Horses of all types of breeds and uses are susceptible to musculoskeletal diseases that result in lameness. Of all reported conditions, lameness ranks as one of the most common causes for poor performance in horses used for racing. Investigators have reported that lameness was ranked as the number 1 health problem affecting horses. Lameness may require veterinary treatment and care and can cause reductions in the time available for use, future athletic ability, and value. Furthermore, a permanent loss of use may be the result of severe musculoskeletal disease.

Lameness-induced pathological bone conditions include, but are not limited to, pedal osteitis, navicular disease, osteochondrosis, osteochondritis, metacarpal disease, sesamoiditis, subchondral bone disease, and fractures. Conventional treatment of lameness is generally implemented after the acute onset of clinical signs. Currently, few strategies exist to prevent development of skeletal disease or to improve or restore bone quality after injury. Tiludronate disodium, a non–nitrogen-containing biphosphonate drug, affects osteoclastic activity and has been used to prevent the resorption of bone in humans. Tiludronate is currently licensed for use in horses in Europe and is authorized by the FDA for compassionate use in the United States. Prospective clinical studies have been conducted to evaluate the use of tiludronate (1 mg/kg, IV, q 24 h for 10 days) in the treatment of navicular disease, arthritis in the distal portion of the tarsus, disuse osteopenia, and osteoarthritis of the thoracolumbar vertebrae, and results determined that the drug was efficacious.

Pharmacokinetics of gallium maltolate after intragastric administration in adult horses

Carolyn Arnold, DVM; M. Keith Chaffin, DVM, MS; Noah Cohen, VMD, MPH, PhD; Virginia R. Fajt, DVM, PhD; Robert J. Taylor, PhD; Lawrence R. Bernstein, PhD

Objective—To determine the pharmacokinetics of gallium maltolate (GaM) after intragastric administration in adult horses.

Animals—6 adult horses.

Procedures—Feed was withheld for 12 hours prior to intragastric administration of GaM (20 mg/kg). A single dose of GaM was administered to each horse via a nasogastric tube (time 0). Blood samples were collected at various time points from 0 to 120 hours. Serum was used to determine gallium concentrations by use of inductively coupled plasma-mass spectroscopy. Noncompartmental and compartmental analyses of serum gallium concentrations were performed. Pharmacokinetic models were selected on the basis of the Akaike information criterion and visual analysis of plots of residuals.

Results—Serum concentration data for 1 horse were such that this horse was considered an outlier and excluded from noncompartmental and compartmental analyses. Noncompartmental analysis was used to determine individual pharmacokinetic parameters. A 1-compartment model with first-order input and output and lag time was selected as the best-fit model for the data and used to determine mean ± SD values for maximum observed serum concentration (0.28 ± 0.09 µg/mL), time of maximum concentration (3.09 ± 0.43 hours), time to the first measurable concentration (0.26 ± 0.11 hours), apparent elimination half-life (48.82 ± 5.63 hours), area under the time-concentration curve (20.68 ± 7.57 h·µg/mL), and apparent volume of distribution (73,493 ± 18,899 mL/kg).

Conclusion and Clinical Relevance—Further studies are necessary to determine the bioavailability of GaM after intragastric administration in adult horses. (Am J Vet Res 2010;71:1371–1376)

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Conclusion and Clinical Relevance—Further studies are necessary to determine the bioavailability of GaM after intragastric administration in adult horses. (Am J Vet Res 2010;71:1371–1376)
Gallium, a trivalent semimetallic element (group IIIa), is a novel therapeutic drug that may be useful in horses for the prevention of skeletal disease or aid in the restoration of bone quality after injury. Gallium was originally used during diagnostic imaging procedures of humans with neoplasia and osteomyelitis. Gallium was found to inhibit bone resorption and thereby lower the plasma concentration of calcium. In human medicine, gallium is approved for use in the treatment of hypercalcemia of malignancy and Paget’s disease. Gallium also affects osteoclastic activity by inhibiting a vacuolar-class ATPase or a surface proton pump while not affecting the recruitment or viability of osteoclasts. To be effective, gallium must adsorb to the cortex of bone to affect osteoclastic activity. Gallium concentrates in regions of bones undergoing increased bone metabolism such as the epiphyseal growth plate of juvenile animals and the periosteal and endosteal surfaces of bone. In addition to modulating bone resorption, GaM was found to inhibit bone resorption and thereby lower the plasma concentration of calcium. In human medicine, gallium is approved for use in the treatment of hypercalcemia of malignancy and Paget’s disease. Gallium also affects osteoclastic activity by inhibiting a vacuolar-class ATPase or a surface proton pump while not affecting the recruitment or viability of osteoclasts. To be effective, gallium must adsorb to the cortex of bone to affect osteoclastic activity. Gallium concentrates in regions of bones undergoing increased bone metabolism such as the epiphyseal growth plate of juvenile animals and the periosteal and endosteal surfaces of bone. In addition to modulating bone resorption by osteoclasts, findings of another study indicate that gallium may have an anabolic effect on bone.

Gallium nitrate, a citrate-chelated solution, is the currently available formulation of gallium approved for use in humans; however, when administered IV, this formulation can form precipitates with calcium and phosphorous in the renal tubules and, thus, can cause nephrotoxicosis. To prevent nephrotoxicosis, gallium nitrate is administered IV as a constant rate infusion (5 mg/kg, q 24 h for 5 days). However, a similar treatment regimen is likely to be impractical when used in horses.

Gallium maltolate (tris [3-hydroxy-2-methyl-4H-pyran-4-onato] gallium [III]) is a novel preparation of gallium that may be an alternative to the use of gallium nitrate. Gallium maltolate is readily absorbed by the gastrointestinal tract, and there is less renal excretion of GaM, compared with the renal excretion of gallium nitrate. In humans, GaM has good oral bioavailability (25% to 57%) with linear rates of absorption and elimination after the administration of doses ranging from 100 to 500 mg. In addition, GaM has been investigated as a novel agent for the prevention and treatment of pneumonia caused by Rhodococcus equi in foals. Furthermore, GaM is readily absorbed and well tolerated after intragastric or oral administration in foals. The purpose of the study reported here was to determine the pharmacokinetics of GaM after intragastric administration in healthy adult horses.

Materials and Methods

Animals—Four mares and 2 geldings that ranged in age from 3 to 17 years old (mean, 9 years old) were included in the study. Breeds of these horses included Quarter Horse (n = 4), Thoroughbred (1), and American Paint Horse (1). A physical examination was performed on each horse 2 days before the start of the study; in addition, body weight of each horse was recorded, and a blood sample was collected for a CBC and serum biochemical analysis. Each horse was housed separately in a box stall for the duration of the study (3 days). The diet consisted of a ration of coastal hay and a commercially available grain-based diet. Feed was withheld for 12 hours prior to the administration of GaM, but horses again were fed 8 hours after GaM administration. Water was not withheld during the study. Horses were observed daily for signs of adverse reactions. This study was approved by the Texas A&M University Institutional Animal Care and Use Committee.

Administration of GaM—Each horse was restrained with a nose twitch for nasogastric intubation with a nasogastric tube equipped with a funnel. A 10 mg/mL solution of GaM was used, and each horse was intragastrically administered a single dose of GaM (20 mg/kg). After the administration of GaM and before the removal of the nasogastric tube, 500 mL of water was used to rinse the funnel and flush the nasogastric tube.

Collection and processing of blood samples—An area over the left jugular vein of each horse was clipped and aseptically prepared on the first day of the study prior to GaM administration. A 14-gauge, 13.3-cm catheter was inserted into the left jugular vein and sutured to the skin of the neck. Prior to collection of each blood sample, a syringe equipped with a hypodermic needle was used to aspirate 10 mL of blood from the catheter, and this volume of blood was discarded to prevent dilution of the blood sample by the residual heparin solution in the catheter lumen. A blood sample (7 mL) was then collected with the same syringe and hypodermic needle before the administration of GaM (0 hours) and at 0.25, 0.5, 1, 1.5, 2, 4, 6, 8, 12, 24, 48, 72, 96, and 120 hours after the administration of GaM. Blood samples were transferred immediately from the syringe into a 9-mL serum separator tube, which was inverted several times and stored on ice for 2 to 4 hours. Clotted blood samples were then centrifuged at 4°C for 10 minutes at 400 g to separate serum from the remaining blood components. Serum was collected, divided into aliquots, placed in storage vials, and stored at –80°C until analysis was performed 90 days later.

Determination of serum gallium concentration by use of ICP-MS—Frozen serum samples were thawed at 37°C and then diluted with 1% ultrapure deionized water. Diluted samples were analyzed by use of ICP-MS and the gallium 71 isotope. Rhodium 103 was included as an internal standard. Weight linear calibration was performed with a blank sample and 4 external standards (0.2, 2, 20, and 200 µg/L). Data were acquired in peak hopping mode by use of the autolens feature and 3 repeat replicate measurements/determination. Calibration and baseline determinations were performed before and after the analytic run. The detection limit and limit of quantitation of the ICP-MS method for gallium in serum were 0.5 and 1.5 ng/mL, respectively. Gallium was not detected in 5 of the 6 method blanks. It was present in the sixth blank at 1.3 times the method detection limit, well below the limit of quantitation of the method. Analytic precision and accuracy were acceptable on the basis of normal criteria for this instrumental method. The mean relative percentage difference of 5 duplicate pairs, calculated by dividing the difference in a duplicate pair by its mean value, was 1.6%, whereas recovery of gallium added to 6 spiked blanks (laboratory control samples) and 5 matrix-spiked samples yielded means of 92% and 91%, respectively. Instrumental response was linear over a calibration range...
of 0 to 20 ng/mL, with a correlation coefficient of 0.999 and a coefficient of variation of 1.4%.

**Pharmacokinetic analysis**—Noncompartmental and compartmental pharmacokinetic analyses of serum gallium concentrations were performed with a commercially available software program. Noncompartmental analysis was used to determine individual pharmacokinetic parameters. Compartmental analysis was used to create pharmacokinetic models. A model was selected on the basis of the Akaike information criterion and visual analysis of plots of residuals. The selected model was then used to simulate a dosing regimen (20 mg/kg, q 24 h for 5 days) from which mean serum concentrations at various time points were calculated.

**Results**

Findings of the physical examinations and results of CBCs and serum biochemical analyses were within the reference limits for all horses. Horses weighed between 430 and 660 kg (mean, 504 kg). Horses appeared to have no adverse effects attributable to the administration of GaM. Physical examination variables and behaviors remained unchanged after intragastric administration of GaM for the duration of the study. One horse had a mild episode of colic on the last day of the study. After treatment, the horse was not observed to have any further signs of colic.

A semilogarithmic plot of the time-concentration curve of mean ± SD serum gallium concentrations with and without inclusion of data for the outlier was pre-

![Figure 1](image)

**Figure 1**—Mean ± SD serum gallium concentrations after intragastric administration of GaM (20 mg/kg) in adult horses. Serum gallium concentrations were determined by use of an ICP-MS analytic method, gallium 71 isotope, and rhodium 103 (internal standard). Data from 1 horse were such that the horse was considered an outlier; therefore, results were determined with (dashed line; n = 6 horses) or without (solid line; B) data for the outlier included.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean ± SD for 6 horses</th>
<th>Mean ± SD for 5 horses†</th>
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</thead>
<tbody>
<tr>
<td>Noncompartmental analysis</td>
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<td></td>
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<tr>
<td>t(0) (h)</td>
<td>0.020 ± 0.016</td>
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<td>Q1 (h)</td>
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<td>tmax (h)</td>
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<td>0</td>
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<tr>
<td>Cmax (µg/mL)</td>
<td>12.0 ± 6.69</td>
<td>9.6 ± 3.58</td>
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<tr>
<td>AUC∞ (h•µg/mL)</td>
<td>36.06 ± 47.35</td>
<td>16.84 ± 5.69</td>
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<td>AUCt (h•µg/mL)</td>
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<td>20.92 ± 6.94</td>
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<td>AUC%Extrapolated</td>
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<td>19.62 ± 6.0</td>
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<tr>
<td>MRT∞ (h)</td>
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</tr>
<tr>
<td>MRTt (h)</td>
<td>66.74 ± 14.37</td>
<td>72.59 ± 1.17</td>
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<tr>
<td>1-compartment model</td>
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<tr>
<td>K1 (h)</td>
<td>1.477 ± 0.731</td>
<td>1.750 ± 0.328</td>
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<tr>
<td>K1 half-life (h)</td>
<td>1.38 ± 2.39</td>
<td>0.41 ± 0.09</td>
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<tr>
<td>K1 (h)</td>
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<td>0.014 ± 0.002</td>
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<tr>
<td>K1 half-life (h)</td>
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<tr>
<td>t1/2 (h)</td>
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<tr>
<td>tmax (h)</td>
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<td>3.09 ± 0.43</td>
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<tr>
<td>Cmax (µg/mL)</td>
<td>0.84 ± 1.37</td>
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<tr>
<td>AUC∞ (h•µg/mL)</td>
<td>36.06 ± 47.35</td>
<td>16.84 ± 5.69</td>
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<tr>
<td>V_F (mL/kg)</td>
<td>35.07 ± 35.88</td>
<td>20.68 ± 7.57</td>
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<tr>
<td>V_F (mL/kg)</td>
<td>61,529 ± 33,830</td>
<td>73,493 ± 18,899</td>
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</tbody>
</table>

*Serum gallium concentrations used in the noncompartmental analysis and 1-compartment model were determined by use of an ICP-MS analytic method, gallium 71 isotope, and rhodium 103 (internal standard).
†Data from 1 horse were such that the horse was considered an outlier and removed from comparison of parameter estimates.

AUC = Area under the time-concentration curve. AUC∞ = Area under the time-concentration curve from time 0 to infinity. AUC%Extrapolated = Proportion of the AUC that was extrapolated. AUC∞ = Area under the time-concentration curve from time 0 to the last detectable serum concentration. Cmax = Maximum observed serum concentration. t(0) = Elimination rate constant for the terminal portion of the time-concentration curve. K1 = Rate at which drug enters the central compartment. K1 half-life = Half-life of the drug entering the central compartment. K2 = Rate at which drug exits the central compartment. K2 half-life = Half-life associated with K2 of drug leaving the central compartment. MRT∞ = Mean residence time from time 0 to infinity. MRTt = Mean residence time from time 0 to the last detectable serum concentration. T1/2 = Apparent elimination half-life. T1/2 = Time to first measurable serum concentration. T1/2 = Time of observed maximum serum concentration. V_F = Apparent volume of distribution.
mean concentrations were plotted for all 6 adult horses (dashed line) and for 5 adult horses with data for the outlier excluded (solid line); concentrations also are plotted for the 1 adult horse that was considered an outlier (dotted-and-dashed line).

pared (Figure 1). Results from 1 horse were such that the horse was considered an outlier; this particular horse had much higher serum concentrations of gallium at 12 and 24 hours (3.38 and 3.63 µg/mL, respectively), compared with mean ± SD concentrations calculated for the other 5 horses at these times (0.2690 ± 0.0895 µg/mL and 0.2290 ± 0.0831 µg/mL, respectively). Therefore, data for this horse were used for comparison of results with and without inclusion of these data. These samples were reanalyzed to ensure that no laboratory error had been made; results of the repeated analyses were similar to results of the initial analyses. For all 6 horses, serum gallium concentrations were detectable in blood samples collected at the first time point (0.25 hours) after intragastric administration of GaM.

Mean ± SD pharmacokinetic parameter estimates derived by use of noncompartmental analysis with and without the inclusion of data for the outlier were summarized (Table 1). A 1-compartment model with first-order input and output and lag time was selected as the best-fit model for the data. The equation for this model was as follows:

\[ C(T) = \left( \frac{D \cdot K_{01}}{V_d \cdot (K_{10} - K_{01})} \right) \left( e^{-K_{10}T} - e^{-K_{01}T} \right) \]

where \( C(T) \) is the serum concentration at time \( T \), \( D \) is the dose, \( K_{01} \) is the rate of drug entering the central compartment, \( V_d \) is the volume of distribution of the central compartment, and \( K_{10} \) is the rate of drug exiting the central compartment. In addition, mean ± SD pharmacokinetic parameter estimates derived from the 1-compartment model with and without the inclusion of data for the outlier were summarized.

The 1-compartment model was used to provide model-predicted serum gallium concentrations in adult horses for a simulated dosing regimen (20 mg/kg, intragastric, q 24 h for 5 days); concentrations were provided with and without data for the outlier and for the outlier alone (Figure 2).

**Discussion**

It is difficult to determine the target serum concentration of gallium required to impact osteoclastic function in horses. Typically, a therapeutic dose range is selected from a combination of in vitro results and information derived from in vivo preclinical and clinical trials. Investigators of an in vitro study detected reversible dose-dependent inhibition of osteoclasts by use of solutions of 15µM gallium (1.046 µg of gallium/mL). A 500-mg dose of gallium in humans with Paget's disease resulted in a mean serum concentration of 569 ng/mL and an apparent improvement in clinical signs during an in vivo clinical trial. The findings of another study indicate that 0.25 or 0.5 mg of gallium nitrate/kg/d greatly reduced the concentrations of biomarkers associated with Paget's disease in humans; the equivalent dose of GaM in humans would be 0.43 or 0.87 mg/kg/d. A previous study conducted by our laboratory group revealed that a target serum concentration of 700 ng of GaM/mL was considered therapeutic against pneumonia caused by *R equi* infection in foals. In other species, the dose of GaM required for an antimicrobial effect is much greater than that needed to affect osteoclastic activity. The authors who performed that study speculated that the dose of GaM required to inhibit osteoclastic activity may be 5% to 10% of the dose required for antimicrobial activity. Therefore, a therapeutic serum concentration would be defined as 70 ng of gallium/mL, which was easily achieved by all horses in the study reported here.

The disposition of GaM is different in adult horses than in neonatal foals. A previous report on the intragastric administration of 20 mg of GaM/kg in foals resulted in higher serum concentrations than those in adult horses. Foals achieved a mean maximum observed plasma concentration of 1.08 µg/mL when administered a 20 mg/kg dose of GaM. Oral administration of a methylcellulose formulation of GaM (20 mg/kg) to foals resulted in a maximum observed plasma concentration of 0.9 µg/mL; at this same dosage, adult horses in the present study achieved a maximum observed serum concentration of 0.28 µg/mL after intragastric administration of GaM. Similarly, the area under the time-concentration curve in foals differs from the area under the time-concentration curve of adult horses. In a previous study, the area under the time-concentration curve in foals after intragastric administration was 40.2 hµg/mL. Other investigators reported the area under the time-concentration curve in foals after oral administration of the methylcellulose formulation of GaM to foals was 24.06 hµg/mL. In the present study, we determined that the area under the time-concentration curve in 5 adult horses after intragastric administration of GaM was 20.68 hµg/mL. Time of observed maximum serum concentration was similar in foals (4.3 hours and 3.5 hours) of other studies and in the adult horses (3.09 hours) of the present study. These differences in the times of observed maximum serum concentration are likely attributable to changes in drug absorption, distribution, metabolism, and excretion between foals and adult horses. The bioavailability of orally administered gallium remains unknown. In addition, a formulation...
for the IV administration of gallium is not available for horses.

Investigators of other studies\textsuperscript{11,12} reported a relatively large variation in plasma concentrations of GaM after intragastric and oral administrations to foals. In the study reported here, 1 horse was considered an outlier. This particular horse had much higher serum concentrations of gallium at 12 and 24 hours (3.38 and 3.63 µg/mL, respectively), compared with mean ± SD serum concentrations calculated for the other 5 horses at these times (mean 12-hour concentration, 0.2696 ± 0.0895 µg/mL; mean 24-hour concentration, 0.229 ± 0.0831 µg/mL). By excluding all data from this horse that was considered an outlier, the degree of individual variation in the mean maximum serum concentration of gallium more closely resembled that reported in other studies.\textsuperscript{13–15} Apparent variability in absorption across age groups results in foals achieving higher maximum serum concentrations than did adult horses in the present study. We are unable to explain this variation in maximum serum concentrations except by individual variability in the absorption of gallium. When the 1-compartment model was used to determine model-predicted serum concentrations of GaM after intragastric administration (20 mg/kg, q 24 h for 5 consecutive days; Figure 2), differences between the model-predicted mean serum concentrations of the other 5 horses and the model-predicted concentrations for the horse considered an outlier may be explained by the considerably longer time to first measurable serum concentration for the horse considered an outlier and the fact that the model-predicted concentrations were based on simulated, not observed, pharmacokinetic parameters.

Other differences between age groups after intragastric administration of GaM included the apparent elimination half-life, mean residence time, and time of observed maximum serum concentration. Investigators have reported a mean elimination half-life of 26.6 hours for GaM in foals after intragastric administration\textsuperscript{23} and have reported a mean elimination half-life of 26.6 hours observed maximum serum concentration. Investigators calculated, not observed, pharmacokinetic parameters. The model-predicted concentrations for the horse considered an outlier may be explained by the considerably longer time to first measurable serum concentration for the horse considered an outlier and the fact that the model-predicted concentrations were based on simulated, not observed, pharmacokinetic parameters.

To our knowledge, this is the first report in which investigators have described the pharmacokinetics of GaM after intragastric administration in adult horses. Gallium was absorbed by adult horses with no overt adverse effects when administered intragastrically once at a dosage of 20 mg/kg. Investigations regarding the efficacy of GaM for use in the treatment of pneumonia in foals are ongoing, and much has yet to be determined regarding the effects of GaM on the osteoclastic activity of horses. Studies conducted to determine the bioavailability of GaM after oral administration will be critical for evaluating the effects of this drug on the osteoclastic activity of horses.

\textbf{References}

16. Schlesinger PH, Teitelbaum SL, Blair HC. Osteoclastic inhibi-