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Effect of Erythromycin and Gentamicin on Abomasal Emptying Rate in Suckling Calves

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Background: Commonly used dosage protocols for antimicrobial agents may alter the rate of gastric emptying.

Hypothesis: Parenteral administration of erythromycin increases and gentamicin decreases the rate of abomasal emptying.

Animals: Five male Holstein-Friesian calves (8–15 days of age).

Methods: Calves received each of the following 4 IM treatments in random order: control, 2 mL of 0.9% NaCl; erythromycin, 8.8 mg/kg; low-dose gentamicin, 4.4 mg/kg; high-dose gentamicin, 6.6 mg/kg. Abomasal emptying rate was assessed by acetaminophen and glucose absorption. Calves were fed 2 L of cow's milk containing acetaminophen (50 mg/kg body weight) 30 minutes after each treatment was administered, and jugular venous blood samples were obtained periodically after suckling. The maximum observed plasma acetaminophen concentration (actual C_{max}) and time of actual C_{max} (actual T_{max}) were determined, and pharmacokinetic modeling was used to calculate model C_{max} and model T_{max}.

Results: Erythromycin increased abomasal emptying rate, as indicated by a shorter time to actual T_{max} and model T_{max} ($P < .05$). Abomasal emptying rate after injection of low-dose gentamicin was similar to that of control. Administration of high-dose gentamicin resulted in a longer time to actual T_{max} ($P = .021$) but did not change model T_{max} ($P = .62$).

Conclusions and Clinical Relevance: IM injection of erythromycin increased abomasal emptying rate in dairy calves, whereas low-dose and high-dose gentamicin did not alter the rate of abomasal emptying as measured by acetaminophen kinetics and glucose absorption. The clinical relevance of these findings remains to be determined.

Key words: Aminoglycoside; Glucose absorption curve; Macrolide; Prokinetic.

Impaired abomasal motility is suspected to play a major role in the development of abomasal disorders in cattle, such as left displaced abomasum in lactating dairy cows and abomasal tympany in calves.[1] A number of factors such as hypocalcemia,[2] endotoxemia,[3] alkalemia,[4] hyperglycemia,[5] and increased abomasal luminal osmolality and energy content[6] have been shown to decrease abomasal emptying rate in cattle, and it would be clinically helpful to identify therapeutic agents that decrease abomasal emptying rate as an unwanted adverse effect. It would also be clinically helpful to identify effective prokinetic agents that stimulate, coordinate, and restore abomasal, pyloric, and small intestinal motility in cattle suspected to have abomasal hypomotility. Currently neostigmine, bethanechol, metoclopramide, and erythromycin are being used as part of the treatment of cattle suspected to have gastrointestinal hypomotility.[7–10, a]

Erythromycin and related macrolides have become the treatment of choice for gastric paresis in humans.[11–13] Erythromycin currently is the most effective gastric prokinetic agent available, in that IV or PO administration increases the rate of gastric emptying in humans by 30 to 60%, which is substantially greater than the effect of other gastric prokinetic agents such as metoclopramide and domperidone.[11,13] Erythromycin has a similar prokinetic effect in domestic animals such as dogs and horses.[14–16] Administration of erythromycin at the labeled antimicrobial dosage (8.8–10 mg/kg, IM) exerted a substantial prokinetic effect in milk-fed calves[17] and adult cattle.[a] Specifically, erythromycin increased the abomasal emptying rate by 37% in calves as assessed by change in abomasal volume that was determined ultrasonographically,[17] and by 44% in adult cattle immediately after surgical correction of left displaced abomasum.[a] The magnitude of the increase in abomasal emptying rate in calves and adult cattle was similar to the effect of erythromycin in humans.[11,13]

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.[18] Gentamicin therefore may be administered to critically ill calves that are suspected to have abomasal hypomotility. However, in vitro gentamicin concentrations of 20 to 400 μg/mL (42–837 μM) decrease the peristaltic response of guinea pig ileum,[19] and gentamicin concentrations of 150 to 300 μM decrease the in vitro contractility of uterine smooth muscle from pregnant and nonpregnant cows.[20,21] Because the smooth muscle in the calf's abomasum may be more sensitive to the effects of gentamicin than uterine smooth muscle, we were concerned that parenterally administered gentamicin might decrease the abomasal emptying rate in the calf. Accordingly, the aims of the study reported here were to determine and compare the effect of administering the recommended parenteral dose of erythromycin (positive control) and 2 different doses of gentamicin (test substance) in healthy suckling dairy calves. We expected the results of the study to confirm previous findings[17] that erythromycin is an effective prokinetic agent in calves, and to determine the effect, if any, that parenteral administration of gentamicin has on abomasal emptying rate.

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Material and Methods

Five male Holstein-Friesian colostrum-fed calves (body weight range, 31–48 kg) were obtained from local farms. Calves at the time of experiments were between 8 and 15 days of age. Calves were kept unrestrained in individual stalls and fed fresh cow's milk twice a day (60 mL/kg body weight) by a bottle with a teat.

Abomasal emptying was measured by acetaminophen absorption and glucose absorption. Acetaminophen is a widely used oral analgesic and antipyretic drug in humans, and its absorption provides an accurate method of determining the emptying rate of liquid phase meals in calves.[22,23] When administered PO, acetaminophen is absorbed in the small intestine[24] with the rate limiting step for absorption being the rate of gastric emptying in animals with normal small intestinal function.[25] Because the apparent rate of absorption is much faster than the rate of elimination in suckling calves,[22] the time to maximal acetaminophen concentration after oral ingestion is primarily dependent on the rate of abomasal emptying. Glucose absorption provides a crude measure of abomasal emptying rate in neonatal calves.[6]

An IV catheter was placed in the jugular vein and secured to the neck. Each calf was given the following 4 IM treatments in randomized order: control, 2 mL of 0.9% NaCl; erythromycin lactobionate[b] (8.8 mg/kg body weight); low-dose gentamicin sulfate[c] (4.4 mg/kg); and high-dose gentamicin sulfate[c] (6.6 mg/kg). Calves were fed by suckling 2 L of whole cow's milk containing acetaminophen (50 mg/kg body weight) 30 minutes after the treatment was administered. This time difference was selected because prokinetic agents usually are administered to humans 15 to 30 minutes before meals[26] and because maximal plasma concentrations of gentamicin occur at 45 minutes after IM administration in cattle.[27] The dosage protocol for erythromycin was based on the results of a previous study in suckling calves.[17] The dosage protocol for gentamicin was based on pharmacokinetic studies in calves and adult cattle.[18,27,28] At least 36 hours elapsed between each study in order to ensure an adequate wash-out period; during this time calves were fed fresh cow's milk.

Venous blood samples for determination of plasma acetaminophen and glucose concentrations were obtained at −30, 0, 15, 30, 45, 60, 90, 120, 150, 180, 210, 240, 300, 360, 420, and 480 minutes after the start of suckling cow's milk. The sampling times were selected in an attempt to have at least 6 data points before and after the time of maximal acetaminophen concentration in order to facilitate nonlinear regression analysis. Samples were collected into 6 mL tubes containing heparin centrifuged at 3000 $\times g$ for 15 minutes and 3 mL of plasma harvested and stored at −20 °C for <4 weeks before analysis.

Plasma was thawed at room temperature and acetaminophen concentrations were determined spectrophotometrically by a colorimetric titration assay as described previously.[22] The maximum observed plasma concentration (actual C_{max}) and time of maximum observed plasma concentration (actual T_{max}) were obtained from a plot of plasma acetaminophen concentration–time data. The first derivative of Siegel's modified power exponential formula was used to model the plasma acetaminophen concentration-time relationship, as described previously.[22] The equation was derived from the fact that the acetaminophen concentration-time relationship represented as a cumulative dose curve is an inverse analog of the scintigraphic curve: $C(t) = mk\beta e^{-kt}(1 - e^{-kt})^{\beta-1}$, where $C(t)$ is the acetaminophen concentration in plasma (μg/mL) at time t in minutes, and m, k, and β are constants; m is the total cumulative recovery of acetaminophen when t is infinite, k is an estimate of the rate constant for abomasal emptying, and β provides an estimate of the duration of the lag phase before an exponential rate of emptying is reached. Nonlinear regression[d] was used to estimate values for m, k, and β, as previously described.[22] The time to calculated C_{max} (model T_{max}) was obtained as follows: model $T_{max} = \ln(\beta)/k$, and the calculated value for model C_{max} determined by applying the values for m, k, β, and t = model T_{max} to the cumulative dosage curve.

Plasma glucose concentration was determined by use of an automatic analyzer.[e] The maximum observed plasma concentration (actual C_{max}) and time of maximum observed plasma concentration (actual T_{max}) were obtained from a plot of the plasma glucose concentration versus time data. Although a delay in actual T_{max} suggests a slower rate of abomasal emptying,[6] actual T_{max} is an insensitive and nonspecific index of abomasal emptying rate. This is because the plasma-glucose time relationship is dependent on the glucose or lactose concentration in the ingested meal, the rate of abomasal emptying, the small intestinal transit time and surface area available for absorption, the rate of glucose entry into cells (which is dependent on the rate and magnitude of insulin release after glucose absorption), and the magnitude of glucose loss in the urine if plasma glucose concentration exceeds the renal threshold of 140–160 mg/dL.[6]

Statistical Analysis

Data were expressed in tabular form as least squares mean and 95% confidence interval for the least squares mean, and graphically as least squares mean and SE. A value of $P < .05$ was considered significant. The primary variables of interest were actual T_{max} and model T_{max} for the acetaminophen absorption curve. Repeated-measures analysis of variance (ANOVA)[f] was used to determine the effect of treatment on actual T_{max} and C_{max} for acetaminophen and glucose absorption, and model T_{max} and C_{max} for acetaminophen absorption. Repeated-measures ANOVA[f] (with repeated measures on treatment and time) was used to determine the main effects of treatment and time and the interaction between treatment and time on plasma glucose concentration. Posthoc contrasts were confined to the following: erythromycin to control, high-dose gentamicin to control, and low-dose gentamicin to control.

Results

All calves remained healthy during the study period. The time taken to suckle 2 L of cow's milk ranged from 1.6 to 3.0 minutes.

Acetaminophen absorption indicated that erythromycin increased the abomasal emptying rate when compared with control (Table 1, Fig 1), as indicated by a shorter time to actual T_{max} ($P < .001$) and model T_{max} ($P < .001$).

The abomasal emptying rate after injection of low-dose gentamicin (4.4 mg/kg) was similar to that of control (actual T_{max}, $P = .21$; model T_{max}, $P = .82$) (Table 1, Fig 1). Administration of high-dose gentamicin decreased abomasal emptying rate when compared with control, as indicated by a longer time to actual T_{max} ($P = .021$) when compared with control. However, high-dose gentamicin did not change the time to model T_{max} ($P = .62$) when compared with control.

The glucose absorption curve was similar for all 4 treatments (Fig 2), with the main effect of treatment ($P = .57$) and treatment-time interaction ($P = .78$) not being significant. The lack of a substantial interaction effect indicated that treatment did not alter the change in glucose concentration over time. There was a substantial main effect of time on the plasma glucose concentration ($P < .001$). Actual T_{max} and C_{max} were similar for all treatments (Table 1).

Table 1. Abomasal emptying rate indices of 5 calves suckling 2 L of cow's milk and administered 4 treatments.

Factor	Control	Erythromycin (8.8 mg/kg)	Low-dose Gentamicin (4.4 mg/kg)	High-dose Gentamicin (6.6 mg/kg)
Acetaminophen absorption				
Actual C_{max} (µg/mL)	30.1 (24.8, 35.4)	33.8 (28.3, 39.1)	27.9 (22.6, 33.2)	33.3 (28.0, 38.6)
Actual T_{max} (minute)	120 (95, 145)	60* (35, 85)	138 (113, 163)	156* (131, 181)
Model C_{max} (µg/mL)	25.9 (20.6, 31.2)	28.9 (23.6, 34.2)	23.7 (18.4, 29.0)	28.4 (23.1, 33.7)
Model T_{max} (minutes)	129 (104, 154)	67* (42, 92)	132 (107, 157)	136 (111, 161)
Glucose absorption				
Actual C_{max} (mg/mL)	136 (120, 152)	125 (109, 141)	123 (107, 139)	121 (105, 137)
Actual T_{max} (minutes)	111 (70, 152)	48 (7, 89)	96 (55, 137)	120 (79, 161)

Abomasal emptying rate was assessed by acetaminophen absorption and glucose absorption. C_{max} is the maximal plasma acetaminophen or glucose concentration and T_{max} is the time at which C_{max} occurred. Model C_{max} and T_{max} were obtained by fitting a nonlinear equation to the cumulative dose curve for acetaminophen (see "Materials and Methods" for details). Data are least squares means and 95% confidence interval for the least squares mean (in parentheses).

*$P < .05$ compared with control.

Discussion

The first major finding of the study reported here in healthy calves was that IM injection of erythromycin increased the rate of abomasal emptying as assessed by acetaminophen absorption. The second major finding was that IM injection of low-dose (4.4 mg/kg) or high-dose (6.6 mg/kg) gentamicin did not alter the rate of abomasal emptying as measured by acetaminophen kinetics (model T_{max}) and glucose absorption.

Gastric emptying rate has been measured by direct and indirect methods. A commonly used method in rodents is removal of the stomach after a fixed time and measurement of the remaining content of the nutrient under investigation,[29] or to use nonabsorbable or poorly absorbable markers such as phenol red[30] or polyethylene glycol.[31] The main problem with these direct methods is the requirement for a large number of animals, because they measure percent emptying at only 1 point in time. In contrast, the acetaminophen absorption method allows the effect of treatment on emptying rate to be compared on different days using each animal as its own control, thereby decreasing the number of animals required for study. Acetaminophen is a widely available and inexpensive drug that is poorly absorbed from the stomach but rapidly absorbed from the small intestine[25,32] and has been widely used as a marker for gastric emptying in horses[33] and humans.[34] The acetaminophen method has been validated against the gold standard method (scintigraphy) in humans,[25,32] horses,[33] and suckling calves.[22]

Antimicrobial agents may have adverse or beneficial properties separate from their antibiotic activity.[35,36] Diarrhea is an adverse effect of penicillin administration in humans and horses.[37–39] Erythromycin and other macrolides have prokinetic effects in humans and animals.[15,17,40] Erythromycin exerts its effect on accelerating gastric emptying by acting as a motilin agonist via binding to motilin receptors on smooth muscle and nerve cells in the pyloric antrum and on smooth muscle cells in the proximal small intestine,[41–43] or by the release of endogenous motilin through cholinergic or serotonergic pathways.[44] Motilin is a 22 amino acid peptide that is periodically released from endocrine cells in the duodeno-jejunal mucosa, thereby initiating the migrating

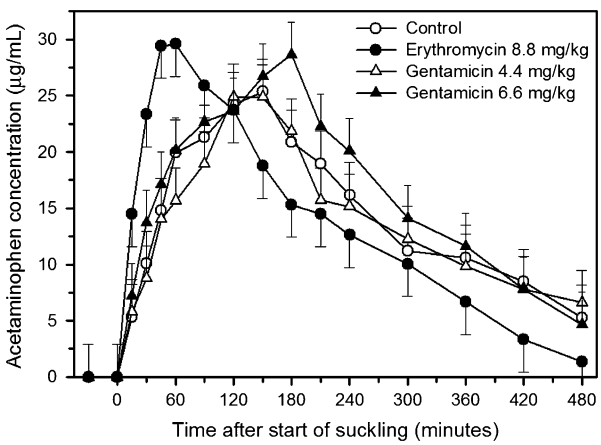

Fig 1. Change in plasma acetaminophen concentration (least squares mean ± SE) in 5 calves, each of which received 1 of 4 treatments in a crossover study 30 minutes before suckling 2 L of milk containing acetaminophen (50 mg/kg body weight).

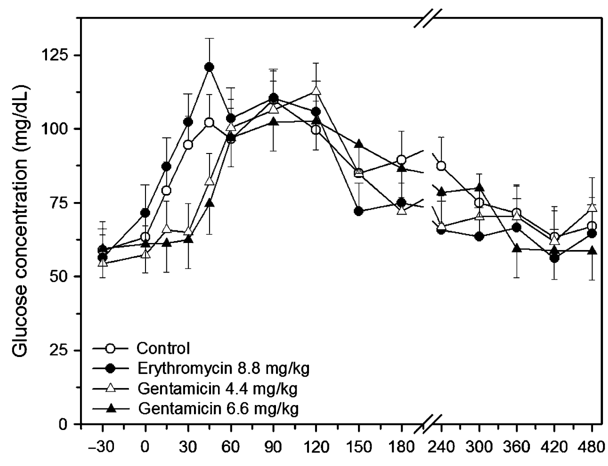

Fig 2. Change in plasma glucose concentration (least squares mean ± SE) in 5 calves, each of which received 1 of 4 treatments in a crossover study 30 minutes before suckling 2 L of milk.

motor complex (MMC) of the mammalian gut during the interdigestive period; the MMC is the so-called ''housekeeper'' of the small intestine. There is considerable interest in the group of nonpeptide motilin agonists, called the motilides (motilin-like macrolides), that interact with the motilin receptor and promote gastric emptying.[41] Abomasal hypomotility and decreased rate of abomasal emptying are complications of some abomasal disorders.[45,46] Acceleration of abomasal emptying may be of therapeutic value in the treatment of animals with delayed abomasal emptying.

Our results clearly demonstrate that the antimicrobial dose of erythromycin is an effective prokinetic agent in healthy suckling calves; this finding was consistent with erythromycin's effect in humans, dogs and horses.[11–15] The findings in this study using acetaminophen absorption to assess emptying rate were similar to those in a previous study in calves that used changes in the ultrasonographic dimensions of the abomasum to assess the effect of erythromycin (8.8 mg/kg, IM) on the rate of abomasal emptying.[17] The results of the ultrasonographic study indicated that a prokinetic effect was not evident when a 10-fold lower dose of erythromycin (0.88 mg/kg, IM) was administered.[17] Erythromycin 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 IM q24h, and meat withdrawal time is 6 days after a 5-day treatment at 8.8 mg/kg.[17] Parenteral administration of erythromycin to calves and adult cattle specifically as a prokinetic agent therefore constitutes extra label drug use. Because the calves in our study were clinically healthy and did not have any apparent signs of abnormal abomasal motility, we cannot directly comment on the prokinetic effect of parenterally administered erythromycin in sick calves. However, erythromycin is highly effective in facilitating gastric motility and increasing gastric emptying rate in humans and dogs with gastric paresis,[47,48] and the treatment of gastric hypomotility is considered the most promising area of application.[49] The results of a recent study indicated that the prokinetic effect of erythromycin is clinically relevant in adult cattle with abomasal hypomotility, in that erythromycin (10 mg/kg IM) increased the rate of abomasal emptying and milk production in the immediate postoperative period of cattle undergoing surgical correction of left displaced abomasum.[a] Whether a similarly beneficial clinical effect is produced by erythromycin in calves suspected to have abomasal hypomotility (such as calves with abomasal tympany) remains to be determined.

Gentamicin was administered in an unapproved and extra label manner to the calves in the study reported here. Because of the potential for causing violative residues in treated animals, the American Association of Bovine Practitioners issued a revised position statement in 2005 regarding the extralabel use of aminoglycosides in cattle:[g] ''The American Association of Bovine Practitioners, being cognizant of food safety issues and concerns, encourages its members to refrain from the intramammary, IM, SC or IV extra label use of the aminoglycoside class of antibiotics in bovines.'' This recommendation is consistent with a 1998 position statement from the American Veterinary Medicine Association and a 2005 consensus statement issued by the American College of Veterinary Internal Medicine.[50] Accordingly, the main purpose in administering gentamicin to the calves in the study reported here was to determine whether the IM administration of gentamicin altered the rate of gastric emptying. Demonstration of such an effect would have clinical implications for the use of gentamicin in sick horses and companion animals.

The recommended IM dosage for gentamicin in adult cattle is 3.5 to 5 mg/kg of body weight[27,28] but because calves have a larger extracellular fluid space than do adult cattle, the recommended dosage should be increased in calves in order to achieve appropriate tissue concentrations.[18] We therefore elected to administer 2 dosages (4.4 and 6.6 mg/kg) of gentamicin. In contrast to the reported contractile effect of erythromycin in uterine smooth muscle,[51,52] gentamicin inhibits spontaneous, KCl-, and agonist-induced contraction of myometrium isolated from nonpregnant cows in a dose-dependent manner.[20,21] However, the inhibitory in vitro effect of gentamicin on the frequency and amplitude of uterine smooth muscle contraction has been documented to occur at gentamicin concentrations of 150 and 300 μM, respectively.[21] The relevance of the observed in vitro effects on cow uterine small muscle to abomasal motility in a calf administered gentamicin at 6.6 mg/kg IM may be questionable, because the highest plasma concentration achieved in cows administered 5.0 mg/kg IM was predicted to be 17.2 μg/mL,[27] equivalent to 36 μM, which is much lower than the concentration required (150 μM) to decrease the frequency of bovine uterine smooth muscle contraction.[21] However, because in vitro gentamicin concentrations of 20 μg/mL (42 μM) decreased the peristaltic response of guinea pig ileum,[19] it remains possible that high-dose administration of gentamicin (particularly when administered IV) might adversely affect gastrointestinal motility. High luminal gentamicin concentrations obtained after PO administration of gentamicin also could decrease gastrointestinal motility; for example, administering gentamicin sulfate PO at a dose of 250 mg (equivalent to 5 mg/kg) in 2 L of milk to a 50-kg calf produces an abomasal luminal concentration of 125 μg/mL (260 μM).

In conclusion, the results of this study indicate that IM injection of erythromycin increased abomasal emptying rate in dairy calves, whereas IM injection of low-dose or high-dose gentamicin did not alter the rate of abomasal emptying as measured by acetaminophen kinetics and glucose absorption. It remains to be determined whether erythromycin-induced alterations in abomasal emptying rate occur in sick cattle and whether this adverse effect of erythromycin treatment is clinically important.

Footnotes

[a] Wittek T, Tischer K, Gieseler T, et al. Effect of erythromycin and flunixin-meglumin on abomasal emptying rate of dairy cows

immediately after surgical correction of left displaced abomasum. Proceedings of the XXIVth World Buiatrics Congress 2006, #385
[b] Erythromycin, Cytochemia, Tehran, Iran
[c] Gentamicin 80, Alborz Daru, Tehran, Iran
[d] PROC NLIN, SAS Inc, Cary, NC
[e] Hitachi 704 automatic analyzer, Hitachi, Tokyo, Japan
[f] PROC MIXED, SAS Inc Cary, NC
[g] http://www.avma.org/onlnews/javma/dec05/051201j.asp; accessed May 2007

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