13] where the plasma potassium-lowering effect of orally administered sodium bicarbonate solutions in non-acidemic calves was predominantly related to plasma volume expansion rather than to increases in base excess.

Another factor that might have had an influence on plasma K^+ was the assumed hypertonicity of extracellular fluid after administration of hypertonic sodium bicarbonate solutions. Hypertonicity has been proposed to result in an increase of intracellular K^+ as a result of cellular dehydration which consequently provokes passive diffusion of potassium out of the cells. This effect was therefore discussed to counteract in part the desired plasma potassium-lowering effect of hypertonic sodium bicarbonate.[27] Although a marked

potassium-lowering effect of sodium bicarbonate was observed in the present study, hypertonicity could be an explanation for the initial increase of plasma K^+ after administration of hypertonic bicarbonate in 1 calf that was presented with concurrent hypernatremia.

Because of the inconsistency of results concerning the potassium-lowering effect of sodium bicarbonate, a hyperkalemic state in human patients is usually corrected by intravenous administration of glucose and insulin in order to achieve an insulin-mediated shift of potassium ions into the cells.[12] In the present study, a total of 12 calves were initially treated with glucose-containing infusion solutions. Insulin was unfortunately not determined, but provided that intravenous administration of glucose induces sufficient endogenous insulin release and insulin increases in parallel to glucose concentration, we would have expected to find a significant correlation between the change of plasma glucose on the one and potassium concentrations on the other hand. The lack of this finding could be related to the fact that glucose-containing infusions were stopped 10 minutes before blood sampling, which might have resulted in normal or only slightly increased glucose concentration in some calves because of the presence of hyperinsulinemia. A statistically significant difference for the change of plasma K^+ was also not found between calves of the HBS + CDI group that received glucose-containing infusions (mixture of saline, glucose and sodium bicarbonate) and those which received glucose-free infusion solutions. Synergistic effects of sodium bicarbonate, glucose and insulin were reported in the treatment of hyperkalemic humans with end-stage renal disease and mild metabolic acidosis,[28] which suggests that simultaneous infusions of sodium bicarbonate and glucose solution might be also advantageous in hyperkalemic neonatal calves with diarrhea. However, the additive plasma potassium-lowering effect of glucose-containing solutions in the present study might have been masked by different dosages of sodium bicarbonate that were administered irrespective of body mass, different osmolarity of infusion solutions or variations in respect to the performed infusion rates, which is clearly a weakness of the present study. Further studies are therefore necessary to determine and especially compare the potassium-lowering effect of sodium bicarbonate, saline and glucose-containing solutions.

Another weakness of this study is that only 20 of 71 calves of this study population were in fact hyperkalemic and that those hyperkalemic calves were unevenly distributed over the 3 treatment group. This is related to the fact that all treatment decisions were based on clinical findings; an attempt that was chosen in the present study in order to simulate a field practice situation where laboratory findings are usually not available.

Our findings suggest, that the change of plasma K^+ during the defined time intervals was also dependent on the initial plasma potassium concentration on admission to the hospital (Table 1, Fig S1). It can be assumed that the organism would rather assist in dropping supranormal values, but would rather resist to lowering of values that are within normal limits for the sake of homeosta-

sis. This is well documented for the insulin-dependent compartmental shift of potassium ions, as a low plasma potassium concentration induces an insulin resistance to cellular potassium uptake, whereas the sensitivity of the carbohydrate metabolism is not affected.[29]

However, even in the 15 non-hyperkalemic calves of the HBS group we observed a median decrease of plasma K^+ of 0.85 mmol/L until T_{60min} which could be also related to alternative treatment effects of hypertonic sodium bicarbonate solutions. As the plasma potassium concentration does not accurately reflect intracellular potassium stores in an acidemic state[30] it is conceivable, that the rapid fall of plasma K^+ and the subsequent hypokalemic state in 12 out of 15 calves in this group at T_{60min} (Fig S1) was also the result of a marked depletion of body potassium stores. This explanation appears plausible as those calves were not clinically dehydrated such that the acidemia induced efflux of potassium ions out of the cells could have been masked by renal elimination, which potentially results in a depletion of potassium stores during ongoing acidosis.

Based on the results of multivariable stepwise linear regression analysis, the decline of serum creatinine concentrations was identified as the most important factor that was associated with the change of plasma K^+ between T_{60min} and T_{24h} in this study population. This finding additionally emphasizes the importance of rehydration and concomitant restoration of renal function in the treatment of hyperkalemic calves. Hypertonic rehydration with 8.4% sodium bicarbonate in a dosage of 10 mL/kg BW in combination with oral rehydration has previously been used for the treatment of hyperkalemic diarrheic calves.[8] This treatment procedure was successful in 11 of 12 calves and was therefore reported to represent a cheap treatment option in dehydrated calves. In the present study, a similar treatment procedure was performed in calves of the HBS group, although the administered amounts of sodium bicarbonate were in most cases higher (range 8.8–20.3 mL/kg BW) and those calves were not or only mildly dehydrated and consequently non-hyperkalemic (plasma K^+ <5.8 mmol/L). Administration of undiluted 8.4% sodium bicarbonate resulted in a comparable expansion of plasma volume in groups HBS and HBS+CDI as determined at T_{10min}. Remarkably, a subsequent decrease of plasma volume was observed in calves of the HBS groups during the time intervals until T_{60min} and T_{180min}, whereas plasma volume was further increased until T_{60min} and remained on the same level at T_{180min} in calves of group HBS+CDI (Table 2). This indicates that dehydrated calves with concurrent hyperkalemia benefit from administration of crystalloid infusion solutions following rapid alkalinization with sodium bicarbonate in order to restore renal function and enhance renal K^+ excretion.

Of relevance is additionally the finding that a significant change in K^+ occurred earlier (T_{60min}) in calves of groups HBS and HBS+CDI compared to calves of the CDI group (T_{180min}). This suggests that conventional intravenous fluid therapy with isotonic or slightly

hypertonic solutions may not directly stimulate a compartmental shift of potassium ions but produces plasma volume expansion thereby stimulating renal K^+ excretion.[11] On the basis of these results, we therefore conclude that the combination of rapid alkalinization with hypertonic sodium bicarbonate followed by a continuous infusion of larger volumes of iso- or slightly hypertonic solutions represents the best treatment strategy in dehydrated neonatal calves with diarrhea and clinical signs of hyperkalemia.

Conclusions

This study emphasizes the importance of alkalinization in the treatment of hyperkalemic calves with concurrent strong ion (metabolic) acidosis. This can be readily achieved by rapid infusions of hypertonic 8.4% sodium bicarbonate solutions in volumes of 250 or 500 mL which is recommended to be followed by the administration of iso- or slightly hypertonic crystalloid solutions in order to correct concomitant dehydration and enhance the renal elimination of potassium ions.

Footnotes

[a] Vasuflo-T G 20 or G 22, Dispomed, Germany
[b] Rapidpoint 405, Siemens Healthcare Diagnostics Inc, Tarrytown, NY
[c] Cobas c 311, Roche Diagnostics, Mannheim, Germany
[d] SPSS 18.0, IBM, New York City, NY

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Supporting Information

Additional Supporting Information may be found online in Supporting Information:

Fig S1. Changes of plasma potassium concentration between the intervals $T_{initial}$ to T_{60min} and T_{60min} to T_{24h} in individual calves of the 3 treatment groups.

Table S1. Overview of the performed treatment procedures during the study period of 24 hours.

Table S2. Median and interquartile ranges of selected variables of clinical pathology and hydration status of calves of the study population at different times of examination.