Assessment of the effects of erythromycin, neostigmine, and metoclopramide on abomasal motility and emptying rate in calves

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Objective—To determine and compare the effects of erythromycin, neostigmine, and metoclopramide on abomasal motility and emptying rate in suckling calves.

Animals—6 male Holstein calves (15 to 40 days of age).

Procedure—Calves were monitored for 1 hour before being fed milk replacer (60 mL/kg; time, 0 minutes) and then were monitored for another 3 hours. Calves received 6 treatments in randomized order: erythromycin (8.8 mg/kg, IM) at –30 minutes; low-dose erythromycin (0.88 mg/kg, IM) at –30 minutes; erythromycin (8.8 mg/kg, IM) at –30 minutes and neostigmine (0.02 mg/kg, SC) at –30 and 90 minutes; neostigmine (0.02 mg/kg, SC) at –30 and 90 minutes; metoclopramide (0.1 mg/kg, IM) at –30 and 90 minutes; and placebo (2 mL of saline [0.9% NaCl] solution, SC) at –30 minutes. Abomasal volume was calculated from ultrasonographic measurements of abomasal width, length, and height. Abomasal motility and emptying rate were assessed by measuring luminal pressure and change in abomasal volume over time.

Results—Administration of erythromycin (8.8 mg/kg) increased the frequency of abomasal luminal pressure waves and the mean abomasal luminal pressure and decreased the half-time of abomasal emptying by 37%. Administration of metoclopramide, neostigmine, and low-dose erythromycin (0.88 mg/kg) did not alter abomasal motility, mean luminal pressure, or emptying rate.

Conclusions and Clinical Relevance—Results indicated that administration of erythromycin at the labeled antimicrobial dose (8.8 mg/kg, IM) exerted an immediate, marked prokinetic effect in healthy suckling calves, whereas administration of metoclopramide or neostigmine did not alter abomasal motility or emptying rate. (*Am J Vet Res* 2005;66:545–552)

Abomasal hypomotility and a decreased rate of abomasal emptying are believed to play important roles in the etiopathogenesis of abomasal disorders in adult cattle and calves.[1] Medical treatment of cattle suspected to have abomasal hypomotility is widely practiced, but few data are available on treatment efficacy.[2] Because abomasal hypomotility has been associated with hypocalcaemia,[3,4] endotoxemia,[5] alkalemia,[6] hyperinsulinemia,[7] and hyperglycemia,[8,9] the current focus of treatment of adult cattle and calves suspected to have abomasal hypomotility is correction of acid-base, electrolyte, and metabolic abnormalities; amelioration of the effects of endotoxemia; and elimination of gram-negative bacterial infections. Some clinicians also administer neostigmine, metoclopramide, or erythromycin to ruminants suspected to have abomasal hypomotility, on the basis of evidence to suggest that these medications have a prokinetic effect in neonatal[10] and adult humans[11] and domestic monogastric animals.[12-15] Prokinetic agents have the ability to stimulate, coordinate, and restore gastric, pyloric, and small intestinal motility.[2] Whether neostigmine, metoclopramide, or erythromycin exert a clinically useful prokinetic effect on the abomasum in adult and neonatal bovids is unknown.

The parasympathomimetic agents neostigmine and bethanechol have been administered to cattle to increase gastrointestinal tract motility. There are uncontrolled clinical reports on the use of neostigmine to treat cecal dilatation in cows[16] and omasal impaction in cattle and water buffaloes[17]; also, administration of neostigmine (0.012 mg/kg, IV) appears to increase abomasal emptying rate in calves.[15] However, in milk-fed calves, neostigmine (0.04 mg/kg, IM) did not shorten the transit time to the ileum,[18] suggesting that the agent does not increase abomasal emptying rate in suckling calves. In a study[19] of yearling cattle, administration of bethanechol (0.07 mg/kg, SC) resulted in an increase in the antral spike rate and total number of antegrade propagating spikes, indicating a possible prokinetic effect; however, because of a lack in coordination, bethanechol did not alter the abomasal emptying rate.

Metoclopramide has been used to treat vagal indigestion of cattle[20] and abomasal emptying defect of sheep,[21] but treatment efficacy of this agent is unknown. The administration of metoclopramide (0.1, 0.2, 0.3, 0.5, 0.8, or 1 mg/kg, IM or IV) to 3- to 6-month-old calves did not alter ruminal motility, fecal characteristics, or the frequency of defecation.[22] Similar results were obtained in a study[23] of the administration of metoclopramide (0.1, 0.3, or 0.5 mg/kg, SC) to 8-week-old calves; the drug did not alter the frequency of forestomach contractions but did decrease the amplitude of intraruminal pressure contractions, which is not consistent with a prokinetic effect. In a study[24] in adult goats, metoclopramide (0.5 mg/kg, IM or IV) did not alter the electromyographic activity of the abo-

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masal body but transiently increased the electrical activity of the pyloric antrum. Administration of metoclopramide (0.1 mg/kg, SC) altered abomasal and duodenal electromyographic activity in yearling cattle,[19] but in another study,[a] lower metoclopramide doses (0.023 and 0.045 mg/kg, administration route not reported) did not alter myoelectrical activity or tension of the pyloric antrum in sheep. Metoclopramide is an antagonist at dopaminergic (D_2) receptors and a serotonin (5-hydroxytryptamine; 5-HT) agonist at 5-HT_4 receptors and antagonist at 5-HT_3 receptors; in humans, it is also a neuroleptic agent that induces extrapyramidal activity (including torticollis, opisthotonus, trismus, and facial spasms), which is more likely to occur in children.[25] Excitement followed by depression and somnolence has been observed in cattle and goats after administration of metoclopramide at doses ≥ 0.3 mg/kg.[22-24,26] Taken together, these results suggest that metoclopramide (0.1 mg/kg, IM) may exert a weak prokinetic effect in ruminants, but higher doses are associated with the occurrence of adverse behavioral effects.

Numerous studies[12,27-31] in monogastric animals have revealed that erythromycin increases the amplitude and frequency of gastric contractions as well as gastric luminal pressure and promotes small intestinal motility by contracting the pyloric antrum and inducing phase III activity, the so-called housekeeper of the gastrointestinal tract. Erythromycin acts as an agonist of the receptors for motilin, which is a 22–amino-acid peptide present in the endocrine cells of the duodenal mucosa. Motilin is periodically released during periods of food withholding, and this release is associated with development of antral contractions and phase III activity.[28,32] In a preliminary study[33] in lactating dairy cows, administration of erythromycin lactobionate at 2 doses (0.1 mg/kg, IV, or 1 mg/kg, IV or IM) or erythromycin base (10 mg/kg, IM) in polyethylene glycol resulted in a large and sustained increase in the myoelectrical activity in the abomasal body, pyloric antrum, and duodenum and an increase in the luminal pressure in the abomasal body, compared with untreated cattle. These effects were accompanied by an increased rate of abomasal emptying, as assessed by change in duodenal pH.[33] Therefore, we hypothesized that erythromycin would increase abomasal motility and emptying rate in suckling calves and that neostigmine or metoclopramide would have little to no prokinetic effect. The purpose of the study reported here was to determine and compare the effects of erythromycin, neostigmine, and metoclopramide on abomasal motility and emptying rate in suckling calves fed a standard meal.

Materials and Methods

Animals—This study was approved by the University of Illinois Institutional Animal Care and Use Committee. Six healthy male Holstein-Friesian calves were obtained from the university dairy farm within the first week after their birth. Each calf had a cannula[b] surgically placed in the abomasal body, as previously described.[34] After the calves recovered from surgery and anesthesia, they were kept unrestrained in individual stalls that were bedded with sawdust; calves were fed (60 mL/kg) twice a day with a commercially available medicated all milk-protein milk replacer[c] (minimum crude protein, 20%; minimum crude fat, 20%; maximum crude fiber, 0.15%; minimum calcium, 0.5%; maximum calcium, 1.0%; minimum phosphorus, 0.6%; and decoquinate 45.4 g/ton [providing 0.5 mg/kg of body weight]) and had access to fresh water at all times. The calves had been used previously in a scintigraphic study[35] to validate ultrasonography as a measure of abomasal location and emptying rate.

Experimental protocol—Calves were studied when they were 15 to 40 days of age. At least 10 hours after the previous meal and at least 48 hours after any previous measurement session in this study, each calf was weighed and placed in a movable calf stall that allowed sitting and standing but prevented excessive lateral and forward movement.

Abomasal luminal pressure was measured via advancement of a 5-F high-fidelity catheter-tip pressure transducer[d] through the abomasal cannula so that the tip was in the abomasal lumen. The catheter tip continuously measured lateral pressure and was connected to a 6-channel recorder.[e] Abomasal luminal pH was measured via advancement of a flexible glass pH electrode[f] through the abomasal cannula so that the tip was in the abomasal lumen. This pH electrode was connected to a pH meter.[g] Correct catheter positioning was determined by examination of the pressure and pH traces and values.

After instrumentation, calves were studied for 4 hours (time, –60 to 180 minutes) and all calves were fed milk replacer (60 mL/kg of body weight) at time 0 minutes. Each calf received all of the following 6 treatments in randomized order with an intertreatment interval of at least 48 hours: the labeled antimicrobial dose of erythromycin[h] (8.8 mg/kg, IM) at –30 minutes; 0.1× the labeled antimicrobial dose of erythromycin (0.88 mg/kg, IM) at –30 minutes; the labeled antimicrobial dose of erythromycin (8.8 mg/kg, IM) at time –30 minutes as well as the recommended dose of neostigmine[i] (0.02 mg/kg, SC) at –30 and 90 minutes; the recommended dose of neostigmine (0.02 mg/kg, SC) at –30 and 90 minutes; metoclopramide[j] (0.1 mg/kg, IM) at –30 and 90 minutes; and placebo (control treatment; 2 mL of saline [0.9% NaCl] solution,[k] SC) at –30 minutes.

Treatments were administered 30 minutes before feeding because prokinetic agents are usually administered to humans 15 to 30 minutes before meals.[36] The dosage protocol for erythromycin was based on the manufacturer's recommended antimicrobial dose (4 mg/lb, which is equivalent to 8.8 mg/kg) and the results of a pharmacokinetic study[37] that indicated erythromycin base (15 mg/kg) was rapidly absorbed after IM injection, with maximal serum concentrations being achieved within 3 hours. The dose was similar to that administered to 2 adult cattle (10 mg/kg, IM) in another study.[33] We also administered 0.88 mg of erythromycin/kg, IM (ie, 0.1× the antimicrobial dose), because erythromycin has prokinetic effects at dosages below the effective antimicrobial dose.[13] The dose of neostigmine (0.02 mg/kg) was selected to assist comparison with the study performed in cows by Steiner et al[38] but was slightly below the dose range (0.025 to 0.050 mg/kg for all mammalian species) recommended by the European Agency for Evaluation of Medical Products (Veterinary Medicines Evaluation Unit).[39] The dose of metoclopramide (0.1 mg/kg) was the highest dose that has not been associated with adverse neurologic effects. Metoclopramide was injected twice because of the short elimination half-life in cattle (53 minutes).[26]

During each 4-hour study period, abomasal luminal pH and pressure were recorded continuously and whether the calves were standing or recumbent was noted. For ultrasonographic evaluation of the abomasum, the hair on the ventral aspect of the abdomen of each calf was clipped. Each calf was gently restrained in a standing position, and a 3.5-MHz ultrasound sector probe[l] was applied to the ventral aspect of the

abdomen in transverse and sagittal planes (as described[35]) to determine the maximal ultrasonographically visible abomasal dimensions (length, width, and height); ultrasonographic measurements were obtained at the beginning of the experiment (60 minutes before the start of suckling); immediately after the end of suckling; and at 10, 20, 30, 45, 60, 90, 120, 150, and 180 minutes after the start of suckling.

Data analyses—The analog outputs of the 6-channel recorder and pH meter were digitized[m] at 1 Hz. Digitized data were stored and analyzed offline by use of commercially available software[m] on a personal computer. The pressure and pH electrode catheters were calibrated immediately before and after each recording period to determine the drift in the signal; drift was < 1 mm Hg/h for pressure and < 0.04 pH units/h for the pH electrode.

For determination of the number and amplitude of abomasal contractions, data were obtained from the 1-Hz pressure signal but only when the calf was standing because sternal recumbency altered the luminal pressure. Abomasal motility was assessed by counting the number of abomasal contractions during each of 5 time periods (–60 to –30 minutes, –29 to 0 minutes, 1 to 60 minutes, 61 to 120 minutes, and 121 to 180 minutes) and by calculating a motility index from the amplitude of each abomasal contraction wave. An abomasal contraction wave was defined as a pressure amplitude > 10 mm Hg with a duration of at least 4 seconds. Any pressure amplitude caused by external movements (ie, sitting down or standing up), coughing, or defecation was not considered to represent an abomasal contraction wave. An abomasal motility index was then calculated as the sum of all pressure wave amplitudes derived from abomasal contractions, as

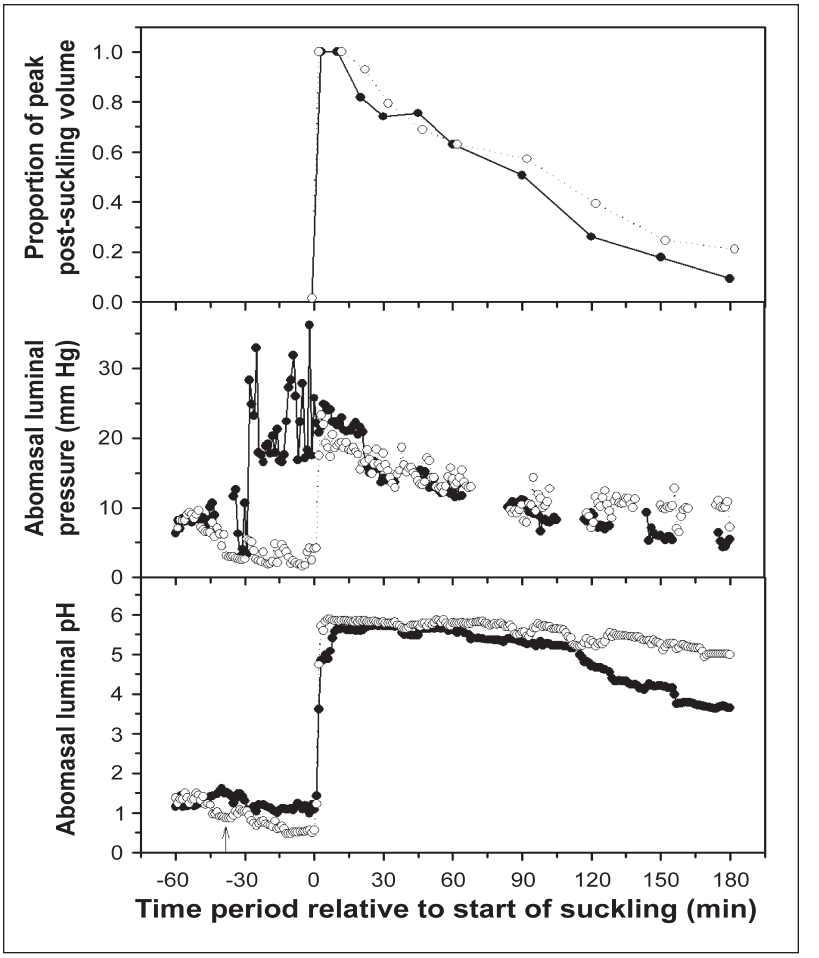

Figure 1—Typical changes in the proportion of peak abomasal volume after suckling and abomasal luminal pressure and pH in a Holstein-Friesian calf before and after administration of erythromycin (8.8 mg/kg, IM; closed circles) or 2 mL of saline (0.9% NaCl) solution (open circles) at time –30 minutes (arrow); the calf was allowed to suckle milk replacer (60 mL/kg) starting at time 0 minutes. Notice that the missing data points in the middle panel represent the times at which the calf was sitting.

Table 1—Mean ± SD number of abomasal pressure waves per minute (count/min) in 5 calves, each of which received treatments (in a crossover study) with erythromycin, neostigmine, erythromycin and neostigmine, metoclopramide, or saline (0.9% NaCl) solution (control) at –30 minutes and were fed milk replacer (60 mL/kg) starting at 0 minutes.

	Time period (min)				
Treatment	**–60 to –30**	**–29 to 0**	**1 to 60**	**61 to 120**	**121 to 180**
Erythromycin (8.8 mg/kg, IM)	0.2 ± 0.2	2.0 ± 1.1†‡	0.7 ± 0.6	0.4 ± 0.2	0.4 ± 0.3
Erythromycin (0.88 mg/kg, IM)	0.7 ± 0.8	0.8 ± 1.1	0.3 ± 0.1	0.2 ± 0.1	0.2 ± 0.2
Erythromycin (8.8 mg/kg, IM) and neostigmine* (0.02 mg/kg, SC)	0.6 ± 0.7	1.3 ± 0.8†	0.5 ± 0.4	0.5 ± 0.4	1.0 ± 0.7†
Neostigmine* (0.02 mg/kg, SC)	0.8 ± 1.1	1.0 ± 1.1	0.2 ± 0.1	0.1 ± 0.03†	0.1 ± 0.1
Metoclopramide* (0.1 mg/kg, IM)	0.6 ± 0.7	0.5 ± 0.4	0.1 ± 0.1†	0.2 ± 0.1	0.2 ± 0.1
Control (2 mL of saline solution, SC)	0.5 ± 0.5	0.5 ± 0.6	0.4 ± 0.4	0.3 ± 0.3	0.2 ± 0.1

*Neostigmine and metoclopramide were administered at –30 minutes and again at 90 minutes. †Value significantly ($P < 0.05$) different from that of the control treatment within the same time period. ‡Value significantly ($P < 0.05$) different from that obtained prior to treatment and suckling (–60 to –30 minutes) within the same treatment.

proposed by Di Lorenzo et al.[40] The motility index was calculated for each of the 5 time periods and then expressed as the mean motility index per minute.

The lowest pressure value for each 60-second interval was used as the pressure value for that minute; this prevented the inclusion of pressure transients associated with a contraction wave in the calculation of mean pressure. The mean abomasal luminal pressure was calculated by use of the value for each minute (after linear correction of the measured values for drift) of the 5 time periods.

Abomasal volume was calculated from the ultrasonographically determined measurements by use of the equation for the volume of an ellipsoid (volume = width × length × height × $\pi/6$, where the constant π is an irrational number approximating 3.142). This method has been validated for use in calves.[35] The modified power exponential equation of Siegel et al[41] was used to calculate the **half-time of abomasal emptying ($t_{1/2}$)** from the abomasal volume, as described previously.[35] Briefly, a volume-versus-time curve was generated for each experiment by use of the following equation:

$$y(t) = 1 - (1 - e^{(-k \bullet time)})^{\beta},$$

where y(t) is the proportion of peak volume after suckling at time t, time is the time interval from the start of suckling in minutes, the constant *e* is an irrational number (approx 2.718), k is the slope of the terminal portion of the emptying curve (min^{-1}), and β is the extrapolated y-intercept for the terminal portion of the curve. Values for k and β obtained from nonlinear regression analysis of experimental data were applied in the calculation as follows:

$$\text{Ultrasonographic } t_{1/2} = (-1/k) \bullet \log_e(1 - 2^{-1/\beta}),$$

where $\log_e$ is the natural logarithm with base e.

The lowest pH value for each 60-second interval was used as the pH value for that minute; this prevented the inclusion of transient high pH values that resulted from the pH electrode contacting the abomasal mucosa. The mean abomasal luminal pH was calculated by use of the value for each minute (without correcting for drift) for the following 5 time periods: –60 to –30 minutes, –29 to 0 minutes, 1 to 60 minutes, 61 to 120 minutes, and 121 to 180 minutes.

Statistical analyses—Data were expressed as mean values ± SD, and a value of $P < 0.05$ was considered significant. A repeated-measures ANOVA (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. Variables with non-normal distributions were log transformed or ranked before statistical analysis was performed. A statistical software program[n] was used for all statistical analyses.

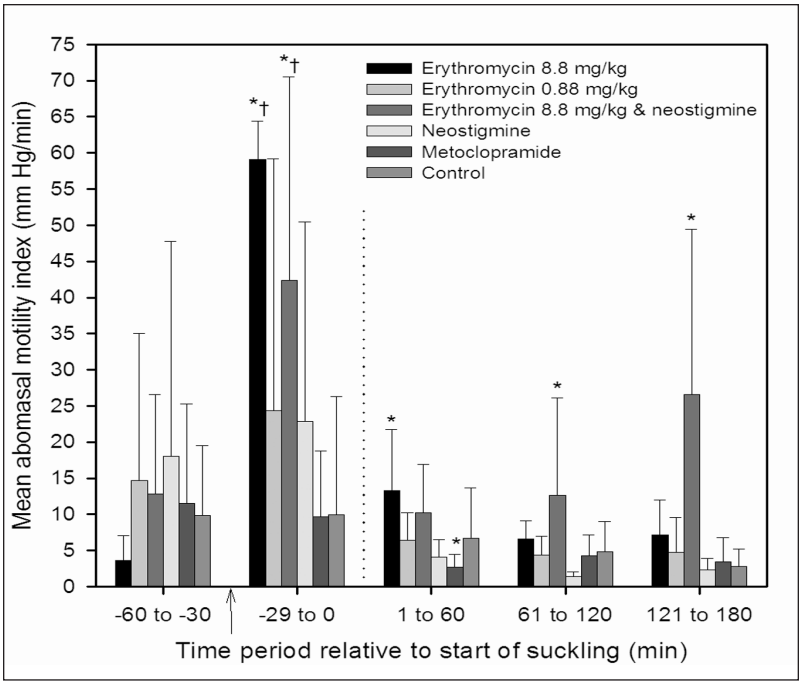

Figure 2—Mean ± SD abomasal body motility index (mm Hg/min) in 5 calves, each of which received treatments (in a crossover study) with erythromycin, neostigmine, erythromycin and neostigmine, metoclopramide, or saline solution (control) at time –30 minutes (arrow; treatments with neostigmine and metoclopramide were repeated at 90 minutes) and were fed milk replacer (60 mL/kg) starting at time 0 minutes (dotted vertical line). *Value significantly ($P < 0.05$) different from that of the control treatment within the same time period. †Value significantly ($P < 0.05$) different from that obtained prior to treatment and suckling (–60 to –30 minutes) within the same treatment group.

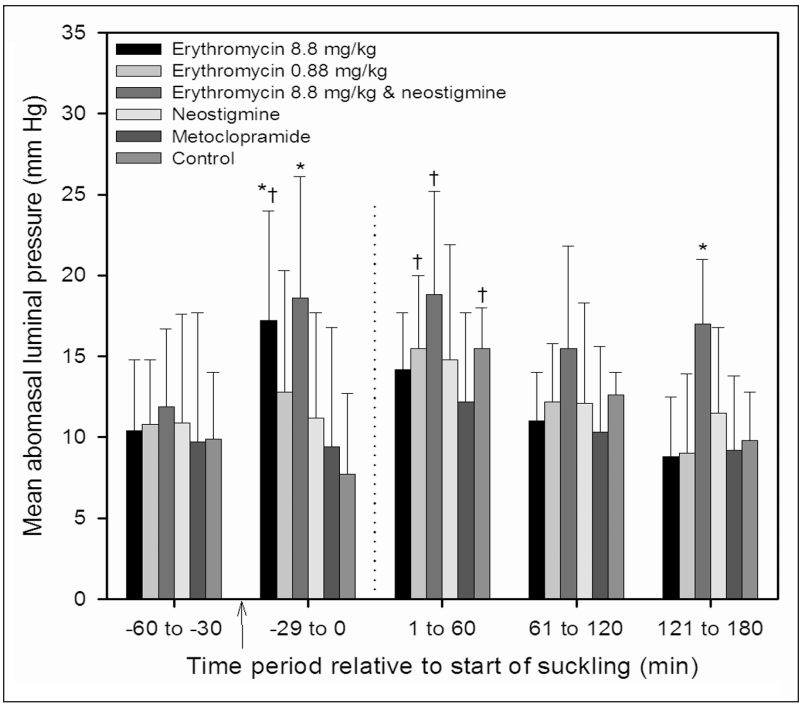

Figure 3—Mean ± SD abomasal body luminal pressure (mm Hg) in 5 calves, each of which received treatments (in a crossover study) with erythromycin, neostigmine, erythromycin and neostigmine, metoclopramide, or saline solution (control) at time –30 minutes (arrow; treatments with neostigmine and metoclopramide were repeated at 90 minutes) and were fed milk replacer (60 mL/kg) starting at time 0 minutes (dotted vertical line). *See* Figure 2 for remainder of key.

Results

During the study periods, abomasal luminal pH and pressure were recorded continuously and whether the calves were standing or recumbent was noted (**Figure 1**). Satisfactory measurements were obtained from 5 calves for all 6 treatments, whereas measurements in 1 calf were obtained for only 4 treatments; therefore, data analyses were confined to the 5 calves that received all treatments.

Abomasal motility—The mean frequency of abomasal contractions before treatment administration did not differ between treatment groups (**Table 1**). The abomasal contraction frequency increased immediately after administration of erythromycin (8.8 mg/kg), with and without neostigmine. In contrast, administration of neostigmine alone, low-dose erythromycin (0.88 mg/kg), metoclopramide, and the control treatment did not alter the contraction frequency. Suckling of milk did not appear to alter the contraction wave frequency.

The mean motility index before treatment administration was similar for all treatment groups (**Figure 2**). Erythromycin (8.8 mg/kg), with and without neostigmine, immediately increased the motility index. Administration of low-dose erythromycin (0.88 mg/kg), neostigmine alone, metoclopramide, and the control treatment did not alter the motility index. Suckling of milk appeared to decrease the motility index in all treatment groups. During the first hour after suckling (1 to 60 minutes), the mean motility index was increased in calves administered erythromycin (8.8 mg/kg) and decreased in calves administered metoclopramide, compared with index values obtained before treatment and suckling (–60 to –30 minutes). From 61 to 180 minutes after suckling, the mean motility index was increased in calves administered the combination of erythromycin (8.8 mg/kg) and neostigmine, compared with index values obtained for the control treatment during the same time period.

Mean abomasal luminal pressure—The mean pressure before treatment administration was similar for all treatment groups (**Figure 3**). After treatment at –30 minutes and before suckling (ie, –29 to 0 minutes), the mean luminal pressure of the abomasum was increased in calves administered erythromycin (8.8 mg/kg), with and without neostigmine, compared with values obtained for the control treatment in the same time period; however, neostigmine alone did not alter mean luminal pressure. After suckling milk replacer, the luminal pressure of the filled abomasum appeared to increase with all 6 treatments; between 1 and 60 minutes after suckling, the mean luminal pressures of the abomasum in the erythromycin (8.8 mg/kg) and neostigmine treatment group, the low-dose erythromycin (0.88 mg/kg) treatment group, and the control treatment group were significantly greater than the values obtained prior to treatment and suckling (–60 to –30 to minutes) in the same treatment group. After suckling, the mean luminal pressure decreased in each treatment group except in calves treated with both erythromycin (8.8 mg/kg) and neostigmine.

Abomasal emptying rate—Administration of erythromycin (8.8 mg/kg) decreased the $t_{1/2}$ value by 37%, compared with that of the control treatment group (64 ± 14 minutes and 101 ± 17 minutes, respectively; **Figure 4**), whereas $t_{1/2}$ values were unchanged with administration of low-dose erythromycin (0.88 mg/kg; 92 ± 35 minutes), neostigmine (89 ± 12 minutes), or metoclopramide (107 ± 23 minutes). Administration of erythromycin (8.8 mg/kg) and neostigmine increased the value of $t_{1/2}$ (76 ± 24 minutes), but this was not significantly different from the value of the control treatment group.

Abomasal pH—Mean luminal pH before suckling was similar for all treatment groups; values increased similarly in all treatment groups after suckling, and there were no differences between groups (**Figure 5**).

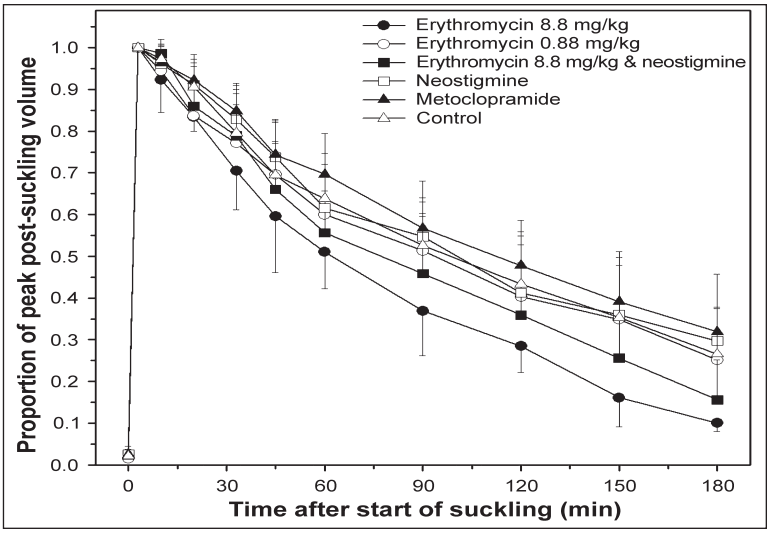

Figure 4—Change in abomasal volume (mean ± SD peak post-suckling volume) in 5 calves, each of which received treatments (in a crossover study) with erythromycin, neostigmine, erythromycin and neostigmine, metoclopramide, or saline solution (control) at time –30 minutes (treatments with neostigmine and metoclopramide were repeated at 90 minutes) and were fed milk replacer (60 mL/kg) starting at time 0 minutes. The data for abomasal volume were normalized to 1 immediately after suckling.

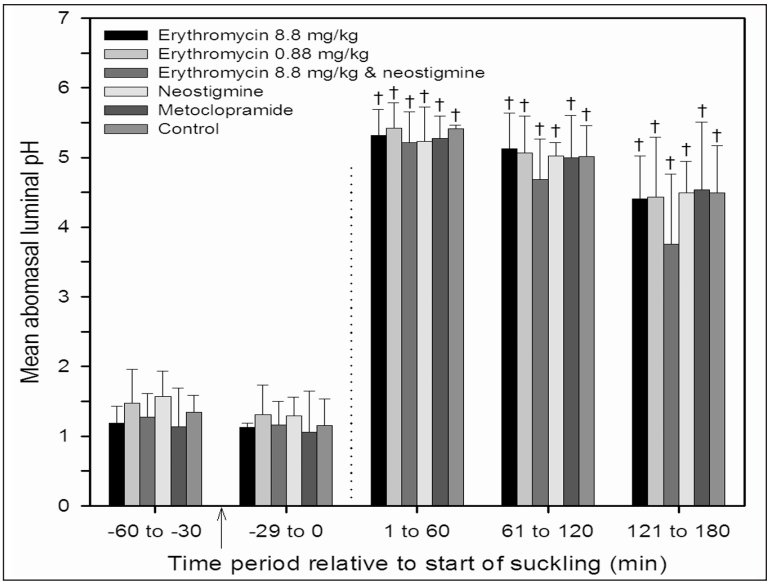

Figure 5—Mean ± SD abomasal body luminal pH in 5 calves, each of which received treatments (in a crossover study) with erythromycin, neostigmine, erythromycin and neostigmine, metoclopramide, or saline solution (control) at time –30 minutes (arrow; treatments with neostigmine and metoclopramide were repeated at 90 minutes) and were fed milk replacer (60 mL/kg) starting at time 0 minutes (dotted vertical line). *See* Figure 2 for remainder of key.

Discussion

On the basis of the results of the present study, erythromycin (administered at the labeled antimicrobial dose) is an effective prokinetic agent in healthy suckling calves; this finding is consistent with the effects of erythromycin in humans, dogs, and horses.[12,27-29] It is very likely that a similar prokinetic effect occurs when erythromycin is administered to healthy adult cattle because the results of a preliminary study[33] in 2 Holstein cows indicated that administration of erythromycin lactobionate (0.1 mg/kg, IV, or 1 mg/kg, IV or IM) or erythromycin base (10 mg/kg, IM) increased the myoelectrical activity in the abomasal body, pyloric antrum, and duodenum as well as increasing abomasal luminal pressure, compared with pretreatment values. It is also likely that the prokinetic effect of erythromycin is still present after repeated administration in calves and adult cattle because a prokinetic effect was maintained in humans with diabetic gastroparesis after 4 weeks of oral administration of erythromycin[42] and clinically relevant concentrations of erythromycin do not alter motilin receptor density in rabbits.[43]

Parenteral administration of erythromycin is labeled in the United States for treatment of pneumonia, pneumonia-enteritis complex, foot rot, metritis, and stress in beef cattle and for treatment of pneumonia, foot rot, metritis, and stress in dairy cattle. The recommended dose rate is 1.1 to 8.8 mg/kg (0.5 to 4 mg/lb), IM, every 24 hours, and meat withdrawal time after 5 days' treatment at 8.8 mg/kg (4 mg/lb) is 6 days. Therefore, parenteral administration of erythromycin to calves and adult cattle as a prokinetic agent constitutes extra-label drug use. In preruminant calves, erythromycin (20 mg/kg) administered via the oral route is absorbed but only when the drug is administered as an acid-resistant ester.[44] Erythromycin should not be administered orally to ruminant cattle because it appears to be degraded by ruminal microflora,[44] and at a dosage of 30 mg/kg, PO, every 24 hours, it induces severe diarrhea and death in beef calves weighing 200 to 250 kg.[37] 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 erythromycin after parenteral administration in calves or adult cattle with abomasal disorders, such as left displacement of the abomasum or abomasal impaction, or after surgical correction of abomasal volvulus. However, erythromycin is highly effective in facilitating gastric motility and increasing gastric emptying rate in humans and dogs with gastric paresis,[32,40,45] and the treatment of gastric hypomotility is considered the most promising area of application.[28]

Our finding that erythromycin decreased the value of $t_{1/2}$ in healthy calves by 37% was similar to the decrease in the half-time of gastric emptying (44%) obtained in a systematic review[11] of results of prokinetic studies in humans. Whether erythromycin is efficacious as a medical treatment for abomasal and small intestinal motility disorders in calves remains to be determined. However, because erythromycin increases phase III activity[28,32,33] and because the duration of the migrating myoelectric complex in calves increases with increased flow[46] but decreases after onset of *Escherichia coli* STa enterotoxin-induced diarrhea,[47] erythromycin administration may be of benefit as part of the treatment of calves with diarrhea.

In the present study, the mechanism by which erythromycin increased abomasal emptying rate, compared with placebo, was probably related to an increased frequency of luminal pressure waves and mean luminal pressure immediately after administration as well as increased contractility of the pyloric antrum and increased antroduodenal coordination,[30] although we did not specifically evaluate the latter effects. It is widely accepted that the rate of gastric emptying is determined by the interaction between the tone of the gastric body, antral contractility, pyloric resistance, duodenal resistance, and gastroduodenal coordination,[48,49] with the pressure gradient between the stomach and duodenum being the most important determinant of emptying rate after ingesting a fluid meal.[50-52] In contrast, the rate of gastric emptying of solid meals is controlled largely by antral contractions.[51,45] After ingestion of a fluid meal, the pressure gradient between the stomach and duodenum is created by rapid phasic contractions of the gastric body superimposed on slower sustained contractions and the rate of liquid emptying increases linearly with luminal pressure.[51] Therefore, in the calves included in our study, the increased luminal pressure after erythromycin (8.8 mg/kg, IM) administration was the most likely reason for the observed increase in emptying rate.

Neostigmine did not alter abomasal motility, pressure, or emptying rate in the calves of the study reported here. Our results were consistent with those observed by Roussel et al[19] after administration of the parasympathomimetic drug bethanechol (0.07 mg/kg, SC) to yearling cattle. Although bethanechol slightly increased the tone and motility of abomasal smooth muscle, that agent did not increase abomasal emptying rate, presumably because of a lack of antroduodenal coordination[19] or induction of pyloric spasm.[53] Our data support the concept that neostigmine may be deleterious to gastric and abomasal emptying because coadministration of neostigmine with erythromycin (8.8 mg/kg) partially ameliorated the prokinetic effect of the latter, even though administration of neostigmine with erythromycin increased the motility index and luminal pressure to a greater extent than did administration of erythromycin alone. A neostigmine-induced increase in pyloric tone provides an explanation for these findings.

Metoclopramide did not exert a prokinetic effect in the calves of the present study and decreased the frequency of abomasal contractions and the motility index during the first hour after feeding; these results contrast with those obtained in studies[52,54,55] of humans and domestic monogastric animals, which indicate that metoclopramide inhibits gastric accommodation, resulting in higher luminal pressures and increased rate of gastric emptying. Gastric accommodation is the process by which an increased gastric volume is accommodated without a large increase in intragastric pressure.[10,48] The lower luminal pressure after suckling

milk in the calves of our study, compared with the value for untreated calves after suckling milk, suggests that metoclopramide facilitated, rather than inhibited, gastric accommodation in neonatal calves. However, our results were consistent with those of Roussel et al,[19] who determined that administration of 0.1 mg of metoclopramide/kg, SC, had no effect on abomasal and duodenal electromyographic activity in yearling cattle. Metoclopramide also induces only minor changes in the electromyographic pattern of the abomasum and duodenum in sheep and goats.[24,a] In our study, the failure to observe a metoclopramide-associated prokinetic effect in calves may have resulted from our selection of a dose rate of 0.1 mg of metoclopramide/kg, IM, which appeared to induce mild and transient restlessness followed by signs of depression in some calves. Because more severe adverse neuroleptic effects occur when doses > 0.1 mg of metoclopramide/kg are administered to ruminants,[22,23] we cannot recommend the use of metoclopramide as a prokinetic agent in calves.

To our knowledge, this is the first report of abomasal luminal pressure changes in calves after suckling a milk meal. In a study[56] of dairy calves, Bell measured the luminal pressure in the abomasal body and antrum after introduction of 1.5 L of saline (0.9% NaCl) solution and observed phasic increases in pressure of 5 cm H_2O(3.7 mm Hg) that were synchronized with antral electromyographic activity. The antral contractions generated pressure amplitudes of as much as 20 cm H_2O (14.7 mm Hg), but usually, the pressure increase was < 10 cm H_2O (7.4 mm Hg). However, that investigator did not report the mean luminal pressure values or the change in luminal pressure after suckling. In another study[57] by Svendson, the mean luminal pressure of the abomasal body of adult cattle was reported to be 2 to 4 mm Hg; however, the reference level for the pressure measurements was not stated and that range of values seems much too low to be physiologic. The luminal pressure values determined in the study by Svendson were also considerably lower than those observed by Huhn et al[33] in 2 adult cows that had been administered erythromycin lactobionate (0.1 and 1.0 mg/kg, IV, respectively); luminal fluid pressures in those cows ranged from 13 to 32 mm Hg with peak values > 100 mm Hg. Transient increases in luminal fluid pressure of 1.2 to 2.2 cm H_2O were reported to occur at a frequency of 1.2 to 2.2 contractions/min in yearling cattle,[58] and pressure changes of 1.5 to 4.8 cm H_2O occurred in dairy cows,[8] but mean luminal pressure was not reported for either of those studies.

On the basis of our data, we conclude that administration of erythromycin (8.8 mg/kg, IM) caused an immediate and profound increase in abomasal motility, mean luminal pressure, and emptying rate in healthy suckling calves. Our results suggest that erythromycin, when administered at the labeled antimicrobial dose, may be a useful prokinetic agent in milk-fed calves.

a. Kopcha M. Myoelectrical and myomechanical response of the pyloric antrum in sheep to metoclopramide (abstr), in *Proceedings.* 6th Annu Vet Med Forum Am Coll Vet Intern Med 1988;733.
b. Percutaneous endoscopic gastrostomy kit, MILA Instruments Inc, Florence, Ky.
c. Agri Master, Supreme All Milk, Blain Supply, Janesville, Wis.
d. Millar mikro-tip catheter, model SPC 460, Millar Instruments, Houston, Tex.
e. Model 5/6H, Gilson Medical Electronics, Middleton, Wis.
f. LoT stomach probe, Medical Instruments Corp, Solothurn, Switzerland.
g. Cole-Parmer pH/mV/rel mV/°C benchtop meter, Cole-Parmer Instrument Co, Vernon Hills, Ill.
h. Gallimycin 100, 100 mg of erythromycin/mL, Bimeda Inc, Riverside, Mo.
i. Neostigmine methylsulfate, 1 mg/mL, American Regent Laboratories Inc, Shirley, NY.
j. Reglan Injectabile, 5 mg/mL, A H Robbins Co, Richmond, Va.
k. 0.9% Sodium chloride USP, Abbott Laboratories, Chicago, Ill.
l. Ultramark 4, 3.5-MHz linear probe, Advanced Technology Laboratories, Tempe, Ariz.
m. Windaq, DATAQ Instruments, Akron, Ohio.
n. SAS 8e, SAS Institute Inc, Cary, NC.

References

1. Constable PD, Miller GY, Hoffsis GF, et al. Risk factors for abomasal volvulus and left abomasal displacement in cattle. *Am J Vet Res* 1992;53:1184–1192.
2. Steiner A, Roussel AJ. Drugs coordinating and restoring gastrointestinal motility and their effect on selected hypodynamic gastrointestinal disorders in horses and cattle. *Zentralbl Veterinarmed [A]* 1995;42:613–631.
3. Daniel RC. Motility of the rumen and abomasum during hypocalcaemia. *Can J Comp Med* 1983;47:276–280.
4. Madison JB, Troutt HF. Effects of hypocalcaemia on abomasal motility. *Res Vet Sci* 1988;44:264–266.
5. Vlaminck K, van Meirhaeghe H, van den Hende C, et al. Einfluss von Endotoxinen auf die Labmagenentleerung beim Rind. *Dtsch Tierarztl Wochenschr* 1985;92:392–395.
6. Poulsen JSD, Jones BEV. The influence of metabolic alkalosis and other factors on abomasal emptying rate in goats and cows. *Nord Vet Med* 1974;26:22–30.
7. van Meirhaeghe H, Deprez P, van den Hende C, et al. The influence of insulin on abomasal emptying in cattle. *Zentralbl Veterinarmed [A]* 1988;35:213–220.
8. Holtenius K, Jacobson SO, Holtenius P. Effects of intravenous infusion of glucose and pancreatic glucagon on abomasal function in dairy cows. *Acta Vet Scand* 1998;39:291–300.
9. Holtenius K, Sternbauer K, Holtenius P. The effect of plasma glucose level on the abomasal function in dairy cattle. *J Anim Sci* 2000;78:1930–1935.
10. Dumont RC, Rudolph CD. Development of gastrointestinal motility in the infant and child. *Gastroenterol Clin North Am* 1994;23:655–671.
11. Sturm A, Holtmann G, Goebell H, et al. Prokinetics in patients with gastroparesis: a systematic analysis. *Digestion* 1999;60:422–427.
12. Ringger C, Lester GD, Neuwirth L, et al. Effect of bethanechol on erythromycin gastric emptying in horses. *Am J Vet Res* 1996;57:1771–1775.
13. Hall JA, Washabau RJ. Diagnosis and treatment of gastric motility disorders. *Vet Clin North Am Small Anim Pract* 1999;29:377–395.
14. Roussel AJ, Hopper RN, Cohen ND, et al. Prokinetic effects of erythromycin on the ileum, cecum, and pelvic flexure of horses during the postoperative period. *Am J Vet Res* 2000;61:420–424.
15. Dardillat C, Ruckebusch Y. Aspects fonctionnels de la jonction gastro-duodenale chez le veau nouveau-ne. *Ann Rech Vet* 1973;4:31–56.
16. Braun U, Steiner A, Bearth G. Therapy and clinical progress of cattle with dilatation and torsion of the caecum. *Vet Rec* 1989;125:430–433.
17. Umakanthan T. Treatment of omasal impaction—a field report. *Indian Vet J* 1997;74:605–606.
18. Smith RH. Passage of ingesta through the calf abomasum and small intestine. *J Physiol* 1964;172:305–320.
19. Roussel AJ, Brumbaugh GW, Waldron RC, et al. Abomasal and duodenal motility in yearling cattle after administration of prokinetic drugs. *Am J Vet Res* 1994;55:111–115.

20. Braun U, Steiner A, Kaegi B. Clinical, haematological and biochemical findings and the results of treatment in cattle with acute functional pyloric stenosis. *Vet Rec* 1990;126:107–110.

21. Ruegg PL, George LW, East NE. Abomasal dilatation and emptying defect in a flock of Suffolk ewes. *J Am Vet Med Assoc* 1988;193:1534–1536.

22. Zdelar F, Hahn V, Martinic B, et al. Effect of the antiemetic metoclopramide on the digestive tract of fattening calves, and its use in digestive disorders. *Veterinarski Glasnik* 1979;33:761–766.

23. Guard C, Schwark W, Kelton D, et al. Effects of metoclopramide, clenbuterol, and butorphanol on ruminoreticular motility in calves. *Cornell Vet* 1988;78:89–98.

24. Huhn JC, Nelson DR. The quantitative effect of metoclopramide on abomasal and duodenal myoelectric activity of goats. *Zentralbl Veterinarmed [A]* 1997;44:361–371.

25. Pinder RM, Brogden RN, Sawyer PR, et al. Metoclopramide: a review of its pharmacological properties and clinical use. *Drugs* 1976;12:81–131.

26. Jones RD, Mizinga KM, Thompson FN, et al. Bioavailability and pharmacokinetics of metoclopramide in cattle. *J Vet Pharmacol Ther* 1994;17:141–147.

27. Itoh Z, Nakaya M, Suzuki T, et al. Erythromycin mimics exogenous motilin in gastrointestinal contractile activity in the dog. *Am J Physiol* 1984;247:G688–G694.

28. Peeters TL. Erythromycin and other macrolides as prokinetic agents. *Gastroenterology* 1993;105:1886–1899.

29. Pilot MA. Macrolides in roles beyond antibiotic therapy. *Br J Surg* 1994;81:1423–1429.

30. Parkman HP, Pagano AP, Vozelli MA, et al. Gastrokinetic effects of erythromycin: myogenic and neurogenic mechanisms of action in rabbit stomach. *Am J Physiol* 1995;269:G418–G426.

31. Lester GD, Merritt AM, Neuwirth L, et al. Effect of erythromycin lactobionate on myoelectric activity of ileum, cecum, and right ventral colon, and cecal emptying of radiolabeled markers in clinically normal ponies. *Am J Vet Res* 1998;59:328–334.

32. Dive A, Miesse C, Galanti L, et al. Effect of erythromycin on gastric motility in mechanically ventilated critically ill patients: a double-blind, randomized, placebo-controlled study. *Crit Care Med* 1995;23:1356–1362.

33. Huhn JC, Nelson DR, Constable PD, et al. Prokinetic properties of erythromycin lactobionate in cattle, in *Proceedings*. 20th World Buiatrics Cong 1998;177–181.

34. Ahmed AF, Constable PD, Misk NA. Effect of orally administered cimetidine and ranitidine on abomasal luminal pH in clinically normal milk-fed calves. *Am J Vet Res* 2001;62:1531–1538.

35. Wittek T, Constable PD, Marshall TS, et al. Ultrasonographic measurement of abomasal volume, location, and emptying rate in calves. *Am J Vet Res* 2005;66:537–544.

36. Ehrenpreis ED, Zaitman D, Nellans H. Which form of erythromycin should be used to treat gastroparesis? A pharmacokinetic analysis. *Aliment Pharmacol Ther* 1998;12:373–376.

37. Burrows CE, Griffin DD, Pippin A, et al. A comparison of the various routes of administration of erythromycin in cattle. *J Vet Pharmacol Ther* 1989;12:289–295.

38. Steiner AS, Roussel AJ, Martig J. Effect of bethanechol, neostigmine, metoclopramide, and propranolol on myoelectric activity of the ileocecocolic area in cows. *Am J Vet Res* 1995;56:1081–1086.

39. European Agency for Evaluation of Medical Products, Veterinary Medicines Evaluation Unit. Neostigmine: summary report. EMEA/MRL/161/96-FINAL, 1997.

40. Di Lorenzo C, Flores AF, Tomomasa T, et al. Effect of erythromycin on antroduodenal motility in children with chronic functional gastrointestinal symptoms. *Dig Dis Sci* 1995;39:1399–1404.

41. Siegel JA, Urbain JL, Adler LP, et al. Biphasic nature of gastric emptying. *Gut* 1988;29:85–89.

42. Janssens J, Peeters TL, Vantrappen G, et al. Improvement of gastric emptying in diabetic gastroparesis by erythromycin. *N Engl J Med* 1990;322:1028–1031.

43. Depoortere I, Peeters TL, Vantrappen G. Effect of erythromycin and of octreotide on motilin receptor density in the rabbit. *Regul Pept* 1991;32:85–94.

44. Soback S, Ziv G, Kurtz B, et al. Age-dependent oral bioavailability of erythromycin thiocyanate in calves. *Zentralbl Veterinarmed [A]* 1987;34:102–107.

45. Desautels SG, Hutson WR, Christian PE, et al. Gastric emptying response to variable oral erythromycin dosing in diabetic gastroparesis. *Dig Dis Sci* 1995;40:141–146.

46. Girard CL, Sissons JW. The role of migrating myoelectric complexes in the regulation of digesta transport in the preruminant calf. *Can J Physiol Pharmacol* 1992;70:1142–1147.

47. Roussel AJ, Woode GN, Waldron RC, et al. Myoelectric activity of the small intestine in enterotoxin-induced diarrhea of calves. *Am J Vet Res* 1992;53:1145–1148.

48. Meyer JH. Motility of the stomach and gastroduodenal junction. In: Johnson LR, ed. *Physiology of the gastrointestinal tract.* 2nd ed. New York: Raven Press, 1987;613–629.

49. Thomas JE. Mechanics and regulation of gastric emptying. *Physiol Rev* 1957;37:453–474.

50. Low AG. Nutritional regulation of gastric secretion, digestion, and emptying. *Nutr Res Rev* 1990;3:229–252.

51. Kelly KA. Gastric emptying of liquids and solids: roles of proximal and distal stomach. *Am J Physiol* 1980;239:G71–G76.

52. Minami H, McCallum RW. The physiology and pathophysiology of gastric emptying in humans. *Gastroenterology* 1984;86:1592–1610.

53. Adams SB, MacHarg MA. Neostigmine methylsulfate delays gastric emptying of particulate markers in horses. *Am J Vet Res* 1985;46:2498–2499.

54. Burrows CF. Metoclopramide. *J Am Vet Med Assoc* 1983;183:1341–1343.

55. Harrington RA, Hamilton CW, Brodgen RN, et al. Metoclopramide. *Drugs* 1983;25:451–494.

56. Bell FR. The pressure relationship in the gastric body, antrum and duodenum during gastric emptying in the calf, in *Proceedings*. 5th Int Symp Ruminant Physiol 1979;485–493.

57. Svendson P. Etiology and pathogenesis of abomasal displacement in cattle. *Nord Vet Med* 1969;21(suppl 1):1–60.

58. Vlaminck K, van den Hende C, Oyaert W, et al. Studies on abomasal emptying in cattle. I. Correlation between abomasal emptying, electromyographic activity and pressure changes in the abomasum. *Zentralbl Veterinarmed [A]* 1984;31:561–566.