Evaluation of acetaminophen absorption in horses with experimentally induced delayed gastric emptying

Katharina L. Lohmann, MedVet; Anne Bahr, DVM; Noah D. Cohen, VMD, PhD; Dawn M. Boothe, DVM, PhD; Allen J. Roussel, DVM, MS

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

Animals—6 mature horses.

Procedure—Delayed gastric emptying was induced by IV injection of atropine sulfate. Twenty minutes later, acetaminophen and technetium Tc 99m pentetate were administered simultaneously via nasogastric tube. Serial lateral images of the stomach region were obtained, using a gamma camera. 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 obtained, 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 480 minutes, and the appearance rate constant were determined, using a parameter estimation program. Correlations were calculated, using a Spearman rank correlation coefficient.

Results—A significant correlation was detected between T_{50} determined by use of scintigraphy and T_{max} determined by use of acetaminophen absorption. Correlation between T_{50} and other absorption variables of acetaminophen was not significant.

Conclusions and Clinical Relevance—The acetaminophen absorption method was a valid technique in this model of delayed gastric emptying in horses. The method may be a valuable tool for use in research as well as in clinical evaluation of gastric emptying in horses. (*Am J Vet Res* 2002;63:170–174)

Abnormal gastric emptying in horses may be a major factor in the pathogenesis of diseases such as gastric ulcers, duodenitis-jejunitis of the proximal portion of the jejunum, and postoperative ileus. Evaluation of gastric emptying in clinical and research settings, however, has been limited by the availability of tests that are easy to administer, reliable, safe, and economical.

Nuclear scintigraphy has become the standard technique for evaluation of gastric emptying, because it is accurate, sensitive, quantitative, and relatively easy to perform.[1] The technique allows determination of emptying variables such as the **half-time of gastric emptying (T_{50})**, which is defined as the time at which 50% of the initially administered volume has emptied from the stomach.[1] It is applicable for liquid as well as solid meals.[2] Evaluation of gastric emptying in horses by use of nuclear scintigraphy has been described.[3] However, lack of availability of equipment and trained personnel as well as health hazards attributable to possible exposure to radioactive material (eg, contaminated reflux) limits its potential for widespread use in horses.

Indirect determination of liquid-phase gastric emptying by measurement of the absorption of orally administered acetaminophen is a useful alternative to nuclear scintigraphy and has been evaluated extensively in human patients.[4-6] After oral administration, acetaminophen is absorbed almost exclusively in the proximal portion of the small intestine.[4] Assuming the small intestinal mucosa is normal, the rate of gastric emptying is the rate-limiting step in acetaminophen absorption.[4,5] The method appears to be limited to the evaluation of liquid-phase gastric emptying, because a correlation was not found between results of scintigraphic evaluation of gastric emptying and acetaminophen absorption after feeding of a semisolid meal.[7] Variables of acetaminophen absorption described in human patients include the **maximum acetaminophen concentration (C_{max})**,[5] **time to reach maximum acetaminophen concentration (T_{max})**,[5] acetaminophen concentration at 30 and 60 minutes,[5] and **area under the concentration-versus-time curve (AUC)** for the first 60 minutes after acetaminophen administration.[6] The acetaminophen absorption method has been described in horses[8] and used to evaluate the effect of prokinetic drugs on gastric emptying.[9-12] In healthy horses, there is a significant correlation between T_{50} of liquid-phase gastric emptying, as determined by use of nuclear scintigraphy, and 2 variables of acetaminophen absorption (ie, T_{max} and the **appearance rate constant [K_a]**).[13] However, C_{max} and AUC for the first 240 minutes after acetaminophen administration are not significantly correlated with T_{50}.[13] These findings indicate validity of the procedure for use in healthy horses when certain variables of

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From the Departments of Large Animal Medicine and Surgery (Lohmann, Bahr, Cohen, Roussel) and Physiology and Pharmacology (Boothe), College of Veterinary Medicine, Texas A&M University, College Station, TX 77843-4475. Dr. Lohmann's present address is Department of Large Animal Medicine, College of Veterinary Medicine, University of Georgia, Athens, GA 30602.
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acetaminophen absorption are used. To our knowledge, validation of the acetaminophen absorption method in horses with abnormal gastric emptying has not been reported.

The objective of the study reported here was to investigate the correlation of T_{50} determined by use of nuclear scintigraphy and variables of acetaminophen absorption in horses with experimentally induced delayed gastric emptying. A model of delayed gastric emptying resulting from the administration of atropine that has been described elsewhere[8] was chosen for the study. We hypothesized that 1 or more absorption variables of acetaminophen would be significantly correlated with T_{50}.

Materials and Methods

Horses—Six horses from the Texas A&M University research herd were used. None of the horses had clinical signs of gastrointestinal tract disease. Horses comprised 4 geldings and 2 mares, and there were 4 Thoroughbreds, 1 Paint, and 1 mixed-breed horse. Horses ranged from 6 to 25 years old (median, 12.5 years), and they ranged in body weight from 389.5 to 495.5 kg (median, 455.5 kg). Horses were kept in paddocks and fed a complete diet of pelleted feed[a] with unlimited access to water. They were allowed to acclimate to the ration for at least 7 days prior to the experiments. After termination of the study, horses were returned to the research herd. The protocol for the study was approved by the Texas A&M University Laboratory Animal Care Committee.

Procedure and instrumentation—All experiments were conducted at the Large Animal Nuclear Scintigraphy facility at the College of Veterinary Medicine, Texas A&M University. During experiments, horses were restrained with a halter and lead rope; tranquilizers were not used. After experiments, horses were given 2 L of mineral oil via nasogastric tube in an attempt to prevent impaction that could have resulted from possible intestinal stasis caused by atropine administration. Horses were fed half their normal ration in the evening after the experiment and were monitored for signs of colic until the next morning, at which time they were returned to the research herd.

Eighteen hours before each experiment, feed and water were withheld to allow maximal emptying of the stomach. A catheter for administration of atropine sulfate and collection of blood samples was inserted aseptically into a jugular vein. Atropine sulfate (0.018 or 0.028 mg/kg of body weight) was administered IV to induce a state of delayed gastric emptying. The dose of atropine was adjusted for each horse to ensure that T_{50} was ≥ 100 minutes. This cut-off value was determined on the basis of another study[13] conducted by our laboratory group in which horses were not treated with atropine, and T_{50} ranged from 10.8 to 74 minutes (median, 21.5 minutes). By ensuring that the T_{50} for all horses in the study was outside that previously observed range of values, we were confident that gastric emptying was indeed delayed in all horses. Unfortunately, it was not possible to use the horses from that study in this study.

Twenty minutes after atropine injection, acetaminophen (20 mg/kg) and technetium Tc 99m pentetate (10 mCi) in 1 L of water were administered via a nasogastric tube. Immediately after administration, the first scintigraphic image was obtained (time 0). At this time point, the stomach region was defined by visual assessment of radiation detected on the monitor of the gamma camera.[b] To facilitate positioning of the camera for subsequent images, the stomach region was outlined, using tape placed on the left side of each horse. Lateral images obtained on the left side were used exclusively, because we had documented previously that lateral images obtained on the right side and the geometric mean (square root of the product of lateral images obtained from the right and left sides) did not accurately reflect gastric emptying.[13] Each image was obtained during a period of 30 seconds, using a 64 × 64 matrix. Images were acquired 0, 10, 20, 30, 45, 60, 75, and 90 minutes after administration of acetaminophen and at 30-minute intervals thereafter until 480 minutes or until the stomach region was not distinguishable from the background. Blood samples were collected from the catheter in the jugular vein prior to administration of acetaminophen (baseline) and at the time each scintigraphic image was acquired.

Serum was harvested, and samples were submitted in duplicate to the Clinical Pharmacology Laboratory at Texas A&M University for determination of serum acetaminophen concentration by use of **fluorescence polarization immunoassay (FPIA)**.[c] Assay validation of the FPIA, using equine serum samples to which known amounts of acetaminophen had been added, yielded a lower limit of quantification of 2 μg/ml. For all control samples with an acetaminophen concentration > 2 μg/ml (ie, 5, 10, 15, 25, and 40 μg/ml), the coefficient of variation was < 10%. Control samples of human serum were used to ensure calibration of the machine each day before samples were analyzed. Control samples of equine serum were analyzed with every 20 test samples.

Analysis of scintigraphic images—Number of counts per pixel of each scintigraphic image was determined, using a nuclear medicine software program.[14] Regions of interest (stomach) were drawn by hand on the computerized scintigraphic images to encompass all pixels containing > 10% of the maximum count per pixel for the respective image. Total number of counts in the region of interest was recorded for each image. Values were corrected for radioactive decay of the isotope, using the following formula:

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

where A is the corrected count at time t, A_0 is the initial count, λ is the decay constant (ie, $0.693/t_{1/2}$; $t_{1/2}$ is the half-life of the isotope), and t is the time of acquisition of the image. Count data were plotted against elapsed time.

Values for T_{50} were estimated from the data by fitting power exponential curves,[15] using the following equation:

$$y = 2^{-(t/t_{50})^{\beta}}$$

where y is the percentage of counts remaining in the stomach at time t, and β is the value for lag time prior to emptying. When $\beta = 1$, the emptying curve is a simple exponential curve. Values of $\beta > 1$ indicate an initial lag period prior to emptying, and values of $\beta < 1$ indicate rapid early emptying. Values for T_{50} and β were estimated by use of nonlinear least-squares regression, using statistical software.[d] Values of a modified R^2 were used as an estimate of goodness-of-fit.

Acetaminophen absorption—Data for serum acetaminophen concentrations were subjected to pharmacokinetic analysis, using a parameter estimation program.[e] Models were defined by exponential equations that had the following general mathematical equation:

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

where C_p is the concentration of acetaminophen at any time (ie, 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, as determined by use of residual analysis, was conducted 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. Values for K_a, C_{max}, T_{max}, and AUC for the first 480 minutes after acetaminophen administration were determined, using the parameter estimation program.

Statistical analysis—Correlations between T_{50} and variables of acetaminophen absorption were evaluated, using a **Spearman rank correlation coefficient (SRCC)**. Results were considered significant for values of $P \le 0.05$.

Results

Horses—None of the horses had clinical signs of colic during the study. We did not detect any complications in the horses during the study period.

Acetaminophen absorption—In 1 of the horses, values for K_a and T_{max} could not be determined for any of the absorption patterns used by the parameter estimation program. Values for variables of acetaminophen absorption were calculated for the remaining 5 horses, and ranges and medians were as follows: K_a, 0.005 to 0.015 and 0.013/min; C_{max}, 5.1 to 11.5 and 9.1 µg/ml; T_{max}, 104.7 to 284.3 and 170.8 minutes; and AUC 1,004 to 3,932 and 2,241 µg/ml/min. Serum acetaminophen concentrations of the 6 horses over time were plotted **(Fig 1)**.

Nuclear scintigraphy—In several horses, acquisition of scintigraphic images was terminated before 480 minutes, because radioactivity had entirely left the stomach, and the stomach region could not be clearly defined. Values of T_{50} in all 6 horses ranged from 118.5 to 214.8 minutes (median, 131.5 minutes). When we considered data from only the 5 horses in which all variables of acetaminophen absorption could be calculated, T_{50} ranged from 118.5 to 214.8 minutes (median, 127.7 minutes). Values for β in all 6 horses ranged

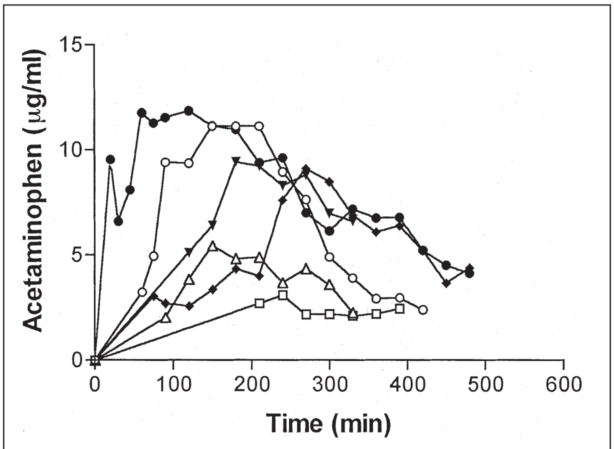

Figure 1—Serum acetaminophen concentrations in 6 horses with experimentally induced delayed gastric emptying. Horses were administered acetaminophen (20 mg/kg of body weight) via a nasogastric tube at time 0. Each symbol represents values for 1 horse. Notice the differences among horses. Values for time until the maximum serum acetaminophen concentration (T_{max}) for 5 of the horses were 144.9, 170.8, 207.4, 284.3, and 104.7 minutes, respectively. Value for T_{max} could not be calculated for the sixth horse (□) because of a flat absorption curve. Lower limit of quantification for serum acetaminophen concentration was 2 µg/ml.

from 1.66 to 9.10 (median, 2.31), indicating that all horses had a lag period prior to gastric emptying.

Correlation between scintigraphy and acetaminophen absorption—Correlations between T_{50} and variables of acetaminophen absorption were calculated, using only the 5 horses for which complete data sets were available. The only significant correlation was between T_{50} and T_{max} (SRCC = 0.9, P = 0.037). Correlation between T_{50} and K_a was of similar magnitude but was not significant (SRCC = –0.821, P = 0.089). Correlation between T_{50} and AUC (SRCC = –0.5, P = 0.391) and between T_{50} and C_{max} (SRCC = –0.6, P = 0.285) was weak in magnitude and not significant. The latter 2 correlations did not improve when data from all 6 horses were used for the analysis (SRCC = –0.37, P = 0.47 for T_{50} and AUC; SRCC = –0.48, P = 0.33 for T_{50} and C_{max}).

Discussion

In the study reported here, we investigated the correlation between nuclear scintigraphy and acetaminophen absorption for use in the determination of liquid-phase gastric emptying in horses with experimentally delayed gastric emptying. The study was performed as a sequel to a similarly designed study[13] in horses with presumably normal gastric emptying in which a significant correlation between T_{50} and T_{max} as well as between T_{50} and K_a was reported.

The study reported here verified the validity of use of the acetaminophen absorption method in horses in an atropine-induced model of delayed gastric emptying by documenting a significant correlation between T_{50} determined by a standard method (ie, nuclear scintigraphy) and 1 variable for acetaminophen absorption (ie, T_{max}). Although we did not detect a significant correlation between T_{50} and K_a, we believe this absorption variable should be evaluated further. Because of the small number of horses used, our analysis may have lacked power to detect a significant correlation. More frequent collection of blood samples during the time period preceding T_{max} also may have been helpful in more accurately determining K_a and may have improved the magnitude of its correlation with T_{50}. For example, only 3 or 4 blood samples were obtained from 3 horses for serum acetaminophen determination before T_{max} was reached. This perceived inaccuracy of K_a determination represents a potential limitation for the use of this variable in a clinical setting, where frequent collection of blood samples may be undesirable. The lack of correlation between T_{50} and C_{max} or between T_{50} and AUC was not surprising in light of the results of our previous study[13] and does not diminish the validity of the acetaminophen absorption method in general.

It was not possible to determine all variables for acetaminophen absorption in all of the horses used in this study. One of the horses had an extremely flat absorption curve, and consequently, none of the absorption patterns provided by the parameter estimation program fit the data appropriately enough to calculate T_{max} and K_a. Possible explanations for the low absolute serum concentrations of acetaminophen in this horse, compared with the concentrations in the other horses, include differences in intestinal permeability, intestinal blood flow, and hepatic metabolism. Because T_{50} of that horse was similar to values for the other horses, excessive prolongation of gastric emptying itself was not believed to be responsible for the low absolute acetaminophen concentration. Interestingly, a similar problem was observed in our previous study[13] in 1 horse that had extremely rapid gastric emptying ($T_{50,}$ 5.5 minutes). Whereas sample collection during the early absorption period may simply have not been sufficiently frequent in that former study, procedural factors were unlikely to be responsible for our inability to calculate variables for acetaminophen absorption in the horse of the study reported here. Unfortunately, we did not repeat the experiment to investigate whether that horse would consistently have lower serum acetaminophen concentrations than the other horses or whether increasing the dose of acetaminophen would improve determination of acetaminophen absorption variables.

We used atropine administered by IV injection to induce delayed gastric emptying in the horses reported here. The drug can delay gastric emptying in humans[16,17] and rats,[18] and its inhibitory effect on gastrointestinal motility in horses has been recognized as a cause of colic.[19] In humans, atropine affects the initial phase of adaptive gastric relaxation and the subsequent phase of mono-exponential gastric emptying.[17] In rats, atropine can delay gastric emptying without altering the type of emptying kinetics.[18] Although atropine may not accurately reflect delayed gastric emptying attributable to gastrointestinal tract disease in horses, its use in experiments has been described.[8] The atropine model was deemed appropriate for the study reported here, because our objective of investigating the correlation between results of 2 simultaneously performed techniques could be fulfilled regardless of the exact pathophysiologic mechanism for delay of gastric emptying. To our knowledge, the effect of atropine on gastric emptying kinetics in horses has not been described. In the study reported here, all calculated power exponential curves had values for $\beta > 1$; however, there did not appear to be a direct correlation between the magnitude of values for β and T_{50}. Therefore, atropine appeared to have a more complex effect than merely increasing the duration of the lag period prior to gastric emptying. However, an increase in duration of the lag period was observed in this study, compared with results for our previous study[13] in which values for β ranged from 0.86 to 2.94 (median, 1.17).

Reference values for variables of gastric emptying that can be used for horses have not yet been established. Although a number of studies have evaluated gastric emptying in horses, only a few horses were used in each study, and the methods used to measure gastric emptying varied. In studies[8-13] that describe the use of acetaminophen absorption, the type and volume of the liquid meal, method used to determine serum acetaminophen concentrations, and duration of the study period differ. Except for 1 study,[13] scintigraphy and acetaminophen absorption have not been performed simultaneously. Despite these concerns, there are similarities in the findings among these studies, which may serve as preliminary guidelines for the evaluation of gastric emptying in horses. Scintigraphic studies[3,13,f] of gastric emptying in horses without pharmacologic alteration of gastric motility yielded values for T_{50} of approximately 30 minutes. Differences among horses appear to be considerable, as indicated by a range of 10.8 to 74 minutes in 1 study.[13] Also, the type of liquid meal appears to influence the rate of gastric emptying, because 1 study[f] revealed a significant increase in mean T_{50} when a 25% dextrose solution was used instead of water as the liquid meal (371.1 vs 26.7 minutes). Using the acetaminophen absorption method, values for T_{max} between 30 and 50 minutes have been reported for clinically normal horses.[8-13] Similar to T_{50}, differences among horses for this variable were considerable, with a range of 27.9 to 87.3 minutes in 1 study.[13] In other studies[9-12] in which gastric emptying was delayed by administration of endotoxin, a significant increase in T_{max} was detected, with values of approximately 130 to 150 minutes. Therefore, those values match the results of the study reported here, although a different model of delayed gastric emptying was used. One study[8] in which atropine was used to induce a delay in gastric emptying had a smaller increase in T_{max} from 31 to 62 minutes. This was surprising, because those investigators used a dose of atropine (0.025 mg/kg) that was similar to the dose used in the study reported here. Some of the factors that may have been responsible for the discrepancy in results are the use of ponies versus horses, differences in feeding regimen prior to evaluation of gastric emptying, and a smaller volume of liquid meal administered (350 ml vs 1 L). Other factors such as environmental conditions or the degree of excitement in the horses may also have played a role.

Overall, it appears premature at this time to define a value for T_{50} or T_{max} beyond which gastric emptying should be considered abnormal. For the purpose of this study, we chose a cutoff value for T_{50} of > 100 minutes to define delayed gastric emptying. This value was based on results of another study[13] in a relatively small number of horses and should, at most, be used as a guideline to define delayed gastric emptying in general. Evaluation of a larger number of animals, using a standardized protocol, is needed before reference ranges can be established for variables of gastric emptying in horses. Future studies also may define additional valid variables for acetaminophen absorption that would allow less frequent collection of blood samples. In human patients, for example, use of the AUC for the first 60 minutes after acetaminophen administration has been described.[6]

Acetaminophen absorption provides a convenient, safe, and relatively inexpensive method for the measurement of liquid-phase gastric emptying and may be applicable in research and clinical settings. Investigations concerning the pathophysiologic characteristics of gastrointestinal tract diseases in horses or the effects of prokinetic drugs should include measurements of liquid- and solid-phase gastric emptying. Although dual-phase scintigraphic studies[g] on gastric emptying have been described in horses, the necessary equipment may not always be available, and alternative means of liquid-phase measurement may be desirable. Clinical conditions in which liquid-phase gastric emptying can be expected to be altered include esophageal, gastric, and duodenal ulcers in suckling foals and adult horses, duodenitis-jejunitis of the proximal portion of the jejunum, and postoperative ileus in colic patients. Although gastric reflux is frequently evident in these conditions and would prevent the use of an absorption method, we believe that delayed gastric emptying may occur even when there is not measurable gastric reflux. Therefore, measurement of liquid-phase gastric emptying may be useful for complete patient evaluation and monitoring of disease progression or response to medication. In postoperative patients, measurements of gastric emptying may further facilitate the assessment of tolerance to enteral feeding. A potential caveat for the acetaminophen absorption method is its use in patients with abnormal absorptive function of the small intestines, such as may develop with inflammatory bowel disease. Additional studies will be necessary to establish the usefulness of the acetaminophen absorption method under such conditions.

[a]Horse Chow No. 100, Purina Mills Inc, St Louis, Mo.

[b]Omega 500, Technicare Corp, Cleveland, Ohio.

[c]List No. 9536, 66-6300/R1, Abbott Laboratories, Diagnostic Division, Abbott Park, Ill.

[d]SAS, version 8.0, SAS Institute Inc, Cary, NC.

[e]RSTRIP, Micromath Scientific Software, Salt Lake City, Utah.

[f]Sojka JE. The effect of dietary composition on gastric emptying rate in ponies (abstr), in *Proceedings*. 3rd Equine Colic Res Symp 1988;24.

[g]Neuwirth L. Dual-phase gastric emptying in horses (abstr), in *Proceedings*. 5th Equine Colic Res Symp 1994;11.

References

1. Thrall JH, Ziessman HA. Gastrointestinal system. In: Thrall JH, ed. *Nuclear medicine—the requisites.* St Louis: Mosby-Year Book Inc, 1995;235–240.
2. Akkermans LMA, Van Isselt JW. Gastric motility and emptying studies with radionuclides in research and clinical settings. *Dig Dis Sci* 1994;39:95S–96S.
3. Ringger NC, Lester GD, Neuwirth L, et al. Effect of bethanecol or erythromycin on gastric emptying in horses. *Am J Vet Res* 1996;57:1771–1775.
4. Clements JA, Heading RC, Nimmo WS, et al. Kinetics of acetaminophen absorption and gastric emptying in man. *Clin Pharmacol Ther* 1978;24:420–431.
5. Heading RC, Nimmo J, Prescott LF, et al. The dependence of paracetamol absorption on the rate of gastric emptying. *Br J Pharmacol* 1973;47:415–421.
6. Tarling MM, Toner CC, Withington PS, et al. A model of gastric emptying using paracetamol absorption in intensive care patients. *Intensive Care Med* 1997;23:256–260.
7. Petring OU, Adelhøj B, Ibsen M, et al. The relationship between gastric emptying of semisolids and paracetamol absorption. *Br J Clin Pharmacol* 1986;22:659–662.
8. Doherty TJ, Andrews FM, Provenza MK, et al. Acetaminophen as a marker of gastric emptying in ponies. *Equine Vet J* 1998; 30:349–351.
9. Valk N, Doherty TJ, Blackford JT, et al. Effect of cisapride on gastric emptying in horses following endotoxin treatment. *Equine Vet J* 1998;30:344–348.
10. Valk N, Doherty TJ, Blackford JT, et al. Phenylbutazone prevents the endotoxin-induced delay in gastric emptying in horses. *Can J Vet Res* 1998;62:214–217.
11. Doherty TJ, Andrews FM, Abraha TW, et al. Metoclopramide ameliorates the effects of endotoxin on gastric emptying of acetaminophen in horses. *Can J Vet Res* 1999;63:37–40.
12. Meisler SD, Doherty TJ, Andrews FM, et al. Yohimbine ameliorates the effects of endotoxin on gastric emptying of the liquid marker acetaminophen in horses. *Can J Vet Res* 2000;64:208–211 .
13. Lohmann KL, Roussel AJ, Cohen ND, et al. Comparison of nuclear scintigraphy and acetaminophen absorption as a means of studying gastric emptying in horses. *Am J Vet Res* 2000;61:310–315.
14. *NUCLEAR MAC user's manual: version 2.7*. Littleton, Colo: Scientific Imaging Inc, 1995;E7.
15. Elashoff JD, Reedy TJ, Meyer JH. Analysis of gastric emptying data. *Gastroenterology* 1982;83:1306–1312.
16. Lidums I, Hebbard GS, Holloway RH. Effects of atropine on proximal gastric motor and sensory function in normal subjects. *Gut* 2000;47:30–36.
17. Rashid MU, Bateman DN. Effect of intravenous atropine on gastric emptying, paracetamol absorption, salivary flow and heart rate in young and fit elderly volunteers. *Br J Clin Pharmacol* 1990; 30:25–34 .
18. Scarpignato C, Girone MG, Tirelli F, et al. Inhibition of gastric emptying and secretion by pirenzepine and atropine in rats. *Eur J Pharmacol* 1984;101:193–200.
19. Ducharme NG. Gastrointestinal complications associated with the use of atropine in horses. *J Am Vet Med Assoc* 1983;182:229–231.