Gentamicin concentrations in synovial fluid and joint tissues during intravenous administration or continuous intra-articular infusion of the tarsocural joint of clinically normal horses

Timothy B. Lescun, BVSc, MS; Michael P. Ward, BVSc, MPVM, PhD; Stephen B. Adams, DVM, MS

Objective—To compare gentamicin concentrations achieved in synovial fluid and joint tissues during IV administration and continuous intra-articular (IA) infusion of the tarsocural joint in horses.

Animals—18 horses with clinically normal tarsocural joints.

Procedure—Horses were assigned to 3 groups (6 horses/group) and administered gentamicin (6.6 mg/kg, IV, q 24 h for 4 days; group 1), a continuous IA infusion of gentamicin into the tarsocural joint (50 mg/h for 73 hours; group 2), or both treatments (group 3). Serum, synovial fluid, and joint tissue samples were collected for measurement of gentamicin at various time points during and 73 hours after initiation of treatment. Gentamicin concentrations were compared by use of a Kruskal-Wallis ANOVA.

Results—At 73 hours, mean ± SE gentamicin concentrations in synovial fluid, synovial membrane, joint capsule, subchondral bone, and collateral ligament of group 1 horses were 11.5 ± 1.5 µg/mL, 21.1 ± 3.0 µg/g, 17.1 ± 1.4 µg/g, 9.8 ± 2.0 µg/g, and 5.9 ± 0.7 µg/g, respectively. Corresponding concentrations in group 2 horses were 458.7 ± 130.3 µg/mL, 496.8 ± 126.5 µg/g, 128.5 ± 74.2 µg/g, 99.4 ± 473 µg/g, and 13.5 ± 7.6 µg/g, respectively. Gentamicin concentrations in synovial fluid, synovial membrane, and joint capsule of group 1 horses were significantly lower than concentrations in those samples for horses in groups 2 and 3.


Septic arthritis causes pain and is a potentially life-threatening disease in horses. It results from bacterial colonization of the synovial membrane, articular cartilage, or subchondral bone of a joint.1,2 Bacteria localize within joint tissues after hematogenous spread, traumatic inoculation from a wound or puncture, or iatrogenic inoculation during joint injection or surgery.3 The severe inflammatory response within an infected joint results in rapid enzymatic degradation of proteoglycan and collagen; loss of integrity of the cartilage matrix; synovial fibrosis; and, ultimately, osteoarthritis.4,5 When infection cannot be eliminated or severe lameness persists, euthanasia may be required for humane or economic reasons.

Treatments for horses with septic arthritis include systemic administration of antimicrobials and anti-inflammatory drugs, joint lavage, arthroscopic debridement, and open joint drainage.6 Local administration of antimicrobials has been combined with these other treatment modalities.7-9 Intra-articular injection10,11,15 intraosseous and regional IV perfusion10,15 implantation of absorbable16 and nonabsorbable17,20 antimicrobial-impregnated polymer beads, and use of gentamicin-impregnated collagen sponges21 have all been reported for the treatment of horses with septic arthritis. The primary advantage of local administration of antimicrobials is the ability to achieve a concentration of drug at the infection site that is considerably higher than that achieved with systemic administration drugs alone.18 A continuous IA infusion system was developed with the goal of maintaining a drug concentration within the joint many times higher than the MIC of common pathogens of horses.22,23 The system achieved a mean steady-state gentamicin concentration of 1.069 µg/mL within the synovial fluid of the tarsocural joint at a mean infusion rate of 1.17 mg/min. It was suggested23 that the high gentamicin concentrations achieved would improve the spectrum and bactericidal activity of the drug during treatment of patients with septic arthritis. The gentamicin concentration achieved in synovial fluid during continuous IA infusion was several-fold higher than that reported23,24 by use of regional perfusion techniques; however, measurement of gentamicin concentrations in synovial tissue and bone was not performed.25

Studies8,9,13,15,18,22 in which investigators assessed methods of local delivery of antimicrobials for the treatment of patients with septic arthritis have primar-
illy focused on the concentration of drug achieved in synovial fluid. Concentrations of antimicrobial achieved in the synovial membrane, subchondral bone, and joint capsule are more appropriate measures to use when evaluating a method of antimicrobial delivery because these are the sites where bacteria localize during infection. 10 Gentamicin concentrations in the synovial membrane 11 and bone 23, 24 have been evaluated during administration by use of regional perfusion techniques; however, concentrations achieved by use of methods for local delivery that rely on passive diffusion of drug from the synovial fluid into synovial tissues would be expected to differ. To our knowledge, there is currently no information available regarding gentamicin concentrations in the synovial membrane, subchondral bone, joint capsule, or collateral ligament after a drug is administered systemically or via continuous IA administration. Extrapolation of gentamicin concentrations in synovial fluid to concentrations in the deeper synovial tissues that are often involved in synovial infections 3 could erroneously lead to a presumption of drug efficacy. Direct measurement of gentamicin concentrations in joint tissues during drug administration would provide more precise information for making therapeutic decisions about the treatment of patients with septic arthritis. Additionally, knowledge of any correlation between gentamicin concentrations in synovial fluid and joint tissues would enable customized monitoring and dosage adjustment during treatment of patients.

The primary objective of the study reported here was to compare gentamicin concentrations achieved in joint tissues during IV administration and continuous IA infusion of the tarsocrural joint in horses. Joint tissues examined were the synovial membrane, joint capsule, subchondral bone, and collateral ligament. Additional objectives were to establish whether a correlation exists between gentamicin concentrations in synovial fluid and synovial tissues during treatment and whether concurrent IV and IA administration affects the gentamicin concentration achieved in joint tissues. Our primary hypothesis was that a continuous IA infusion of gentamicin into the tarsocrural joint would achieve higher drug concentrations in joint tissues than would be achieved by IV administration alone. We also hypothesized that concurrent administration via continuous IA infusion and IV injection would achieve higher drug concentrations in the joint tissues than would be achieved by continuous IA infusion alone.

**Materials and Methods**

**Animals**—Eighteen horses between 4 and 20 years of age that had been donated to Purdue University for reasons other than tarsocrural joint disease were used for the study. All horses were to be euthanized because of chronic, incurable, or unmanageable conditions (15 musculoskeletal conditions and 3 behavioral conditions). Horses weighed between 410 and 584 kg and were considered generally healthy. Before inclusion in the study, all horses had to have results within the respective reference ranges for a CBC, urinalysis, BUN concentration, serum creatinine concentration, and ratio for urine γ-glutamyltransferase activity to urine creatinine concentration. The study protocol was approved by the Purdue University Animal Care and Use Committee.

**Experimental design**—Horses were randomly assigned to 1 of 3 treatment groups (6 horses/group). Group 1 horses were administered gentamicin (6.6 mg/kg, IV, q 24 h for 4 days [ie, at 0, 24, 48, and 72 hours]). Group 2 horses were administered a continuous IA infusion of gentamicin into a single tarsocrural joint (50 mg/h for 73 hours). Group 3 horses were administered a continuous IA infusion of gentamicin plus IV administration of gentamicin. The initiation of gentamicin administration was designated as time 0.

Synovial fluid and serum samples were collected throughout the 73-hour study period. Horses were euthanized by IV injection of an overdose of barbiturate immediately after conclusion of the study, and a necropsy was performed immediately thereafter. Joint tissue samples were collected to measure gentamicin concentrations. To enable assessment of expected peak gentamicin concentrations in synovial fluid and joint tissues, a 1-hour delay was chosen as the interval from the last IV administration of gentamicin until horses were euthanized and tissue samples were collected.

**Preparation of horses**—The joint infusion system used in the study was designed to deliver a continuous fluid flow rate of 0.5 mL/h. It comprised an expandable latex balloon attached to flow control tubing and a catheter adapted for IA use. The IA catheter can remain patent within the tarsocrural joint of horses for 5 days. 12 A catheter was inserted in the left jugular vein of each horse and secured in position for IA administration of gentamicin. Horses in groups 2 and 3 were sedated, injected SC at the insertion site with a local anesthetic, and had a catheter placed aseptically into the planterolateral pouch of the left tarsocrural joint. The catheter and attached infusion system were sutured in place and secured by use of cyanoacrylate. The balloon reservoir was filled with 40 mL of gentamicin solution (100 mg/mL). The IA catheter, infusion tubing, and balloon were secured beneath a bandage on the distolateral aspect of the crus.

**Collection of samples during the period of gentamicin administration**—Samples of synovial fluid were collected from the dorsomedial pouch of the tarsocrural joint at 0, 1, 3, 6, 12, 25, 49, and 73 hours. Hemorrhagic synovial fluid samples were centrifuged at 1,500 × g for 5 minutes. Supernatant was then harvested, placed into a plastic tube, and frozen at −20°C until analyzed. Blood samples were collected at 0, 1, 6, 24, 25, 48, 49, 72, and 73 hours. Serum was harvested, placed into plastic tubes, and frozen at −20°C until analyzed. Serum samples for trough gentamicin concentrations were those collected immediately before each IV administration, and serum samples for peak gentamicin concentrations were collected 1 hour after each IV administration of gentamicin to enable correlation with expected peak gentamicin concentrations in tissues.

**Collection of samples during necropsy**—Horses were euthanized 73 hours after initiation of gentamicin administration by IV injection of an overdose of barbiturate. Samples (approx 0.5 to 1 g) of the synovial membrane (dorsolateral and plantarolateral aspects), joint capsule (dorsal aspect), and long head of the lateral collateral ligament were collected immediately after horses were euthanized. Samples of subchondral bone of the distal lateral trochlea ridge were collected by resecting a triangular wedge from the trochlea and then cutting this wedge into 3 to 5 pieces of subchondral bone (approx 0.5 cm/piece). All tissue samples were collected into plastic tubes and frozen at −20°C until analyzed.

**Preparation of samples**—Samples of synovial membrane, joint capsule, and collateral ligament tissue were thawed and
weighed prior to processing. We added 0.5 mL of collagenase (5 mg/mL) and 0.5 mL of dilution buffer to each sample; samples were then incubated at 37°C for 24 hours. Following incubation, samples were homogenized by use of an electric tissue homogenizer. The tissue slurry was centrifuged at 1,500 × g for 5 minutes. Supernatant was harvested, placed into plastic tubes, and frozen at −20°C until analyzed.

Bone samples were prepared in a manner similar to that described elsewhere. Specifically, each small bone piece (approx 0.5 cm³) was placed into a sterile, thick plastic bag; covered by a towel; and then pulverized into grains < 2 mm by use of a mallet. Each resultant sample was weighed and soaked in 1 mL of dilution buffer for 24 hours. Supernatant was then harvested and frozen at −20°C until analyzed.

One milliliter of each sample of synovial fluid and 1 mL of 10% methanol solution were added to a centrifugal filter unit (10,000 MW). The samples were vortexed and then centrifuged at 1,500 × g for 45 minutes in a fixed-angle, rotor-adapted centrifuge. Ultrafiltrate was harvested and used to measure gentamicin concentrations in synovial fluid.

Gentamicin assay—A fluorescence polarization immunoassay was used to measure the gentamicin concentration in samples of synovial fluid, serum, and supernatant of tissues. A calibration curve for the assay was established by use of 6 human serum standards for each gentamicin reagent pack used, as has been described elsewhere. Coefficient of variation for the assay was established for synovial fluid and synovial and joint tissues by preparing 6 samples that contained 4 known concentrations of gentamicin (0, 5, 50, and 500 mg/mL or µg/g). The coefficient of variation ranged from 1.1% to 10.2% for the 4 concentrations tested. Extraction efficiency for the synovial tissue samples tested was 89.2 ± 3.6%. Similar to the procedure reported by Werner et al., subsequent incubation of bone samples in 1 mL of dilution buffer for 24 hours and assay of supernatant were used to evaluate additional elution of gentamicin. This additional incubation failed to yield substantial amounts of gentamicin.

Statistical analysis—Gentamicin concentrations in samples of synovial membrane obtained from the dorsolateral and plantarolateral collection sites were compared within each group by use of a paired t test. Subsequently, data for synovial membrane samples from each joint were combined for comparison among groups. Serum peak and trough gentamicin concentrations and gentamicin concentrations in samples of synovial fluid were compared by use of a repeated-measures ANOVA. Gentamicin concentrations in samples of serum, synovial fluid, synovial membrane, joint capsule, subchondral bone, and lateral collateral ligament obtained during necropsy (73 hours after initiation of gentamicin administration) were compared among groups; data were assessed for normality by use of a Shapiro-Wilk test and then analyzed by use of a Kruskal-Wallis 1-way nonparametric ANOVA. Values of P ≤ 0.05 were considered significant. The r value was used to describe relationships among gentamicin concentrations in serum, synovial fluid, and synovial tissues at 73 hours. All analyses were performed by use of commercially available statistical software program.

Results

IA infusion—The joint infusion system delivered a mean ± SE volume of 32.3 ± 1.4 mL of gentamicin during the administration period to horses of groups 2 and 3, which resulted in a mean infusion rate of 0.44 ± 0.07 mL/h. Mean dosing rate was 0.09 ± 0.001 mg/kg/h. There was no difference in volume of infusion, infusion rate, or dosing rate between groups 2 and 3.

Necropsy—All catheters for IA infusion remained within the plantarolateral pouch of the tarsocrural joint for the entire administration period. Two catheters (1 in group 2 and 1 in group 3) had evidence of kinking or flattening when removed during necropsy (Figure 1). One of these horses had the lowest gentamicin concentration in synovial fluid at 73 hours (70 µg/mL), compared with values for the other horses in that group. There were 2 horses in which leakage of infusion fluid was suspected because of moisture on the inner layer of the bandage corresponding to the location of the junction between the infusion tubing and IA catheter. Both of these horses were in group 2, and both had gentamicin concentrations in synovial fluid (254 and 284 µg/mL, respectively) that were less than the mean for the group (459 µg/mL) in samples obtained at 73 hours.

We did not detect gross lesions in the tarsocrural joints attributable to IA catheters. All IA catheter sites had mild edema in the subcutaneous tissues at the time of necropsy. All dorsomedial arthrocentesis sites had gross hemorrhage evident within the synovial membrane. No other complications were observed in association with the IA catheters.

Gentamicin concentration in serum samples—Within each group, peak gentamicin concentration in serum samples obtained at 73 hours was significantly higher for group 2 horses, compared with concentrations for horses of groups 1 and 3 (Table 1). Trough gentamicin concentration in serum samples for group 1 horses increased significantly (P = 0.007) from 24 to 72 hours (Figure 2). Gentamicin concentrations measured in serum samples obtained at 72 hours did not differ significantly (P = 0.61) among groups. There were no other significant effects of time on serum gentamicin concentrations.
Gentamicin concentrations in samples of synovial fluid—Within each group, peak gentamicin concentration in synovial fluid during the 73-hour administration period did not differ significantly over time. Gentamicin concentration measured in synovial samples obtained at 73 hours was significantly (P = 0.006) lower for group 1 horses, compared with the concentrations for horses in groups 2 and 3 (Table 1).

Gentamicin concentration in samples of joint tissues—Mean gentamicin concentration in samples of synovial membrane obtained from the dorsolateral and plantarolateral collection sites did not differ significantly within groups, and data were subsequently combined for comparison of gentamicin concentrations in synovial membranes among groups. Gentamicin concentration in synovial membrane was significantly (P < 0.001) lower for group 1 horses, compared with concentrations for group 2 and 3 horses (Table 1). Gentamicin concentration in samples of joint capsule was significantly (P = 0.006) lower for group 1 horses, compared with concentrations for group 2 and 3 horses. Gentamicin concentration in samples of lateral collateral ligament was significantly lower for group 1 horses, compared with the concentration for group 3 horses. There was no significant difference detected between groups 1 and 2, nor between groups 2 and 3, for gentamicin concentration in samples of the lateral collateral ligament.

Gentamicin concentration in samples of subchondral bone—Gentamicin concentration in samples of subchondral bone was significantly (P = 0.017) lower for group 1 horses, compared with the concentration for group 3 horses. There was no significant difference detected between groups 1 and 2, nor between groups 2 and 3.

Correlations of gentamicin concentrations among serum, synovial fluid, and synovial and joint tissues—A significant correlation (r, 0.94; P = 0.005) was found between gentamicin concentrations in serum and the lateral collateral ligament in group 1 horses. A significant correlation was also found in group 2 horses between gentamicin concentrations in synovial fluid and synovial membrane (r, 0.83; P = 0.03) and between synovial fluid and subchondral bone (r, 0.87; P = 0.02). No other significant correlations were detected for gentamicin concentrations in serum, synovial fluid, and synovial and joint tissues.

Discussion

Gentamicin is a concentration-dependent, bactericidal aminoglycoside that is commonly used in the treatment of horses with joint infections. It is a polycationic molecule with poor lipid solubility that is primarily distributed within the extracellular tissue space. There is relatively sparse information available regarding gentamicin distribution within joint tissues for systemically or locally administered drug. In which investigators evaluated gentamicin in horses have primarily used gentamicin concentrations in synovial fluid to assess its distribution to joint tissues and predict efficacy of the drug for treating synovial infections. However,
because bacteria primarily localize within the synovial membrane, subchondral bone, and other soft tissues of the joint during infection, \(^1\) we elected to investigate gentamicin distribution within these tissues by direct measurement following administration of gentamicin in accordance with 3 dosing protocols. Analysis of the results supports our hypothesis that a continuous IA infusion of gentamicin achieves higher concentrations of the drug in joint tissues than is achieved by use of IV administration alone. However, the hypothesis that a combination of both methods of drug delivery (ie, IA and IV) would achieve higher tissue concentrations than continuous IA infusion alone was rejected.

In horses, the most common pathogens have an MIC < 4 µg/mL for gentamicin, \(^2\) although development of resistant organisms and strains of bacteria with a higher MIC has been reported.\(^3\) All gentamicin concentrations measured in tissues in the study reported here exceeded 4 µg/g. Gentamicin concentrations during continuous IA infusion ranged from 3 times the MIC for common pathogens in samples of lateral collateral ligament to 125 times the MIC in samples of synovial membrane.

The bactericidal action of gentamicin involves ionic binding to the outer bacterial membrane followed by internalization through 2 energy-dependent processes.\(^4\) The initial ionic binding process is a concentration-dependent event, whereas the active-transport processes are limited in rate and independent of drug concentration. This sequence of passive ionic binding followed by energy-dependent internalization explains the concentration-dependent activity as well as the postexposure effects (ie, postantibiotic effects) for aminoglycosides.\(^5\) Clinical efficacy of aminoglycosides in humans correlates with the ratio of peak serum concentration to MIC.\(^6\) Duration of the postantibiotic effect is also related to peak serum concentrations of aminoglycosides, with a plateau of this effect suggested at 10 times the MIC.\(^7\)

Synovial membranes are of mesenchymal origin and considered highly permeable because of the lack of a basement membrane.\(^8\) There is a complex capillary network within the subsynovium,\(^9\) and transsynovial flow of fluid is principally governed by Starling's forces.\(^10\) However, hyaluronan in synovial fluid can alter the reflection coefficient of synovial membranes\(^11\) and may affect synovial distribution of gentamicin. Movement of gentamicin into and out of the synovial cavity is believed to take place via diffusion down a concentration gradient.\(^12\) Our finding of a strong correlation between gentamicin concentrations in samples of synovial fluid, synovial membrane, and subchondral bone in horses administered gentamicin via a continuous IA infusion was most likely attributable to the establishment of a steady-state gentamicin concentration within the synovial fluid.\(^13\) This is supported by the finding that the gentamicin concentration in the synovial fluid of groups 2 and 3 did not vary significantly over time. This removes the effect of diffusion rate from the correlation analysis. At a steady-state condition, diffusion of drug out of the synovial cavity (and into synovial membrane, subchondral bone, surrounding tissues, and lymphatic vessels) would equal the infusion rate for the joint infusion system. Assuming steady-state conditions, evaluation of gentamicin concentration in the synovial fluid provides an indication of gentamicin concentrations achieved in synovial membranes and subchondral bone during a continuous IA infusion. If required, adjustments in dosage and infusion rate could be used\(^14\) to achieve higher (or lower) gentamicin concentrations in the synovial fluid (and hence in the adjacent tissues) than those reported here.

Mean gentamicin concentration in samples of synovial membrane obtained 1 hour after IV administration for group 1 horses was 21 µg/g. This value was higher than the corresponding gentamicin concentration in synovial fluid and similar to the corresponding gentamicin concentration in serum samples. In 1 study,\(^15\) lymph and plasma gentamicin concentration-versus-time curves crossed between 1 and 2 hours after IV administration at a dosage of 2.2 mg/kg, and the time to peak gentamicin concentration in lymph fluid was 1.2 hours. In another study,\(^16\) time to peak gentamicin concentration in tissue-cage fluid after IV administration at a dosage of 6.6 mg/kg was 1.4 hours. Although the gentamicin concentration in synovial fluid samples obtained 1 hour after IV administration should be effective against most pathogens of horses, use of the gentamicin half-life of 1.4 hours in tissues\(^17\) reveals that the concentration would be < 4 µg/g within 6 hours after administration. Alternatively, use of the gentamicin half-life of 3.1 hours in lymph fluid\(^18\) reveals that the gentamicin concentration would be < 4 µg/g within 11 hours after treatment. Duration of the postantibiotic effect required to extend gentamicin activity to a 24-hour dosing interval would be between 13 and 18 hours by use of these calculations. For bacteria with an MIC > 4 µg/mL that cause a synovial infection, we propose that IV administration of gentamicin at a dosage of 6.6 mg/kg once daily may be insufficient for successful treatment. However, it is recognized that a synergistic effect exists between aminoglycosides and ß-lactam antimicrobials.\(^19\) Because of the common clinical practice of combining these antimicrobial classes for treatment of patients with septic arthritis,\(^1\) the efficacy of systemically administered aminoglycosides may be attributable in part to this effect. Such combinations may also contribute to the successful treatment of patients infected with highly susceptible organisms. In other studies,\(^14\) investigators have suggested that IV administration of gentamicin alone at recommended doses is likely to be ineffective in the treatment of patients with septic arthritis, and analysis of our results supports this contention. In contrast, continuous IA infusion resulted in a mean gentamicin concentration of 497 µg/g in samples of synovial membrane, which would be maintained during the period when the infusion was in steady-state equilibrium and provide effective and rapid bacterial killing.

A limitation of the study reported here and other studies in which investigators investigated gentamicin concentrations in synovial fluid and tissues of horses was the use of normal joints. Investigators in 1 study\(^19\) reported that during regional limb perfusion of the carpus in horses with experimentally induced septic arthritis, the mean gentamicin concentrations in syn-
of synovial fluid were less than those reported by use of the same technique in normal joints. In a study in which investigators evaluated antimicrobial absorption from infected and normal joints in rabbits, gentamicin absorption was slower from the infected joints. In a series of related studies, mean peak gentamicin concentration in joints infected with Escherichia coli was similar to that found in normal joints after IA injection of 150 mg of gentamicin. However, the mean apparent half-life of gentamicin in synovial fluid was longer and mean clearance of gentamicin from synovial fluid was lower in the infected joints. The authors of those studies concluded that fluid secretion and removal were substantially altered during joint sepsis. Clearly, infection is expected to change the distribution of gentamicin within synovial tissues; however, it is not clear to what degree the distribution is altered. This fact further supports the use of continuous IA infusion and other local treatments in which the difference between expected gentamicin concentrations in tissues and the MIC is larger than that with IV administration and provides a margin of safety with respect to any possible reduction of gentamicin concentrations in infected tissues. We believe that results of the study reported here should be viewed only as a guide to anticipated gentamicin concentrations in tissues during treatment of horses with septic arthritis and that additional investigations of antimicrobial concentrations achieved in joint tissues by use of various local treatment modalities for patients with septic arthritis are warranted.

In 1 study, gentamicin concentration was measured in bone of horses following IA injection or regional IV perfusion of the metacarpophalangeal joint. Both groups in this study also received concurrent systemic administration of gentamicin (6.6 mg/kg, IV) 1 hour before the local administration to mimic the clinical situation of combining local and systemic treatments. Mean peak gentamicin concentration in bone was 39 µg/g (IA injection) and 32 µg/g (regional IV perfusion) at 1 hour after administration. Gentamicin concentrations in samples of subchondral bone for group 2 and 3 horses of our study (99 and 163 µg/g, respectively) were considerably higher. Although the bone samples were obtained from different locations in our study and the aforementioned study and should not be compared directly, gentamicin concentrations in bone following IA injection or IV regional perfusion were less than the reported MIC of 8 µg/g by 12 hours after administration. Considering that bone infection increases morbidity and mortality associated with septic arthritis, a continuous IA infusion could provide more effective gentamicin penetration into areas of subchondral bone than would be achieved by use of other local delivery techniques and offer advantages in the treatment of patients with septic arthritis complicated by osteomyelitis.

One aspect of continuous IA infusion of antimicrobials that requires further investigation is the type of antimicrobial used. Several gram-negative bacterial species have developed unstable adaptive resistance to aminoglycosides following exposure, which can be enhanced and prolonged by continued drug exposure. It was speculated that the clinical use of aminoglycosides in combination with other antimicrobials has prevented this phenomenon from becoming clinically recognized, and to our knowledge, there is currently no evidence supporting this phenomenon as a clinical problem. Investigators in 1 study stated that this phenomenon was not true resistance (in which an increase in MIC is induced) and that it may reflect a typical mechanism of aminoglycoside action. However, an alternative approach to continuous IA antimicrobial infusion for the treatment of patients with septic arthritis would be to use time-dependent drugs, such as a β-lactam antimicrobial, in combination with aminoglycosides. By use of this approach, a continuous infusion of a time-dependent drug could be complemented with an intermittent infusion of a high dose of a concentration-dependent drug, such as an aminoglycoside.

The use of aminoglycosides for local antimicrobial treatment has the benefits of inducing their concentration-dependent activity and concurrently minimizing the potential for nephrotoxic effects. It has been suggested that a trough serum concentration of < 2 µg/mL could minimize the possibility of gentamicin-induced nephrotoxicosis. Trough serum concentration of gentamicin was monitored in the 3 treatment groups and was consistently < 2 µg/mL, which suggested that at the dosages used, the risk of nephrotoxic effects should be small. However, the mean trough serum concentrations of gentamicin in group 3 horses throughout the study period reflected the addition of IV administration and IA infusion. Local delivery of gentamicin should be considered in the pharmacokinetic analysis when it is combined with systemically administered drug, and appropriate dosing adjustments should be made for patients in which renal function or systemic status are less than optimal.

We found a strong correlation between gentamicin concentrations in samples of lateral collateral ligament and serum in horses receiving gentamicin by IV administration alone. The lateral collateral ligament of the tarsocrural joint is extracapsular, and perfusion and drug distribution for this structure should not be influenced by the synovial environment after systemic delivery of drug. There was no significant correlation between gentamicin concentrations in samples of serum or synovial fluid and synovial membrane, joint capsule, or subchondral bone following IV administration alone. These findings agree with results of other studies in which investigators assessed the relationship among gentamicin concentrations in serum, synovial fluid, and joint tissues. In 1 study, investigators measured gentamicin concentrations in synovial and lymph fluids after IV drug administration to determine whether drug concentrations in synovial fluid could be used as an indicator of the drug concentration in interstitial tissues. Although it was stated that a sample of plasma, synovial fluid, or lymph could serve as a good index for the other 2, the authors concluded that gentamicin concentration in synovial fluid had limited value for use in predicting the gentamicin concentration in tissue fluid. In another study in which investigators evaluated the pharmacokinetics of ampicillin and gentamicin, it was found that predictions from serum concentrations of gentamicin overestimated.
gentamicin concentrations in synovial fluid, and those authors concluded that drug concentrations in synovial fluid could not be predicted through pharmacokinetic analysis of the peripheral compartment alone.

The joint infusion system used in the study reported here was more reliable than a prototype system initially evaluated for continuous IA infusion in which 29% of catheters developed complications. There were 2 catheters in our study that had evidence of kinking or flattening when examined during necropsy; however, both were still patent and considered to be functioning on the basis of evaluation of the catheter and gentamicin concentrations in the synovial fluid and tissues. There were also 2 horses in which leakage at the junction of the infusion tubing and IA catheter was suspected during necropsy. These horses had gentamicin concentrations in synovial fluid and tissues that were at the lower end of the values for their group. Despite these technical difficulties, the infusion system delivered a mean of 0.44 mL/h, which was slightly lower than the expected 0.5 mL/h. In our experience, we have found that there is a low rate (6%) of technical problems (primarily leakage) with the clinical use of this system. We believe that the ideal continuous IA infusion system should have a reliable catheter system that can also be used for high-volume synovial lavage. Furthermore, it should be able to deliver more than 1 antimicrobial, and clinicians or researchers should be able to adjust the dosage of antimicrobial delivered. The joint infusion system used in our study meets several of these criteria; however, additional development and evaluation of other available systems are necessary to advance this method of local administration of antimicrobials.

Results from the study reported here provide information regarding gentamicin concentrations that could be achieved in joint tissues by use of the same infusion rate and gentamicin dosing rate when other systems are used for continuous IA delivery.

The purpose of the study reported here was to compare the gentamicin concentration achieved in the synovial membrane, joint capsule, subchondral bone, and lateral collateral ligament of the tarsocrural joint of clinically normal horses during IV administration and continuous IA infusion. Analysis of the results revealed that continuous IA infusion achieved significantly higher gentamicin concentrations in joint tissues, compared with concentrations achieved by use of IV administration alone. We also found that the addition of IV administration of gentamicin to continuous IA infusion does not significantly increase the gentamicin concentrations achieved in joint tissues of horses.

References