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Effect of abomasal emptying rate on the apparent efficiency of colostral immunoglobulin G absorption in neonatal Holstein-Friesian calves

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ABSTRACT

Inadequate absorption of colostral IgG in calves increases the risk of morbidity and death and is an important source of economic loss to the dairy industry. We hypothesized that an increased rate of abomasal emptying in colostrum-fed calves would be associated with an increased apparent efficiency of absorption (AEA) of colostral IgG. This is because an increase in abomasal emptying rate causes IgG to reach the site of absorption in the small intestine earlier and at a higher luminal concentration. The main objective was, therefore, to determine the association between the AEA of colostral IgG and abomasal emptying rate in neonatal calves. Twenty-four neonatal Holstein-Friesian calves were randomly assigned to one of the following treatments: control, 2 mL of 0.9% NaCl intramuscularly; erythromycin, 8.8 mg/kg of body weight intramuscularly; ivermectin, 200 μg/kg intravenously; and gentamicin, 6.6 mg/kg intramuscularly. These treatments were selected because we have previously demonstrated that erythromycin and ivermectin increase, and gentamicin decreases, the rate of abomasal emptying in milk-fed calves. Calves were fed 3 L of pooled cow colostrum containing acetaminophen (50 mg/kg of body weight) by oroesophageal intubation at 1 h of age and 30 min after each treatment was administered. Jugular venous blood samples were obtained periodically after the start of feeding. Abomasal emptying rate was assessed by the time to maximal plasma acetaminophen concentration. Erythromycin increased and gentamicin decreased the abomasal emptying rate and AEA of colostral IgG compared with control, respectively, whereas ivermectin had no effect. Using data from all 24 calves, the AEA of colostral IgG was linearly and negatively associated with abomasal emptying rate ($R^2 = 0.22$). We conclude that the abomasal emptying rate is an important determinant of the AEA of colostral IgG. Identifying a non-antimicrobial method for increasing abomasal emptying rate will provide a practical and effective method for facilitating transfer of passive immunity in colostrum-fed dairy calves.

Key words: erythromycin, ivermectin, gentamicin, prokinetic

INTRODUCTION

Neonatal calves must ingest colostrum during the first 24 h after birth to acquire passive immunity via the active uptake of maternal IgG across small intestinal epithelial cells (Stott et al., 1979a; Bush and Staley, 1980; Matte et al., 1982). The mass of IgG absorbed from the small intestine of the colostrum-fed calf depends on the IgG concentration in colostrum, the volume of colostrum administered, and the apparent efficiency of absorption (**AEA**) of ingested IgG (Stott et al., 1979c; Rajala and Castren, 1995). Although the AEA ranges from 6 to 66% for calves <24 h of age (Bush et al., 1971; Stott and Menefee, 1978; Matte et al., 1982), typical mean values for AEA are 30 to 35% for fresh colostrum and 20 to 30% for colostral replacement products (Morin et al., 1997; Quigley and Drewry, 1998; Jones et al., 2004; Gvozdic et al., 2007) with an AEA of 33 to 45% appearing to be near the practical biologic limit when 2 L or more of colostrum is fed shortly after birth (Bush et al., 1971; Baumwart et al., 1977; Stott and Fellah, 1983; Besser et al., 1985; Quigley et al., 2000; Godden et al., 2009a,b).

The rate of abomasal emptying influences the rate at which colostral IgG is delivered to the site of IgG absorption, which is the small intestine. Bovine colostrum contains nutrients such as proteins, fats, lactose, vitamins, and minerals and a large variety of nonnutrients including biologically active peptides, growth factors, hormones, cytokines, immunoglobulins, and maternal leukocytes, with marked variability in the protein and fat percentages and, therefore, the caloric content (Maunsell et al., 1998; Quigley and Drewry, 1998; Georgiev, 2008). The volume, caloric density and content (fat or protein concentration and type), and osmolality

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of an ingested fluid meal are important determinants of abomasal emptying rate in neonatal calves (Bell and McLeay, 1978; Sen et al., 2006; Marshall et al., 2008). We were, therefore, interested in determining the effect of experimentally induced changes in abomasal emptying rate on the AEA in newborn calves fed a standardized colostrum meal. We hypothesized that an increased rate of abomasal emptying would be associated with an increased AEA because colostral IgG reaches the site of absorption in the small intestine earlier and at a higher luminal concentration, which will result in a higher AEA and plasma IgG concentration (Stott and Fellah, 1983). Support for our hypothesis was provided by a study that demonstrated curd formation after colostrum ingestion results in a higher AEA because the IgG containing whey phase of colostrum leaves the abomasum very soon after coagulation (Cruywagen, 1990). Additional support for our hypothesis was provided by the results of a recent study in neonatal calves that demonstrated that an increase in colostral osmolality of 560 mOsm/L decreased the AEA (Cabral et al., 2011); we have previously demonstrated that an increase in solution osmolality from 300 to 600 mOsm/kg markedly decreased abomasal emptying rate in calves (Sen et al., 2006). We investigated our hypothesis in healthy neonatal calves fed a standardized colostrum meal by pharmacological alteration of the abomasal emptying rate.

MATERIALS AND METHODS

Animals

Twenty-four newborn Holstein-Friesian calves, ranging in BW from 32 to 41 kg (mean, 37 kg), were obtained from a local dairy farm in the winter of 2010 and spring of 2011. Calves had an unassisted delivery and normal adaptation to extra-uterine life; all stood within 3 h of birth. Calves were separated from their dam immediately after birth and housed unrestrained in separate stalls that were bedded with wood shavings. Calves were fed fresh cow milk (60 mL/kg of BW) 3 times a day after their initial feeding of colostrum. Calves had access to fresh water at all times, but a calf starter ration was not fed. The study protocol was approved by the institutional animal care and use committee.

Experimental Design

A 16- or 18-gauge catheter was inserted in the right jugular vein within 30 min of birth after clipping and aseptic preparation of the catheter site. One milliliter of lidocaine hydrochloride was injected subcutaneously (**SC**) over the right jugular vein, and the skin was incised (1 cm in length) with a scalpel blade to assist in catheter placement. An extension set was attached to the catheter and secured to the neck. The catheter was flushed every 12 h with heparinized saline solution (40 U of heparin/mL).

Calves were randomly assigned to receive 1 of 4 treatments using a random number generator (Excel spreadsheet, Microsoft Corp., Redmond, WA). Each calf was weighed and then assigned to receive one of the following treatments 1 h after birth: 2 mL of 0.9% NaCl solution i.m. (control treatment); erythromycin lactobionate (8.8 mg/kg of BW, i.m.; Hospira, Royal Leamington Spa, UK); ivermectin (200 μg/kg, i.v.; Ivomec injection, 1% solution, Merck & Co. Inc., Rahway, NJ); gentamicin (6.6 mg/kg, i.m.; Gentamicin 80, Alborz Daru, Tehran, Iran). These 3 treatments were selected because erythromycin is a strong prokinetic agent in milk-fed calves (Wittek and Constable, 2005; Nouri and Constable, 2007; Nouri et al., 2008; Afshari et al., 2009) and adult cattle (Wittek et al., 2008a,b; Constable et al., 2012), and ivermectin increased and gentamicin decreased the rate of abomasal emptying, respectively, in milk-fed calves (Nouri et al., 2008; Afshari et al., 2009). Thirty minutes after administration of each treatment, the calves were esophageally intubated and administered 3 L of pooled first-milking colostrum at 39°C that contained a dose of acetaminophen (50 mg/kg, Ramopharmin Co., Tehran, Iran). Pooled colostrum was obtained by harvesting 2 L of first-milking colostrum from 40 multiparous Holstein-Friesian cows immediately after parturition, mixing the 2-L colostrum samples, and packaging the pooled colostrum in 1-L plastic bags before storing at −20°C. Venous blood samples for determination of plasma IgG concentration were obtained immediately before colostrum administration (at 1 h) and at 3, 6, 9, 12, 18, 24, 36, and 48 h after birth and on d 5 and 7. Blood samples were collected into 6-mL partially evacuated tubes containing sodium heparin and centrifuged at 1,000 × *g* for 15 min at room temperature. Three milliliters of plasma was harvested and stored at −20°C until analysis was performed.

Abomasal emptying rate was measured by use of acetaminophen and glucose absorption techniques as previously described (Marshall et al., 2005; Nouri and Constable, 2006). Venous blood samples for determination of plasma acetaminophen and glucose concentrations were obtained at −30, 0, 15, 30, 45, 60, 90, 120, 240, 300, 360, 420, and 480 min (start of intubation was designated as time 0 min). These time points for obtaining samples were selected in an attempt to provide

at least 6 data points before and after the time to maximal (**Tmax**) of acetaminophen to facilitate nonlinear regression analysis for pharmacokinetic modeling.

Plasma IgG Concentration–Time Relationship

A commercial radial immunodiffusion kit (Purified IgG and Anti Bovine IgG; AbD Serotec, Raleigh, NC) was used to measure total IgG concentration in plasma and colostrum. Plasma was thawed at room temperature, and 5 μL of serum then was transferred into wells of an immunodiffusion plate. Colostrum was thawed at room temperature and diluted 1:6 with sterile saline (0.9% NaCl) solution, and 5 μL of diluted colostrum then was transferred into wells of the immunodiffusion plate. Three reference samples were included on each plate to enable us to generate a standard curve. Plates were allowed to incubate for 24 h at 19 to 22°C before results were interpreted. The diameter of each ring was measured, and total IgG concentrations were calculated by extrapolation from the standard curve.

AEA of Colostral IgG

The AEA of IgG absorption was calculated from the measured plasma total [IgG] in grams per liter at 24 h, the estimated plasma volume (**PV**) in liters, and the IgG intake in grams as AEA = (Plasma [IgG]) × PV/(IgG intake) (Quigley et al., 1998). The PV was calculated as PV = 0.089 × (BW at birth, kg) (Quigley et al., 1998). This calculation assumed that IgG absorption from the intestinal tract was minimal after 24 h and that PV expansion due to absorption of colostral constituents had stabilized (Sasaki et al., 1977). Plasma IgG concentration usually peaks at 24 h of age in colostrum-fed calves; the decrease in plasma IgG concentration after this time has been attributed to transfer to other pools and catabolism of IgG (Bush et al., 1971; Grongnet et al., 1986; Rajala and Castren, 1995). The IgG intake was calculated by multiplying the IgG concentration (g/L) in pooled colostrum by the volume of colostrum administered (L).

Plasma Acetaminophen Concentration–Time Relationship and Abomasal Emptying Rate

Plasma was thawed at 19 to 22°C and the acetaminophen concentration analyzed spectrophotometrically by use of a colorimetric nitration assay (Jenway, Stone, UK) as described elsewhere (Marshall et al., 2005). Actual maximal plasma concentration (**Cmax**) and actual Tmax were derived from a plot of the plasma acetaminophen concentration versus time data. The first derivative of Siegel's modified power exponential formula was used to model the acetaminophen time curve (Marshall et al., 2005; Nouri and Constable, 2006). The equation was derived from the fact that the acetaminophen concentration versus time curve represented as a cumulative dose curve is an inverse analog of the scintigraphic curve with the following equation: $C(t) = m \times k \times \beta \times e^{-k\times t} \times (1 - e^{-k\times t})^{\beta-1}$, where C(t) is the acetaminophen concentration in plasma at a specified time point, t is time, m [unit (μg/mL) × min] is the area under the acetaminophen concentration–time curve when time is infinite, k (min^{-1}) is an estimate of the rate constant for abomasal emptying, β is a constant that provides an estimate of the duration of the lag phase before an exponential rate of emptying is reached, and e is the natural logarithm. Nonlinear regression (PROC NLIN, SAS, version 9.2, SAS Institute Inc., Cary, NC) was used to estimate values for m, k, and β as described (Marshall et al., 2005). Values for model Cmax and model Tmax were obtained by fitting the estimated values for k, β, and m in the nonlinear equation to the cumulative dose curve equation for acetaminophen.

Plasma Glucose Concentration–Time Relationship

Plasma glucose concentration was determined using an automatic analyzer (Hitachi 704 automatic analyzer, Hitachi, Tokyo, Japan). Actual Cmax and actual Tmax were derived from a plot of the plasma glucose concentration versus time data, and the area under the plasma glucose concentration–time curve was calculated from 0 to 6 h by using the trapezoid method; this area provides a crude index of the amount of glucose absorbed for each treatment (Nouri and Constable, 2006; Sen et al., 2006; Constable et al., 2009).

Statistical Analysis

Data were expressed as mean ± SD, and a value of $P < 0.05$ was considered significant for all statistical analyses. The primary variables of interest were the plasma IgG concentration–time relationship, abomasal emptying rate as assessed by the mean value for Tmax calculated by modeling the acetaminophen concentration–time relationship (model Tmax), and the AEA. A repeated-measures ANOVA was used to determine the main effects of treatment using a compound symmetry covariance matrix (PROC MIXED, SAS, version 9.2). Untransformed values for most variables were used in the repeated-measures ANOVA because distributions were approximately normal and variances were homogeneous. Time to maximal glucose concentration was log transformed for analysis and expressed as geometric mean and range. Post hoc tests were conducted to com-

pare erythromycin, ivermectin, and gentamicin with the control treatment whenever the value for the *F*-test for treatment was significant. Previous studies by the investigators have indicated that a crossover study involving 6 calves per group was sufficient to provide adequate statistical power to detect a prokinetic effect at $\alpha = 0.05$ and $\beta = 0.80$ (Wittek and Constable, 2005; Nouri and Constable, 2007; Nouri et al., 2008; Afshari et al., 2009). Repeated-measures ANOVA was used to determine the main effects of treatment and time, as well as the interaction between treatment and time, for the plasma IgG, acetaminophen, and glucose–time relationships using an autoregressive(1) covariance matrix. Appropriate post hoc tests were conducted (within group to time = 0 value; between groups to control group at the same time) when indicated by the *P*-value for the *F*-test using Bonferroni-corrected *P*-values. A statistical software program (SAS, version 9.2) was used for all comparisons.

RESULTS

Plasma IgG Concentration–Time Relationship and AEA

The measured IgG concentration in pooled colostrum was 60.5 g/L. Therefore, calves were administered a standardized IgG mass of 181.5 g by oroesophageal intubation.

The *P*-values for the *F*-test for the main effect of treatment and time, and for the interaction between treatment and time, on plasma IgG concentration were <0.0001, <0.0001, and 0.0003, respectively. Plasma IgG concentration peaked at 12 to 24 h of age in all 4 groups (Figure 1); however, a marked difference in the plasma IgG concentration–time relationship was observed between groups. Compared with control calves, plasma IgG concentration was increased in calves administered erythromycin at 1 h and at all measured time points from 9 h to d 7. Plasma IgG concentration was increased in calves administered ivermectin at 12 h, compared with control calves.

The AEA was higher ($P = 0.0012$) for calves administered erythromycin and lower ($P = 0.014$) for calves administered gentamicin (Table 1) when compared with control calves. The AEA for calves administered ivermectin was similar ($P = 0.10$) to that for control calves.

Plasma Acetaminophen Concentration–Time Relationship and Abomasal Emptying Rate

The *P*-values for the *F*-test for the main effect of treatment and time, and for the interaction between treatment and time, on plasma acetaminophen concentration were <0.0001, <0.0001, and 0.024, respectively. Erythromycin increased the rate of abomasal emptying, as assessed by actual Tmax ($P = 0.0022$) and model Tmax ($P = 0.049$; Figure 2, Table 1). Ivermectin also increased the rate of abomasal emptying, as assessed by actual Tmax ($P = 0.0022$) but not by model Tmax ($P = 0.11$; Figure 2, Table 1). In contrast, gentamicin did not alter the rate of abomasal emptying, as assessed by actual Tmax ($P = 1.00$) or model Tmax ($P = 0.39$; Figure 2, Table 1),

Relationship Between AEA of IgG and Abomasal Emptying Rate

The AEA was linearly and negatively associated with abomasal emptying rate ($R^2 = 0.22$; $P = 0.020$) as assessed by model Tmax for acetaminophen absorption (Figure 3). Whereby, AEA = 0.58 − 0.00056 × (model Tmax).

Plasma Glucose Concentration–Time Relationship

The *P*-values for the *F*-test for the main effect of treatment and time, and for the interaction between treatment and time, on plasma glucose concentration

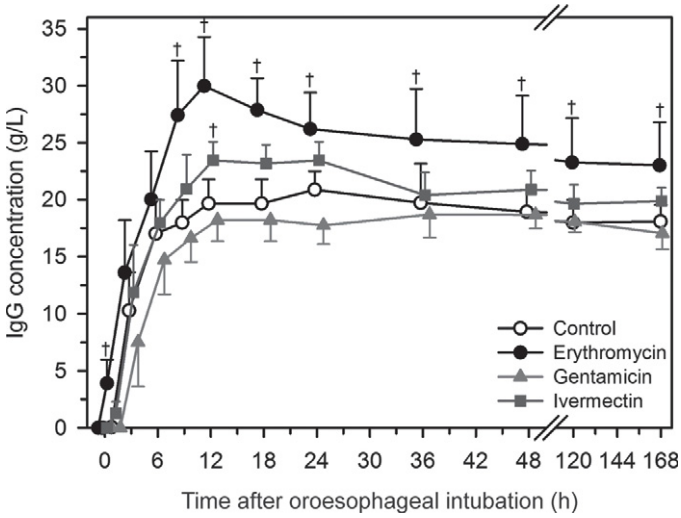

Figure 1. Mean ± SD plasma IgG concentration in 24 Holstein-Friesian calves receiving 3 L of pooled colostrum containing acetaminophen (50 mg/kg) by oroesophageal intubation. Calves were randomly assigned to receive 1 of the following 4 treatments 30 min before oroesophageal intubation of 3 L of colostrum: 2.0 mL of 0.9% NaCl solution i.m. (control treatment; n = 6, open circles), erythromycin lactobionate (8.8 mg/kg, i.m.; n = 6, filled circles), gentamicin (6.6 mg/kg, i.m.; n = 6, filled triangles), or ivermectin (200 μg/kg, i.v.; n = 6, filled squares). Data are slightly offset for each group with respect to time to improve readability. †$P < 0.017$ (Bonferroni corrected) compared with control treatment at the same time.

Table 1. Abomasal emptying rate indices (mean ± SD) of 24 Holstein-Friesian calves receiving 3 L of pooled colostrum containing acetaminophen (50 mg/kg) by oroesophageal intubation[1]

Factor[2]	Control	Erythromycin	Gentamicin	Ivermectin	*P*-value: *F*-test treatment
BW (kg)	37.8 ± 3.2	37.7 ± 2.3	36.8 ± 2.4	37.3 ± 3.2	0.93
IgG absorption					
Apparent absorption efficiency (%)	38.7 ± 4.2	48.2 ± 5.0*	31.9 ± 1.5*	43.0 ± 5.6	<0.0001
Acetaminophen absorption					
Actual Cmax (μg/mL)	20.4 ± 2.3	28.5 ± 2.2*	18.6 ± 1.8	23.6 ± 0.9*	<0.0001
Actual Tmax (min)	370 ± 53	235 ± 67*	370 ± 80	235 ± 64*	0.0009
Model Cmax (μg/mL)	19.9 ± 2.1	22.0 ± 3.5	16.9 ± 1.5*	21.4 ± 1.3	0.0046
Model Tmax (min)	340 ± 62	278 ± 39*	368 ± 57	289 ± 47	0.023
AUC_{480} (g × min/dL)	7.8 ± 0.5	9.7 ± 0.9*	6.6 ± 0.4*	8.8 ± 0.3*	<0.0001
k (min^{-1})	0.0019 ± 0.0007	0.0022 ± 0.0005	0.0019 ± 0.0006	0.0019 ± 0.0005	0.71
β	1.88 ± 0.28	1.84 ± 0.21	1.98 ± 0.25	1.70 ± 0.13	0.22
m (mg/mL) × min	21.5 ± 5.6	19.7 ± 4.6	18.7 ± 4.4	22.0 ± 4.2	0.60
Glucose absorption					
Actual Cmax (mg/dL)	124 ± 54	123 ± 55	94 ± 29	113 ± 31	0.62
Actual Tmax (min)	43 (15, 90)	59 (15, 270)	78 (15, 480)	43 (30, 45)	0.65
AUC_{480} (g × min/dL)	39.7 ± 11.8	44.3 ± 18.0	35.1 ± 10.2	39.2 ± 9.5	0.67

[1]Calves were randomly assigned to receive 1 of the following 4 treatments 30 min before oroesophageal intubation of 3 L of colostrum: 2.0 mL of 0.9% NaCl solution i.m. (control treatment; n = 6), erythromycin lactobionate (8.8 mg/kg, i.m.; n = 6), gentamicin (6.6 mg/kg, i.m.; n = 6), or ivermectin (200 μg/kg, i.v.; n = 6). Abomasal emptying rate was assessed by acetaminophen absorption and glucose absorption.

[2]Actual Cmax is the maximal plasma acetaminophen or glucose concentration, and Actual Tmax is the time at which Actual Cmax occurred. Model Cmax and Tmax for acetaminophen were obtained by fitting a nonlinear equation to the first derivative of Siegel's modified power exponential formula for acetaminophen (see Materials and Methods for details). AUC_{480} is the area under the acetaminophen concentration–time curve, or the glucose concentration–time curve, for the first 8 h after intubation. k = an estimate of the rate constant for abomasal emptying; β = constant that provides an estimate of the duration of the lag phase before an exponential rate of emptying is reached; m = area under the acetaminophen concentration–time curve when time is infinite. For glucose absorption, area under the curve is the area under the plasma glucose concentration–time relationship for the 6-h period after suckling. Actual Tmax for glucose absorption is geometric mean with range in parentheses.

*Mean values within a row are significantly different ($P < 0.05$) from the control value.

were 0.57, <0.0001, and 0.41, respectively. Plasma glucose concentration was increased at all time points from 15 to 90 min in the control, erythromycin, and gentamicin groups and at all time points from 15 to 60 min in the ivermectin group (Figure 4). No significant effect of treatment on the glucose absorption curve was observed (Figure 4, Table 1).

DISCUSSION

The major finding of the study reported here was that the AEA of colostral IgG was linearly and negatively associated with abomasal emptying rate in dairy calves, with abomasal emptying rate explaining 22% of the variation of AEA. This new finding is consistent with long-held beliefs that the rate of gastrointestinal motility, and, therefore, the rate of abomasal emptying, is an important determinant of the AEA of colostral IgG (Morin et al., 1997; Kaske et al., 2005). Stott and Fellah concluded in 1983 that age at first feeding, concentration of IgG in colostrum, and volume of colostrum fed (within limits) were the 3 major factors affecting colostral IgG absorption (Stott and Fellah, 1983). Our results indicate that the rate of abomasal emptying should be considered as an additional fourth major factor affecting colostral IgG absorption.

Calorically inert isotonic fluids, such as isotonic $NaHCO_3$, are emptied from the abomasum of the milk-fed calf rapidly and in an exponential manner (Marshall et al., 2008). Caloric fluids, such as cow milk and milk replacer, are emptied in a more linear manner (Nouri and Constable, 2006; Marshall et al., 2008); this is a physiologic response to ensure that nutrients are presented to the small intestine at a relatively constant rate. Because colostrum is calorically more dense than cow milk, colostrum is widely believed to be emptied more slowly from the abomasum than cow milk or milk replacer. This study is the first to permit a comparison of an index of abomasal emptying rate in calves fed colostrum, cow milk, or all-milk-protein milk replacer. The mean time to maximum acetaminophen concentration in calves receiving 3 L of colostrum in the study reported here was 340 min; this should be compared with mean times of 129, 187, and 191 min in dairy calves suckling 2 L of cow milk (Nouri et al., 2008; Afshari et al., 2009; Constable et al., 2009) and 190, 201, and 206 min in dairy calves suckling 2 L of milk replacer containing 20% fat and 20% protein (Sen et

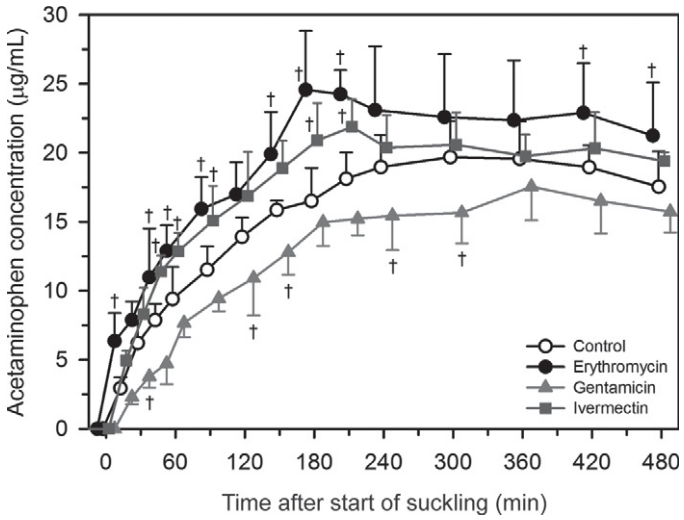

Figure 2. Mean ± SD plasma concentration of acetaminophen in 24 Holstein-Friesian calves receiving 3 L of pooled colostrum containing acetaminophen (50 mg/kg) by oroesophageal intubation. Calves were randomly assigned to receive 1 of the following 4 treatments 30 min before oroesophageal intubation of 3 L of colostrum: 2.0 mL of 0.9% NaCl solution i.m. (control treatment; n = 6, open circles), erythromycin lactobionate (8.8 mg/kg, i.m.; n = 6, filled circles), gentamicin (6.6 mg/kg, i.m.; n = 6, filled triangles), or ivermectin (200 µg/kg, i.v.; n = 6, filled squares). Data are slightly offset for each group with respect to time to improve readability. †$P < 0.017$ (Bonferroni corrected) compared with control treatment at the same time.

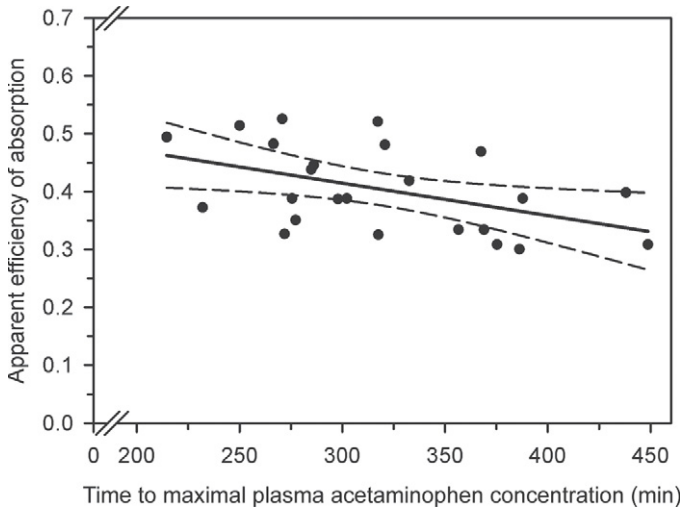

Figure 3. Scatter plot of the relationship between apparent efficiency of absorption (AEA) of colostral IgG and abomasal emptying rate, as assessed by the time to maximal plasma acetaminophen concentration (model Tmax) in 24 Holstein-Friesian calves receiving 3 L of pooled colostrum containing acetaminophen (50 mg/kg) by oroesophageal intubation. Calves were randomly assigned to receive 1 of the following 4 treatments 30 min before oroesophageal intubation of colostrum: 2.0 mL of 0.9% NaCl solution i.m. (control treatment; n = 6), erythromycin lactobionate (8.8 mg/kg, i.m.; n = 6), gentamicin (6.6 mg/kg, i.m.; n = 6), or ivermectin (200 µg/kg, i.v.; n = 6). The AEA was linearly and negatively associated with abomasal emptying rate ($R^2 = 0.22$; $P = 0.020$), whereby AEA = 0.58 − 0.00056 × (model Tmax).

al., 2006; Nouri and Constable, 2007; Marshall et al., 2008). Because the rate of abomasal emptying is faster when larger volumes are fed, the results of this study indicate that the rate of abomasal emptying is much slower in colostrum-fed calves, most likely because of the higher fat and protein percentage in colostrum. It remains to be determined whether the fat or protein content plays the primary role in determining the rate of abomasal emptying.

Inadequate absorption of colostral IgG in dairy calves increases the risk of morbidity and death (Tyler et al., 1999) and is an important source of economic loss to the dairy industry. To reduce the risk of failure of transfer of passive immunity in dairy calves, producers should harvest colostrum as soon after parturition as possible, and preferably within 2 h after calving if the cow is strong enough to permit milking (Morin et al., 2010). This is because colostral IgG concentration decreases by 3.7% during each subsequent hour after calving because of postparturient secretion of milk by the mammary glands (Morin et al., 2010). Holstein-Friesian calves should be fed at least 153 g of total IgG within the first 2 h after birth, equivalent to 3 L of first-milking colostrum (Chigerwe et al., 2008). This is because transfer of passive immunity is optimized when

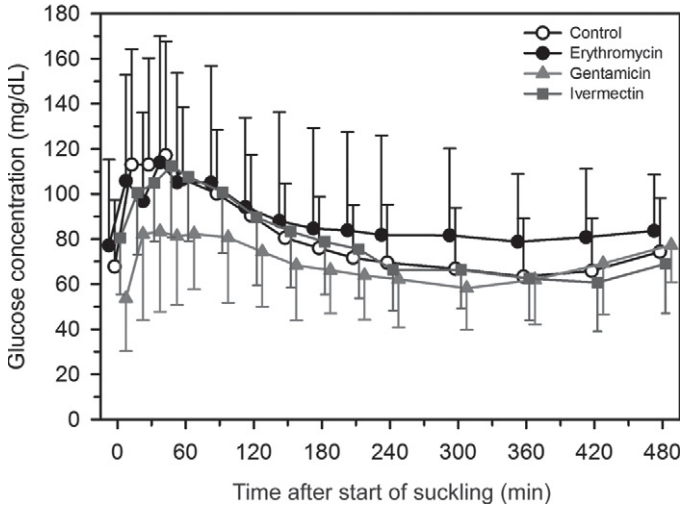

Figure 4. Mean ± SD plasma glucose concentration in 24 Holstein-Friesian calves receiving 3 L of pooled colostrum containing acetaminophen (50 mg/kg) by oroesophageal intubation. Calves were randomly assigned to receive 1 of the following 4 treatments 30 min before oroesophageal intubation of 3 L of colostrum: 2.0 mL of 0.9% NaCl solution i.m. (control treatment; n = 6, open circles), erythromycin lactobionate (8.8 mg/kg, i.m.; n = 6, filled circles), gentamicin (6.6 mg/kg, i.m.; n = 6, filled triangles), or ivermectin (200 µg/kg, i.v; n = 6, filled squares). Data are slightly offset for each group with respect to time to improve readability.

colostrum is fed to calves within the first 2 h after birth (Stott et al., 1979b; Chigerwe et al., 2008).

We administered pooled colostrum by oroesophageal intubation to all calves in this study to standardize the time of administration and the volume present in the abomasum at the start of emptying. Administration of fluids to neonatal calves by esophageal intubation does not induce esophageal groove closure and, therefore, the fluid initially is deposited in the reticulorumen (Lateur-Rowet and Breukink, 1983; Chapman et al., 1986). Movement of fluid from the reticulorumen into the abomasum immediately follows esophageal intubation (Chapman et al., 1986; Ahmed et al., 2002) in response to a pressure gradient between the reticulorumen and the abomasum because the reticulum and rumen are dorsal to the abomasum in the neonatal calf (Wittek et al., 2005). Although esophageal intubation of 2 L of an electrolyte solution has been shown to result in similar abomasal volumes in calves 7 to 17 d of age to that obtained after suckling, intubation did delay the rate of abomasal emptying (Nouri and Constable, 2006). This result was attributed to differences in the central control of the pyloric motor profile or suckling-induced changes in the concentration–time profile of insulin, gastrin, cholestokinin, and oxytocin (Nouri and Constable, 2006).

The AEA is dependent on the age of the calf at first feeding, volume and IgG concentration fed, the presence or absence of factors in colostrum including non-IgG proteins, a low molecular weight protein, and a phosphate compound (Balfour and Comline, 1962; Besser and Osborn, 1993), calf factors such as postnatal respiratory acidosis (Besser et al., 1990) and inadequate curd formation (Gregory, 2003), environmental factors, and route of administration (suckled or oroesophageal intubation; Stott and Menefee, 1978; Stott et al., 1979a,b; Bush and Staley, 1980; Stott and Fellah, 1983; Besser et al., 1985; Grongnet et al., 1986; Gvozdic et al., 2007). Intubation of newborn calves with approximately 2.6 and 1.7 L of colostrum at 2 and 14 h after birth, respectively, resulted in a numerically lower AEA at 24 h of age that was not statistically significant (Lee et al., 1983). Intubation of newborn calves with approximately 1.5 and 1.0 L of colostrum at 2 and 8 h after birth, respectively, resulted in lower serum IgG_1 concentrations at 24 h of age (Zaremba et al., 1984). In a 1985 study containing a total of 52 calves (esophageal intubation of calves with colostrum at 10% of metabolic size at approximately 1, 13, and 25 h after birth) resulted in a numerically lower serum IgG concentration from 20 to 32 h of age that was not statistically significant (Adams et al., 1985). A recent study by Kaske and his colleagues indicated that esophageal intubation of 4 L of colostrum at 1 h after birth slightly delayed the initial increase in serum IgG concentration and resulted in a numerically lower AEA at 24 h than calves permitted to suckle all or most of 2 L of colostrum at 1 h after birth (Kaske et al., 2005). Although collectively these studies demonstrate that suckling of $\leq$2.6 L of colostrum provides higher serum IgG concentrations at 24 h and higher AEA than does esophageal intubation, 2 recent studies have demonstrated that intubation of 3 L of colostrum provided similar serum IgG concentrations at 24 h and similar AEA to that produced by suckling (Godden et al., 2009b; Chigerwe and Coons, 2012).

Erythromycin increased the AEA of colostral IgG and serum IgG concentration at 24 h of age by 25% relative to control calves, which is a clinically relevant increase. Similar increases in AEA have been observed by adding the natural mineral adsorber zeolite (clinoptilolite) or selenium to colostrum. Addition of zeolite to colostrum at 5 g per feeding increased the absorption of colostral IgG in neonatal calves by 20 to 39% through an unidentified mechanism (Natalija et al., 2005; Gvozdic et al., 2007, 2008). Doses of zeolite exceeding 5 g decrease AEA and are deleterious to calf health (Sadeghi and Shawrang, 2008). Addition of selenium to colostrum at 1 to 4 mg/kg increased the absorption of colostral IgG in neonatal calves by 20 to 42%, possibly by increasing the rate of pinocytosis by small intestinal epithelial cells (Kamada et al., 2007).

The glucose concentration–time relationship has been used as an index of abomasal emptying rate in milk-fed calves (Nouri and Constable, 2006; Sen et al., 2006; Nouri et al., 2008; Afshari et al., 2009; Constable et al., 2009) but appears to lack the sensitivity of the acetaminophen concentration–time relationship. This is because glucose is a homeostatically regulated metabolite that is also osmotically active (thereby altering its extracellular concentration via osmotically driven shift of free water) and capable of being excreted in the urine when plasma concentrations exceed 140 to 160 mg/dL in the calf (Nouri and Constable, 2006; Sen et al., 2006). Similar to the findings in the study reported here, 2 previous studies conducted by our laboratory in milk-fed calves failed to identify a significant effect of erythromycin on shortening the time to maximal plasma glucose concentration (Nouri et al., 2008; Afshari et al., 2009). The plasma glucose concentration–time relationship appears to be more helpful to identify changes in the abomasal emptying rate when oral rehydration solutions are administered with or without milk (Constable et al., 2001; Nouri and Constable, 2006; Sen et al., 2006; Constable et al., 2009).

Erythromycin, gentamicin, and ivermectin were administered in an extra-label manner to calves in this study to demonstrate proof of concept. Our results confirm previous findings in neonatal calves fed cow milk or

milk replacer that erythromycin base (8.8 mg/kg, i.m.; Wittek and Constable, 2005) and erythromycin lactobionate (8.8 mg/kg, i.m.; Nouri and Constable, 2007; Nouri et al., 2008; Afshari et al., 2009) are effective prokinetic agents (Constable et al., 2012). An erythromycin formulation consisting of the base in a nonaqueous, buffered, alcohol-base sterile solution is labeled in the United States for the treatment of pneumonia and bovine respiratory disease caused by susceptible bacteria. The recommended dosage is 2.2 to 8.8 mg/kg i.m. every 24 h, and meat withdrawal time is 6 d after a 5-d treatment at 8.8 mg/kg (Wittek and Constable, 2005). We are not aware of any studies in calves that directly compared the prokinetic effects of erythromycin base in a nonaqueous, buffered, alcohol-base sterile solution to that of erythromycin lactobionate. Examination of indices of abomasal emptying rate in published studies suggests that the erythromycin lactobionate formulation may be a more effective prokinetic agent, based on reductions in abomasal emptying rate of 46 to 48% as assessed by model Tmax for acetaminophen absorption (Nouri and Constable, 2007; Nouri et al., 2008; Afshari et al., 2009) compared with a 37% reduction when erythromycin base in propylene glycol formulation is administered, as assessed by reduction in the time required for the abomasal volume to decrease by half (Wittek and Constable, 2005).

Gentamicin is an aminoglycoside antibiotic effective against most gram-negative and some gram-positive bacterial infections and has been used in the past as part of the treatment of sick neonatal calves with septicemia or calf diarrhea. Because of the potential for causing violative residues in treated animals, the American Association of Bovine Practitioners has issued a position statement regarding the extra-label use of aminoglycosides in cattle (Kahler, 2005): "The American Association of Bovine Practitioners, being cognizant of food safety issues and concerns, encourages its members to refrain from the intramammary, i.m., s.c., or i.v. extra-label use of the aminoglycoside class of antibiotics in bovines." Accordingly, the main purpose in administering gentamicin to the calves in the study reported here was to determine whether the i.m. administration of gentamicin altered the rate of gastric emptying. It is clearly inappropriate to administer an antimicrobial for a non-antimicrobial effect (such as altering abomasal emptying rate) in a food-producing animal as such use may unnecessarily promote the development of antimicrobial resistance (Nouri and Constable, 2007; Nouri et al., 2008; Wittek et al., 2008a,b; Afshari et al., 2009).

The dosage rate of ivermectin administered in the study reported here reflected current label recommendations except that ivermectin was administered i.v. instead of SC to maximize plasma ivermectin concentrations, which were likely to be >1,000 ng/mL during the period when abomasal emptying was assessed (Wilkinson et al., 1985). Assuming a dose-dependent response to i.v. administration of ivermectin, it is likely that the weak prokinetic effect of ivermectin detected after i.v. administration does not result after SC injection. Results of the study reported here should not be construed as promoting the extra-label use of ivermectin as a prokinetic agent. The prokinetic effect after i.v. administration of ivermectin is weak (Afshari et al., 2009) and likely to be even weaker when ivermectin is administered via the labeled routes of administration (SC, oral, or topical). Moreover, extra-label use of ivermectin as a prokinetic agent is not appropriate because it may contribute to the development of ivermectin resistance by some intestinal nematodes.

CONCLUSIONS

The findings of the study reported here demonstrate, for the first time, that the AEA of colostral IgG administered by oroesophageal intubation is influenced by the abomasal emptying rate. This finding has 2 major implications: (1) identification of an effective, practical, and low-cost non-antimicrobial agent, such as bethanechol or cisapride (Constable et al., 2012), that increases abomasal emptying rate in neonatal calves has the potential to improve calf health by increasing the AEA of colostral IgG; and (2) the relatively low and variable AEA of IgG in colostral replacers may be due, in part, to a solution osmolality in excess of 300 mOsm/kg that results in a decreased abomasal emptying rate (Sen et al., 2006). Additional studies demonstrating that the AEA of colostral IgG is influenced by abomasal emptying rate in calves suckling 3 L of colostrum appear indicated.

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