Antibiotic Intravenous Regional Perfusion for Successful Resolution of Distal Limb Infections: Two Cases

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Source: Journal of Zoo and Wildlife Medicine, 39(3) : 438-444

Published By: American Association of Zoo Veterinarians

URL: https://doi.org/10.1638/2007-0177.1
ANTIBIOTIC INTRAVENOUS REGIONAL PERFUSION FOR SUCCESSFUL RESOLUTION OF DISTAL LIMB INFECTIONS: TWO CASES


Abstract: Intravenous regional perfusion is a common technique for treating infections of the extremities in humans and horses. It has the advantage of achieving very high antibiotic concentrations in affected tissues. This technique was used to clinically resolve deep, mixed infections involving bones and joints in a swamp wallaby and a lesser kudu. Both infections were severe and considered life-threatening, because amputation was not feasible, systemic antibiotic treatment had failed, and both animals were in pain and had evidence of the systemic effects of the infections. In the wallaby, once daily treatments with imipenem for 5 days resulted in a return to normal function within 1 mo. In the kudu, four treatments using both ampicillin/sulbactam followed by enrofloxacin were performed every 2 days, followed by two treatments with ampicillin/sulbactam alone 2 wk later. Resolution of this case was achieved in less than 2 mo. The only adverse effect noted was phlebitis in the kudu, which resolved with conservative therapy. Healing was rapid in both cases and was apparent after two treatments. This report demonstrates the efficacy and flexibility of intravenous regional perfusion for the treatment of severe infections of the digits in nondomestic species.

Key words: Anaerobic infections, digital infections, intravenous regional perfusion, kudu, osteomyelitis, wallaby.

INTRODUCTION

Distal limb infections in captive nondomestic species can be challenging to manage for both biological and logistic reasons. With severe infections, blood flow to and perfusion of tissues in distal limb segments may be decreased, thus limiting the effectiveness of systemic antimicrobial drugs. Frequent topical therapy and daily administration of oral medications may not be possible due to logistic and compliance issues. Intravenous regional perfusion (IRP) may be a useful technique in these species because although it requires immobilization, it does not require daily handling and does not rely on cooperation of the patient. This technique is used in human medicine and domestic animal medicine, because it has the advantage of achieving high local concentrations of antimicrobial drugs that cannot be attained with systemic routes of administration. This paper describes the use of IRP for the successful resolution of distal limb bacterial infections in two unrelated species.

CASE REPORTS

Case 1

A 14-kg, 10-yr-old male swamp wallaby (Wallabia bicolor) housed at a zoological institution presented to the University of Florida Veterinary Medical Teaching Hospital (UFVMTH) for a swollen right foot and progressive lameness. The foot had been swollen for approximately 3 wk and had been treated by the UF zoological medicine field service 11 days prior to presentation with topical povidone-iodine and a single dose of i.m. procaine penicillin G (Fort Dodge Laboratories, Fort Dodge, Iowa 50501, USA). The animal’s caretaker reported that 2 days prior to presentation, the foot seemed more swollen and the wallaby had stopped bearing weight on the foot. This animal had a previous history (1 yr prior to this episode) of a bony swelling on the right mandible, consistent with “lumpy jaw,” and this was treated successfully with surgical debridement and oral azithromycin (Pfizer Animal Health, Exton, Pennsylvania 19341, USA).

The wallaby was anesthetized with ketamine (Fort Dodge Laboratories, Fort Dodge, Iowa 50501, USA) 50 mg, medetomidine (Pfizer Animal Health, Exton, Pennsylvania 19341, USA) 0.72 mg, and midazolam (Abbott Laboratories, North Chicago, Illinois 60064, USA) 0.7 mg i.m., followed by endotracheal intubation and maintenance on isoflurane (Abbott Laboratories, North Chicago, Illinois...
60064, USA). Physical examination findings confirmed swollen toes on the right foot, with maximal swelling around the fourth digit. Radiographs of the right foot revealed focal soft tissue swelling surrounding the distal interphalangeal joint of the fourth digit as well as mineralization in the soft tissues, consistent with chronic osteomyelitis. An indwelling i.v. catheter was placed aseptically, and blood was submitted for complete blood count (CBC), biochemistry panel, and culture. Metronidazole (Hospira Healthcare, Saint Laurent QC H4M 2X6, Canada) therapy was instituted at 420 mg i.v. b.i.d. for 2 days. The CBC revealed a mild anemia (packed cell volume (PCV) 30, reference range 35.5 – 45.0; red blood cell count (RBC) 4.67 × 10^12/l, reference range 4.67 ± 0.91; hemoglobin 11.4, reference range 11.0 – 13.0 g/dl). No other abnormalities were found and the blood culture was negative.

The following day the wallaby was anesthetized again for surgical exploration and debridement of the foot. The distal phalanx of the fourth digit appeared necrotic and therefore was amputated. The surgical site was debrided, flushed copiously, and bandaged. Tissue was submitted for aerobic and anaerobic culture as well as histopathology. Therapy with azithromycin (125 mg p.o. s.i.d.) and meloxicam (Metacam, Merial Ltd., Duluth, Georgia 30096, USA) (2.3 mg p.o. s.i.d.) was initiated the next morning. The aerobic culture grew a mixture of Streptococcus, Staphylococcus, Escherichia coli, and Corynebacterium organisms; only the E. coli isolate was assessed for susceptibility and was sensitive to all antibiotics tested. Unfortunately, the anaerobic culture was lost. Histopathologic analysis of the tissue confirmed the clinical diagnosis of chronic osteomyelitis.

Two days later the wallaby was anesthetized with ketamine 50 mg and midazolam 1.5 mg i.m. and isoflurane via face mask for a bandage change and evaluation. Upon bandage removal, purulent material was draining from the amputation site and the swelling appeared increased. Amputation of additional phalanges was considered but rejected due to the importance of the digit in weight bearing. In consultation with a surgeon, IRP therapy using imipenem (Merck & Co., Inc., Whitehouse Station, NJ 08889, USA) was elected. A catheter was placed just distal to the stifle in the lateral saphenous vein of the right hind limb. The limb was wrapped tightly distal to the catheter site, and a tourniquet was placed at the stifle. The bandage was removed and 500 mg of imipenem was infused into the catheter. After 10 min the tourniquet was removed, the catheter was flushed with heparinized saline, the toe was bandaged, and the wallaby recovered from anesthesia. This treatment was repeated once a day for 4 additional consecutive days.

Four days after initiating the IRP therapy, the toe appeared greatly improved. Purulent material was not observed and the swelling had decreased markedly. Oral azithromycin and meloxicam treatment were continued for 6 wk, although the meloxicam dose was decreased to 1.5 mg after 2 wk. The animal was discharged from the hospital 4 wk after admission, at which time he was bearing weight normally on the right hind foot. Although some soft tissue swelling persisted, he remained free of clinical signs for the subsequent 2 yr, at which time he was transferred to another institution and lost to follow up.

Case 2

A 12-yr-old, approximately 68-kg male lesser kudu (Tragelaphus imberbis) housed at a private conservation center presented for a swelling over the left rear pastern. This animal had a previous history of an abscess on the left rear lateral hoof wall 10 mo prior to presentation. He was immobilized with carfentanil (Wildlife Pharmaceuticals, Fort Collins, Colorado 80522, USA) 1.8 mg, medetomidine 2.2 mg, and ketamine 100 mg delivered by dart and supplemented with nasal oxygen throughout the procedure. Abnormalities on physical examination included overgrowth of all four hooves, an abscess on the right rear lateral claw, fair-to-thin body condition, and severe, fluctuant swelling of the left rear pastern, extending to the fetlock. All hooves were trimmed and debrided where indicated. The left pastern joint was prepared aseptically and tapped for culture and cytology, then opened surgically. A large volume of purulent material was drained, and the joint was flushed with copious amounts of dilute povidone-iodine solution. A Penrose drain was placed to facilitate drainage and the foot was bandaged. Blood was collected for CBC and biochemistry panel. Anesthesia was reversed with naltrexone (Wildlife Pharmaceuticals, Fort Collins, Colorado 80522, USA) 90 mg i.v., naltrexone 90 mg s.c., and atipamezole (Pfizer Animal Health, Exton, Pennsylvania 19341, USA) 11 mg i.v. Treatments included routine vaccinations for rotavirus-coronavirus, clostridial agents, and Salmonella, as well as tetanus toxoid, tocopherol, and doramectin. In addition, the animal was given penicillin G benzathine/procaine (Fort Dodge Laboratories, Fort Dodge, Iowa 50501, USA) 1,620,000 IU s.c., amikacin sulfate (Phoenix Pharmaceutical, Inc., St. Joseph, Missouri 64506, USA) 700 mg i.v., long-acting ceftiofur (Pfizer Animal Health, Exton,
Pennsylvania 19341, USA) 600 mg s.c., and flunixin meglumine (Schering-Plough Animal Health, Union, New Jersey 07083, USA) 150 mg i.m. Oral treatment with sulfamethoxazole/trimethoprim (Hofmann-La Roche, CH-4070, Basel, Switzerland; 960 mg b.i.d. for 14 days) and phenylbutazone (Phoenix Pharmaceutical, Inc., St. Joseph, Missouri 64506, USA; 600 mg s.i.d. for 3 days) was instituted the following day.

Cytology results revealed large numbers of a mixed population of Gram-negative bacteria, degraded cells, neutrophils, and lymphocytes as well as small numbers of Gram-positive cocci. Aerobic culture grew *Morganella morganii* sensitive to aminoglycosides, chloramphenicol, fluoroquinolones, sulfamethoxazole/trimethoprim, and imipenem but intermediate to ceftiofur and resistant to cephalosporins, penicillins, extended-spectrum penicillins, and rifampin. Two anaerobic organisms, *Clostridium bifermaments* and *Fusobacterium necrophorum*, also were identified, and both were beta-lactamase negative. Complete blood count revealed a mild anemia (PCV 36, reference range 45.7 ± 5.9; RBC 7.76 × 10¹²/ml, reference range 9.75 ± 1.34; hemoglobin 12.8 g/dl, reference range 15.8 ± 1.8). Biochemistry panel abnormalities included hypocalcemia (5.6 mg/dl, reference range 7.9 ± 0.9), unfavorable calcium/phosphorus ratio (0.629), increased fibrinogen (700 mg/dl), and increased aspartate aminotransferase (AST; 645 IU/L, reference range 269 ± 169).

At a recheck exam 3 days later, the swelling on the left foot was greatly decreased and no drainage was noted. The foot was bandaged, the long-acting ceftiofur injection was repeated, and phenylbutazone treatment was discontinued. However, when the animal was immobilized after an additional 4 days, the abscess appeared much worse. A new draining tract had opened laterally over the joint, and a moderate amount of purulent material was expressed. Some skin surrounding the wound had sloughed. Furthermore, it was apparent that there was continued extensive involvement of the pastern joint, making the prognosis for this animal guarded. The wounds were debrided, flushed, and bandaged as before. The ceftiofur and flunixin meglumine treatments were repeated, and calcium carbonate (600 mg p.o. s.i.d. for 3 wk) was prescribed. Blood work was repeated and results were essentially unchanged.

Within 3 days, and 10 days following original presentation, the animal was immobilized for IRP therapy. The wound appeared unchanged from the last exam, with copious amounts of purulent discharge and evidence of tissue necrosis. The left limb was wrapped tightly to just above the hock (Fig. 1). A tourniquet was placed at the hock and a catheter was placed in a lateral vein (Fig. 2). The wrap was removed and 20 ml of a 30 mg/ml solution of ampicillin/sulbactam (Abbott Laboratories, North Chicago, Illinois 60064, USA) was infused. Due to concerns about perivascular infiltration, a second catheter was placed in a more distal vein, and an additional 40 ml of the ampicillin/sulbactam solution was infused. After 10 min, the tourniquet was removed and the limb massaged for 5 min. The procedure was then repeated, this time using a solution of enrofloxacin (Bayer Healthcare, Shawnee Mission, Kansas 66201, USA) diluted to 10 mg/ml in the proximal catheter. The tourniquet and i.v. catheters were removed after 10 min, and the limb was again massaged. The wound was bandaged and the ceftiofur and flunixin treatments were repeated.

The regimen described was repeated 14, 16, 18, 32, and 38 days after initial presentation. Marked improvement in the appearance of the left limb was first noted on day 16, and weight gain and body condition improvement (based on estimated weights and condition scoring) were noted on day 29. In general, blood parameters improved slowly, although the fibrinogen dropped after only one IRP treatment, from 800 mg/dl on day 7 to 500 mg/dl on day 14, and remained ≤500 mg/dl for the remainder of treatment. On day 22, the PCV was 27.4, hemoglobin was 8.7 g/dl, RBC was 6.26 × 10¹²/ml, AST was 572 IU/L, calcium was 6.1 mg/dl, and the Ca:Ph was 0.884. On day 59, the final immobilization for this problem, the PCV was 36.4, hemoglobin was 12.3 g/dl, RBC was 8.14 × 10¹²/ml, AST was 555 IU/L, calcium was 6.8 mg/dl, and the Ca:Ph was 1.06.

Overall, treatment was tolerated well. However, on day 22, after four IRP treatments, inflammation was noticed along the veins on the lateral aspect of the affected limb, and increased warmth in the limb distal to the hock was readily appreciated on palpation. Phlebitis was the main differential, and IRP was not performed. On days 25 and 29, IRP was not performed, and dimethyl sulfoxide (Fort Dodge Laboratories, Fort Dodge, Iowa 50501, USA) was applied to the limb to help decrease inflammation. Intravenous regional perfusion therapy was resumed on day 32, but the enrofloxacin infusion was omitted for this and the following treatment. Also on day 32, the long-acting ceftiofur injections were discontinued, and florfenicol (Schering-Plough Animal Health, Union, New Jersey 07083, USA; 1,200 mg s.c. for four treatments) was initiated. The final immobilization of this animal for this problem was
on day 59 following initial presentation. At that time, all draining tracts were closed and granulating in well. No evidence of infection remained and the kudu’s body condition was good. A final dose of florfenicol was administered, and the problem was considered resolved. This animal was immobilized 8 mo later for a routine exam and hoof trim, and there was no evidence of infection in the limb. He died 17 mo after initial presentation as a result of complications of a chronic oral infection, presumed to be fusobacteriosis.

**DISCUSSION**

Intravenous regional perfusion is a proven technique in human and equine medicine. Retrospective studies examining the use of intravenous antimicrobial regional perfusion of horses with severe naturally occurring septic conditions of the extremity had reported overall survival rates ranging from 75–89%. Resolution of human chronic limb infections after treatment including IRP also have been reported. In the two cases of the present report, IRP therapy proved effective in returning animals back to full function when surgical debridement and systemic antibiotic therapy failed.

In both the wallaby and the kudu, the distal extremity infections were severe, contained multiple pathogenic organisms, and involved bone and joints. Because amputation was not a viable option in either situation, euthanasia may have been re-
required if medical treatment had not succeeded. Both animals also exhibited systemic effects, as evidenced by anemia in both animals and poor body condition in the kudu. Anaerobic pathogens were suspected in both cases, although only proven to be involved in the kudu. Because infections with anaerobic bacteria tend to be deep-seated and are, by definition, in tissues that are poorly perfused (and therefore poorly oxygenated), the effectiveness of systemic antibiotics was in question. Nonetheless, due to concerns regarding repeated anesthetic events, in both cases topical wound care and single-dose intravenous antibiotic injection followed by oral (and in the kudu, long-acting parenteral) antibiotics was the initial therapy chosen. Both animals showed improvement at the first recheck examination, but the infections progressed rapidly thereafter. Failure of the initial therapy may have been due to inadequate antibiotic tissue levels, due to poor compliance, unknown idiosyncrasies of pharmacokinetics in these species, or the presence of infected tissue with large quantities of exudates. Sulfa drugs, used orally in the kudu, tend to have poor activity against anaerobes. However, ruminant physiology severely limits drug choice; few oral antibiotics are effective after passage through the rumen. Had it been feasible to maintain these patients on continuous, or at least daily, intravenous antibiotics, the infections may have resolved.

There are few published guidelines for the duration and frequency of treatments when using IRP. The protocol used in the wallaby, once daily infusions for 5 days, was based on the protocol used in small animals at the UFVMTH (Farise, pers. com.). Treatment of the kudu, however, presented additional challenges due to the drugs necessary for immobilization. Carfentanil is a long-acting, ultrapotent opioid and requires reversal with a long-acting antagonist, naltrexone. Due to concerns that the naltrexone would still be present at opioid receptors and interfere with the action of carfentanil, it was necessary to wait at least 48 hr between immobilizations. Neither the wallaby nor the kudu exhibited any adverse reactions that were attributed to the frequent immobilizations.

Drug choice in IRP is generally based on culture and sensitivity, and a water-soluble, isotonic solution is preferred. Both species in this report, the wallaby as a foregut fermentor and the kudu as a true ruminant, are animals that rely on enteric bacterial processing of ingesta. Inappropriate destruction of gastrointestinal flora was a potential problem that had to be weighed against the severity of the infections when choosing antimicrobials. The use of the intravenous route made this less of a

Figure 2. The tourniquet was tightened and the gauze wrap was removed before infusion of the antibiotic.
Concern and represents another advantage of this treatment modality. For the wallaby, an anaerobic culture was not available, so an antibiotic was chosen empirically. Imipenem was selected for its broad spectrum, availability, and known effectiveness against anaerobes. Appetite, fecal consistency, and weight were monitored carefully during therapy, but no apparent adverse effects on gastrointestinal flora were observed. Drug selection was more complicated for the kudu, because an antibiotic effective against anaerobes and the Morganella morganii cultured from the wound was not available. Therefore, two drugs were used in its therapy. Ampicillin/sulbactam was chosen based on its availability and because the two anaerobic organisms cultured were beta-lactamase negative, thus making a beta-lactam a good choice. Although amikacin was considered as a second drug, it was rejected for two reasons. First, there was concern that the repeated immobilizations necessary for the IRP treatment would put this older animal at higher risk of kidney damage from an aminoglycoside. Second, the effectiveness of aminoglycosides can be diminished in vivo both by beta-lactam antibiotics and the presence of necrotic tissue. Chloramphenicol also was considered but was rejected due to concerns with inactivation by penicillins, as well as the anemia already present in this patient. Enrofloxacin was chosen based on culture and sensitivity and because it is generally safe in ruminants and older animals. Again, no gastrointestinal side effects were noted, and in fact the kudu's body condition improved during therapy.

Adverse effects of IRP are rarely reported. A transient fever following regional perfusion has been reported in several human subjects, but most animal studies have reported no complications resulting from IRP. In the patients discussed here, treatment was very well tolerated, and the frequent anesthetic events did not cause any apparent problems. The only significant adverse reaction was seen in the kudu, in the form of phlebitis. Although of concern at the time, it did not result in lymphenopathy, and it resolved completely and did not recur when IRP was reinstated. The likely cause of the phlebitis was the enrofloxacin, which is not labeled for i.v. use and can be irritating when given intravenously. A transient, self-resolving vasculitis occurred following IRP with 1.5 mg/kg enrofloxacin in three out of six healthy horses. Due to potential damage to vessels, synovial structures, and chondrocytes from high concentrations of enrofloxacin, this drug has generally not been recommended for regional perfusion. The phlebitis in the kudu may have been avoided with the use of amikacin; however, the consequences of phlebitis are much less significant than renal damage. In fact, when the animal died a year and half later due to complications of an oral infection, azotemia was found antemortem and kidney lesions consistent with chronic renal failure were noted on necropsy, illustrating that kudu certainly are susceptible to kidney disease.

The response to IRP was rapid in both cases. After one (kudu) or two (wallaby) treatments, the wounds had less purulent exudate and swelling, and both animals appeared to be in less pain. The infection in the wallaby showed steady improvement, and although some residual swelling remained a month after presentation, the animal was ambulating normally. The kudu's recovery was more prolonged. This may have been due to longer intervals between treatments, a more severe infection, a poorer immune response, concurrent stressors, or the phlebitis and cessation in treatment for 2 wk. Interestingly, the kudu suffered a lice infestation a few weeks prior to his initial presentation. This was successfully treated with topical doramectin, but the severity of the infestation was unexpected and may have been reflective of a diminished immune system competence.

The source of the infection in both cases is unknown. Hematogenous spread to joints is a reported sequela of fusobacteriosis in humans; however, this is unlikely in the wallaby because of the long interval (1 yr) between the mandibular infection and the foot infection. Similarly, the presumed Fusobacterium infection that resulted in the kudu's death occurred more than 1 yr after the original hoof abscess was resolved. On the other hand, acquisition from the pasture is very likely, because the sites of the infections—feet and oral cavity—are the anatomic locations with the most intense contact with the ground. Unfortunately, pasture contamination is difficult to manage in the captive environment.

Successful use of IRP has been reported in other nondomestic species. Repeated infusions with gentamicin and cefoxitin were used in adjunctive treatment of a captive African elephant with severe cellulitis and osteomyelitis involving all three phalanges of the third digit. More recently, a captive Asian elephant with a severe foreign body–induced sole abscess was treated with regional perfusion of gentamicin and ceftiofur, in addition to systemic sulfamethoxazole–trimethoprim. A second perfusion was performed 15 days after the initial treatment, although by this time the abscess had almost completely resolved.

In conclusion, IRP therapy should be considered a valuable tool for infections of the distal extrem-
ities in nondomestic species. The two animals successfully treated in this report suffered life-threatening infections and had exhausted other medical and surgical options. The technique is performed easily and is well tolerated, does not require specialized equipment or training, is flexible enough to be adjusted to suit different management limitations, and may result in a successful outcome when systemic antibiotic treatment has failed.

Acknowledgments: The authors thank Dr. J. Fa-rese for his expert assistance with the wallaby case; Dr. J. Siegal-Willott, Dr. D. Heard, D. Peck, C. Teare, A. Whitaker, the students and technicians of the UFVMTH Zoological Medicine Service, the hoofstock crew at White Oak Conservation Center; and the Mammal and Bird Department staff at St. Augustine Alligator Farm for assistance with these cases.

LITERATURE CITED

Received for publication 13 December 2007