Influence of exercise on the distribution of technetium Tc 99m medronate following intra-articular injection in horses

Jennifer A. Dulin, DVM; W. Tod Drost, DVM; Mitch A. Phelps, PhD; Elizabeth M. Santschi, DVM; Maria I. Menendez, BVSc; Alicia L. Bertone, DVM, PhD

Objective—To determine the effects of exercise on the distribution and pharmacokinetics of technetium Tc 99m medronate (99mTc-MDP) following intra-articular (IA) injection in horses.

Animals—5 horses.

Procedures—1 antebrachiocarpal joint (ACJ)/horse was assigned to the exercised group (n = 5), and the contralateral ACJ was evaluated in the nonexercised group (5) after a minimum washout period of 7 days. Following IA injection of 99mTc-MDP (148 MBq), blood and scintigraphic images of the carpus were obtained at 5, 10, 15, 20, 30, 45, 60, 90, 120, 240, 360, 480, 600, 720, and 1,440 minutes. Plasma and scintigraphic radioactivity were determined over time, and pharmacokinetic parameters were generated via noncompartmental and compartmental analyses. Each horse was monitored via physical and lameness examination and ACJ synovial fluid analysis before injection and at days 1, 2, 3, and 7.

Results—Lameness was not observed. Mean ± SD synovial fluid WBC count increased at day 1 (exercised, 721 ± 234 cells/µL; nonexercised, 948 ± 223 cells/µL), but returned to baseline at days 3 and 7. Mean time to maximum plasma radioactivity was earlier in the exercised group (16.00 ± 2.35 minutes) than the nonexercised group (43.75 ± 3.64 minutes). Linear regression of the scintigraphic radioactivity-time curves revealed a greater negative slope in the exercised group within the first 25 minutes. There was no difference in absorption or elimination rate constants in a 2-compartment model.

Conclusions and Clinical Relevance—IA injection of 99mTc-MDP was safe and effective for evaluating synovial solute distribution. Exercise significantly increased early transfer of 99mTc-MDP from the ACJ into plasma, although absorption and elimination rate constants were not affected. Exercise may affect synovial clearance and withdrawal times of medications administered IA. (Am J Vet Res 2012;73:418–425)
and longitudinally within an individual.\textsuperscript{7–10} These articular clearance values have not been investigated in horses. Clearance rates of \textsuperscript{99m}technetium (as \textsuperscript{99m}Tc-DTPA), a freely diffusible water-soluble molecule, have been used to represent other synovial molecules that equilibrate with plasma in human studies. This method provides a measurement of joint perfusion and drainage and subsequent transfer of solutes from the IA joint space to circulating blood. Clearance of IA-administered \textsuperscript{99m}technetium, measured by serial counts of emitted \(\gamma\) rays, is significantly increased by dynamic exercise in humans with knee joint effusion.\textsuperscript{31} It is thought that increased clearance of synovial fluid and solutes following exercise is directly related to increased blood flow to the synovium as well as increased IA hydrostatic pressure leading to altered Starling forces across the synovium.\textsuperscript{12–22} These studies of joint fluid dynamics support the notion that exercise of a cyclic nature leads to earlier synovial solute clearance, compared with synovial solute clearance without exercise.

Although various human, canine, and rabbit studies have used radiopharmaceuticals for investigating synovial fluid exchange, a similar technique for evaluating the distribution of IA administered \(\gamma\)-emitting radioisotopes in horses has not been reported. The goals of the study reported here were to evaluate the safety of \textsuperscript{99m}Tc-MDP IA injection in clinically normal horses and to define the effect of exercise on the blood and joint distribution of \textsuperscript{99m}Tc-MDP by use of both noncompartmental analysis and compartmental modeling. The hypotheses were that \textsuperscript{99m}Tc-MDP is safe when administered IA in clinically normal horses and that exercise affects the distribution and pharmacokinetics of \textsuperscript{99m}Tc-MDP following IA injection in horses.

\section*{Materials and Methods}

\textbf{Experimental design—}The study was performed as a randomized, controlled, crossover trial. One randomly selected ACJ per horse was assigned to the exercised group protocol (n = 5), and the contralateral ACJ was evaluated in the nonexercised group protocol (5) after a washout period of a minimum of 7 days. The experimental protocol was approved by The Ohio State University Institutional Animal Care and Use Committee.

\textbf{Horses—}Five female Thoroughbred horses (mean ± SD age, 3.2 ± 1.6 years; body weight, 478.2 ± 20.7 kg) were included in the study. Prior to enrollment, all horses were considered healthy and free from lameness or ACJ inflammation as determined on the basis of inspection by an experienced examiner (ALB). Each carpus was examined by a diplomate of the American College of Veterinary Radiologists (WTD) and determined to be free of visible radiographic abnormalities on the basis of a single flexed lateromedial view. Horses were exercised for at least 2 weeks on a high-speed equine treadmill\textsuperscript{4} prior to initiation of the study. Horses were exercised 3 times/wk with the following regimen to simulate the exercise of race training: walking (9 km/h) for 5 minutes, followed by trotting (16 km/h) for 5 minutes, galloping (32 km/h) for 5 minutes, and walking (9 km/h) for 5 minutes. Throughout the experiment, horses were housed individually in stalls in a temperature-controlled environment, fed a commercial grain mixture twice daily, and provided access to hay and water ad libitum.

\textbf{IA administration of \textsuperscript{99m}Tc-MDP—}On day 0 of each protocol, a 14-gauge, 5.25-inch peripheral venous catheter\textsuperscript{5} was placed by use of aseptic technique in either jugular vein. Prior to IA injection, the skin over the dorsolateral pouch of the appropriate ACJ was clipped free of hair and aseptically prepared. Approximately 1 mL of 2% mepivacaine hydrochloride was infiltrated SC over the joint pouch. A 20-gauge, 1.5-inch needle was steriley inserted into the dorsolateral ACJ pouch, and 0.5 to 1 mL of synovial fluid was aspirated and placed in an EDTA-containing tube\textsuperscript{6} for analysis of WBC count and total protein concentration. One author (JAD), who was included in the academic nuclear medicine permit designated by Environmental Health and Safety—Radiation Safety, administered 148 MBq (4 mCi; total volume, 5 mL) of \textsuperscript{99m}Tc-MDP IA. All personnel wore adequate personal protective equipment during injection as outlined in the academic nuclear medicine permit. The total dose of radiopharmaceutical was determined to be appropriate for imaging on the basis of unpublished pilot data, and a small volume was used to avoid increased IA volume and increased IA hydrostatic pressure.

\textbf{Blood and image collection—}Following injection, horses in the exercised group protocol were immediately trotted on a high-speed equine treadmill\textsuperscript{4} for 5 minutes at 16 km/h. Blood collection began immediately at termination of treadmill exercise. In both groups, 2 mL of blood was obtained from the indwelling jugular vein catheter at 5, 10, 15, 20, 25, 30, 45, 60, 90, 120, 240, 360, 480, 600, 720, and 1,440 minutes following injection. The blood was placed directly into individual sodium heparin blood collection tubes\textsuperscript{7} and stored at room temperature (23°C) for processing within 6 hours after collection. Prior to initiating image collection, each horse was sedated with detomidine hydrochloride (0.01 mg/kg, IV) and butorphanol tartrate (0.01 mg/kg, IV). Additional sedation was administered throughout image collection and consisted of 0.002 to 0.004 mg of detomidine/kg, and butorphanol IV as needed, to acquire the images. Static, 90-second, dorsal scintigraphic images of both forelimbs, from midradius to proximal metacarpus (Figure 1), were obtained beginning 5 minutes after injection in the nonexercised group protocol and 10 minutes after injection in the exercised group protocol to permit travel between the treadmill and nuclear medicine suite. The \(\gamma\) camera\textsuperscript{8} was placed at a similar distance dorsal to the carpi during each image acquisition. Scintigraphic imaging occurred at 5 (non-exercised group only), 10, 15, 20, 25, 30, 45, 60, 90, 120, 240, 360, 480, 600, 720, and 1,440 minutes following injection.

\textbf{Evaluation of joint inflammation—}Within 2 hours prior to \textsuperscript{99m}Tc-MDP injection on day 0 and at days 1, 2, 3, and 7 after injection for both protocols, each horse was assessed at a trot in a straight line on a hard ground surface for forelimb lameness and graded on a
0 to 5 scale as described by the American Association of Equine Practitioners. The tissues over the ACJ were palpated and visually inspected for swelling on days 0, 1, 2, 3, and 7. The swelling was scored as follows: 0, no subcutaneous swelling; 1, minor (1-cm-diameter) subcutaneous swelling at injection site; 2, mild (1- to 3-cm-diameter) subcutaneous swelling at injection site; 3, moderate (extending past the dorsolateral ACJ pouch or > 3-cm-diameter) subcutaneous swelling; and 4, severe (entire dorsal surface of carpus) subcutaneous swelling. The circumference of the carpus at the ACJ was measured on days 0, 1, 2, 3, and 7 by placing a measuring tape around the ACJ over the widest part of the accessory carpal bone. All clinical assessments were performed by the same examiner (JAD). Synovial fluid WBC count and total protein concentration were evaluated by use of repeated arthrocentesis prior to injection on day 0 and at days 1, 3, and 7 after injection by means of an automated cell counter and refractometry. Reference limit WBC count was considered ≤ 500 cells/µL, and reference limit total protein concentration was considered ≤ 2.5 g/dL.

**Blood sample processing**—Heparinized blood samples were centrifuged for 5 minutes at 1,000 X g. Then, 0.5 mL of the plasma supernatant was pipetted into a plastic test tube for each sample, which was placed into a liquid scintillation well counter. The well counter was calibrated daily by use of a known cesium source and was set to record CPM within a range of 119 to 162 keV. Technetium emits γ ray energy at 140 keV. All CPM measurements were converted to DPM on the basis of a known 77.3% efficiency of the well counter for detecting technetium disintegrations. Finally, all plasma radioactivity data (DPM/mL of plasma) were corrected for radioisotope decay by use of the following formula:

\[ A_0 = A/e^{-\lambda t} \]

where \( A_0 \) is the activity at the time of IA injection, time 0 (decay-corrected DPM); \( A \) is the activity at time \( t \) (uncorrected DPM); \( \lambda \) is the decay constant (0.693/half-life); and \( t \) is the time after injection when the blood was acquired (minutes). The half-life of \( \text{⁶⁷} \text{Tc} \)-MDP is 363 minutes.

**Image processing**—The static, 90-second, scintigraphic images were processed by use of software to determine radioactivity within the ACJ over time (decay-corrected CPM/ROI point). An ROI was drawn by 1 author (JAD) outlining the ACJ (Figure 1). The author was unaware of treatment group assignment at the time the ROIs were drawn. The total number of counts within each 90-second ROI was determined by use of the software, and the counts were multiplied by 0.66 to provide an uncorrected CPM value. The CPM value was then corrected for radioactive decay. To account for unavoidable variability in hand-drawn ROIs, the decay-corrected CPM values were divided by the total number of points (pixels) per ROI, yielding a final measurement of radioactivity within the ACJ (CPM/point).

To assess the distribution of the radiopharmaceutical in the joint and surrounding bone and soft tissues, a separate set of ROIs were produced from the same images at the 20- and 360-minute time points (Figure 1). These time points were chosen to represent early and delayed phases of radiopharmaceutical distribution. Four rectangular ROIs of the following sizes were drawn over each static image: 7 × 7 mm (ROI 1), 10.75 × 13.25 mm (ROI 2), 20.5 × 22.75 mm (ROI 3), and 36.5 × 39 mm (ROI 4). All size measurements were made by use of a digital caliper with 0.01-mm resolution and accuracy to 0.02 mm. Mean ± SE CPM values were determined for each ROI; ROI 1 and 2 represented the activity within the ACJ, and ROI 3 and 4 represented the activity within the surrounding bone and soft tissues.

**Noncompartmental pharmacokinetic analysis and compartmental modeling**—Noncompartmental and compartmental pharmacokinetic parameters were generated by use of a computer software program for plasma radioactivity as well as activity within the scintigraphic ROI in the exercised and nonexercised groups. Uniform weighting was used throughout the analysis. Compartmental model selection was guided by the Akaike information criterion and parameter SEs of estimate.

**Statistical analysis**—Statistical analyses were performed by use of commercially available software. Pharmacokinetic parameter estimates as well as ROI data were compared between groups by use of a paired \( t \) test. Serial quantitative data (percentage change in joint circumference, synovial fluid WBC counts, and total protein concentrations) were analyzed by use of 2-way repeated-measures ANOVA with Bonferroni posttests. Scored data (edema and lameness scores) were analyzed by use of the Kruskal-Wallis test for nonparametric data with a Dunn multiple comparison posttest. Values of \( P \leq 0.05 \) were considered significant for all tests.

**Results**

Evaluation of joint inflammation—All horses had normal results of preinjection physical, radiographic, and lameness examinations and synovial fluid analyses, and all completed both study protocols with no lameness or physical examination abnormalities. There was no significant difference between exercised and nonexercised groups for swelling score, percentage change in ACJ circumference, or synovial fluid WBC count and
total protein concentration at any examination time. Joint circumference at day 7 was slightly increased (mean ± SD 1.79 ± 1.11%), compared with preinjection (0 ± 0%) and day 1 (–0.13 ± 0.30%) values in the exercised group (P < 0.05). Preinjection synovial fluid WBC counts were less than the reference limit in both the exercised (130 ± 61 cells/µL) and nonexercised groups (113 ± 32 cells/µL). In the exercised (721 ± 234 cells/µL; P < 0.05) and nonexercised (948 ± 223 cells/µL; P < 0.01) groups, WBC count increased, with a peak at 24 hours after injection, compared with preinjection values. In both groups, WBC values returned to preinjection concentrations at 3 and 7 days after injection. Synovial fluid total protein concentration did not increase over the examination period in either group.

**Scintigraphic analysis**—Radioactivity remaining within the ACJ was higher in the exercised group at 360 (P = 0.04), 600 (P = 0.02), 720 (P = 0.02), and 1,440 (P = 0.03) minutes. There was no difference in CPM per point between the groups at any other time. However, linear regression of the curve from 5 through 25 minutes revealed a greater negative slope in the exercised group (P = 0.03). The line of best fit for the exercised group was y = -7.94x + 824 (r² = 0.93). The line of best fit for the nonexercised group was y = -3.20x + 732 (r² = 0.83). Both slopes were considered nonzero, with 95% confidence interval of -14.55 to -1.33 for the exercised group and -5.82 to -0.58 for the nonexercised group (Figure 2).

The distribution of radioactivity within the joint and surrounding tissues was analyzed at 20 and 360 minutes in both groups. At 20 minutes after injection, there were no differences between groups in radioactivity remaining within the joint (ROI 1, P = 0.50; ROI 2, P = 0.71) or the surrounding tissues (ROI 3, P = 0.30; ROI 4, P = 0.34; Figure 3). At 6 hours after injection, more radioactivity remained in both the joint (ROI 1, P = 0.03; ROI 2, P = 0.04) and the surrounding tissues (ROI 3, P < 0.01; ROI 4, P < 0.001) in the exercised group.

**ROI noncompartmental analysis of ⁹⁹mTc-MDP**—Noncompartmental pharmacokinetic parameters of technetium activity within the scintigraphic ROI were summarized (Table 1). The AUC last was higher in the exercised group than in the nonexercised group (P = 0.05). The Cl, determined by dose divided by AUC last, was lower in the exercised group (P < 0.01). The Vz was lower in both groups. The Lz was calculated from 8 to 24 hours.

![Figure 2](https://example.com/figure2.png)

Figure 2—Scintigraphic radioactivity-time curve following injection of ⁹⁹mTc-MDP into the ACJ in exercised and nonexercised horses. *Significant (P < 0.05) differences between exercised (circles) and nonexercised (squares) groups. Values are expressed as mean ± SE.

![Figure 3](https://example.com/figure3.png)

Figure 3—Mean ± SE radioactivity (CPM) within 4 ROIs representing the ACJ (regions 1 and 2) and the tissues surrounding the ACJ (regions 3 and 4) at 20 (A) and 360 (B) minutes after IA injection of ⁹⁹mTc-MDP in horses. Black bars = exercised horses; gray bars = nonexercised horses. See Figure 2 for remainder of key.

### Table 1—Noncompartmental pharmacokinetic parameters (mean ± SE) of ⁹⁹mTc-MDP activity in a scintigraphic ROI after injection into the ACJ in exercised and nonexercised horses.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Exercised</th>
<th>Nonexercised</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (CPM/point)</td>
<td>665.6 ± 52.4</td>
<td>726.8 ± 93.4</td>
</tr>
<tr>
<td>L1 (1/min)</td>
<td>0.001 ± 0</td>
<td>0.001 ± 0</td>
</tr>
<tr>
<td>Cl (mL/min)</td>
<td>1.256 ± 0.156</td>
<td>1.676 ± 0.092*</td>
</tr>
<tr>
<td>Vz (mL)</td>
<td>2.615 ± 426</td>
<td>3.940 ± 727</td>
</tr>
<tr>
<td>AUC last (min*CPM/point)</td>
<td>447,871 ± 50,499*</td>
<td>321,800 ± 40,974</td>
</tr>
</tbody>
</table>

*Significant (P < 0.05) difference between groups.

### Table 2—Noncompartmental pharmacokinetic parameters (mean ± SE) of ⁹⁹mTc-MDP activity in plasma after injection into the ACJ in exercised and nonexercised horses.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Exercised</th>
<th>Nonexercised</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (DPM/mL)</td>
<td>22,485 ± 6,305</td>
<td>22,706 ± 7,430</td>
</tr>
<tr>
<td>Tmax (min)</td>
<td>2.35* ± 0.092*</td>
<td>43.75 ± 3.64</td>
</tr>
<tr>
<td>Cl (1/min)</td>
<td>0.001 ± 0</td>
<td>0.001 ± 0</td>
</tr>
<tr>
<td>V/F (mL/min)</td>
<td>0.069 ± 0.009</td>
<td>0.061 ± 0.008</td>
</tr>
<tr>
<td>Vz/F (mL)</td>
<td>91.54 ± 11.83</td>
<td>139.80 ± 30.77</td>
</tr>
<tr>
<td>AUC last (min*DPM/mL)</td>
<td>9,654,907 ± 8,891,620</td>
<td>5,59,163</td>
</tr>
</tbody>
</table>

The L1 was calculated from 8 to 24 hours in the exercised group and from 10 to 24 hours in the nonexercised group. F = Bioavailability. Tmax = Time to Cmax.

See Table 1 for remainder of key.
was not different between groups. Furthermore, the Lz, calculated from 8 to 24 hours after injection, was not different between groups.

Plasma noncompartmental analysis and compartmental modeling of 99mTc-MDP—Noncompartmental pharmacokinetic parameters of technetium activity in plasma following IA injection were summarized (Table 2). The value of Cmax was not different between the exercised and nonexercised groups. However, Cmax occurred earlier in the exercised group (P < 0.001). There were no detectable differences in AUClast, Cl, Vz, or Lz between groups. More radioactivity per milliliter of plasma was present in the exercised group at 360, 480, 600, and 720 minutes after injection (P < 0.05; Figure 4).

A 2-compartment pharmacokinetic model of 99mTc-MDP activity following IA injection was produced by use of plasma data, describing absorption from the ACJ to plasma, distribution within peripheral tissues, and renal elimination (Figure 5). Compartmental parameter estimates of 99mTc-MDP in plasma were summarized (Table 3). There was no difference between groups for rate constants of absorption of 99mTc-MDP from joint to plasma, transfer of 99mTc-MDP between plasma and peripheral tissues, or elimination of the technetium from plasma.

Discussion

Previous human and canine studies 10,11,24,25 have evaluated the use of radioactive compounds administered IA, including 99mTc-DTPA, to delineate the effects of various pathological and physiologic conditions on synovial fluid and solute dynamics. Specifically, studies by Wisham et al25 and James et al11 that used radioactive sodium and 99mTc-DTPA, respectively, revealed increased clearance of the markers in the immediate postexercise period in human knee joints; these findings are similar to the results of the present study. Although radiopharmaceuticals have been used IA in other species, the effect of exercise on their distribution has only been defined in humans. The present study revealed the safety and usefulness of 99mTc-MDP for examining the effects of exercise on synovial solute distribution in horses and for potential future application in equine joint disease. Technetium Tc 99m medronate administered IA, with or without exercise immediately after injection, was well tolerated in horses of the present study. A mild, transient local inflammatory response occurred in both groups, evidenced by a small increase in joint circumference and a mild increase in synovial fluid WBC count. The synovial fluid changes were consistent with those reported for repeated arthrocentesis and were markedly less than those reported for saline (0.9% NaCl) solution injection. Arthrocentesis alone results in a mild increase in synovial WBC count (2,380 WBCs/µL) without substantial increase in pro-

Table 3—Compartmental parameter estimates (mean ± SE) of 99mTc-MDP in plasma after injection into the ACJ in exercised and nonexercised horses.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Exercised</th>
<th>Nonexercised</th>
</tr>
</thead>
<tbody>
<tr>
<td>K0 (1/min)</td>
<td>0.153 ± 0.047</td>
<td>0.063 ± 0.023</td>
</tr>
<tr>
<td>K1 (1/min)</td>
<td>0.002 ± 0.001</td>
<td>0.001 ± 0.001</td>
</tr>
<tr>
<td>K2 (1/min)</td>
<td>0.015 ± 0.008</td>
<td>0.005 ± 0.002</td>
</tr>
<tr>
<td>V1/F (mL)</td>
<td>41.59 ± 9.36</td>
<td>37.12 ± 8.09</td>
</tr>
<tr>
<td>V2/F (mL)</td>
<td>58.13 ± 16.21</td>
<td>143.60 ± 34.69</td>
</tr>
</tbody>
</table>

K1 and K2 = Rate constants for intercompartmental transfer of 99mTc-MDP between plasma and peripheral tissues and interstitium. K0 = Rate constant for absorption of 99mTc-MDP from joint to plasma. K1 = Rate constant for elimination of 99mTc-MDP from plasma. V1/F = Observed apparent volume of distribution for plasma corrected for bioavailability. V2/F = Observed apparent volume of distribution for peripheral tissues and interstitium corrected for bioavailability. See Table 1 for remainder of key.
Intra-articular injection of saline solution elicits moderately increased synovial WBC (31,388 WBCs/µL) and protein (3.9 g/dL) concentrations at 24 hours after injection, both of which return to baseline values within 7 days afterward. The minor changes in clinical variables, along with a lack of lameness during the study period, suggest that IA administration of 99mTc-MDP is safe in clinically normal horses.

Regional scintigraphic analysis indicated that exercise resulted in redistribution of 99mTc-MDP from the joint into the surrounding tissues after exercise. These findings suggest that IA-administered 99mTc-MDP may be driven by exercise from the ACJ into the surrounding tissues and interstitium, followed closely by absorption into lymphatic and the venous systems. Exercise is thought to increase synovial clearance through increased synovial blood flow, resulting in greater transport of solutes from the joint into circulation. A study evaluating articular blood flow in exercising and resting dogs revealed increased blood flow to all articular soft tissues with exercise. Also, exercise increases distal limb perfusion and subsequent radiopharmaceutical uptake into bone in horses undergoing nuclear scintigraphy. In addition to increased cardiac output and peripheral perfusion during exercise, changes in IA pressure during cyclic flexion and extension of the joint are hypothesized to stimulate joint clearance. The pumping action of the joint during motion is thought to drive synovial fluid from the joint, resulting in the creation of subatmospheric IA pressure when the joint is in a neutral position at rest. Increasing IA pressure by infusion of saline solution leads to fluid transport out of the joint, and it is thought that increasing IA pressure by joint flexion most likely does the same. Flexion of the metatarsophalangeal joint in anesthetized ponies leads to a reliable increase in IA pressure. Furthermore, a study by Macoris and Bertone revealed that cyclic motion of effused joints (baseline IA pressure > 30 mm Hg) results in peak pressures > 100 mm Hg. These changes in IA pressure alter Starling forces across the synovium, increasing IA hydrostatic pressure, which ultimately leads to fluid exchange between the synovial fluid and plasma. Intra-articular volume can affect IA pressure and synovial clearance. Because of this, a small and uniform volume (net volume, 4 mL) was used for radiopharmaceutical injection. The mean ± SD synovial fluid volume in healthy antebrachio-carpal joints was estimated to be 11.67 ± 3.28 mL by Smith et al. In a pilot study, the addition of 4 mL to the ACJ did not result in increased IA pressure as determined by manometer measurement in 2 horses with joint angles of approximately 180°. Furthermore, addition of 4 mL to the midcarpal joint in anesthetized horses with joint angles of 135° (mild flexion) resulted in increase of IA pressure to approximately 14 mm Hg. Even without a large change in IA pressure following addition of 4 mL of fluid, the extra fluid may have altered synovial fluid flow following injection. Synovial membrane has a low osmotic reflection coefficient and high permeability, and injection of fluid into the joint may have altered the initial clearance of the marker. However, the effect would have been uniform between groups; therefore, any differences in early radiopharmaceutical distribution can be attributed to the effect of exercise. Although the approximately 4-mL net volume gain in the present study may seem like a large volume with respect to the normal IA volume, the effects of the volume gain were...
uniform between groups and should have been minimal. A combination of increased synovial perfusion and increased IA pressure leading to altered Starling forces likely led to the distribution of \(^{99m}\)Tc-MDP from the joint to surrounding tissues and vasculature following exercise. \(^{99m}\)Tc is a readily available isotope commonly used in both clinical and research settings for nuclear scintigraphy. The radioisotope can be bound to various pharmaceuticals, which target specific tissues or organ systems to enhance imaging studies. One of the most common applications is \(^{99m}\)Tc-MDP, in which \(^{99m}\)Tc, a metastable isomer of \(^{99}\)Tc, is bound to the bone-seeking pharmaceutical methylene-diphosphonate. The resulting radiopharmaceutical is water soluble, with a molecular weight of 485.94 g/mol. In the present study, the \(^{99m}\)Tc-MDP radiopharmaceutical was chosen because of its commonality as well as its similarity with physical characteristics of some medications administered IA. For instance, the molecular weights of methylprednisolone acetate (416.51 g/mol) and triamcinolone acetonide (434.50 g/mol), 2 corticosteroids commonly administered IA, are similar, and triamcinolone is also water soluble. Furthermore, the bone-seeking pharmaceutical was chosen to best assess the distribution of the compound to surrounding tissues. Other radiopharmaceuticals, such as \(^{99m}\)Tc-DTPA, undergo little distribution to tissues and have more rapid elimination via glomerular filtration. Such compounds may have allowed for a more simplified pharmacokinetic profile, and the use of \(^{99m}\)Tc-MDP may limit the conclusions of the present study for this reason. The short half-life, accessibility, and physical characteristics of \(^{99m}\)Tc-MDP are useful in applications such as pharmacokinetics research, in addition to clinical uses.

A 2-compartment model, characterized by distinct absorption-distribution and elimination phases, best described the plasma radioactivity data in the present study as determined by use of standard pharmacokinetic analyses. The left shift of the plasma radioactivity-time curve of the exercised group in the present study may be explained by an earlier absorption of technetium from the joint into plasma. Likely because of our inability to fully separate and accurately calculate the rate constants for the absorption and distribution phases in plasma, no significant difference was found between groups for the rate constant for absorption of \(^{99m}\)Tc-MDP from joint to plasma. However, the noncompartmental analysis and linear regression analysis both revealed earlier technetium appearance in plasma. It could be possible to detect \(^{99m}\)Tc-MDP earlier in plasma without a change in the absorption rate constant if the IA pressure changes associated with joint motion result in earlier movement of the pharmaceutical through the interstitial space and into the vasculature. Increased IA pressure increases interstitial fluid transport. This earlier passage through the interstitium would also be expected to be associated with changes in the microvascular pressure profiles and fluid transport, compared with static, normal joints as described in the isolated joint model. The joint arterial, venous, and capillary pressures and flows; microvascular resistance; net filtration pressure; transitional microvascular pressure; vascular and tissue compliances; and osmotic reflection coefficient could all potentially be altered by exercise, although they were not evaluated in the present study. Any of the changes associated with joint motion, particularly increased IA pressure, could lead to earlier transfer of synovial fluids and solutes, without a change in the rate constant for absorption of \(^{99m}\)Tc-MDP from joint to plasma. Therefore, the left shift in the radioactivity-time curve can best be explained by earlier absorption of \(^{99m}\)Tc-MDP from the ACJ to plasma in the early postexercise period.

Technetium Tc 99m medronate exists in plasma as free and protein-bound forms. The free form is eliminated via glomerular filtration and is therefore dependent on kidney function and glomerular filtration rate. Noncompartmental analysis of plasma data revealed no difference in \(L_z\) from 8 to 24 hours after injection. Furthermore, compartmental analysis revealed no difference between groups for the rate constant for elimination of technetium from plasma, which represents the rate of renal elimination of \(^{99m}\)Tc-MDP. Exercise decreases renal arterial blood flow via sympathetic nervous system stimulation, which could potentially result in a decreased glomerular filtration rate if the autoregulatory function is overcome. Consequently, elimination of renally cleared compounds, such as \(^{99m}\)Tc-MDP, could be expected to decrease in exercised animals. However, the lack of difference between groups in \(L_z\) and the rate constant for elimination of technetium from plasma does not support decreased renal elimination in exercised horses of the present study. In fact, the short exercise period (5 minutes) may have had no effect on renal blood flow or glomerular filtration of \(^{99m}\)Tc-MDP. Future studies incorporating additional data collection and pharmacokinetic analysis, such as urine radioactivity measurements or IV administration, would enable further interpretation of these results by providing additional distribution and elimination data. Also, studies involving a more intense or prolonged exercise protocol may be necessary to further examine the effects of exercise on renal elimination.

The IA administration of \(^{99m}\)Tc-MDP was found to be a safe and effective method for evaluating the effects of exercise on synovial transport. Clearance of the radiopharmaceutical from the ACJ was increased immediately after exercise, but this effect appeared to wane after approximately 25 minutes. The resulting plasma radioactivity-time curve had a left shift in the exercised group, compared with the nonexercised group, and there was no apparent difference between groups for absorption, intercompartmental transfer, and elimination rate constants in the 2-compartment model. In contrast, the data suggested this was a result of earlier appearance of \(^{99m}\)Tc-MDP in plasma after exercise. Additional studies to evaluate the effect of more intense exercise on elimination rate constants would be warranted. Further research may be necessary to define the effects of exercise on pharmacokinetics of IA-administered solutes, including joint medications, which may have an effect on treatment of clinical disease states and competition withdrawal times.

---

b. BD Angiocath, BD, Franklin Lakes, NJ.
References