Comparison of nuclear scintigraphy and acetaminophen absorption as a means of studying gastric emptying in horses

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Objective—To evaluate the correlation between half-time of liquid-phase gastric emptying (T_{50}), determined with nuclear scintigraphy using technetium Tc 99m pentetate, and absorption variables of orally administered acetaminophen.

Animals—6 mature horses.

Procedure—Technetium Tc 99m pentetate (10 mCi) and acetaminophen (20 mg/kg of body weight) were administered simultaneously in 200 ml of water. Serial left and right lateral images of the stomach region were obtained with a gamma camera, and T_{50} determined separately for counts obtained from the left side, the right side and the geometric mean. Power exponential curves were used for estimation of T_{50} and modified R^2 values for estimation of goodness of fit of the data. Serial serum samples were taken, and acetaminophen concentration was determined, using fluorescence polarization immunoassay. Maximum serum concentration (C_{max}), time to reach maximum serum concentration (T_{max}), area under the curve for 240 minutes and the absorption constant (K_a) were determined, using a parameter estimation program. Correlations were calculated, using the Spearman rank correlation coefficient.

Results—Correlations between T_{50} and T_{max} and between T_{50} and K_a were significant.

Conclusions and Clinical Relevance—T_{max} and K_a are valuable variables in the assessment of liquid-phase gastric emptying using acetaminophen absorption. Acetaminophen absorption may be a valuable alternative to nuclear scintigraphy in the determination of gastric emptying rates in equine patients with normally functioning small intestine. (*Am J Vet Res* 2000;61:310–315)

Gastric emptying disorders have been associated with different disease syndromes in horses. Murray[1] suggests abnormal gastric emptying as a possible underlying problem causing gastric and esophageal ulceration. Additionally, pyloric stricture subsequent to severe ulceration can lead to mechanical obstruction and gastric outflow disorders.[1] Although the role of gastric emptying in syndromes such as duodenitis/proximal jejunitis and postoperative ileus has not been fully characterized, altered gastric emptying likely may be a component of these disorders.

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Clinically, it has been challenging to assess gastric emptying in horses. Gastric intubation and aspiration methods are laborious and require horses to be compliant. Contrast radiographic studies are often unsatisfactory, because they can define anatomy and reveal mechanical obstructions but cannot provide quantitative information on the rate of gastric emptying.[2] Objective evaluation of response to treatment to promote gastric emptying has the same limitations. Nuclear scintigraphy greatly improves diagnosis of impaired gastric emptying, because it allows calculation of emptying variables, such as the half-time of gastric emptying (ie, the time at which 50% of the initially administered volume has emptied from the stomach).[3] It has become the standard technique for evaluation of gastric emptying, because it is accurate, sensitive, quantitative, and easy to perform.[2] Nuclear scintigraphy, however, has certain limitations for its clinical use. The necessary equipment is expensive to acquire and maintain, and special training of personnel is needed to work with radioactive materials and to operate this equipment. The procedure involves oral administration of a radioactive isotope with subsequent serial imaging of the stomach region. Exposure of horses and personnel involved in the procedure to radioactive material (eg, contact with contaminated reflux) must be considered. In some instances, cost and effort associated with the procedure may be deemed prohibitive. Alternative methods for the evaluation of gastric emptying in horses are therefore desirable.

Indirect determination of the gastric emptying rate by evaluating the absorption rate of orally administered **acetaminophen (AP)** has been investigated in humans.[4] Following oral administration, AP is absorbed almost exclusively in the proximal portion of the small intestine[5] and can be measured in the serum or plasma. Study results indicate that the rate-limiting step for absorption of AP is the rate of gastric emptying[5] so long as the small intestine is functioning normally. Significant correlations have been demonstrated between the half-time of liquid-phase gastric emptying (determined by sequential scintiscanning technique, using indium In 113m pentetate) and the maximum plasma concentration of AP, time to reach the peak concentration, and the plasma concentrations at 30 and 60 minutes after administration to humans.[4] No correlation between gastric emptying half-time and any of the AP absorption variables could be determined in an experiment using a semi-solid meal in humans.[6] Acetaminophen, therefore, appears to be a reliable marker only of liquid-phase gastric emptying. Because this test is cheaper, safer and easier to perform than nuclear scintigraphy, it could potentially be beneficial in measuring gastric emptying in experimental studies and clinical trials in the horse. Acetaminophen absorption has been used in horses to investigate the effect of different potentially prokinetic drugs on the rate of gastric emptying.[7,a] To our knowledge, validation of this method in horses, using an accepted standard such as nuclear scintigraphy, has not been reported.

The objective of our study was to investigate the correlation of the half-time of gastric emptying determined by nuclear scintigraphy using technetium Tc 99m pentetate with pharmacokinetic variables of AP in horses. The purposes of our study were to investigate whether the AP assay was a valid test to measure gastric emptying of liquids in horses and to determine which of the absorption variables most accurately reflected the rate of gastric emptying.

Materials and Methods

Horses—Six horses from the Texas A&M University research herd were used for the study. None of the horses had clinical signs of gastrointestinal tract disease. There were 5 geldings and 1 mare of different breeds (3 Quarter Horses, 2 draft horses, and 1 Arabian). Median age of these horses was 10.5 years (range, 6 to 24 years). Body weight ranged from 378 to 665.9 kg (median, 491.4 kg). The protocol for the study was approved by the Texas A&M University Laboratory Animal Care Committee. Horses were kept in paddocks and fed a complete diet of pelleted feed.[b] They were adapted to the ration for at least 7 days prior to the experiments. The horses had free access to water. After termination of the study, the horses were returned to the research herd.

Procedure and instrumentation—All experiments were conducted at the Texas A&M University College of Veterinary Medicine. For all experiments, the room and equipment used and the people conducting the experiment were the same. The experimental protocol was performed twice on each horse with a period of at least 3 days in between trials. Eighteen hours before each experiment, feed and water were withheld to allow emptying of ingesta from the stomach. The horses were brought into the large animal nuclear scintigraphy room where they were restrained with a halter and lead rope. An intravenous catheter for blood sampling was inserted aseptically into a jugular vein. A total of 20 mg of AP/kg of body weight and 10 mCi of technetium Tc 99m pentetate, in a volume of 200 ml of water, were administered simultaneously via nasogastric intubation. Immediately after administration, the first scintigraphic image was obtained (time 0). The gamma camera[c] was positioned for sequential acquisition of right and left lateral images. Images were obtained for 30 seconds each, utilizing a 64×64 matrix. Acquisition times were at 0, 10, 20, 30, 45 and 60 minutes after administration of the radioisotope, and every 30 minutes thereafter for a total of 240 minutes.

Blood samples for determination of serum AP concentration were taken from the intravenous catheter at baseline (time 0), and at 5, 10, 20, 30, 45, 60, 75 and 90 minutes after administration of AP, and every 30 minutes thereafter until 240 minutes. Serum concentration of AP was determined by use of **fluorescence polarization immunoassay (FPIA)**.[d] Assay validation of the FPIA produced a lower limit of quantification of 2 µg/ml in horse serum. Human control samples were used to assure machine calibration on each day before samples were run. Equine control samples were run with every 20 test samples. The coefficient of variation for the medium (15 µg/ml) control concentration in horse serum was 3.465%.

Data analyses—Regions of interest (stomach) were drawn on the computerized scintigraphic images using a nuclear medicine software program.[8] The total number of counts in the region of interest was recorded for each image and the geometric mean (square root of the product of counts from the left and right sides) determined for each time point. Values were corrected for radioactive decay of the isotope, using the following formula:

$$A = A_0 e^{-\lambda t}$$

with A = corrected count at time t, A_0 = initial count, λ = decay constant ($0.693/t_{0.5}$ with $t_{0.5}$ = half-life of isotope), and t = acquisition time point in minutes after time 0. Count data were plotted against elapsed time.

The half-time of gastric emptying was estimated from the data by fitting power exponential curves using the following equation:

$$y = 2^{-(t/t50)^{\beta}}$$

where y = percentage of counts remaining in the stomach at time t, t_{50} = estimated time at which 50% of counts remain in the stomach (half-time) and β = indicator of lag time prior to gastric emptying.[3] $\beta = 1$ makes the emptying curve a simple exponential curve, $\beta > 1$ indicates an initial lag period prior to emptying, and $\beta < 1$ indicates rapid early emptying. Values for t_{50} and β were estimated with nonlinear least squares regression using statistical software.[e] Values of a modified R^2 were used as an estimate of the goodness-of-fit.[3] **Gastric emptying half-times (t_{50})** were calculated separately, using counts obtained from the right side only, the left side only, and the geometric mean.

Acetaminophen absorption—Serum samples were submitted in duplicate to the Texas A&M University clinical pharmacology laboratory for determination of serum AP concentration using FPIA. Data were subjected to pharmacokinetic analysis using a parameter estimation program.[f] The models were defined by exponential equations having the general mathematic formula as follows:

$$C_p = \sum_{i=0}^{n} A_i e^{-ki(t)}$$

where C_P is the concentration of AP at any time (t), the coefficient A_i is the y intercept of the ith exponential term, and k_i is the slope of the ith exponential term (ie, the terminal elimination rate constant). Selection of the best-fit model using residual analysis was done on the basis of statistical model selection criteria that relate the number of exponential terms in the model to the total variance accounted for by the model. Using the parameter estimation program, the **appearance rate constant (K_a), maximum serum concentration (C_{max}), time until maximum serum concentration (T_{max})**, and the **area under the curve for 240 minutes (AUC_{240})** were determined.

Statistical analyses—Correlations between the half-time for gastric emptying and the AP absorption variables were evaluated, using **Spearman rank correlation coefficient (SRCC)**. Correlations between results of the 2 study days for each variable (T_{50}, K_a, T_{max}, C_{max}, AUC_{240}) were calculated for each horse, using SRCC. Correlations between values for T_{50} obtained from the left side only, the right side only, and the geometric mean were calculated, using SRCC. Results were considered significant for values of $P \leq 0.05$.

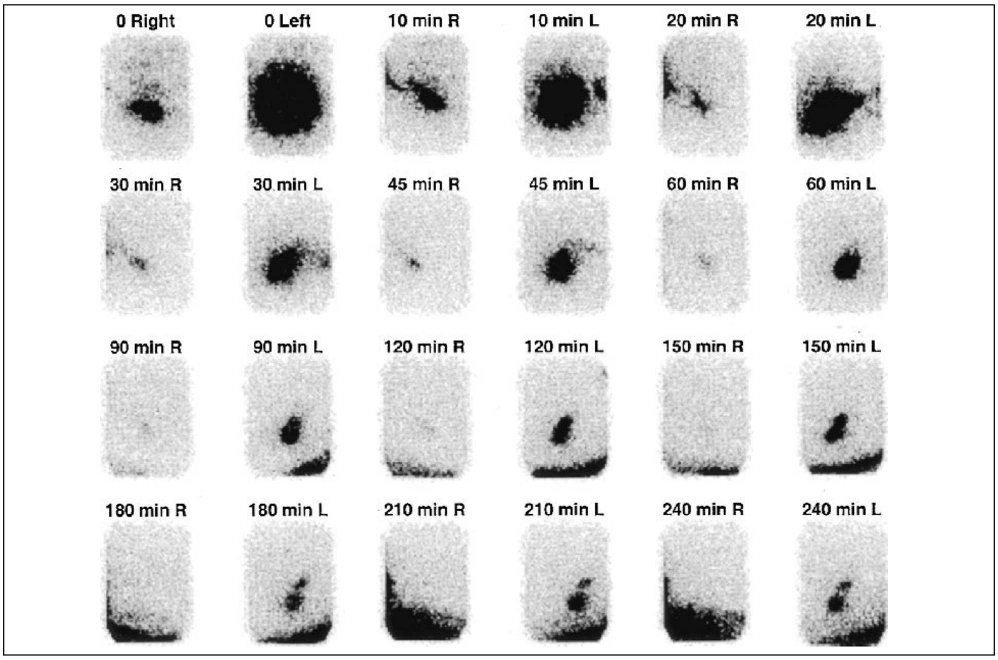

Figure 1—Left and right lateral nuclear scintigraphic images of the stomach region of a horse after 20 mg of acetaminophen/kg of body weight and 10 mCi of technetium Tc 99m pentetate, in a volume of 200 ml of water, were administered simultaneously via nasogastric intubation. The gastric emptying study included right and left lateral acquisitions; times after administration of isotope are indicated. Notice the difference in image quality of the right versus the left lateral views at a given time point.

Table 1—Nuclear scintigraphic variables used to determine gastric emptying in 6 horses (A–F) after technetium Tc 99m pentetate (10 mCi, PO) administration

	Trial 1 horses						Trial 2 horses				
Measurements	**A**	**B**	**C**	**D**	**E**	**F**	**A**	**B**	**C**	**D**	**F**
Left side											
T_{50}*	14.0	71.7	29.1	10.8	39.6	21.5	19.2	74.0	47.5	11.6	16.6
β	1.22	1.82	0.95	0.86	1.14	1.14	1.17	1.26	2.94	0.91	1.2
R^2	0.99	0.99	0.99	0.98	0.99	0.99	0.99	0.99	0.99	0.98	0.99
Right side											
T_{50}	16.7	45.0	26.8	26.3	23.2	70.2	31.4	6.8	44.6	30.3	30.0
β	4.76	753.7	2.73	3.09	2.53	22.19	1.32	0.79	37.15	8.38	70.18
R^2	0.99	0.41	0.99	0.99	0.99	–0.79	0.99	0.99	0.56	0.89	0.71
Geometric mean†											
T_{50}	13.9	45.1	27.8	16.6	26.2	21.6	23.3	14.3	44.9	21.2	22.9
β	2.0	29.78	1.69	1.24	1.91	15.89	1.14	0.79	43.26	1.68	1.25
R^2	0.99	0.72	0.92	0.98	0.99	0.02	0.99	0.99	0.88	0.99	0.96

*Only values for T_{50} obtained from left lateral images were used for statistical analysis. †Geometric mean was determined from the square root of the product of counts from the left and right sides.

T_{50} = Estimated time in minutes at which 50% of counts remain in the stomach (half-time). β = Indicator of lag time prior to gastric emptying (β = 1 indicates a simple exponential curve, β > 1 indicates an initial lag period prior to emptying, and β < 1 indicates rapid early emptying). R^2 = Goodness of fit by sides.

Results

All horses remained free of gastrointestinal disorders during the study period. One horse was fed a modified ration,[g] because it would not eat the standard ration. No adverse reactions were identified following nasogastric administration of technetium Tc 99m pentetate and AP.

Eleven experiments with 6 horses in 2 trials were used for statistical analysis. Data from the second trial for 1 horse could not be used, because the obtained AP concentrations did not fit into any drug-absorption model using the parameter estimation program. There was no significant correlation between study days for values of T_{50} and AP absorption variables. Consequently, we treated the 2 observations obtained from each horse as independent. The net effect of this assumption would have been to overestimate the observed correlations between nuclear scintigraphy and AP absorption.

Nuclear scintigraphy—Right lateral images did not allow definition of an area of interest past 60 minutes in most instances. Consistently, the area of interest was smaller when seen from the right side than it was in the equivalent left lateral image (**Fig 1**). Calculations using left lateral images resulted in higher modified R^2 values than calculations using right lat-

Table 2—Pharmacokinetic variables used to determine gastrointestinal absorption of acetaminophen (20 mg/kg of body weight, PO) in 6 horses (A–F)

	Trial 1 horses						Trial 2 horses				
Variable	A	B	C	D	E	F	A	B	C	D	E
C_{max} (µg/ml)	21.64	13.1	16.64	15.72	20.29	19.63	21.49	13.18	16.54	16.71	19.61
T_{max} (min)	31.28	87.27	47.7	34.25	62.15	64.03	44.0	57.04	74.48	35.13	27.89
AUC_{240} (µg/ml/min)	2,885.9	1,791.6	2,411.3	1,939.6	3,339.9	3,022.6	3,132.8	2,676.5	2,117.5	2,157.1	2,779.0
K_a (/min)	0.06	0.045	0.094	0.116	0.043	0.073	0.082	0.065	0.043	0.091	0.464

C_{max} = Maximum serum concentration. T_{max} = Time until maximum serum concentration. AUC_{240} = Area under the concentration-time curve for 240 min. K_a = Appearance rate constant.

eral images or the geometric mean, indicating that imaging of the stomach region from the left side yielded better fitting of the models to the data. Correlations between values for T_{50} from the right side, the left side, and the geometric mean were of low magnitude and not significant. Consequently, only values of T_{50} obtained from the left side were used for analysis. Half-times of gastric emptying (determined from left lateral images) ranged from 10.8 to 74.0 minutes with a median of 21.5 minutes (**Table 1**).

Acetaminophen absorption—The median K_a was 0.073/min^{-1} (range, 0.043 to 0.464/min^{-1}). Values for C_{max} were between 13.1 and 21.6 µg/ml (median, 16.71 µg/ml). The T_{max} ranged from 27.9 to 87.3 minutes (median, 47.7 minutes). The AUC_{240} was between 1,719.6 and 3,339.9 µg/ml/min (median, 2,676.5 µg/ml/min; **Table 2**).

Correlation between scintigraphy and AP data—The only significant correlations were between T_{50} and K_a (SRCC = –0.63, P = 0.037) and between T_{50} and T_{max} (SRCC = 0.79, P = 0.004). Correlations between T_{50} and C_{max} (SRCC = –0.47, P = 0.19) and between T_{50} and AUC_{240} (SRCC = –0.04, P = 0.916) were weak in magnitude and not significant.

Discussion

Our study investigated the correlation between 2 techniques (AP absorption[4] and nuclear scintigraphy[9]) to measure liquid phase gastric emptying in horses. Nuclear scintigraphy has been considered the standard for measuring gastric emptying in many species.[9-11] It has been used in horses to measure both gastric and cecal emptying in experimental studies assessing the effects of potential gastrointestinal tract prokinetic substances.[8,11-13,h] There are, however, substantial limitations to its clinical usefulness in regard to cost, efficacy and safety. Absorption of AP also has been used to measure gastric emptying in different species.[5,7,14] Different variables, such as maximum plasma concentration, time to reach maximum plasma concentration, and area under the concentration-time curve correlate with the rate of gastric emptying, as measured by scintigraphy, in humans.[4] Although the AP absorption has been validated in other species by comparing it with nuclear scintigraphy, there have been, to our knowledge, no such studies in the horse.

There was a wide inter- and intra-individual range of values for pharmacokinetic variables in our study. The T_{max}, for example, ranged from 27.9 to 87.3 minutes. Similar variability in pharmacokinetic variables of AP was found in a study to determine gastric emptying rates of healthy human volunteers.[15] The values of AP absorption measurements for horses in our study were different from values found in other equine studies.[7,8,h] Possible explanations for these differences include different volume of fluid administered, influence of breed, size, and age of horses; and differences in environmental circumstances and study conditions (eg, ambient temperature, time of day, influence of the study room). Because our study was limited to evaluating the correlation between 2 methods, further studies will be necessary to establish a reference range of gastric emptying values in clinically normal horses. Investigation of the possible influence of type and volume of the liquid meal on gastric emptying variables will be helpful to establish a standard test protocol. This was, however, not intended in our study. Values for T_{50} and AP variables reported in this study may, therefore, not be representative of the clinically normal equine population and should not be used as reference values. In our study, because the methods were applied simultaneously, any circumstances that would have altered the rate of gastric emptying would have had concomitant effects on results obtained by both methods. Therefore, the influence of study conditions, test meal, and test subjects on the rate of gastric emptying did not alter interpretation of results.

In one experiment, the AP concentrations from 1 horse could not be fit into any of the absorption patterns using the parameter estimation program, and, consequently, absorption variables could not be determined. This poor fit may have been attributable to abnormal absorption, enterohepatic circulation of AP, or technical error. The latter explanation was considered unlikely because of frequent verification of test accuracy. This finding indicates that AP absorption may not always yield interpretable results in each horse. Interestingly, this experiment was the only one for which it was impossible to define areas of interest in right lateral images. Calculations using counts obtained from left side images yielded the shortest emptying half-time of all experiments (5.5 minutes, data not shown). We suspect, therefore, that the unusual AP absorption data were attributable to the emptying or absorption pattern rather than to test inaccuracy.

In the study reported here, significant correlation of a given AP absorption variable with the half-time of gastric emptying, as measured by nuclear scintigraphy, was interpreted as proof of usefulness of the AP absorption variable to measure gastric emptying. Our results indicated that K_a as well as T_{max} of AP absorption were valid indicators of the rate of gastric emptying, because the only significant correlation was between T_{50} of scintigraphy and K_a and T_{max} of AP absorption, respectively. The magnitude of correlation between T_{50} and K_a (SRCC = –0.63, $P = 0.037$) was not as great as it was between T_{50} and T_{max} (SRCC = 0.79, $P = 0.004$). This may have been the result of inaccuracy in determining K_a because of poor definition of the early AP absorption curve in some instances. Seven of 11 experiments had a T_{max} of less than 60 minutes. There were, however, only 6 serum samples taken during this period, with even fewer having concentrations of AP greater than the lowest detectable concentration. To achieve accurate K_a values, more frequent sampling before T_{max} would be helpful.

Acetaminophen absorption has been used to demonstrate that cisapride[16] and yohimbine hydrochloride[a] can attenuate endotoxin-mediated delay in gastric emptying in the horse. Results of another study indicate that metoclopramide hydrochloride has prokinetic effects and atropine has inhibitory effects on gastric emptying in ponies.[7] The variables of AP absorption used to evaluate changes in the rate of gastric emptying in these studies were T_{max}, C_{max}, and AUC. If results of our study were extrapolated to other studies in which AP absorption was employed to assess gastric emptying, interpretation of some results of these studies would be different. For example, in 1 study using T_{max}, C_{max}, and AUC as variables indicating gastric emptying, significant effects were seen for atropine (T_{max}, C_{max}, and AUC), metoclopramide (T_{max}), and yohimbine (AUC).[7] If, however, according to our conclusions, AUC does not accurately reflect gastric emptying, yohimbine would not be considered to have significantly altered the rate of gastric emptying.

In this study, technetium Tc 99m pentetate and AP were administered in solution. A liquid-phase meal was chosen because of certain physical properties of AP that make it a reliable marker of gastric emptying for liquid substances[4] but not solid meals.[6] Because we were comparing AP absorption with nuclear scintigraphy, it was crucial that both methods measured the same phase.

We worked under the assumption that withoholding food for a period of 18 hours was sufficient to achieve complete emptying of the stomach. This assumption was not verified by gastroscopy; therefore, it was possible that some of the horses had residual feed in their stomach when radioisotope and AP were administered. Even if there had been residual solid feed material in the stomach of our research horses, technetium and AP would have remained in the liquid volume that was administered. Dilutional effects of residual liquid stomach contents would have influenced results of both methods equally. It is, however, possible that residual solid or liquid material in the stomach influenced the rate of gastric emptying. This may account for some of the variability between our results and the results of other studies.

The value of assessing liquid-phase gastric emptying in horses could be questioned. As the role of gastric emptying disorders in equine disease has not been investigated extensively, it is not yet certain whether emptying of solid- versus liquid-phase meals is of lesser or greater importance. In our opinion, evaluating liquid-phase gastric emptying would be clinically useful in certain conditions. Foals with severe gastric and duodenal/esophageal ulceration, for example, can have gastric emptying disorders even though they only consume a liquid (milk) diet. Similarly, postoperative ileus develops in horses that do not ingest solid feed. The ability of these horses to tolerate oral administration of fluids is often used to clinically assess when they may be started on solid food. The methods investigated in this report would be applicable to such circumstances. Clearly, it is possible that emptying disorders involving only solid-phase gastric emptying exist. This has been described in humans with diabetic gastroparesis[17] as well as in dogs with pyloric obstruction.[18] Such cases would likely need to be evaluated with techniques other than AP absorption.

Clinically normal horses were used in our study. Whether similar correlations would be observed in horses with abnormal gastric emptying remains to be determined.

It is our conclusion that AP absorption may be a valid method for evaluating gastric emptying rates in horses. Results of our study indicate that T_{max} and K_a were the pharmacokinetic measurements that best correlated with scintigraphic estimation of gastric emptying rate.

[a]Meisler SD, Doherty TJ, Abraha T, et al. The effects of yohimbine on endotoxin-induced delayed gastric emptying in horses (abstr), in *Proceedings*. 15th Am Coll Vet Intern Med Forum, 1997.
[b]Horse Chow #100, Purina Mills Inc, St Louis, Mo.
[c]Omega 500, Technicare Corp, Cleveland, Ohio.
[d]List No. 9536, 66-6300/R1, Abbott Laboratories, Diagnostic Division, Abbott Park, Ill.
[e]SAS PROC NLIN, SAS Institute Inc, Cary, NC.
[f]RSTRIP, Micromath Scientific Software, Salt Lake City, Utah.
[g]50% Horse Chow #100, 50% Omolene #200, Purina Mills Inc, St Louis, Mo.
[h]Doherty TJ, Abraha T, Keaffaber S, et al. Metoclopramide ameliorates the effect of endotoxin on gastric emptying in horses (abstract), in *Proceedings*. 15th Am Coll Vet Intern Med Forum, 1997.

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