Effect of parenteral administration of erythromycin, tilmicosin, and tylosin on abomasal emptying rate in suckling calves

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Objective—To determine the effect of parenteral administration of erythromycin, tilmicosin, and tylosin on abomasal emptying rate in suckling calves. 

Animals—8 male Holstein-Friesian calves < 35 days old. 

Procedures—Calves received each of 4 treatments in random order (2 mL of saline [0.9% NaCl] solution, IM [control treatment]; erythromycin, 8.8 mg/kg, IM; tilmicosin, 10 mg/kg, SC; and tylosin, 176 mg/kg, IM). Calves were fed 2 L of milk replacer containing acetaminophen (50 mg/kg) 30 minutes later. Jugular venous blood samples and transabdominal ultrasonographic abomasal dimensions were obtained periodically after suckling. Abomasal emptying rate was assessed on the basis of the time to maximal plasma acetaminophen concentration and ultrasonographic determination of the half-time of abomasal emptying. One-tailed Dunnett post tests were conducted whenever the F value for group was significant. 

Results—Emptying rate was faster for erythromycin, tilmicosin, and tylosin than for the control treatment, as determined on the basis of time to maximal plasma acetaminophen concentration. Ultrasonography indicated that the half-time of abomasal emptying was significantly shorter for erythromycin than for the control treatment. Tylosin and tilmicosin accelerated the abomasal emptying rate, but not significantly, relative to the emptying rate for the control treatment. 

Conclusions and Clinical Relevance—Administration of erythromycin, tilmicosin, and tylosin at the label dosage increased abomasal emptying rate in calves. The clinical importance of an increase in abomasal emptying rate in cattle remains to be determined. (Am J Vet Res 2007;68:1392–1398)

Irreversible abomasal motility is a common event in cattle and is suspected to play a major role in the development of left displaced abomasum, abomasal volvulus, and abomasal impaction in adult cattle and abomasal tympany in calves. Abomasal emptying rate is decreased in cows with left displaced abomasum and is further decreased immediately after surgical correction of the condition. Administration of an effective prokinetic agent that stimulates, coordinates, and restores abomasal, pyloric, and small intestinal motility may have clinical use in cattle with abomasal hypomotility. Erythromycin is an effective prokinetic agent in humans and domestic animals, including adult cattle and calves. Erythromycin exerts its effect to accelerate 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 portion of the small intestine or by the release of endogenous motilin through cholinergic or serotonergic pathways. Motilin is a peptide comprising 22 amino acids that is periodically released from endocrine cells in the duodenoejunal mucosa, thereby initiating the MMC of the mammalian gastrointestinal tract during the interdigestive period; the MMC is the so-called housekeeper of the gastrointestinal tract. There is considerable interest in the group of nonpeptide motilin agonists, referred to as the motilides (ie, motilin-like macrolides), that interact with the motilin receptor and promote gastric emptying. Structure-activity studies have indicated that motilides have 3 main structural requirements to enable them to interact strongly with the motilin receptor: a ring structure (typically a 14-membered lactone ring), an amino sugar bound at C-5 of the ring in a glycosidic linkage, and a neutral sugar bound at C-3 of the ring.

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ABBREVIATIONS

<table>
<thead>
<tr>
<th>MMC</th>
<th>Migrating motor complex</th>
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<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt;</td>
<td>Maximal plasma acetaminophen concentration</td>
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<td>T&lt;sub&gt;max&lt;/sub&gt;</td>
<td>Time at which the maximal plasma acetaminophen concentration was detected</td>
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<td>t&lt;sub&gt;1/2&lt;/sub&gt;</td>
<td>Half-time</td>
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in a glycosidic linkage.11,12 Based on this 3-part structure, the potency of a motilide is influenced primarily by modifications to the dimethylamino group at the 3’ position of the amino sugar and, to a lesser extent, the size and configuration of the lactone ring structure (particularly C-6 through C-9). Inclusion of a neutral sugar at C-3 that is parallel to the amino sugar at C-5 also increases potency of motilides.13,14 Interestingly, the dimethylamino group of the amino sugar bound at C-3 is also important in determining the antimicrobial activity of macrolides.11,14

In another study6 conducted by our laboratory group, we determined that parenteral administration of erythromycin at the labeled dose for cattle (8.8 mg/kg, IM) caused an immediate and profound increase in abomasal motility and emptying rate in milk-fed calves. Erythromycin has a 14-membered enol ether lactone ring with a dimethylamino sugar (desosamine) at C-5 and a neutral sugar (cladinose) at C-3 in parallel with desosamine. We were interested in determining whether the macrolides tylosin and tilmicosin also promote abomasal emptying in milk-fed calves. Tylosin has a 16-membered ring with 2 double bonds, an amino sugar at C-5 with a neutral sugar attached in serial glycosidic linkage, a hydroxyl group instead of a neutral sugar at C-3, and a side-chain sugar at C-14. Tilmicosin is synthesized from tylosin and has a 16-membered ring, an amino sugar at C-5, a hydroxyl group instead of a neutral sugar at C-3, a dimethylamino-piperidonoxyethyl group at C-6, and a side-chain sugar at C-14.

Ultrasonographic measurement of abomasal dimensions provides an accurate method of determining abomasal volume and location in suckling calves. The change in calculated abomasal volume after suckling provides an accurate method for determining the abomasal emptying rate in calves.15 Acetaminophen is a widely used orally administered analgesic and antipyretic in humans, and acetaminophen absorption provides an accurate method of determining the emptying rate of liquid-phase meals in humans,16 horses,17 and calves.18 When administered orally, acetaminophen is absorbed in the small intestine,19 with the rate-limiting step for absorption being the rate of gastric emptying in animals with normal small intestinal function.20 Because the apparent rate of absorption is much faster than the rate of elimination in suckling calves,17 the Cmax and Tmax after oral ingestion are primarily dependent on the rate of abomasal emptying.

For the study reported here, we hypothesized that tylosin and tilmicosin would increase the abomasal emptying rate in milk-fed calves relative to that for untreated control calves, but to a lesser extent than that induced by erythromycin. The hypothesis was tested via 2 methods for assessing abomasal emptying rate (ie, acetaminophen absorption and ultrasonography).

**Materials and Methods**

**Animals**—Eight healthy colostrum-fed male Holstein-Friesian calves were obtained from a local source at 2 to 4 days of age. Body weight of these calves ranged from 39 to 51 kg on arrival.

Calves were individually housed unrestrained in stalls that were bedded with wood shavings. Calves were sedated to ensure an adequate washout period. A catheter was placed in a jugular vein of each calf at least 18 hours before the first experiment. When necessary, additional catheters were inserted at least 12 hours before any subsequent experiment. To perform venous catheterization, calves were sedated by administration of xylazine hydrochloride (0.20 mg/kg, IM). The skin over the right jugular vein, was clipped and aseptically prepared. One milliliter of lidocaine was injected SC over the jugular vein, and a skin incision (1 cm in length) was made with a scalpel blade to assist in catheter placement. A 16- or 18-gauge catheter was then inserted in the jugular vein, an extension set was attached to the catheter, and the catheter and extension set were secured to the calf’s neck. The catheter was flushed every 12 hours with heparinized saline (0.9% NaCl) solution (40 U of heparin/mL).

**Experimental design**—Beginning when calves were at least 12 days old and at least 12 hours had elapsed since the previous feeding of milk replacer, each calf was weighed and placed in a movable calf stall that allowed it to sit and stand but prevented excessive lateral and forward movement. Calves received each of 4 treatments in random order (duplicated Latin-square design). The 4 treatments were 2 mL of saline solution, IM (control treatment), erythromycin (8.8 mg/kg, IM), tilmicosin (10 mg/kg, SC), and tylosin (17.6 mg/kg, IM). The dosage protocol for tilmicosin and tylosin reflected label recommendations for cattle.

Thirty minutes after treatment, each calf was allowed to suckle milk replacer (milk replacer was room temperature [19° to 22°C]). Onset of suckling was designated as time 0. Abomasal emptying rate was measured on the basis of acetaminophen absorption and transabdominal ultrasonographic examination. For subsequent treatments in each calf, at least a 48-hour interval was used after the administration of erythromycin, tylosin, or saline solution and at least a 72-hour interval was used after administration of tilmicosin to ensure an adequate washout period.

**Acetaminophen absorption**—Venous blood samples for determination of plasma acetaminophen concentrations were obtained before and 0, 15, 30, 45, 60, 90, 120, 180, 210, 240, 300, 360, 420, and 480 minutes after the start of suckling. These sample collection time points were selected in an attempt to provide 6 or more data points before and after the time of maximal acetaminophen concentration to facilitate nonlinear regression analysis. Blood samples were col-

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lected into 6-mL tubes that contained sodium fluoride and potassium oxalate and then centrifuged at 1,000 X g for 15 minutes. Plasma (3 mL) was harvested and stored at −20°C until analysis.

Plasma was thawed at approximately 22°C and analyzed spectrophotometrically by use of a colorimetric nitration assay, as described elsewhere.20 Values for actual C_max and actual T_max were obtained from a plot of the plasma acetaminophen concentration–time data. The first derivative of the Siegel modified power exponential equation was used to model the acetaminophen time curve, as described elsewhere.21 Equation 1 was derived from the fact that the acetaminophen-time curve represented as a cumulative dose curve is an inverse analogue of the scintigraphic curve as follows:

\[ C(t) = m \times k \times \beta \times e^{(-k \times t)} \times (1 - e^{(-k \times t)})^{1/2} \]

where \( C(t) \) is the acetaminophen concentration in plasma at time \( t \); \( m, k, \) and \( \beta \) are constants (\( m \) is the total cumulative recovery of acetaminophen when time is infinite, \( k \) is an estimate of the rate constant for abomasal emptying, and \( \beta \) provides an estimate of the duration of the lag phase before an exponential rate of emptying is reached); and \( e \) is the base of the natural logarithm. Nonlinear regression was used to estimate values for \( m, k, \) and \( \beta \), as described elsewhere.19

The time to calculated C_max (Model T_max) was obtained as follows:

\[ \text{Model } T_{\text{max}} = \frac{(\ln \beta)}{k} \]

where \( \ln \beta \) is the natural logarithm of \( \beta \). The calculated value for Model C_max was then calculated by applying the values for \( m, k, \beta, \) and \( t = \text{Model } T_{\text{max}} \) to the acetaminophen-time curve.

Ultrasoundography—For ultrasonographic evaluation of abomasal emptying, 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 ultrasonographic sector probe was applied to the ventral aspect of the abdomen in transverse and sagittal planes to determine the maximal ultrasonographically visible abomasal dimensions (length, width, and height). Ultrasonographic measurements were obtained before the start of suckling to determine the preprandial volume and 15, 30, 45, 60, 90, 120, 150, 180, 210, and 240 minutes after the start of suckling.

Abomasal volume was calculated from the ultrasonographically determined length, width, and height measurements by use of the equation for the volume of an ellipsoid as follows:

\[ \text{Volume} = \text{width} \times \text{length} \times \text{height} \times \left(\frac{\pi}{6}\right) \]

where \( \pi \) is 3.142. This method has been validated for use in calves.15 A modified power exponential equation was used to calculate the \( t_{1/2} \) of abomasal emptying from the abomasal volume by use of nonlinear regression, as described elsewhere.19 Briefly, a volume-versus-time curve was generated for each experiment by use of the following equation:

\[ y(t) = 1 - \left(1 - e^{(-k \times t)}\right)^{1/2} \]

where \( y(t) \) is the proportion of peak volume after suckling at time \( t \) (the time interval from the start of suckling), \( e \) is the base of the natural logarithm, \( k \) is the slope of the terminal portion of the emptying curve, and \( \beta \) is the extrapolated y-intercept for the terminal portion of the curve. Values for \( k \) and \( \beta \) obtained from nonlinear regression analysis of experimental data were applied in the calculation of the \( t_{1/2} \) of abomasal emptying by use of the following equation:

\[ \text{ultrasonic} \ t_{1/2} = \left(-\frac{1}{k}\right) \times \log (1 - 2^{-1/\beta}) \]

Statistical analysis—Data were expressed as least squares means and SE. The primary variables of interest were acetaminophen absorption \( T_{\text{max}} \) and ultrasonographic \( t_{1/2} \) because these 2 variables are most highly correlated with scintigraphic determination of \( t_{1/2} \) for abomasal emptying.15,19 Repeated-measures ANOVA (with repeated measures on treatment) was used to determine the main effects of treatment. Variables with non-normal distributions were logarithmically transformed or ranked before statistical analysis. One-tailed Dunnett post tests were conducted to compare erythromycin, tilmicosin, or tylosin values with control values whenever the \( F \) test value for treatment was significant. A value of \( P < 0.05 \) was considered significant. A statistical software program was used for all statistical comparisons.

Results

Animals—All calves remained healthy during the study period. Experiments were conducted on calves at a median age of 21 days (range, 13 to 32 days), with a median body weight of 50 kg (range, 39 to 56 kg). The mean time to suckle 2 L of milk replacer ranged from 1.5 to 3.0 minutes. The IM administration of erythromycin caused restlessness for several minutes in most calves; administration of tilmicosin or tylosin had no observable effect on behavior. Blood samples could not be collected into 6-mL tubes that contained sodium fluoride and potassium oxalate and then centrifuged at 1,000 X g for 15 minutes. Plasma (3 mL) was harvested and stored at −20°C until analysis.

Plasma was thawed at approximately 22°C and analyzed spectrophotometrically by use of a colorimetric nitration assay, as described elsewhere. Values for actual C_max and actual T_max were obtained from a plot of the plasma acetaminophen concentration–time data. The first derivative of the Siegel modified power exponential equation was used to model the acetaminophen time curve, as described elsewhere. Equation 1 was derived from the fact that the acetaminophen-time curve represented as a cumulative dose curve is an inverse analogue of the scintigraphic curve as follows:

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where \( y(t) \) is the proportion of peak volume after suckling at time \( t \) (the time interval from the start of suckling), \( e \) is the base of the natural logarithm, \( k \) is the slope of the terminal portion of the emptying curve, and \( \beta \) is the extrapolated y-intercept for the terminal portion of the curve. Values for \( k \) and \( \beta \) obtained from nonlinear regression analysis of experimental data were applied in the calculation of the \( t_{1/2} \) of abomasal emptying by use of the following equation:

\[ \text{ultrasonic} \ t_{1/2} = \left(-\frac{1}{k}\right) \times \log (1 - 2^{-1/\beta}) \]
be consistently obtained for 1 calf; therefore, statistical analysis was based on 8 calves for ultrasonography and 7 calves for acetaminophen analysis.

**Acetaminophen absorption**—Erythromycin (P < 0.001), tylosin (P = 0.008), and tilmicosin (P = 0.048) caused significantly faster abomasal emptying, compared with the rate for the control treatment, on the basis of model \( T_{\text{max}} \) values (Figure 1; Table 1). Actual \( T_{\text{max}} \) for erythromycin was also significantly less than for the control treatment.

**Ultrasonography**—Preprandial and maximal abomasal volumes were similar for the 4 treatments (Table 1). Mean change in abomasal volume after suckling 2 L of milk replacer was similar for all treatments, ranging from 1,980 to 2,018 mL.

The \( t_{1/2} \) of abomasal emptying for erythromycin was significantly (P < 0.001) less than the value for the control treatment (Figure 2). Tylosin and tilmicosin also accelerated the emptying rate, but not significantly (P = 0.052 and 0.078, respectively), compared with the rate for the control treatment.

**Discussion**

The major findings of the study reported here were that erythromycin, tylosin, and tilmicosin increased the abomasal emptying rate in suckling calves. Macrolides are categorized on the number of elements in the giant macrocyclic lactone ring of the aglycone as 12-, 14-, 15-, or 16-membered macrolides. Our findings are contrary to long-held beliefs that 16-membered macrolides (such as tyllosin and tilmicosin) have no motilide activity."
dance between the 2 methods used to assess emptying rate. Milk-fed calves may provide a more sensitive in vivo method for evaluating prokinetic agents than adult dogs because a calf’s abomasum can be rapidly primed with a large fluid volume (approx 4% of body weight within 3 minutes), and the ingested meal is a fluid and not a semisolid or solid.

It is possible that macrolides altered receptive relaxation without inducing an MMC. Support for this possibility was provided by a study in fed dogs in which spiramycin augmented the amplitude of gastric pressure changes and another study in suckling calves in which erythromycin increased luminal pressure before feeding and immediately after suckling. It is also possible that an increase in abomasal emptying rate induced by macrolides is unrelated to the MMC because the results of a study in suckling calves indicated that abomasal flow is inversely related to the number of MMCs.

Both tilmicosin and tylosin have a dimethylamino group on the amino sugar desosamine, and this group plays an important role in increasing the potency of motilides. The motilin receptor is a class A G-protein–coupled receptor that contains 7 transmembrane segments and 3 extracellular loops. An ionic interaction between the protonated dimethylamino group of desosamine in motilin or motilides and the negatively charged glutamic acid at position 119 of the second extracellular segment appears to be important for receptor activation. In particular, the size and shape of the electron cloud around the nitrogen atom on desosamine appear to be more important than the electrostatic effect of attached alkyl groups. Because erythromycin, tilmicosin, and tylosin all possess a dimethylamino group on desosamine attached to C-5, it should not be surprising that they exert a prokinetic effect, with the magnitude of the effect dependent on the side chains surrounding the protonated dimethyl amino group. In particular, a neutral sugar on C-3 appears to optimize the charge distribution on the amino group; a neutral sugar attached to desosamine (such as in tylosin) most likely impairs the charge distribution slightly, whereas an organic group on C-5 (such as dimethylpiperidino-ethyl in tilmicosin) could hinder the ionic interaction between the protonated dimethylamino group on the motilide and the negatively charged glutamic acid at position 119. Analysis of our results suggested that 2 other commercially available macrolides labeled for use in cattle (spiramycin and tulathromycin) may also have prokinetic activity. Spiramycin has a 16-membered ring, and tulathromycin has a 15-membered ring, a dimethylamino group on desosamine at C-5, and a structure at C-3. On a structure-activity basis, tulathromycin is likely to have stronger prokinetic effects than the 16-membered rings of tylosin and tilmicosin, although this supposition needs to be verified.

Macrolides were administered 30 minutes before suckling to ensure that maximal serum concentrations were achieved during the first 3 hours after suckling. Administration of erythromycin base (15 mg/kg, IM) in propylene glycol resulted in peak serum concentrations of 2.0 and 3.4 µg/mL at 3 to 5 hours after injection in 200-kg beef calves and 8-week-old Holstein-Friesian bull calves, respectively. For comparison, the serum erythromycin concentration at 30 minutes after injection in those calves was 0.7 µg/mL. Administration of tilmicosin (10 mg/kg, SC) into the neck of Angus cows resulted in peak serum concentrations of 0.9 µg/mL at 30 minutes after administration. Administration of tylosin base (17.6 mg/kg, IM) in propylene glycol to Holstein-Friesian calves that were 1 to 3 weeks old and weighing 38 to 56 kg resulted in peak serum concentrations of 2.3 µg/mL at 2 hours after administration. By comparison, the serum tylosin concentration at 30 minutes after injection was estimated to be 0.6 µg/mL.

Because we used similar formulations, dosing rates, and routes of administration to those reported for the pharmacokinetic studies, we believe that serum concentrations of erythromycin, tilmicosin, and tylosin were maximal in the calves at the time we measured the abomasal emptying rate. The mean t1/2 of elimination for erythromycin is 4.7 hours. The mean t1/2 of elimination for tilmicosin in adult Angus cows is 29.4 hours. The mean t1/2 of elimination for tylosin in Holstein-Friesian calves is approximately 6.0 hours. Duration of the washout period was determined on the basis of the standard assumption of negligible carryover effects after 7 half-lives, which provided a minimum washout period of 33 hours for erythromycin, 206 hours for tilmicosin, and 42 hours for tylosin. On this basis, 48 hours provided an adequate washout period after erythromycin, tylosin, and saline solution injections, but there may have been an inadequate washout period after tilmicosin injection. This was not considered to be of major importance because a duplicated Latin square design was used that minimized the effect of an inadequate washout period. Moreover, because the prokinetic effect of tilmicosin was small for the first 12 hours after injection, the effect of tilmicosin injection on abomasal emptying rate at 72 hours after injection was likely to be negligible.

It is possible the investigators were aware of the treatment groups, and there existed a potential for subjectivity in ultrasonographic determination of abomasal dimensions. However, ultrasonographic T1/2 values were similar in ranking and magnitude to the effect on emptying because the percentage reduction in emptying rate for erythromycin, tylosin, and tilmicosin assessed by ultrasonographic T1/2 (30%, 15%, and 15%, respectively) approximated the values obtained for acetaminophen T1/2 (46%, 14%, and 23%, respectively). It is unlikely that concurrent administration altered the pharmacokinetics of acetaminophen because acetaminophen and macrolides are metabolized by different cytochrome P450 microsomal systems.

We do not believe that the few administrations of xylazine to facilitate IV catheterization at least 12 hours before the start of an experiment confounded our results, even though xylazine prolongs gastrointestinal transit time in a number of species. The T1/2 of elimination of xylazine in cattle is approximately 30 minutes, and it is standard practice to assume negligible carryover effects of a drug after 7 half-lives, which is equivalent to 3.5 hours for xylazine. Xylazine decreases reticuloruminial motility in ruminating cattle in a dose-dependent manner. The IV administration of xyl-
lazine (0.05 mg/kg) to 3-month-old calves and adult cattle inhibited ruminal motility for a mean of 32 and 48 minutes, respectively, whereas higher doses of xylazine (0.10 and 0.26 mg/kg, IV) decreased ruminal motility in adult cattle for approximately 125 minutes and 140 minutes, respectively. The IM administration of a combination of atropine (0.05 mg/kg) and xylazine (0.20 mg/kg) resulted in decreased abomasal and duodenal motility for up to 6 hours in adult cattle. Therefore, it is likely that gastrointestinal tract motility had returned to a normal physiologic state by 6 hours after IM injection of xylazine at a dosage of 0.20 mg/kg.

We believe the results of the study reported here, which was conducted in calves suckling milk replacer, can be extrapolated to adult cattle that have a functional forestomach for 3 reasons. First, the abomasal volume of adult cattle contains approximately 2 to 3 L of fluid, which is similar to the 2-L volume of milk replacer suckled by the calves. Second, abomasal emptying in suckling calves and adult cattle is best characterized as liquid-phase emptying because milk is a fluid and abomasal contents in adult ruminants are 95% to 97% water. Finally, administration of erythromycin (10 mg/kg, IM) to lactating dairy cows after surgical correction of left displaced abomasum causes the time to maximal α-xylene concentration to be decreased by 41% relative to untreated control cattle. The magnitude of the change in Tmax induced by erythromycin in adult cattle of that study was similar to that observed in the study reported here in suckling calves (46% reduction in acetaminophen Tmax). Additional studies are required to confirm that lacosam and tulathromycin exert a weak prokinetic effect in adult cattle, similar to the effect in suckling calves.

Erythromycin lactobionate was used in the study reported here instead of erythromycin base in propylene glycol because of the temporary unavailability of the commercial product. We elected to use the same dose rate (8.8 mg/kg) and route of administration (IM) that have been reported elsewhere to assist in comparison between studies and because IM administration results in a longer duration of effects in adult cattle than does IV administration. Erythromycin is labeled for the treatment of cattle with pneumonia and respiratory tract disease; tylosin is labeled for the treatment of cattle with pneumonia and respiratory tract disease; and tilmicosin is labeled for treating adult cattle of that study to assist in comparing the results of this study with those of the study conducted in calves suckling milk replacer. Second, abomasal emptying rate is clinically important. Therefore, we administered the 3 macrolides in an extralabel manner. It is clearly inappropriate to administer an antimicrobial for a nonantimicrobial effect (such as increasing abomasal emptying rate) because such use may unnecessarily promote the development of antimicrobial resistance. However, cattle severely affected with pneumonia, calf diphtheria, foot rot, and metritis typically have decreased reticulorumininal motility and are therefore likely to have a decrease in gastrointestinal tract motility. Accordingly, the beneficial effect of macrolide administration in sick cattle may be an increase in abomasal emptying rate. However, it remains to be determined whether macrolide-induced acceleration of the abomasal emptying rate is clinically important.

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