Effects of continuous intra-articular infusion of gentamicin on synovial membrane and articular cartilage in the tarsocrural joint of horses

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Objective—To determine the effects of a continuous intra-articular infusion of gentamicin on the synovial membrane and articular cartilage in the tarsocrural joint of horses.

Animals—6 healthy adult horses.

Procedure—A balloon infusion system attached to a catheter placed in the plantarolateral pouch of both tarsocrural joints in each horse was used for continuous gentamicin solution (GM) or balanced electrolyte solution (BES) delivery for 5 days. Cartilage and synovial membrane specimens were collected on day 5 from 3 horses and on day 14 from the remaining 3 horses. Both infused joints from each horse were assessed, using gross evaluation and histologic scoring systems.

Results—Significant differences in the histologic scores of synovial membrane specimens between the GM- and BES-treated joints at either 5 or 14 days were not observed. Safranin-O-fast green staining scores were similar between cartilage specimens from GM- and BES-treated joints. Although the synovial membrane histologic scores and safranin-O-fast green staining scores improved from day 5 to 14, the changes in scores were not significant. Loss of synovial intimal cells from villi was found more commonly in sections of synovial membrane from GM-treated joints, compared with BES-treated joints.

Conclusions and Clinical Relevance—Continuous infusion of GM into the tarsocrural joint of horses does not have significant effects on histologic scores of articular cartilage or synovial membrane, compared with those infused with BES. Continuous infusion of GM into the tarsocrural joint of horses for 5 days is an acceptable method for the treatment of septic arthritis. (*Am J Vet Res* 2002;63:683–687)

Intra-articular administration of antimicrobials for the treatment of septic arthritis in horses has been recommended in recent years.[1-3] The advantages of intra-articular treatment include achieving high concentrations of the drug at the site of infection, the ability to use cost-prohibitive drugs in small doses, and a reduction in systemic adverse effects. Aminoglycosides have a concentration-dependent bactericidal action[4] and are recommended for treatment of septic arthritis in horses.[1,2,5] The effect of a single 150 mg dose of gentamicin into the antebrachiocarpal joint on the synovial membrane has been reported.[6]

Articular cartilage **glycosaminoglycan (GAG)** depletion develops rapidly in horses with septic arthritis as a result of the severe inflammatory response within the joint.[2] Matrix depletion is an early biochemical change in the pathogenesis of osteoarthritis in horses.[7] Rapid resolution of infection and control of the inflammatory process within the joint are essential for successful treatment of septic arthritis and preservation of normal joint function. However, any treatment aimed at resolving the infection within the joint should not cause further irreversible damage to the articular cartilage or synovial membrane. We have previously reported the use of an infusion catheter for continuous infusion of gentamicin into the tarsocrural joint of 12 horses for 5 days.[8] Gentamicin concentrations as high as 3,510 µg/ml were obtained, and the mean steady state synovial fluid gentamicin concentration was 1,069 µg/ml. The purpose of the study presented here was to determine the effect of this continuous infusion of gentamicin on the synovial membrane and articular cartilage in the tarsocrural joint of horses.

Materials and Methods

Horses—Six healthy adult horses of either sex and various breeds were used in our study. Mean age of the horses was 9.5 years, ranging from 2 to 23 years old. Horses did not have any tarsocrural joint disease, as determined by complete physical and lameness examinations, and results of CBC were normal. Horses were confined to box stalls throughout our study. The Purdue University Animal Care and Use Committee approved the study protocol. All 6 horses were included in a concurrent previously reported study[8] on use of the continuous infusion system for delivery of gentamicin into the tarsocrural joints.

Experimental protocol—All 6 horses had both tarsocrural joints catheterized. The joint catheter was created by cutting off the adapter on the end of commercially available flow control tubing.[a] The flow control tubing was connected to a 36-ml latex balloon infuser,[b] using an extension set with a T-connector.[c] Catheters were placed aseptically in the plantarolateral pouch of each joint under local anesthesia with the horses standing in stocks and sedated. Continuous infusion of either 100-mg/ml **gentamicin solution (GM)** in the treatment limb or **balanced electrolyte solution (BES)** in the contralateral limb was maintained for 5 days, at which time all catheters were removed. The GM (pH 3.2) infused at a mean (± SD) rate of 16.4 ± 2.5 ml/d, and BES (pH 7.4) infused at a rate of 24.4 ± 7.7 ml/d. The different infusion rates were caused by the difference in fluid viscosity of the 2 solutions.[d] Daily arthrocentesis of the dorsomedial pouch of each joint was performed for synovial fluid collection during

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the entire infusion period.[8] To evaluate synovial structures, horses 1 to 3 were euthanatized upon completion of the 5-day infusion period, and horses 4 to 6 were euthanatized on day 14.

Gross examination and specimen collection—All catheterized joints were examined by use of a systematic dissection from the dorsomedial surface, reflecting the soft tissues of the dorsal tarsus laterally. The plantarolateral pouch was approached separately. Synovial membrane specimens were taken for histologic examination from 4 separate sites: dorsomedial, dorsodistal, dorsolateral, and plantarolateral (directly over the catheter site; **Fig 1**). These specimens were fixed in neutral-buffered 10% formalin, sectioned, and stained with H&E for histologic examination. An osteochondral specimen (10 × 10 × 5 mm) was taken from the middle of the lateral trochlea ridge of the talus, fixed in neutral-buffered 10% formalin, and then decalcified in citrate-buffered formic acid, embedded in paraplast, sectioned, and stained with H&E as well as safranin-O-fast green stain for histologic and histochemical evaluation.

Evaluation of synovial membrane—All specimens were evaluated histologically without knowledge of treatment allocations, using a modification of a previously reported grading system.[9] Four separate categories were graded as 0 (absent or no proliferation), 1 (mild proliferation, inflammatory infiltrate, or fibrin accumulation), 2 (moderate proliferation, inflammatory infiltrate, or fibrin accumulation), or 3 (severe or the predominant histologic feature). These categories were proliferation of synovial intimal cells and villi, presence and location of fibrin, number and location of mononuclear cells, and number and location of neutrophils. The presence of hemorrhage, blood clots, hemosiderophages, bacteria, or granulation tissue was also recorded. The sum of the scores from each category was calculated for each site, allowing a maximum score of 12/site.

Evaluation of articular cartilage—Articular cartilage of the osteochondral specimens stained with safranin-O-fast green was scored, using a scale of 0 (no interterritorial matrix staining), 1 (mild interterritorial matrix staining), 2 (moderate interterritorial matrix staining), and 3 (maximal interterritorial matrix staining) in 3 separate zones (superficial, intermediate, and deep).[9] Sections of tracheal cartilage were mounted on each slide and served as a positive control for staining of GAG.[10] Specimens were also assessed for histologic abnormalities such as surface fibrillation, erosions, cluster formation, and chondrocyte death. A count of nonfunctional and functional chondrocytes was made in each specimen and expressed as a percentage to further assess the cartilage response. This was performed by counting from the articular surface to the tidemark over a fixed width of the specimen at a site approximately 10 mm to the lateral side of the lateral trochlea. Chondrocytes were considered nonfunctional if they appeared dead (loss of cellular integrity or absence of a clearly defined nucleus) or were surrounded by a zone of poorly staining territorial matrix. This procedure was also performed separately for the intermediate layer of articular cartilage. Counting for the intermediate layer began where superficial chondrocytes became rounded and continued down to a point where chondrocytes began to align perpendicular to the articular surface over a fixed width of the specimen.[11]

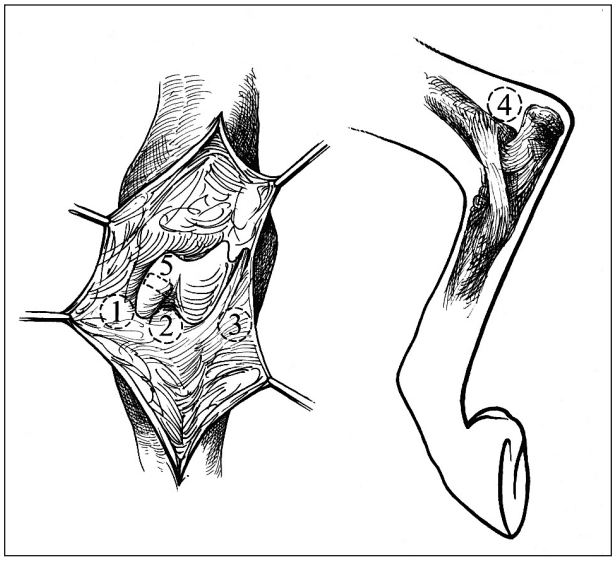

Figure 1—Drawing of the tarsocrural joint of a horse (left, dorsal view; right, lateral view). Notice the sites of specimen collection for evaluation of the synovial membrane. 1 = Dorsolateral site. 2 = Dorsodistal site. 3 = Dorsomedial site. 4 = Plantarolateral site. 5 = Lateral trochlea ridge of the talus (osteochondral specimen).

Statistical analysis—Synovial membrane histologic scores were determined for each site by adding the score from each category. An ANOVA was performed to compare the histologic score from the 4 separate sites from all joints with each other. Following this comparison, histologic scores from the 4 separate sites were added to obtain a total histologic score for each joint. The maximum score possible was 48/joint. A paired *t*-test was used to compare total histologic scores from GM- and BES-treated joints. A Student *t*-test was used to compare day-5 with day-14 scores. Safranin-O-fast green staining scores were added for each zone to obtain a total score for each joint. The maximum score possible was 9/joint. Percentage of nonfunctional chondrocytes was calculated for each joint. A paired *t*-test was used to compare GM- and BES-treated joints. A Student *t*-test was used to compare day 5 with day 14. Results are expressed as mean (± SD). Significance was set at $P < 0.05$.

Results

Gross evaluation—All catheterized joints examined had mild-to-moderate hemorrhage and edema associated with the arthrocentesis sites within the dorsomedial pouch. On gross examination of the dorsomedial pouch a difference was not observed between GM- and BES-treated joints. One joint (horse 4, GM-treated joint) had moderate edema associated with the catheter site in the plantarolateral pouch. The end of the catheter had displaced from the joint to a position in the subcutaneous tissues at some point prior to the end of the infusion period, resulting in fluid from the infusion system entering the tissues rather than the joint. The dorsomedial arthrocentesis sites and the plantarolateral catheter sites had mild local fibrin accumulation on the synovial membrane surface and occasional adherent blood clots. On gross examination a difference was not observed between GM- and BES-treated joints.

Evaluation of synovial membrane—Histologic scores from synovial membrane specimens were determined (**Table 1**). The results of an ANOVA indicated no significant differences in histologic scores between the 4 synovial membrane sites chosen for evaluation ($P = 0.91$). Histologic scores between the GM- and BES-treated joints were not significantly different

(P = 0.35). Scores for GM- and BES-treated joints were combined to compare day-5 with day-14 specimens. Histologic scores improved by day 14, but not significantly (P = 0.08).

Synovial membrane specimens from the plantarolateral pouch were predominantly classified as fibrous synovium with flattened or sparse villi. Several sections were taken directly through the catheter site, which was surrounded by an intense localized inflammatory response within the fibrous capsule. Most of the sections had fibrin accumulation on the surface, and various amounts of granulation formation were observed. One GM-treated joint (horse 2) had a notably flattened synovial lining and approximately 50% loss of the synovial intimal cells from the surface.

Synovial membrane specimens from the dorsomedial pouch were classified as areolar, adipose, or fibrous synovium. Day-5 specimens had moderate-to-severe neutrophilic inflammation associated with hemorrhage and clot formation on the synovial membrane surface. Hemorrhage often continued into the deeper tissue layers of the fibrous joint capsule. Day-14 specimens from the dorsomedial pouch contained hemosiderin within the fibrous capsule and occasionally within synovial intimal cells. Areas of granulation were seen at the synovial surface in 2 of 6 joints evaluated at day 14 (1 GM treated joint and 1 BES treated joint). Inflammatory infiltrates at day 14 were predominantly mononuclear and mild in severity.

Synovial membrane specimens from the dorsodistal synovial reflection were classified predominantly as areolar synovium, with occasional areas of adipose infiltration. Evidence of loss of synovial intimal cells lining the villi in 4 of 6 GM-treated joints was observed. Horses 1 and 5 were estimated to have lost 20% of synovial intimal cells, whereas horse 3 lost 30% and horse 4 lost 40% of the intimal cells lining the villi. Inflammatory response was a mixture of neutrophilic and mononuclear cells in day-5 specimens and predominantly mononuclear cells in day-14 specimens. Considerably less hemorrhage and clot and fibrin accumulation were observed, compared with dorsomedial and plantarolateral sites.

Synovial membrane specimens from the dorsolateral pouch were all classified as fibrous synovium. Approximately 20% of synovial intimal cells from the villi in 1 of the GM-treated specimens were lost (horse 5). Inflammatory changes were similar to those seen in the dorsodistal sites.

Evaluation of articular cartilage—The GAG content of articular cartilage in safranin-O-fast green stained specimens revealed no difference between GM- and BES-treated joints (P = 0.81). Safranin-O-fast green matrix staining between day-5 and day-14 specimens increased, but not significantly (P = 0.07). Scores in the 3 layers of articular cartilage from each horse were determined (**Table 2**). One GM-treated joint (horse 6) had superficial erosion in the middle of the specimen. Three GM-treated and 4 BES-treated joints had mild superficial fibrillation. Occasional cluster formation was observed in 4 GM- and 3 BES-treated joints. Comparison of the percentage of nonfunctional chondrocytes revealed no difference between GM-treated (19.7 ± 4.7%) and BES-treated (18.6 ± 2.3%) joints (P = 0.65) for the total thickness of articular cartilage. The percentage of nonfunctional chondrocytes in the intermediate layer were not significantly different between GM-treated (16.8 ± 4.3%) and BES-treated (17.9 ± 4.9%) joints (P = 0.60). The per-

Table 1—Histologic scores* of the tarsocrural joint synovial membrane following a 5-day continuous infusion of gentamicin solution (GM) or balanced electrolyte solution (BES) in 6 horses

	Horse 1 (day 5)		Horse 2 (day 5)		Horse 3 (day 5)		Horse 4 (day 14)		Horse 5 (day 14)		Horse 6 (day 14)	
Location†	GM	BES	GM	BES	GM	BES	GM	BES	GM	BES	GM	BES
Dorsodistal site	3	8	3	7	6	2	2	1	2	6	3	5
Dorsolateral site	3	7	6	4	3	6	3	1	4	4	4	2
Dorsomedial site	5	8	4	7	6	1	4	3	4	5	2	4
Plantarolateral site	7	5	4	5	4	4	2	2	5	8	3	3
Total score	**18**	**28**	**17**	**23**	**19**	**13**	**11**	**7**	**15**	**23**	**12**	**14**

*Scores for each location were obtained by adding the individual scores for each histologic category evaluated. Categories were graded on a scale of 0 (absent or no proliferation) to 3 (severe or the predominant histologic feature). Categories evaluated were proliferation of synovial intimal cells and villi, presence and location of fibrin, number and location of mononuclear cells, and number and location of neutrophils. †Synovial membrane specimens were taken for histologic examination from 4 separate sites: dorsomedial, dorsodistal, dorsolateral, and plantarolateral (directly over the catheter site; *See* Figure 1).

Table 2—Safranin-O-fast green staining scores* for articular cartilage specimens from the lateral trochlea ridge of the talus following a 5-day continuous infusion of GM or BES in 6 horses

	Horse 1 (day 5)		Horse 2 (day 5)		Horse 3 (day 5)		Horse 4 (day 14)		Horse 5 (day 14)		Horse 6 (day 14)	
Zones	GM	BES	GM	BES	GM	BES	GM	BES	GM	BES	GM	BES
Superficial	0	0	1	1	0	0	0	0	1	0	0	1
Intermediate	1	1	1	1	1	1	1	1	2	1	1	2
Deep	2	2	2	2	2	2	3	3	3	3	2	3
Total score	**3**	**3**	**4**	**4**	**3**	**3**	**4**	**4**	**6**	**4**	**3**	**6**

*Scores were obtained by assessing interterritorial matrix staining on a scale of 0 (no staining) to 3 (dark pink staining).

centage of nonfunctional chondrocytes from day 5 (20.6 ± 4.5%) to day 14 (17.8 ± 2.0%) decreased ($P = 0.21$) in the overall cartilage thickness. Within the intermediate layer the percentage of nonfunctional chondrocytes decreased ($P = 0.14$) from day 5 (19.3 ± 4.8%) to day 14 (15.4 ± 3.3%). None of these changes were considered significant.

Discussion

Results of our study indicate that a continuous 5-day infusion of gentamicin into the tarsocrural joint of horses does not cause substantial deterioration in the synovial membrane histologic scores or articular cartilage GAG content, compared with BES infusion. Further, the synovial membrane histologic scores and articular cartilage safranin-O-fast green staining scores improved by 9 days after completion of the infusion period, but not significantly. This improvement, although not significant, may suggest that changes seen during our study may be transient and potentially reversible.

Our observation of a greater loss of intimal cells from the synovial lining of GM treated joints, compared with BES treated joints, is consistent with a previous report. Stover and Pool[6] found that a single injection of 150 mg of gentamicin into the antebrachiocarpal joint caused loss of synovial intimal cells, with areas of necrosis observed at the tips of synovial villi 24 hours following injection. These investigators also noticed that 2 and 3 days following injection of gentamicin, the number of synovial intimal cells lining the villi was decreased, compared with control joints, and synovial inflammation had resolved within 7 days. In our study, longer duration of exposure to gentamicin resulted in greater loss of synovial intimal cells than that reported from a single injection, with all GM-treated joints having some loss and 4 of 6 GM-treated joints having greater than 20% loss of synovial intimal cells from the villi in the dorsodistal synovial reflection. Despite this, we believe the effects of synovial intimal cell loss are mild and transient, particularly when the severe changes caused by a septic inflammatory process are used for comparison. Synovial regeneration in horses has been studied[12] following arthroscopic synovectomy. Despite slower regeneration, compared with other species, the synovial intimal lining had regenerated 120 days following synovectomy. Synovial intimal cells were metabolically active and able to maintain a normal joint environment. Synovial membrane specimens from our study had improvement on histologic scores between days 5 and 14.

Synovial intimal cell damage may be caused by direct toxic effects of gentamicin, ischemic damage, decreased pH within the joint, inflammation within the joint, or a combination of mechanisms. Gentamicin causes renal tubular necrosis following endocytosis of the drug by proximal tubular cells and incorporation into cellular lysosomes.[13,14] Gentamicin and other aminoglycosides become highly cationic within lysosomes (pH 5 to 6) and inhibit phospholipase activity through strong binding of phospholipids. Accumulation of phospholipids results in eventual lysosomal rupture and cell death.[13,14] It is possible that the same events occur in the synovial intimal cells following exposure to gentamicin in the synovial fluid.

Decreased synovial fluid pH has previously been considered a cause of synovial damage following intra-articular gentamicin administration.[3,6,15] Mean synovial fluid pH in GM-treated joints of our study ranged from 7.13 (day 1) to 7.43 (day 0), whereas in BES-treated joints it ranged from 7.33 (days 1 and 4) to 7.44 (day 0).[8] It seems unlikely that a lowered pH alone could account for substantial loss of synovial intimal cells in our study, because the lowest mean pH value in the treated joints was 7.13, and a pH of 5.98 has been previously reported following intra-articular gentamicin use without mention of substantial loss of synovial intimal cells[15]. Previous studies also reported a more severe inflammatory response[15] and reduced ability to eliminate experimental septic arthritis in horses[3] when gentamicin was buffered with sodium bicarbonate and the pH of the synovial fluid was maintained close to normal values.

Another possible mechanism of cellular injury within the synovial intima is ischemia as a result of vascular thrombosis. Stover and Pool[6] observed thrombosis of subintimal capillaries associated with the tips of villi where synovial intimal cells were necrotic. Although an occasional microthrombus was found in some of the synovial membrane specimens of our study, these were not consistently located in areas of synovial intimal cell loss. It is unlikely that ischemic injury alone is the cause of the observed intimal cell damage. It is possible that a combination of factors is responsible; however, the exact mechanism of loss of the synovial intimal cells remains unclear.

Articular cartilage matrix GAG content was assessed indirectly in our study by histochemical staining. Loss of GAG staining has historically been a hallmark of the initial histochemical events in the onset of osteoarthritis in humans and more recently in horses.[7] Although there appeared to be some loss of safranin-O-fast green staining in the day-5 specimens, improvement in staining in the day-14 specimens suggests that loss of GAG was transitory. Failure to detect a significant difference between GM- and BES-treated joints suggests that GAG depletion may have occurred as a result of the inflammatory response within the joints. Catheter placement and maintenance within the joint, continuous fluid infusion, and daily arthrocentesis produced a synovitis that resolved following the end of the infusion period in GM- and BES-treated joints.[8] Parallel with the resolution of synovitis and a probable reduction of inflammatory mediators within the joint,[7] an improvement in safranin-O staining of the articular cartilage was observed. In light of the severe and rapidly irreversible changes seen in the articular cartilage of septic joints,[2] it is suggested that the continuous gentamicin infusion used in our study is acceptable for the intra-articular delivery of gentamicin in horses with septic arthritis and does not have permanent detrimental effects on the articular cartilage.

In an attempt to combine the cartilage degradation feature of matrix depletion and any possible direct cellular effects of gentamicin on chondrocytes, a classification was developed to estimate nonfunctional chondro-

cytes. This assessment was used over the entire thickness of the cartilage and also over the depth of the intermediate layer, because this is the most metabolically active layer of articular cartilage[11] and, therefore, considered the most likely to have a direct effect of gentamicin on the chondrocytes. In agreement with the findings of safranin-O-fast green staining, a difference between the GM- or BES-treated joints in either full thickness or intermediate layers was not observed, and the percentage of nonfunctional chondrocytes had decreased by day 14, though this finding was not significant.

Previous studies[6,9,16-19,e] have evaluated various joint lavage and intra-articular treatments to determine their safety and efficacy. The synovial inflammation seen in GM- and BES-treated joints in our study may have been caused by a number of factors. Our study does not adequately distinguish between the effects of daily arthrocentesis, joint catheterization, and GM or BES infusion despite histologic assessment of 4 separate areas of the synovial membrane. It is clear that an inflammatory response should be expected any time a synovial cavity is entered and that some effect on the synovial membrane and articular cartilage can be anticipated to result from the induced inflammation. Results of our study suggest that a continuous 5-day infusion of gentamicin into the tarsocrural joint of horses produced mild yet transient changes in the synovial membrane and articular cartilage. The use of a short-term (5 days or less) continuous intra-articular infusion for local antimicrobial treatment in horses with septic arthritis may be helpful as an adjunct to systemic antimicrobial treatment and joint lavage.

[a]Flow control tubing, Mila International Inc, Erlanger, Ky.

[b]Latex balloon infuser, Cat. No. VB101, Mila International Inc, Erlanger, KY.

[c]Minivolume extension set, Baxter Healthcare Corp, Deerfield, Ill.

[d]Flowline fluid delivery systems informational brochure, Pacific Medical Supplies Pty Ltd, Richmond, Victoria, Australia.

[e]Mills ML, Moore BR, St Jean G, et al. Synovial fluid concentrations, cytologic characteristics, and effects on synovium of ceftiofur sodium after intra-articular injection in horses (abstr), in *Proceedings*. Vet Orthop Soc 1997;59.

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