Morphine Synovial Fluid Concentrations After Intravenous Regional Limb Perfusion in Standing Horses

Barbara G. Hunter, DVM, MS, Jill E. Parker, VMD, Diplomate ACVS, Rita Wehrman, DVM, Bernadette Stang, MS, and Christopher K. Cebra, VMD, MS, Diplomate ACVIM

Department of Clinical Sciences, College of Veterinary Medicine, Oregon State University, Corvallis, Oregon

Corresponding author: Barbara Hunter, DVM, MS, Matamata Veterinary Services, Matamata, New Zealand. E-mail: Barbara.hunter21@gmail.com

Submitted January 2013
Accepted July 2014

DOI:10.1111/j.1532-950X.2015.12314.x

Objective: To determine synovial concentrations of morphine after intravenous regional limb perfusion (IVRLP) with morphine or morphine in combination with gentamicin in clinically healthy, standing sedated horses.

Study Design: Experimental.

Animals: Adult horses (n = 6).

Methods: IVRLP was performed using 0.1 mg/kg morphine (M) in standing sedated horses. After a 3-week washout period, IVRLP was performed on the same forelimb with a combination of 0.1 mg/kg morphine and 1 g gentamicin (M/G). Synovial fluid from the middle carpal joint of the perfused limb and jugular blood samples were collected immediately before each perfusion and 20 minutes, and 2, 8, and 24 hours after IVRLP. Morphine and gentamicin concentrations were determined by ELISA.

Data were assessed using 2-way repeated measures ANOVA with significance set at P ≤ .05.

Results: Synovial fluid morphine concentrations were greatest 20 minutes after perfusion. Mean ± SD peak synovial morphine concentrations over 12 perfusions were 3903 ± 4881 ng/mL. There was no significant difference in morphine synovial concentrations after M or M/G. Plasma morphine concentrations peaked within 2 hours of perfusion (range, 11–63 ng/mL). Mean peak gentamicin concentrations in synovial fluid were 76,315 ± 39,809 ng/mL. IVRLP morphine did not cause clinically apparent adverse effects.

Conclusions: IVRLP in standing sedated horses results in measurable levels of morphine in synovial fluid and synovial concentrations of gentamicin after perfusion in combination with morphine are equivalent to those previously reported.

Intravenous regional limb perfusion (IVRLP) with antibiotics is a well-established technique in horses. Multiple studies have shown that high concentrations can be reached within synovial structures and the other tissues of a perfused area. Regional limb perfusion (RLP) with antibiotics, by either an intravenous or an intraosseous route, is an effective adjunct therapy for treatment of septic arthritis, physisis, or osteomyelitis. When RLP was included in the treatment protocol, 87% of synovial injuries that had sepsis or contamination and involved the distal aspect of the limb resolved. A survival rate of ~92% has been reported after RLP treatment for horses with lacerations or acute minimally contaminated synovial lacerations of the distal aspect of the limb. Synovial inflammation has been shown to improve the uptake of antibiotics into a joint when administered by IVRLP.

Complications associated with IVRLP are minor with hematoma and phlebitis of the perfused vein being most common. An incidence of 12% minor and no major complications was associated with daily IVRLP (1–7 days) in 155 horses. Despite the common use of RLP with antibiotics, reports in horses on the use of IVRLP with other therapeutic agents are limited to recent reports evaluating the scintigraphic distribution of technetium-labeled mesenchymal stem cells and use of amphotericin B for treatment of pythiosis.

The administration of opioids to horses by IVRLP has not been reported, but it has potential benefits. A µ-receptor agonist, morphine can activate peripherally located µ-receptors without exerting central effects. Peripheral µ-receptors in the horse have been found in the synovium and inflammation has been shown to upregulate those receptors. In other species, µ-receptors are present on corneal epithelium, granulocytes, plasma cells, and macrophages. Morphine is an effective intra-articular analgesic in horses when used alone or in combination with local anesthetics. In equine models of experimentally induced synovitis, morphine also has potent anti-inflammatory effects. After induction of synovitis with lipopolysaccharide, intra-articular morphine improved the level of clinical lameness, decreased joint effusion, and reduced total nucleated
cell counts and inflammatory cytokines within synovial fluid in comparison to placebo controls. Although intra-articular morphine is beneficial, administration by joint injection may not be appropriate for some painful conditions of the distal aspect of the limb. For example, traumatic wounds and cellulitis are common in horses, and underlying synovial structures are likely to be painful and inflamed, but injection through infected tissue into an uninfected joint would not be appropriate. IVRLP with antibiotics in these cases, and cases of septic arthritis or osteomyelitis, is common practice. Adding morphine to these perfusions could provide analgesia and decrease inflammation while potentially limiting the negative effects reported with systemic administration. As horses with pain in a single limb are at risk for life threatening support limb laminitis, techniques that may improve analgesia have greater impact. Support limb laminitis is the most common complication of prolonged non-weight bearing lameness, and its development decreases prognosis for survival regardless of the prognosis associated with the original condition.

Morphine has been used systemically to treat musculoskeletal pain, but concentrations of morphine in synovial fluid after systemic administration are considerably lower than those obtained with intra-articular injection. Epidural morphine is also an effective analgesic for both hind limb and forelimb pain. The anti-inflammatory effects of morphine administered epidurally on synovitis are unexplored, but given the indirect route of administration, a reduction in joint inflammation after epidural morphine seems unlikely. The ability of morphine to penetrate synovial structures when administered by IVRLP has not been evaluated in horses; however, based on results obtained with IVRLP with antibiotics, there is a potential to achieve higher levels than with systemic administration. IVRLP may also result in therapeutic levels in all the tissues in the perfused region, not only synovial structures. Thus, our purpose was to determine synovial morphine concentrations after IVRLP with morphine alone or in combination with gentamicin in clinically healthy horses. Our 1st hypothesis was that morphine would be present in synovial fluid of the perfused limb after IVRLP. Upon demonstration of our 1st hypothesis, our 2nd hypothesis was that addition of gentamicin to the perfusate would not significantly affect the synovial concentrations of morphine achieved with IVRLP.

MATERIALS AND METHODS

Six healthy, adult horses (mean weight, 572 kg; range, 509–636 kg) were studied. Horses were 1 Thoroughbred, 3 Quarter Horses, 1 Paint horse, and 1 Quarter Horse cross. All horses were healthy on clinical examination and were sound at a walk and trot on a paved surface, and were negative to carpal flexion.

Each horse was administered IVRLP during 2 separate experimental phases. In Phase 1, morphine alone (M) was used for perfusion. In Phase 2, a combination of morphine and gentamicin was used (M/G). Phases were non-randomized as Phase 1 was designed to be the pilot study for Phase 2. If no morphine was detected in synovial fluid with Phase 1, Phase 2 would not have been pursued. Horses were housed in box stalls for 72 hours starting 4–6 hours before IVRLP perfusion. Between Phase 1 and 2, horses were turned out on pasture for a ≥3 week washout period. All experimental procedures were performed with the approval of the Institutional Animal Care and Use Committee.

Phase 1: IVRLP with Morphine (M)

Horses had either a left or right forelimb assigned as the perfusion limb. The left forelimb was randomly chosen by coin toss for the 1st horse. After that, forelimbs were alternated such that horse 1, 3, and 5 had left forelimbs used and horse 2, 4, and 6 had right forelimbs used during each experimental phase. Horses were sedated with detomidine (0.01–0.015 mg/kg intravenously [IV]) and were administered additional doses of detomidine and/or xylazine (0.3–0.5 mg/kg IV) as needed. A synovial fluid sample was collected from the aseptically prepared middle carpal joint of each horse, and blood was collected from the jugular vein immediately before performing IVRLP. Synovial fluid was aspirated with a 3 mL syringe after insertion of a 20 g 3.81-cm needle into the dorsal aspect of the middle carpal joint while the carpus was flexed. Two 10.2-cm wide rubber tourniquets (Esmark Bandage; Cardinal Health, McGraw Park, IL) were placed on the limb: 1 covering 15–18 cm of the proximal half of the metacarpus and 1 on the radius starting at the chestnut and extending proximally for 15–18 cm. A 1 cm thick × 10.2-cm long pad of gauze was placed over the cephalic vasculature and 10.2 cm long gauze pads rolled to 1 cm thickness were placed on either side of the flexor tendons on the metacarpus. Before application of the rubber tourniquets, a 10.2-cm pneumatic tourniquet (Inflato-matic 3000; Zimmer-USA, Warsaw, IN) was placed over the proximal tourniquet and insufflated to 400 mmHg. All tourniquets were applied by the same investigator (B.H.) and rubber tourniquets were applied as tightly as possible. After aseptic preparation of the cephalic vein, a 21 g 1.9-cm butterfly catheter was inserted, left in place for the duration of the IVRLP, then removed after tourniquet removal. IVRLP was administered with preservative-free morphine sulfate (Morphine Sulfate Injection, USP; Hospira, Inc., Lake Forest, IL) at a dose of 0.1 mg/kg diluted to a total volume of 50 mL with sterile saline (0.9% NaCl) solution. The perfusate was drawn into a 60 mL syringe and injected by hand over 3–4 minutes. Tourniquets were left in place for 30 minutes. Synovial fluid samples from the middle carpal joint and blood samples from the jugular vein were collected into tubes containing EDTA (Monoject; SensLabGmbh, Leipzig, Germany) at 20 minutes, 2, 8, and 24 hours after tourniquet release. Blood samples were centrifuged at 3500×g for 5 minutes within 30 minutes of collection, and plasma aliquots were removed. All samples were frozen at −20°C until analysis. Analysis was done within 3 weeks of sample collection. Horses were administered 2 g phenylbutazone intravenously and 500 mg of amikacin was
Hunter et al. Morphine Synovial Fluid Concentrations After Intravenous Regional Limb Perfusion

Injected into the middle carpal joint after collecting the 24-hour samples. Horses were assessed every 12 hours for the first 48 hours after IVRLP for signs of lameness at the walk or phlebitis of the cephalic vein. Physical examinations were performed every 24 hours for 48 hours, and the amount of manure passed over 24 hours was noted to be adequate or inadequate for 48 hours after IVRLP.

Phase 2: IVRLP with Morphine and Gentamicin (M/G)

IVRLP was performed using morphine at 0.1 mg/kg and gentamicin (1 g; gentamicin sulfate; VetOne, MWI, Boise, ID) diluted to a total volume of 50 mL with sterile saline solution. Each horse had IVRLP performed in the same forelimb used in Phase 1 (M). All horses were sedated with detomidine (1 μg/kg IV) and maintained on detomidine constant rate infusion (CRI; 0.6 μg/kg/min). Sample collection times, handling and storage of samples, and monitoring of horses were identical to Phase 1.

Sample Analysis

Synovial fluid and plasma morphine concentrations were analyzed using a direct ELISA (Morphine Specific Direct ELISA; Bio-Quant, San Diego, CA). The assay had been validated for use on human serum, whole blood, oral fluids, plasma and urine, but had not been validated for horses. For validation in horses, standard curves (range 0–50 ng/mL) were created by adding known quantities of morphine to synovial fluid and plasma drawn from untreated horses. Synovial fluid for this purpose was obtained from the middle carpal joint of 3 horses euthanatized for reasons unrelated to this study. The standard curve made from equine synovial fluid was identical to the standard curve made with morphine controls supplied by the assay. The standard curve made from equine plasma consistently produced absorbance readings that were 0.05–0.1 absorbance units lower than those seen with synovial fluid or the kit standards. To maintain consistency, all synovial samples were compared with standard curves made in equine synovial fluid, whereas plasma samples were compared with curves made in equine plasma. Samples were diluted with phosphate buffered saline to achieve values within the standard curves. Plasma samples were run in triplicate whereas synovial samples were run in quadruplicate. Two sets of control plasma and synovial fluid samples infused with morphine and diluted to known concentrations (5 ng/mL and 12.5 ng/mL) were run on each morphine ELISA plate to assess inter-assay consistency. Intra-assay consistency was assessed by coefficients of variation that were computer generated for quadruplicate and triplicate samples at the time of absorbance reading.

Synovial fluid gentamicin concentrations were analyzed using a competitive ELISA (MaxSignal Gentamicin ELISA Test Kit; Bioo Scientific Corp, Austin, TX) that was validated for horses as described in previous paragraphs. Synovial fluid samples were diluted with phosphate buffered saline to achieve values within the standard curve (curve range 0–25 ng/mL) and samples were run in triplicates. Inter- and intra-assay consistency was determined using the same protocol used in the morphine ELISA, with assay controls that were infused with either 5 ng/mL or 50 ng/mL gentamicin.

Absorbances were read at 450 nm using an automated plate reader (Multiskan GO; Thermo Fisher Scientific Oy, Vantaa, Finland) for both morphine and gentamicin. Concentrations were determined using linear regression from absorbances by extrapolating concentrations of unknowns from standard curves run with each ELISA plate.

Statistical Analysis

Synovial fluid and plasma morphine concentrations were normally distributed and were compared over time and between experimental phases 1 and 2 (M vs. M/G) using a 2-way repeated measures ANOVA. Morphine and gentamicin concentrations in phase 2 (M/G) were compared over time using a Pearson product moment correlation. All data were analyzed using statistical software (Sigma Stat 2.0, SPSS Inc, Chicago, IL) Results are reported as mean±SD and significance was set at P<.05.

RESULTS

Assay Validation

The percent coefficients of variation are reported in Table 1 and were considered to be within acceptable limits for this study.

Morphine Concentrations in Synovial Fluid

Measurable concentrations of morphine were achieved in the middle carpal joints of all horses after IVRLP. In all perfusions (n = 12), morphine concentrations were greatest in the sample collected 20 minutes after perfusion, and concentrations diminished temporally (Fig 1). Morphine concentrations in M/G were lower than M; however, this difference was not significant (P=.06). Two horses (horses 1, 4) in group M/G had morphine and gentamicin concentrations that were substantially lower compared with the other 4 horses at 20 minutes (Fig 2). These horses were presumed to have tourniquet failure because of these substantial differences (93 and 64 ng/mL in horses 1 and 4 versus 500–4540 ng/mL for horses 2, 3, 5, 6) in combination with the fact that plasma concentrations of morphine were much higher at 20 minutes compared with the other 4 horses (64 and 60 ng/mL for horses 1 and 4 vs. 37–41 ng/mL for horses 2, 3, 5, 6). When samples from these 2 horses were excluded from the repeated measures ANOVA, there was no significant difference between groups (P=.32). Morphine was not present in any pre-perfusion synovial samples.
Morphine Concentrations in Plasma

Measurable levels of morphine were present in the plasma of all horses at 20 minutes after tourniquet release with peak plasma concentrations being reached at 20 minutes post perfusion in most horses (Fig 3). Two horses (horses 3, 5) in the M/G phase did not reach peak plasma morphine concentration until 2 hours post IVRLP. Peak concentrations ranged from 11–63 ng/mL. Plasma morphine concentrations diminished temporally, and in 5 of 12 cases, measurable concentrations (>1 ng/mL) were absent from plasma at 24 hours. There was no significant difference in morphine plasma concentrations between M versus M/G when all horses were included in analysis (P = 0.35). When horses 1 and 4 were excluded, M/G had significantly greater plasma morphine concentrations than M (P = 0.005).

Gentamicin Concentrations in Synovial Fluid

Peak synovial fluid concentrations of gentamicin were measured at 20 minutes and decreased temporally (Fig 4). Comparison of post-perfusion concentrations of morphine and gentamicin temporally revealed a Pearson correlation coefficient of 0.88 (P < 0.001). Similar to the morphine concentrations in group M/G, horses 1 and 4 had considerably lower concentrations of gentamicin in synovial fluid than the other 4 horses. In all cases, pre-perfusion samples yielded gentamicin concentrations of 0 ng/mL.

Discussion

We found that morphine, a drug with both analgesic and anti-inflammatory potential after administration by IVRLP either alone or in combination with gentamicin, is present in synovial fluid. Mean (± SD) synovial morphine concentrations after IVRLP at 0.1 mg/kg were considerably greater (M = 7532 ± 6992 ng/mL, M/G = 1924 ± 1823 ng/mL) at 20 minutes than previously reported 20 minutes after IV administration (~100 ng/mL in plasma) at the same dose, thus IVRLP with morphine may have greater analgesic potential for treatment of synovial pain of the distal aspect of the forelimb than systemic morphine. Additionally, gentamicin concentrations achieved when gentamicin and morphine were combined in the same perfusate were equivalent to synovial concentrations reported after IVRLP with gentamicin alone. Our results suggest that treatment of painful conditions involving the distal aspect of the limb (e.g., septic joints) can potentially be treated with both antibiotic and analgesic/anti-inflammatory medications combined in the same perfusate, a circumstance that would make IVRLP an even more potent tool than it currently is for treatment of infection of the distal aspect of the limb.

This study was designed as a proof of concept study and, as such, does have some limitations. One limitation is that the 2 study phases were not randomized. Although randomization will be ideal for future trials, in this study the 1st trial phase (M) was meant to be the pilot for phase 2 (M/G). Because IVRLP with morphine has not been previously evaluated, we felt it prudent to establish whether morphine was present in synovial fluid after IVRLP in phase M and then evaluate whether it was present in synovial fluid when administered in combination with an antibiotic in phase M/G.

A 2nd limitation was the small number of horses studied, a factor which was made more pertinent by the elimination of 2 horses from phase 2 because of tourniquet failures. When comparing the 2 phases, morphine concentrations in synovial fluid were not significantly different; however, morphine concentrations in joints perfused with morphine plus gentamicin were lower overall when compared with perfusion with morphine alone. Because of the small number of horses, the power of the analysis was low, and future studies with
larger sample sizes are necessary to determine if co-administration of morphine and gentamicin consistently results in lower morphine concentrations in the sampled joint. IVRLP with combined amikacin and ticarcillin/clavulanic acid has been shown to decrease amikacin concentrations in synovial fluid, suggesting that combining antibiotics can interfere with IVRLP efficacy.\(^{30}\) Whereas potential interaction between morphine and gentamicin may decrease morphine uptake into synovial fluid, the synovial concentrations of gentamicin we obtained are similar to previous reports, suggesting that morphine does not limit uptake of gentamicin.\(^{1}\) Because gentamicin targets bacteria whereas morphine targets \(\mu\)-receptors, it seems unlikely that one drug would decrease the efficacy of the other once both are present in synovial fluid. Regardless of potential morphine/gentamicin interaction, if therapeutic concentrations of gentamicin are reached in synovial fluid, the combination of morphine and gentamicin should be clinically effective.

A 3rd and important limitation was that the synovial fluid concentrations of morphine achieved varied greatly among horses. Previous IVRLP studies with antimicrobials have shown that variability is common,\(^{3,11,32}\) and the variability in synovial fluid gentamicin concentrations in our study are similar to those previously reported.\(^{1}\) Differences in tourniquet efficacy can contribute to variability in antibiotic penetration.\(^{29}\) Efforts to minimize the effect of tourniquet on variability were made by using wide rubber tourniquets in addition to a pneumatic tourniquet. Movement has been thought to be an important factor in decreasing tourniquet efficacy. In phase M, some horses moved their perfused limb despite detomidine sedation. To reduce movement in the M/G trial, sedation was maintained with a detomidine CRI. We acknowledge that changing sedation protocols between phases is a weakness in our experimental protocol; however, despite this revision in protocol, the degree of limb movement observed in the 2 trials was subjectively equivalent. This finding supports recent work by Mahne et al.,\(^{32}\) who found that use of perineural blocks was significantly more

---

**Figure 1**  Mean morphine concentrations in synovial fluid for 6 horses after perfusion with morphine alone (A) or morphine with gentamicin (B). Mean morphine concentrations in synovial fluid after perfusion with morphine and gentamicin with horses 1 and 4 excluded (C).

**Figure 2** Synovial fluid morphine concentrations in morphine (M) and morphine/gentamicin (M/G) in synovial fluid at 20 minutes post-perfusion for individual horses.
effective in reducing limb movement in standing sedated horses undergoing IVRLP than additional sedation. They also found no significant difference in synovial fluid amikacin concentrations regardless of whether IVRLP was done under general anesthesia, standing with sedation, or standing with sedation and local anesthesia, suggesting that repeating this study with additional efforts to limit limb movement may not decrease variability in morphine synovial fluid concentrations. Other factors that could affect synovial fluid concentrations of morphine and gentamicin after IVRLP include the maximum venous pressure reached during IVRLP. Once maximum venous pressure is reached, fluid will leak under the tourniquet. This pressure could be affected by blood pressure of the horse, vascular holding volume of the limb, rate of injection and volume of injection, in addition to the width and tightness of the tourniquet. Recently it was reported that there is a trend for lower perfusate volumes to result in higher synovial fluid drug concentrations. For our study, the perfusate volume chosen was similar to previous reports for antibiotic IVRLP. Other individual horse factors such as synovial circulation and synovial \( \mu \)-receptor concentrations may play a role in morphine synovial fluid concentration variability. Future studies aimed at evaluating these factors would be valuable.

It should be noted that tourniquet failure in horses 1 and 4 was presumed based on the extremely low concentrations of both gentamicin and morphine in synovial fluid and the high concentrations of both drugs in plasma 20 minutes after IVRLP in comparison to the other four horses. Sampling jugular blood before tourniquet release would have shown more conclusively whether tourniquet failure had occurred, and failure to obtain these samples is noted as a weakness.

Despite these weaknesses, there are a few clinically important questions that arise and should be addressed. The 1st of these is whether the concentrations of synovial fluid morphine achieved in this study are analgesic. The minimum synovial fluid concentration of morphine needed for analgesia has not been reported in any species to our knowledge. With that lack, clinical trials or further studies using synovitis pain models are needed to determine if the morphine synovial fluid concentrations are analgesic.
concentrations achieved in this study are within a clinically effective range. The pharmacokinetics of morphine in synovial fluid after intra-articular injection at 0.05 mg/kg have been reported.\textsuperscript{25} As would be expected, IVRLP results in substantially lower synovial fluid morphine concentrations than intra-articular injection shortly after administration.\textsuperscript{25} However, IVRLP may sustain morphine in synovial fluid longer than intra-articular injection as 8 hours after IVRLP with only morphine, synovial fluid concentrations were ~6 times higher than those reported with intra-articular injection.\textsuperscript{25} Important to note is that our samples were taken from normal joints whereas the pharmacokinetics of intra-articular morphine was evaluated on synovial fluid drawn from joints with synovitis. The effusion associated with synovitis may have a diluting effect on drug concentrations, and if that is the case, concentrations achieved by Lindegaard et al.\textsuperscript{22} may be lower than what might be expected in a non-effused joint. Also, synovitis has been shown to increase synovial \( \mu \)-receptors.\textsuperscript{16} If increased \( \mu \)-receptors result in increased attraction of morphine, then concentrations achieved by Lindegaard et al.\textsuperscript{25} may be higher than would be expected in non-inflamed joints. Thus, comparison of synovial fluid morphine concentrations in our study to pharmacokinetics data after intra-articular injection in effort to surmise potential clinical effect is not straightforward.

Another clinically relevant conundrum is the effect that synovitis might have on uptake of pharmaceuticals into synovial fluid after IVRLP. Increased concentrations of amikacin in synovial fluid have been shown in joints with synovitis when compared to normal joints after IVRLP.\textsuperscript{11} It is possible that increased blood flow associated with inflammation may result in increased synovial drug concentrations after IVRLP. If this is the case, morphine concentrations after IVRLP of inflamed joints are likely to be greater than those achieved in this study.

The combination of gentamicin with morphine in phase M/G of this study gives rise to the clinically important question of whether morphine limits uptake of gentamicin into synovial fluid. Aminoglycosides are a common 1st choice for IVRLP clinically because of their concentration-dependent mechanism of action and their post-antibiotic effect. In our study, mean peak gentamicin concentrations were >10 times previously published mean inhibitory concentrations (MIC) of 2–4 \( \mu \)g/mL for common equine pathogens and remained so for at least 2 hours.\textsuperscript{29} The duration that gentamicin must be maintained above MIC in synovial fluid has not been precisely elucidated to our knowledge, but mechanism of action assessment in serum has shown that greater peak concentrations of gentamicin are associated with improved bactericidal and post-antibiotic effects.\textsuperscript{31} Peak concentrations of gentamicin in our study were similar to those of Werner et al.,\textsuperscript{1} but the time above MIC in this study was not as prolonged.\textsuperscript{1} The reason for this difference is not immediately evident. Horses in the study by Werner et al.\textsuperscript{1} were administered a systemic dose of gentamicin at 6.6 mg/kg 1 hour before IVRLP, and it is possible that this systemic dose combined with IVRLP resulted in prolongation of synovial fluid gentamicin above MIC for a greater length of time. It is also possible that gentamicin dissipates from the joint faster when morphine is present, although the mechanism of action by which this could occur is not apparent. Although the initial synovial concentrations of gentamicin in our study were equivalent to previous reports after a single IVRLP with gentamicin alone,\textsuperscript{1} further studies verifying the therapeutic efficacy of gentamicin when administered in combination with morphine by single IVRLP may be prudent before clinical use.

An important component of our study was the demonstration of safety of the procedure. We found that IVRLP with morphine is a clinically safe procedure in healthy adult horses. Phlebitis is the most commonly reported complication with IVRLP, particularly with repeat IVRLP.\textsuperscript{10,35} In addition, some pharmacological results in vasculitis.\textsuperscript{2} None of the 12 perfusions resulted in clinical signs of phlebitis or vasculitis. Systemic administration of morphine has also been reported to decrease gastrointestinal transit time.\textsuperscript{23} None of our horses had signs of colic at any time after perfusion. All horses had normal gastrointestinal sounds during physical examination, and normal manure production and appetite after perfusion. Whereas it is not possible to comment on the effect that repeated perfusions with morphine may have on gastrointestinal motility, the systemic levels of morphine achieved with single perfusions in combination with repeated sedation did not result in a subjective decrease of gastrointestinal sounds or in manure production in any of the horses.

This study represents an initial step in evaluating the potential application of opioids for analgesic and anti-inflammatory effects when administered by IVRLP. Morphine synovial fluid concentrations after IVRLP with a dose that is commonly used systemically for clinical analgesia were several thousand times greater than can be achieved with IM or IV administration regardless of whether gentamicin was present in perfusates.\textsuperscript{23} Concurrently, systemic plasma concentrations of morphine after IVRLP were similar to concentrations reported in serum after IM or IV administration at 0.1 mg/kg.\textsuperscript{23} This supports the theory that RLP results in higher concentrations of morphine within the perfused area than the concentrations achieved with systemic administration, when used alone or in combination with gentamicin. Consequently, IVRLP with morphine may have better local analgesic and anti-inflammatory properties than IV or intra-muscular administration, but further studies are needed to determine the degree of effect that can be achieved.

DISCLOSURE

The authors report no financial or other conflicts related to this report.

REFERENCES


