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Effects of profound acidemia on the dynamic glucose and insulin response and plasma potassium and phosphorus concentrations during an intravenous glucose tolerance test in neonatal calves

F. M. Trefz,*[1] I. Lorenz,† and P. D. Constable‡
*Clinic for Ruminants with Ambulatory and Herd Health Services at the Centre for Clinical Veterinary Medicine, Ludwig-Maximilians-Universität (LMU) Munich, Sonnenstraße 16, 85764 Oberschleißheim, Germany
†Bavarian Animal Health Service (Tiergesundheitsdienst Bayern e.V.), Senator-Gerauer-Str. 23, 85586 Poing, Germany
‡College of Veterinary Medicine, University of Illinois, Urbana-Champaign 61802

ABSTRACT

Acidemia and electrolyte imbalances such as hyperkalemia are common in neonatal calves with diarrhea. Acidemia negatively affects the cellular response to insulin and may therefore result in deranged glucose, potassium, and phosphorus homeostasis. The primary aim of this study was to compare indices that characterize the dynamic glucose and insulin response between acidemic and nonacidemic neonatal diarrheic calves and a healthy control group during an intravenous glucose tolerance test (IVGTT) that consisted of i.v. administration of 0.3 g of glucose per kg of body weight. Secondary aims were to characterize the associated changes in plasma potassium and phosphorus concentrations. The effect of correction of profound acidemia with a sodium bicarbonate containing infusion on these parameters was also assessed. Thirty calves (age $\leq$21 d) were purposively assigned to one of the following groups: 10 calves with diarrhea and profound acidemia (venous blood pH <7.20) where an IVGTT was performed before and after treatment with sodium bicarbonate, 10 calves with diarrhea and minimal acid-base disturbance (venous blood pH >7.35), and 10 healthy control calves. Profoundly acidemic diarrheic calves (jugular venous blood pH 6.99 $\pm$ 0.10) had a similar initial increase in plasma insulin concentration to that in healthy control calves or nonacidemic calves with diarrhea. However, insulin concentrations remained relatively stable in acidemic calves between 15 and 60 min after the start of the IVGTT, whereas a marked decrease in plasma insulin concentrations occurred in all other groups during the same period of time. We conclude that acidemia does not alter cell glucose availability or the dynamic response of glucose, phosphorus, and potassium to insulin; however, acidemia markedly prolongs plasma insulin concentrations following an IVGTT through an unidentified mechanism. Results of this study emphasize the importance of correcting acidemia and metabolic acidosis in neonatal calves with diarrhea.

Key words: calves, insulin resistance, glucose, potassium, phosphorus

INTRODUCTION

Dehydration, azotemia, and development of a hyponatremic strong ion (metabolic) acidosis with variable degrees of hyper D-lactatemia are well-known complications in neonatal calves with diarrhea (Lorenz, 2004; Constable et al., 2005; Trefz et al., 2015a). Electrolyte imbalances such as hyperkalemia are also common in diarrheic calves and can result in skeletal muscle weakness and life-threatening cardiac conduction abnormalities and arrhythmias (Lewis and Phillips, 1973; Weldon et al., 1992; Trefz et al., 2013b).

Potassium is predominantly an intracellular cation and hyperkalemia in neonatal diarrheic calves has traditionally been attributed to an acidemia-induced dysregulation of internal potassium balance. Intracellular buffering of hydrogen ions and impaired Na^+/K^+-ATPase activity have therefore been proposed as underlying mechanisms for hyperkalemia in diarrheic calves (Lewis and Phillips, 1973; Sweeney, 1999; Constable, 2002). However, recent research indicates that the occurrence of hyperkalemia in neonatal diarrheic calves is primarily dependent on the degree of dehydration and to a lesser extent on the cause of the acidemia (Trefz et al., 2013a,b). Decreased renal perfusion and glomerular filtration rate therefore appear to play decisive roles in the development of hyperkalemia. Nevertheless, other factors still have the potential to play an important pathophysiological role in the development of hyperkalemia in diarrheic calves.

The mechanism linking acidemia and altered intracellular potassium homeostasis is not fully understood.

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[1]Corresponding author: Florian.Trefz@campus.lmu.de

Insulin is involved in the regulation of internal potassium balance by providing a net cellular uptake of potassium (Cox et al., 1978; Bia and DeFronzo, 1981). As even mild acidemia (blood pH, 7.27 ± 0.01 and 7.37 ± 0.02) has been associated with insulin resistance in humans (DeFronzo and Beckles, 1979; Mak, 1998), it is likely that insulin-dependent cellular potassium uptake is impaired in the presence of acidemia (Constable and Grünberg, 2013). Impaired cellular responsiveness to insulin provides a potential explanation for the association between acidemia and hyperkalemia. Feeding a low DCAD (−41 mEq/100 g) ration to nonlactating nonpregnant dairy cows induced acidemia (blood pH, 7.32), metabolic acidosis (plasma HCO_3^-, 17.8 mmol/L; urine pH, 5.4), and decreased insulin responsiveness, as assessed by higher peak plasma glucose and lower peak plasma insulin concentrations in response to an intravenous glucose tolerance test (**IVGTT**; Bigner et al., 1996). We therefore hypothesized that neonatal calves with diarrhea and profound acidemia and hyperkalemia have decreased insulin responsiveness and a slower rate of decrease in plasma potassium concentration, compared with diarrheic calves with minimal disturbances in acid-base balance and healthy calves without diarrhea.

Combined administration of insulin and glucose is a well-established treatment for hyperkalemia in humans (Weisberg, 2008). Evaluation of indices that characterize the dynamic glucose and insulin response to an IVGTT in acidemic neonatal calves should improve our understanding of the pathophysiology of potassium balance disorders in neonatal calves with diarrhea and therefore improve treatment protocols for hyperkalemia in acidemic calves. Although it is well known that restoration of potassium homeostasis in diarrheic acidemic calves can be achieved by rehydration and alkalinization using intravenous solutions containing sodium bicarbonate (Koch and Kaske, 2008; Coskun et al., 2010; Trefz et al., 2015b), we hypothesized that intravenous administration of a glucose-containing solution induces endogenous insulin release and thereby exerts a potassium-lowering effect. This might be especially of relevance in the initial treatment of affected calves, where treatment objectives focus on the rapid correction of hyperkalemia, hypoglycemia, and profound acidemia (Constable and Grünberg, 2013; Lorenz and Trefz, 2016). This research question is also of interest because administration of glucose containing infusion solutions to diarrheic calves that require intravenous fluid therapy is popular in ambulatory field practice. Intravenous glucose is administered to counteract negative energy balance and provide a readily utilizable energy source when calves are housed in cold ambient conditions (Berchtold, 2009).

The major objectives of the study reported here were therefore to administer an IVGTT to characterize the dynamic glucose and insulin response and changes in plasma potassium concentrations between acidemic and nonacidemic neonatal diarrheic calves and a healthy control group. Because insulin also induces a compartmental shift of inorganic phosphorus (**P_i**) into insulin-responsive cells in cattle (Knochel, 1977; Grünberg et al., 2006) by upregulating Na/P_i co-transporter gene expression (Li et al., 1996), we also examined the P_i concentration-time relationship during an IVGTT. An additional objective was to determine whether correction of profound acidemia with a sodium bicarbonate-containing infusion has an immediate effect on these parameters.

MATERIALS AND METHODS

The methods of this study were approved by the Animal Welfare and Ethics Committee of the government of Upper Bavaria (permit: 55.2–1-54–2532–11–14) according to German Animal Welfare Legislation.

Calves

An IVGTT was performed in 30 neonatal calves up to 21 d of age. Calves were purposively selected to be assigned to one of the following 3 groups:

1. Ten calves with diarrhea and profound acidemia (venous blood pH <7.20; acidemic group; group A). An IVGTT was performed before treatment (**A-BT**) and after treatment (**A-AT**) with intravenous sodium bicarbonate as described below.
2. Ten calves with diarrhea and minimal acid-base disturbance (venous blood pH >7.35; nonacidemic group; group **NA**).
3. Ten healthy calves with normal fecal consistency and volume (control group; group **C**).

Before inclusion into the study, calves underwent a thorough physical examination that included the assessment of the general condition and examination of the respiratory, gastrointestinal, and cardiovascular system as well as palpation of navel structures and joints. Physical examination included the clinical assessment of posture/ability to stand, behavior, rectal temperature, and extent of enophthalmos (mm). Physical examination was repeated in calves of group A before start of the second IVGTT. Posture was scored as 1 = standing securely; 2 = insecurely, able to correct position; 3 = insecurely, unable to correct position; and 4 = unable to stand. Behavior was scored as 1 = adequate reaction, very bright and alert; 2 = adequate reaction;