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Risk Factors for the Development of Hypokalemia in Neonatal Diarrheic Calves

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Background: Neonatal diarrheic calves have a clear negative potassium balance because of intestinal losses and decreased milk intake but in the presence of acidemia, they usually show normokalemic or hyperkalemic plasma concentrations.

Objectives: To assess whether marked hypokalemia occurs in response to the correction of acidemia and dehydration and to identify factors that are associated with this condition.

Animals: Eighty-three calves with a clinical diagnosis of neonatal diarrhea.

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, 0.9% saline and 40% dextrose infusion solutions.

Results: The proportion of hypokalemic calves after 24 hours of treatment (19.3%) was twice as great as it was on admission to the hospital. Plasma K^+ after 24 hours of treatment was not significantly correlated to venous blood pH values at the same time but positively correlated to venous blood pH values on admission ($r = 0.51$, $P < .001$). Base excess on admission (Odds ratio [OR] = 0.81, 95% confidence interval [CI] = 0.70–0.94), duration of diarrhea (OR = 1.37, 95% CI = 1.05–1.80), milk intake during hospitalization (OR = 0.54, 95% CI = 0.37–0.79) and plasma sodium concentrations after 24 hours (OR = 1.12, 95% CI = 1.01–1.25) were identified to be independently associated ($P < .05$) with a hypokalemic state after 24 hours of treatment.

Conclusions and Clinical Importance: Findings of this study suggest that marked depletion of body potassium stores is evident in diarrheic calves that suffered from marked metabolic acidosis, have a low milk intake and a long history of diarrhea.

Key words: Acidemia; Body potassium depletion; D-lactate; Potassium homeostasis.

Physiologically, the extracellular potassium concentration (K^+) represents only 2% of the total body potassium content[1] and it has been proposed that plasma K^+ represents only an indicator of intracellular potassium stores as long as blood pH and glucose concentrations are in the reference range.[2] Neonatal diarrheic calves have a clear negative potassium balance because of intestinal losses and decreased milk intake.[3] However, they usually show normokalemic or hyperkalemic plasma concentrations, which is very likely to occur in spite of a depletion of intracellular potassium stores.

Elevated plasma potassium concentrations in calves with neonatal diarrhea were traditionally attributed to an acidemic state with intracellular buffering of hydrogen ions in exchange for potassium ions and impairment of the Na^+/K^+-ATPase (responsible for the distribution of potassium between intracellular and extracellular space) as the proposed underlying mechanisms.[4–6] However, recent research has shown that dehydration and concomitant impairment of renal function represents an important mechanism in the pathogenesis of hyperkalemia in such animals. Additionally, the presence of hyperkalemia was reported to be dependent on the nature of an existing acidosis in such that D-lactic acidosis is only rarely associated with a hyperkalemic state.[7,8]

The acidemia-induced efflux of potassium ions out of the cells and a potential subsequent renal elimination in an attempt to prevent life-threatening hyperkalemia likely contributes to intracellular K^+ depletion in diarrheic calves. This mechanism might be especially of relevance in calves with D-lactic acidosis, because this condition is not necessarily associated with clinical dehydration[9] and might therefore explain the reported lower incidence of hyperkalemia in such animals.[8] Considering these pathophysiological mechanisms, the question arises if marked hypokalemia occurs in neonatal calves with diarrhea in response to the correction of acidemia and dehydration.

In general, hypokalemia is a commonly observed electrolyte imbalance in critically ill cattle and has been reported in conjunction with clinical disorders such as hepatic lipidosis, downer cow syndrome and abomasal displacement or volvulus.[10–13] Clinicopathological findings in a large study population of dairy cattle with abomasal displacement or volvulus recently suggested that hypovolemia, a decreased feed intake and acid-base imbalances play an important role in determining the plasma potassium concentration in such animals.[12]

Consequently, this study aims to document the dynamics of plasma K^+ in neonatal diarrheic calves during the course of treatment with special regard to the occurrence of hypokalemia and the identification of factors associated with this condition.

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).

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Calves

Between November 2012 and September 2013 a prospective study was conducted involving 83 calves that were admitted to the Clinic for Ruminants, LMU Munich, with a clinical diagnosis of neonatal diarrhea. Exclusion criteria of calves were concurrent health problems requiring specific therapeutic interventions, euthanasia or death on grounds of severe concurrent disease during the first 48 hours of hospitalization, failure to receive the entire determined infusion volume, or marked hypernatremia (>170 mmol/L).

Because of regional preferences, 91.6% (n = 76) of those 83 calves were Simmental (German Fleckvieh), the most common dairy breed in Bavaria. The medians and interquartile ranges for age (days) and body mass (kg) of the calves were 10.0 (7.0–14.0) and 42.8 (37.6–47.8), respectively. The median and interquartile range of the reported duration of diarrhea in 82 calves prior to hospitalization was 3 (2–5) days.

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 according to an established treatment protocol[15] for the dosage of sodium bicarbonate based on the clinical assessment of posture/ability to stand, hydration status, and the degree of loss of the palpebral reflex without considering laboratory findings. Briefly, calves that were neither dehydrated nor assumed to be acidemic were intended to be treated with an oral rehydration solution (ORS) as sole treatment. In cases in which correction of acidosis was deemed necessary, calves were treated with commercially available 8.4% sodium bicarbonate solutions in a total amount of 250–750 mmol. Calves with signs of marked clinical dehydration were infused with 0.9% saline in an amount of 5–10 L that was spiked with 250 mmol of the intended amount of 8.4% sodium bicarbonate solution. A volume of 0.5 L of a 40% dextrose was added to the saline solution in cases of hypothermia (<37°C), lack of milk intake for more than 24 hours before admission or suspected septicemia.

All calves received meloxicam at a dosage of 0.5 mg/kg IV immediately after the admission examination. Antimicrobial treatment with amoxicillin at a dosage of 15 mg/kg body weight was initiated in 38 calves during the first 24 hours, and in an additional 16 calves during the subsequent 24 hours, because predefined criteria were fulfilled.[15]

After a period of 24 hours clinical signs of calves were reevaluated and treatment was continued by the repeated use of the treatment protocol. Calves were exclusively treated with an electrolyte solution if the offered amount of milk and ORS was suckled well and entirely in the two preceding feeding times before the reevaluation. At that point of time, three calves were treated differently from the clinical treatment protocol and laboratory findings were included in the decision-making. In two acidotic calves with base excess values less than −10 mmol/L, where the follow-up treatment would have exclusively consisted of oral rehydration, infusions with 250 and 500 mmol of sodium bicarbonate were performed to prevent a potential deterioration of the general condition. Another calf which was unable to stand because of aortic thrombosis (later confirmed by necropsy), which would therefore have been treated with high amounts of sodium bicarbonate, was switched to oral rehydration. An overview of the performed treatment procedures and the infused amounts of saline, glucose, and sodium bicarbonate at $T_{initial}$ and T_{24h} can be found in Table 1.

Table 1. Overview of the performed treatment procedures in calves of the present study population (n = 83).

	Initial Treatment (n)	Treatment after 24 hours (n)
Oral rehydration[a]	12	41
$NaHCO_3^-$		
250 mmol	22	38
500 mmol	24	4
750 mmol	25	–
0.9% Saline		
5 L	47	40
10 L	9	–
40% dextrose		
0.5 L	12	2

Intravenous fluids were administered over a period of 24 hours.
[a]As sole treatment.

Feeding

Depending on the initially determined body weight of calves, 1.5 L (≤40 kg) or 2 L (>40 kg) of whole milk was offered 3 times a day (7:00 AM, 12:00 PM, and 7:00 PM), which corresponded to a median offered milk volume of 12.6% of body weight. An oral rehydration solution was additionally offered 3 times a day (10:00 AM, 3:00 PM, and 11:00 PM) in a total volume of 4 L per day. Depending on the time of arrival at the clinic some calves of the ORS group initially received an additional liter of ORS to test the intake of the solution. 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. Calves had access to fresh water throughout the study period. The intake of milk and ORS was determined and recorded and the respective values presented as the intake in percent of body weight.

Sampling Conditions and Laboratory Analyses

For the present analysis, blood samples were taken from the jugular vein on admission to the hospital ($T_{initial}$) as well as 24 hours (T_{24h}) and 48 hours (T_{48h}) after the initiation of treatment. 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 determined using a blood pH, gas, and electrolyte analyzer with ion selective electrodes.[a] Blood samples were kept at room temperature and analyzed within 15 minutes. Blood pH and pCO_2 were corrected for rectal temperature using standard algorithms.[16]

An automatic analyzing system was used for the biochemical analysis.[b] 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.[17,18]

Calculations

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

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

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 mg/dL) photometrically, blood base excess (in vitro base excess) was also automatically calculated in units of mmol/L using the van Slyke equation with measured blood pH at 37°C and the determined actual bicarbonate concentration:

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

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

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

The strong ion gap (SIG) was calculated from total protein concentrations to obtain an estimate of the unmeasured strong anion concentration by using the following equation[19]:

$$SIG = c\text{Total protein} \times (0.343/\{1 + 10^{(7.08 - pH)}\}) - AG \quad (4)$$

Statistical Analysis

Based on previously published reference ranges[20] hypokalemia was defined as a plasma potassium <3.9 mmol/L, hyperkalemia as a plasma potassium concentration >5.8 mmol/L and acidemia as a venous blood pH ≤ 7.30. 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. Spearman's coefficients of correlation were calculated to determine associations between parameters. Potential differences of clinical categories of posture, behavior, and suckling reflex between hypokalemic and nonhypokalemic calves were assessed by a chi-square test. A Mann-Whitney U-test was used to determine statistically significant differences of continuous variables between groups. In order to identify optimal cut-off values of potentially useful predictors of a hypokalemic state at T_{24h} a receiver operating characteristics (ROC) analysis was performed for those variables with a statistically significant difference between hypokalemic and nonhypokalemic calves. The comparative accuracy of those variables was assessed by calculation of the area under the curve (AUC) and the associated 95% confidence interval (95% CI).

A stepwise forward binary logistic regression analysis was additionally used to identify factors that were independently associated with a hypokalemic state at T_{24h} and T_{48h}. For this purpose, clinical or clinicopathological variables with a statistically significant difference in the Mann-Whitney U-test were entered into the model. If two variables were closely correlated to each other ($r_s > 0.75$ or < -0.75), only that variable was entered into the model which had the lowest P-value in the preliminary univariable analysis to minimize the effects of collinearity. The software package SPSS 18.0[c] was used for the statistical analysis of the results and P-Values ≤. 05 were considered as statistically significant.

Results

On admission to the hospital, hyperkalemia was present in 20 calves (24.1%), normokalemia in 55 calves (66.3%), and hypokalemia in 8 calves (9.6%). The correlation between plasma potassium concentration and venous blood pH values on admission is shown in Figure 1. At that point of time plasma potassium concentrations were also weakly correlated to base excess values ($r_s = -0.22$, $P = .05$), whereas no significant correlation to bicarbonate concentrations was seen.

Venous blood pH and plasma potassium concentrations of calves after 24 hours of treatment are depicted in Figure 2. At that point of time a total of 31 calves (37.3%) were still acidemic (venous blood pH ≤ 7.30) and hypokalemia was observed in 16 calves (19.3%). Venous blood pH and plasma K^+ at T_{24h} were not significantly correlated. However, a moderate correlation ($r = 0.512$; $P < .001$) between plasma K^+ at T_{24h} and venous blood pH on admission was seen (Fig 2). This coefficient of correlation was higher ($r = 0.601$, $P < .001$) in the subset of 52 calves with a measured blood pH > 7.30 at T_{24h}. All calves with a hypokalemic state at T_{24h} were acidemic on admission to the hospital and had plasma potassium concentrations ranging from 3.47 to 7.32 mmol/L. Four of those 16 calves were already hypokalemic on admission to the hospital, while eight calves were initially presented in a normokalemic and four calves in a hyperkalemic state (Fig 3).

After 48 hours of treatment a hypokalemic state was still evident in 13 calves. Plasma K^+ at T_{48h} was also not significantly correlated to venous blood pH at that point of time, but significantly correlated ($r = 0.374$; $P < .001$) to venous blood pH on admission (Fig 2). The latter coefficient of correlation was slightly higher ($r = 0.411$; $P < .001$) in a subset of 68 calves with a measured blood pH > 7.30 at T_{48h}.

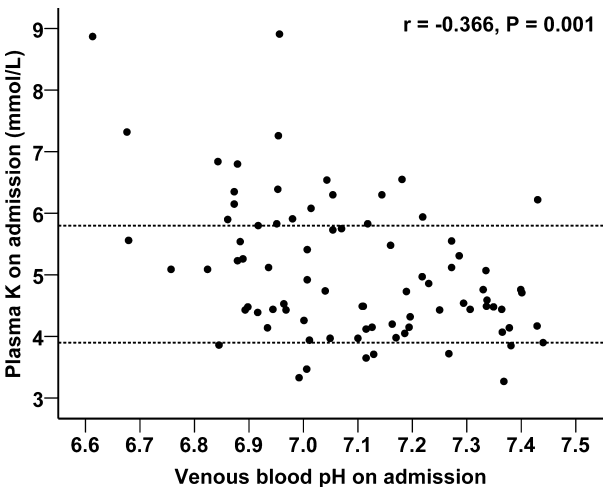

Fig 1. Scatterplot of initial plasma potassium concentrations and venous blood pH values of calves of the present study population (n = 83). The calculated Spearman rho coefficient indicated a weak correlation between the parameters. Dashed horizontal lines indicate the upper and lower limit of the reference range for plasma potassium concentrations.

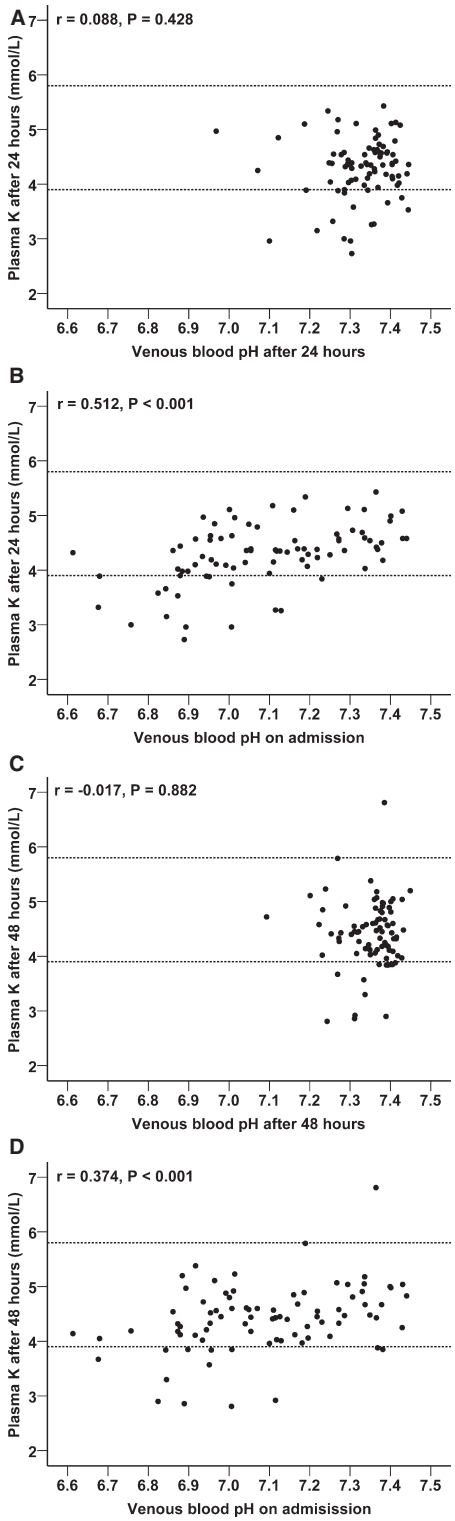

Fig 2. Scatterplots showing the relationship between venous blood pH values and plasma potassium concentrations of 83 calves with neonatal diarrhea at different times of examination. Plasma potassium concentrations that were determined after a period of 24 and 48 hours after initiation of treatment were not correlated to venous blood pH values at the same point of time, but were significantly correlated to venous blood pH determined on admission to the clinic. Dashed horizontal lines indicate the upper and lower limit of the reference range for plasma potassium concentrations.

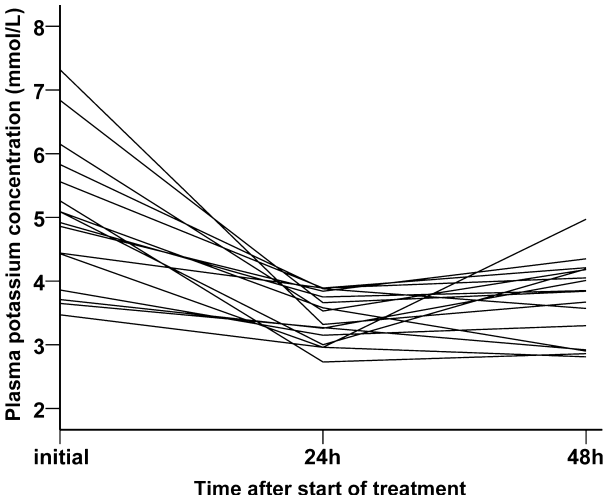

Fig 3. Dynamics of plasma potassium concentrations during the study period in 16 neonatal diarrheic calves with an observed hypokalemic state (plasma potassium concentration < 3.9 mmol/L) after 24 hours of treatment.

Clinical and clinicopathological variables in relation to categories of plasma K^+ after 24 hours of treatment are presented in Table 2. Calves with a hypokalemic state at T_{24h} had a significantly longer history of diarrhea and a significantly lower intake of milk during hospitalization. On admission to the hospital those calves had also significantly higher plasma D-lactate and chloride concentrations, higher values for AG and serum urea concentrations, and significantly lower values for venous blood pH, pCO_2, base excess, SIG and bicarbonate concentration. At T_{24h} significantly higher plasma sodium and chloride concentrations, higher values for AG and significantly lower values for base excess, SIG and bicarbonate concentration in the group of the 16 hypokalemic calves were found. Different cut-off points of those variables that optimized the resulting sensitivity and specificity for the prediction of a hypokalemic state at T_{24h} are shown in Table 3. The highest AUC values were found for venous blood pH, base excess, bicarbonate, and chloride concentration at $T_{initial}$ as well as milk intake until T_{24h}.

Since variables of acid-base status (BE, HCO_3^-, venous blood pH, AG, and SIG) as well as sodium and chloride concentrations were closely correlated to each other, only BE and SIG at $T_{initial}$ and BE and AG at T_{24h} were included in the subsequent multivariable stepwise binary logistic regression model. In the final model base excess on admission, duration of diarrhea before admission, milk intake per body weight until T_{24h} and sodium concentration at T_{24h} were identified as independent factors associated with a hypokalemic state after 24 hours of treatment (Table 4).

Plasma K^+ at T_{24h} was the only factor (OR = 0.061; 95% CI = 0.015–0.255; $P < .001$) that predicted a hypokalemic state after 48 hours in a comparative

Table 2. Clinical and clinicopathological findings of 83 calves with neonatal diarrhea in relation to categories of plasma K^+ after 24 hours of treatment with a clinical protocol using hypertonic (8.4%) sodium bicarbonate solution.

	Categories of Plasma K^+ at T_{24h}		
	Median (Q_{25}/Q_{75})		
Variables	Hypokalemia (n = 16)	Normokalemia (n = 67)	*P*-Value
General findings			
History of diarrhea[a] (days)[b]	4.5 (3/6.8)	3 (1/5)	.031
Milk intake/BW (%)[b]	7.9 (4.7/8.7)	11.3 (8.0/12.5)	.001
ORS intake/BW (%)	6.8 (4.0/8.5)	8.2 (5.8/10.3)	.067
Hydration status and laboratory findings on admission			
Enophthalmos (mm)	5 (2/6)	4 (2/5)	.25
Skin tent duration (seconds)	6.8 (3.7/10)	6.3 (3.2/10)	.30
Venous blood pH	6.89 (6.83/7.0)	7.13 (6.98/7.29)	<.001
pCO_2 (mmHg)[b]	42.0 (32.4/52.8)	53.4 (39.2/62.5)	.015
HCO_3^- (mmol/L)	7.8 (5.2/11.1)	16.5 (10.0/26.6)	<.001
Base excess (mmol/L)[b]	−25.0 (−28.9/−19.6)	−12.6 (−20.1/0.6)	<.001
AG (mEq/L)	27.1 (23.4/30.0)	23.1 (15.4/28.6)	.029
SIG (mEq/L)[b]	−19.4 (−23.0/−15.0)	−14.1 (−18.7/−4.5)	.005
D-lactate (mmol/L)[b]	7.6 (3.8/11.4)	3.6 (0.5/9.4)	.022
L-lactate (mmol/L)	1.1 (0.7/2.7)	1.5 (1.0/3.2)	.14
Glucose (mmol/L)	4.9 (4.2/5.9)	4.7 (4.1/5.4)	.54
Phosphorus (mmol/L)	3.9 (2.8/5.0)	2.9 (2.3/4.1)	.084
Urea (mmol/L)[b]	19.3 (9.3/38.9)	10.6 (7.1/19.5)	.051
Creatinine (μmol/L)	170.4 (106.1/390.8)	135.6 (88.5/287.9)	.22
Na^+ (mmol/L)	143.0 (135.1/150.0)	136.4 (133.3/142.2)	.066
K^+ (mmol/L)	5.0 (4.0/5.8)	4.71 (4.17/5.80)	.97
Cl^- (mmol/L)[b]	112.0 (106.3/119.3)	101.0 (94.0/111.0)	.001
Hydration status and laboratory findings after 24 hours			
Enophthalmos[a] (mm)	1 (0/2)	2 (1/2)	.13
Skin tent duration[a] (seconds)	2.8 (2.4/3.7)	2.9 (2.3/4.2)	.77
Venous blood pH	7.30 (7.26/7.36)	7.36 (7.30/7.39)	.11
pCO_2 (mmHg)	48.6 (41.7/56.5)	53.2 (48.1/57.4)	.21
HCO_3^- (mmol/L)	26.0 (18.0/29.3)	28.2 (23.2/32.7)	.044
Base excess (mmol/L)[b]	0.1 (−7.1/4.1)	1.1 (−2.4/7.1)	.044
AG (mEq/L)[b]	16.1 (11.9/18.4)	12.2 (9.5/15.0)	.021
SIG (mEq/L)	−7.5 (−9.8/−1.0)	−2.1 (−5.7/0.5)	.022
D-lactate (mmol/L)	3.4 (1.2/5.0)	1.6 (0.2/4.4)	.073
L-lactate (mmol/L)	1.3 (1.0/2.3)	1.3 (1.1/1.7)	.59
Glucose (mmol/L)	4.1 (3.7/4.6)	4.3 (3.7/4.9)	.49
Phosphorus (mmol/L)	2.2 (2.0/2.7)	2.1 (1.9/2.5)	.67
Urea (mmol/L)	7.1 (3.8/19)	6.2 (3.8/10.7)	.33
Creatinine (μmol/L)	97.5 (60.1/175.8)	83.3 (62.8/117.5)	.36
Na^+ (mmol/L)[b]	145.1 (141.6/152.9)	138.4 (134.7/144.6)	.002
K^+ (mmol/L)	3.4 (3.0/3.8)	4.4 (4.2/4.7)	<.001
Cl^- (mmol/L)	111.0 (103.3/116.5)	102.0 (97.0/109.0)	.002

Milk intake/BW, milk intake per body weight until T_{24h} (=24 hours after initiation of treatment); ORS intake/BW, intake of the offered oral rehydration solution until T_{24h}; pCO_2, partial pressure of carbon dioxide; AG, Anion gap; SIG, strong ion gap.

[a]Information was missing in one calf.

[b]Factors that were entered in the subsequent stepwise forward binary logistic regression analysis.

logistic regression model (data of preliminary univariable analysis not shown).

Clinical findings including posture, behavior and the suckling reflex were not significantly different between hypo- and normokalemic calves after 24 and 48 hours of treatment, respectively.

Discussion

In this population of neonatal calves with diarrhea we found that the proportion of hypokalemic calves after 24 hours of treatment was twice as high as on admission to the hospital. Central findings of this study

Table 3. Results of a receiver operating characteristics analysis for determining optimal cut-off values and the area under the curve of potentially useful predictors of a hypokalemic state after 24 hours of treatment in calves of the study population.

Variable	Cut-off	Sensitivity %	Specificity %	AUC	95% CI for AUC	*P*-Value
General findings						
Duration of diarrhea	≥2 days	100	30.3	0.673	0.541–0.804	.033
Milk intake/BW	≤9.3%	87.5	68.7	0.765	0.639–0.892	.001
Hydration status and laboratory findings on admission						
Venous blood pH	≤6.95	68.8	83.6	0.821	0.710–0.933	<.001
pCO_2	≤53 mmHg	81.3	52.2	0.696	0.568–0.825	.015
HCO_3^-	≤11.3 mmol/L	81.3	70.1	0.808	0.697–0.919	<.001
Base excess	≤−19.1 mmol/L	81.3	74.6	0.823	0.712–0.935	<.001
AG	≥22.5 mEq/L	87.5	47.8	0.677	0.552–0.802	.029
SIG	≤−11.3 mEq/L	100	37.3	0.729	0.607–0.850	.005
D-lactate	≥2.8 mmol/L	100	43.3	0.685	0.566–0.803	.022
Urea	≥21.1 mmol/L	50	77.6	0.658	0.501–0.814	.051
Cl^-	≥101.5 mmol/L	93.8	52.2	0.770	0.662–0.878	.001
Hydration status and laboratory findings after 24 hours						
HCO_3^-	≤30.9 mmol/L	93.8	41.8	0.663	0.526–0.799	.044
Base excess	≤6.2 mmol/L	100	34.3	0.663	0.528–0.798	.044
AG	≥14.8 mEq/L	62.5	73.1	0.687	0.553–0.822	.021
SIG	≤−3.8 mEq/L	68.8	68.7	0.685	0.543–0.826	.022
Na^+	≥141.4 mmol/L	81.3	67.2	0.746	0.615–0.878	.002

AUC, area under the curve; 95% CI for AUC, 95% confidence interval for the area under the curve.

Table 4. Results of a stepwise forward binary logistic regression analysis of clinical and clinicopathological variables as predictors of a hypokalemic state after 24 hours of treatment with a clinical protocol using hypertonic (8.4%) sodium bicarbonate solution (n = 82).

Variable	Estimate	±SE	OR	95% CI	*P*-Value
Intercept	−17.99	7.80			0.021
Base excess ($T_{initial}$)	−0.21	0.07	0.811	0.703–0.936	0.004
Duration of diarrhea before admission	0.32	0.14	1.374	1.050–1.796	0.020
Milk intake per body weight until T_{24h}	−0.62	0.20	0.537	0.367–0.788	0.001
Na^+ (T_{24h})	0.12	0.06	1.122	1.007–1.251	0.036

The Nagelkerke Pseudo R^2-value of the model was 0.62. The Hosmer-Lemeshow Goodness-of-Fit-test indicated a good fit ($P = .96$) to the final logistic regression model. Information about the duration of diarrhea was missing in one calf.

suggest that this condition was associated with a more pronounced metabolic acidosis on admission to the hospital, a lower intake of milk during hospitalization and a longer duration of diarrhea than in calves with a normokalemic state.

It has been proposed that plasma K^+ represents an indicator of body potassium stores as long as blood pH and glucose concentrations are in the reference range and that a linear interrelation between plasma K^+ and body potassium deficit exists.[1,2] Classic papers also stated[2,21] that metabolic acidosis causes an increase of plasma K^+ independently of intracellular potassium stores. This is supported by our finding that a decline of plasma K^+ during the first 24 hours of treatment occurred even in calves that were presented with normokalemia and that a hypokalemic state with plasma $K^+ < 3.9$ mmol/L was evident in 19.3% of calves at $T_{24h.}$ Although hypokalemia after 24 and 48 hours of treatment could be associated to the parenteral administration of sodium bicarbonate or the development of mild alkalemia, the absence of a significant association between the blood pH and the plasma potassium concentration at 24 hours suggests that depletion of the body's potassium stores could indeed be an important causative factor for the observed hypokalemia after 24 and 48 hours of treatment. However, a high proportion of calves had still venous blood pH values ≤ 7.30 and a hypokalemic state in response to body potassium depletion could have therefore been masked by a still existing acidemic state, which is clearly a weakness of this study. Bicarbonate requirements were exclusively determined on the basis of clinical findings (except of three calves at T_{24h}) and irrespective of individual body weight; an approach that was chosen in the present investigation to simulate a field practice situation where diarrheic calves are usually treated in the absence of laboratory findings.

Binary logistic regression analysis indicated that a long duration of diarrhea, a low base excess on admission, a low milk intake during hospitalization,

and high sodium concentrations at T_{24h} were factors that were independently associated with a hypokalemic state at T_{24h}, which strongly suggests that marked depletion of intracellular potassium stores was evident in those calves. The findings that venous blood pH values on admission were moderately correlated to plasma K^+ at T_{24h} and that a significant correlation was still evident at T_{48h} additionally imply that a depletion of body potassium stores occurred in response to an acidemia-induced shift of potassium ions between the intra- and extracellular spaces which might be enhanced by intestinal losses or alternatively by renal elimination to prevent a life-threatening hyperkalemic state. The observed correlation between venous blood pH values on admission and plasma K^+ at T_{24h} could be also an explanation for the observed association between high plasma sodium and low potassium concentrations at T_{24h} in the binary logistic regression model, since calves with a more pronounced acidemia were treated with higher amounts of hypertonic sodium bicarbonate which could have resulted in higher sodium concentrations after 24 hours of treatment.

The inverse relationship between plasma K^+ and pH was traditionally thought to be related to impairments of Na^+/K^+-ATPase on cell membranes and intracellular buffering of hydrogen ion in exchange for potassium ions[4,5] although the latter mechanism does not seem to have a sound physiological basis because the increase of hydrogen ions occurs in units of nEq/L.[22] Classic papers stated that a 0.1 unit reduction in venous blood pH results in an increase of plasma K^+ of 0.3–0.5 mmol/L[23] or 0.6 mmol/L.[21] However, it was recently reported[8] that this linear interrelation does not reflect the situation in diarrheic calves and that the presence of hyperkalemia depended on the nature of an existing acidosis but more importantly on the degree of dehydration. It was found that the presence of D-lactataemia in acidemic calves resulted in significantly lower odds for hyperkalemia but significantly higher odds for the presence of hypokalemia.[8] This is in line with the results of experimental studies which reported that a hyperkalemic state can be induced by infusions with inorganic acids such as HCl or ammonium chloride but not if organic acids such as lactic acid, acetic acid or ß-hydroxybutyrate are infused.[24–26] This disparate effect on K^+ homeostasis was related to intracellular moving of organic anions which is believed to result in a higher degree of intracellular acidosis and Na^+ loading and consequently a higher Na^+/K^+-ATPase activity resulting in a net cellular uptake of potassium ions.[27] An alternative explanation is provided by the central role that dehydration plays in the pathogenesis of hyperkalemia in neonatal diarrheic calves. Since D-lactic acidosis in neonatal diarrheic calves is not necessarily associated with clinical dehydration[9,15] the acidemia-induced efflux of potassium ions could have been masked by the ability to eliminate potassium ions by the kidneys which would have resulted in marked K^+ wasting during an ongoing acidosis. In the present study, calves with a hypokalemic state at T_{24h} had significantly higher D-lactate concentrations on admission than nonhypokalemic calves. However, D-lactate was not of predictive value in the binary logistic regression analysis, so further studies appear necessary which aim to assess the impact of increased blood D-lactate concentrations on intracellular potassium concentrations.

The finding that a low milk intake and long duration of diarrhea were associated with a hypokalemic state at T_{24h} strongly indicates that the potassium homeostasis in neonatal diarrheic calves is not only determined by internal (ie, transcellular shifts) but also by external potassium imbalances (ie, net difference between intake and elimination). Diarrheic calves have a clear negative potassium balance[3] because of intestinal losses and a long duration of diarrhea therefore likely results in a depletion of potassium stores. The association between a low milk intake and a hypokalemic state at T_{24h} has some commonalities to the situation in adult cattle with abomasal displacement or volvolus where hypokalemia was also associated with decreased feed intake relative to the amount of milk produced, in addition to alkalemia in response to sequestration of chloride in the abomasum, and hypovolemia.[12]

Severe hypokalemia in cows has been associated with clinical signs of depression, skeletal muscle weakness and recumbency[10,13] although such findings have not been consistently observed[28] and concurrent problems and metabolic imbalances were also reported in affected animals.[10] In the present study clinical findings including posture, behavior and strength of the suckling reflex were not significantly different between hypo- and nonhypokalemic calves at T_{24h} and T_{48h} which might be related to the fact that plasma K^+ in hypokalemic calves (median: 3.4 mmol/L at T_{24h}) was not as low as in reports about dairy cattle with clinical signs of severe hypokalemia. However, clinical signs in dairy cattle that were experimentally depleted of potassium also included reduced appetite[29] such that the lower milk intake observed in hypokalemic calves could be an effect of whole-body potassium depletion.

In conclusion, findings of this study indicate that neonatal diarrheic calves which suffered from marked metabolic acidosis, have a low intake of milk and a long history of diarrhea are at special risk for the development of hypokalemia during the course of treatment, which could be related to a marked depletion of body potassium stores. Further studies appear therefore necessary to determine whether hypokalemic calves with neonatal diarrhea benefit from oral or parenteral substitution of potassium ions.

Footnotes

[a] Rapidpoint 405, Siemens Healthcare Diagnostics Inc., Tarrytown, NY
[b] Cobas c 311, Roche Diagnostics, Mannheim, Germany
[c] SPSS 18.0, IBM, New York City, NY

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Conflict of Interest Declaration: The authors disclose no conflict of interest.

Off-label Antimicrobial Declaration: The authors declare no off-label use of antimicrobials.

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