INTRA-SYNOVIAL IMPENEM THERAPY IN 4 HORSES WITH SEVERE SEPTIC ARTHRITIS OR TENOSYNOVITIS NON-RESPONSIVE TO CONVENTIONAL TREATMENT

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Summary

Synovial sepsis in horses may be a treatment challenge that includes different approaches such as synovial lavage, local antimicrobial therapy with intra-synovial injections and/or regional limb perfusions and systemic administration of broad-spectrum antimicrobials. This report describes positive clinical experience after injecting intra-synovial imipenem in 3 septic joints and 1 septic tendon sheath as the last treatment resort in 3 foals and 1 adult horse.

Keywords: imipenem; intra-synovial; horse; septic arthritis; septic tenosynovitis.

Introduction

Synovial sepsis is a serious, common clinical problem in horses and foals that can lead to chronic lameness or euthanasia if not treated promptly or if it becomes refractory to treatment (Schneider et al., 1992; Steel et al., 1999; Sanchez et al., 2008; Richardson and Ahern, 2011). Early diagnosis and aggressive therapy is therefore warranted in all cases of synovial infection in order to improve the prognosis for survival and athletic performance. In addition to systemic antimicrobial therapy, current treatments for these conditions include: arthroscopic/tenoscopic lavage, through and through needle lavage or open drainage, combined with direct intra-synovial antimicrobial injections, intravenous regional limb perfusions, continuous intra-synovial infusion systems, intra-articular implantation of antimicrobial impregnated beads or collagen sponges to maintain an effective high local concentration of antibiotics (Richardson and Ahern, 2011).

The administration route of the antibiotics has evolved considerably and is focused on methods of local drug delivery. Local administration of antimicrobials can achieve extremely high concentrations at the site of the infection and are a vital component of modern treatment of synovial sepsis (Richardson and Ahern, 2011). Intra-synovial injection of several antibiotics such as gentamicin, amikacin and cefazolin have been used to treat severe septic arthritis/tenosynovitis (Schneider et al., 1992) without causing significant inflammatory side effects on equine synovium of healthy joints (Lloyds et al., 1998; Mills et al., 2000).

Imipenem is a beta-lactam carbapenem antibiotic with a wide spectrum of antibacterial activity against Gram-negative and Gram-positive aerobic and anaerobic bacteria, effective against some multi-resistant beta-lactamase producing bacteriae. Imipenem is registered for human use only and is administered intravenously or intramuscularly in combination with cilastatin (imipenem/cilastatin sodium) to reduce toxicity. As imipenem is rapidly inactivated by renal dehydropeptidase I (DHP-I), it is given in combination with cilastatin, a DHP-I inhibitor which increases half-life and tissue penetration of imipenem.

It is considered to be an effective antibiotic for the treatment of severe infections in the majority of body systems (except for meningitis, as imipenem does not cross the haematoencephalic barrier) but it is reserved for treatment of organisms that are resistant to the usual...
antibiotics. Imipenem has also been locally administered by continuous regional arterial infusion for treating severe human acute pancreatitis (Plaschl et al., 2010) or in continuous ambulatory peritoneal dialysis in human patients with septic peritonitis (Lui et al., 1994).

Imipenem is also used in veterinary medicine although it is left as a ‘last resort’ treatment due to the increased multiple antimicrobial drug resistances (Prescott et al., 2002). Imipenem has been pharmacokinetically tested following intravenous administration in healthy adult horses and its adequate diffusion into synovial fluid is proven (Orsini et al., 2005). Although systemic imipenem administration in adult horses might be economically prohibitive, responsible use of this potent antimicrobial could also have a place in equine critical care (Orsini et al., 2005), especially in neonates.

Local use of imipenem/cilastatin (Primaxin IV) was reported for successfully treating a marsupial’s distal limb infection by means of regional perfusions (Fiorello et al., 2008), but did not have any effect in a foal with a *Rhodococcus equi* septic physisitis/arthritis even after injecting it (250 mg) directly into the infected joint (Kelmer and Hayes, 2009).

Current bibliography (Richardson and Ahern, 2011) describes imipenem as being administered intra-synovially or by regional perfusions, but we are not aware of any previous reports that have described the successful management of severe septic arthritis or tenosynovitis in horses after intra-synovial imipenem treatment.

**Case 1**

**Clinical history.**
A 40 kg, 12-hour-old Arabian male foal was presented to the Fundació Hospital Clinínic Veterinari de Barcelona with a history of trauma and severe marked weakness. The problems diagnosed upon admission based on clinical physical exam, complete blood count, biochemical profile, and abdominal and thoracic ultrasound were the following: septicaemia with anphylaxis and pneumonia, ischemic hypoxic encephalopathy, bilateral forelimb flexor tendon retraction, polytraumatism and failure of passive transfer of immunity. Blood culture results revealed Klebsiella oxytoca that was sensitive to most of the antibiotics tested.

Initially, the foal responded favourably to critical intensive medical treatment. Systemic antibiotic therapy consisted of sodium penicillin (22,000 UI/kg, i.v. every 6 hours) and amikacin (25 mg/kg, i.v. every 24 hours).

**Clinical/laboratorial work up and diagnosis.**

Twelve days after admission, a sudden hot, painful and moderately distended femoro-patellar joint (FPJ) associated to a 5/5 grade right hind limb (RH) lameness was observed. Ultrasound of the joint showed increased amount of anechoic synovial fluid and no significant alterations were observed on the radiologic study of the right stifle. Arthrocentesis revealed a slightly cloudy synovial fluid with an increased total nucleated cell count (TNCC) (34,620 nucleated cells/µl, 4 g/dl TP and 97% neutrophils). A positive synovial culture isolated a Klebsiella oxytoca sensitive to amikacin, cefiotiofur and imipenem, and the diagnosis of septic arthritis of the right FPJ was confirmed.

**Treatment and outcome.**

Joint infection worsened (persistent synovial fluid distension and TNCC: 55,000 cells/µl) despite having performed two through and through articular lavages followed by local intra-articular 1g amikacin injections, every other day. An arthroscopic lavage was performed under general anaesthesia but no clinical or laboratory improvement was observed. Five days later, a second arthroscopic lavage was performed but infection continued worsening (TNCC: 167,200 cells/µl, 4 g/dl TP and 97% neutrophils with intracellular bacteria) and, based on initial culture results and sensitivity, the local antibiotic was finally changed to imipenem (50mg).

Synovial fluid analysis performed after the second imipenem intra-articular injection showed marked improvement: 3,700 nucleated cells/µl, 2.8 g/dl TP and 77% neutrophils. Four intra-articular injections were performed in total every other day. Neither stifle effusion nor lameness was longer evident and the foal was successfully discharged one week later. One month later the owner and referring veterinarian reported complete recovery of the foal.

**Case 2**

**Clinical history.**
A 60 kg, 30-day-old Andalusian female foal was re-admitted to the hospital with an acute RH lameness of 24 hours duration. She had been recently treated for septicaemia and was still under systemic antibiotic therapy with cefiotiofur (10 mg/kg bwt i.m.) based on previous blood culture results (Klebsiella oxytoca).

**Clinical/laboratorial work up and diagnosis.**

On admission, the foal was mildly febrile (39.6 ºC) and presented marked hyperfibrinogenemia (900 mg/dl). A hot, painful and severely distended RH tarsocural joint (TCJ) and a 3/5 grade lameness was observed. Ultrasound of the joint showed a thickened articular capsule and synovial fluid with increased cellularity and hyperechoic floccules. Arthrocentesis revealed a slightly cloudy, orange, watery synovial fluid with an increased TNCC (9,040 cells/µl), TP (4.7 g/dl) and high cell neutrophil differential (92%) was obtained. A second positive synovial fluid culture with a resistant *Salmonella sp*, sensitive only to amikacin and imipenem, confirmed septic arthritis of the right TCJ. Radiographic studies of the RH tarsus revealed the presence of a radiolucent defect on the medial malleolus of the tibia, compatible with septic physisitis of the mentioned region.

**Treatment and outcome.**

Initial systemic treatment consisted of amikacin (25mg/kg bwt i.m. every 24 hours), cefiotiofur (10mg/kg bwt i.m. every 12 hours), flunixin meglumine (0.5mg/kg bwt i.m. every 12 hours) and omeprazole (2mg/kg bwt oral every 24 hours). An arthroscopy on the dorso-medial pouch of the joint and every 48 hours articular lavages and regional limb perfusions with amikacin (1g) of the tarsus were performed while the joint was still open.

Despite treatment, the foal continued to worsen to a non-bearing RH lameness and a subcutaneous abscess on the distal medial aspect of the tibia developed. A synovial culture analysis revealed increased TNCC (107,000 cells/µl), TP (3.2 g/dl) and 98% neutrophil cell differential. Joint distension and an altered synovial fluid analysis (28,000 nucleated cells/µl and 3.6 g/dl TP) of the contralateral hind limb (left-LH) TCJ were also noticed. Local antibiotic therapy (1g amikacin) was finally changed to intra-articular imipenem (25 mg), the only other sensitive antibiotic, which was injected daily, during 4 days, in both TCJ joints. The foal was carefully monitored during the first 24 hours and neither increased lameness or evident local inflammatory reaction was detected. After this period, synovial fluid of the LH TCJ had normalized (500 cells/µl and 2.2 g/dl TP) and RH distension and TNCC synovial fluid analysis had both improved (43,920 cells/µl). Despite excellent clinical progression of the polyarthritis, 4 days later, systemic antibiotic therapy was also changed to imipenem (20 mg/Kg bwt i.v. every 8 hours) (Orsini et al., 2005) during 5 days due to severe leukocytosis (23,850 cells/µl) and neutrophilia (18,603 cells/µl). However, 24 hours after starting the systemic treatment the foal presented ataxia and left head tilt. A presumptive diagnosis of...
septic intracranial meningitis was made and the foal was euthanized.

**Post-mortem findings.**
Cerebrospinal fluid revealed intra-cytoplasmic bacteria consistent with an infectious meningoencephalitis. Macroscopic right joint examination revealed multiple articular erosions and a deep osseous defect was found in the medial physeal part of the tibia which communicated with the TCJ. The left joint showed mild synovial membrane congestion but no other evident joint lesions were macroscopically observed.

**Case 3**

**Clinical history.**
A 300 kg, 9-month-old Andalusian female filly was presented with an acute wound on the plantar aspect of the RH pastern.

**Clinical/laboratorial work up and diagnosis.**
On admission, the filly presented a 1/5 grade RH lameness with moderate soft tissue swelling and an acute haemorrhage associated with a deep transverse wound on the plantar aspect of the pastern. Visual and digital palpation of the wound confirmed flexor tendon sheath involvement and a partial superficial digital flexor tendon (SDFT) laceration proximal to its insertion on the first phalanx. Traumatic tendonitis with wound communicated tenosynovitis of the RH was diagnosed.

**Treatment and outcome.**
Tenoscopic lavage of the flexor tendon sheath was immediately performed under general anaesthesia. Systemic antimicrobial therapy consisted in sodium penicillin (22,000 UI/kg bwt i.v. every 6 hours), gentamicin (6.6 mg/kg bwt i.v. every 24 hours), phenylbutazone (2.2 mg/Kg bwt i.v. every 12 hours). Initial evolution was satisfactory but after 15 days, the filly started to be severely lame of the RH (5/5) and a second tenoscopic surgical lavage was performed. A positive coagulase Staphylococcus was isolated from the synovial fluid culture and was only sensitive to enrofloxacin and rifampicin. Culture of the wound isolated a Pseudomonas aeruginosa that was only sensitive to amikacin and gentamicin. Systemic antimicrobial therapy was consequently changed to oral enrofloxacin (7.5 mg/kg bwt orally every 24 hours) and gentamicin (6.6mg/kg bwt i.m. every 24 hours). During the first week, daily amikacin (1g) regional perfusions were performed but no improvement was observed. Control synovial fluid analysis revealed: 11,000 nucleated cells/μl, and 4.4 g/dl TP. A positive coagulase Staphylococcus was again isolated from a second synovial fluid culture but this time was only sensitive to cephalexin and imipenem. Systemic treatment was changed to oral cephalexin (30 mg/kg bwt orally, every 8 hours) and local therapy with imipenem (10 mg), which was injected into the RH flexor tendon sheath through a proximal lateralized tendon sheath access due to the pastern plantar wound. The sheath was injected 3 more times with imipenem, every 48 hours, and posteriorly no more synovial fluid could be collected again for further analysis due to lack of sheath distension. The filly improved considerably showing that infection had definitely been controlled and was consequently discharged a week later with oral cephalexin for a minimum of 15 extra days. A year later the filly was known to be pasture sound.

**Case 4**

**Clinical history.**
A 500 kg, 8-year-old Warmblood gelding was presented for an open, articular, comminute and displaced fracture of the right ulna of 7-day duration together with a fracture of the left maxillary bone.

**Clinical/laboratorial work up and diagnosis.**
On admission, the horse showed a 5/5 grade lameness of the right forelimb (RF). A deep, oblique, 7 cm long elbow joint communicated wound was evident on the lateral aspect of the forearm, distal to the elbow. Further radiographs of the RF elbow confirmed the diagnosis of comminute, articular displaced open ulnar fracture with joint elbow wound communication.

**Treatment and outcome.**
Surgery consisted in fracture internal fixation with two (caudal and lateral) locking compression plates and flushing of the right elbow joint with 10 litres of Ringer’s Lactate solution plus a joint injection of amikacin (1g) after synovial fluid sample withdrawal. The horse was treated with sodium penicillin (22,000 UI/kg bwt i.v. every 6 hours), gentamicin (6.6 mg/kg bwt i.v. every 24 hours), phenylbutazone (2.2 mg/kg bwt i.v. every 12 hours) and morphine (0.1 mg/kg, i.m. every 8 hours). The right elbow joint was flushed daily for the first 5 days and 5 alternate more days. The joint was initially injected with 1g amikacin but was changed to imipenem due to severe RF worsening lameness (non-related to the fracture fixation based on good post-operative radiologic stability of fracture reduction) and synovial fluid culture isolation of Gram-negative bacillus Enterobacteria. The elbow joint was injected with a total volume of 30 ml with imipenem (75 mg) during 2 consecutive days, and every 48 h for 5 more days. Unfortunately the horse developed severe laminitis on the contralateral limb and, following the owner’s requirement, the horse was euthanized due to bad sport future prognosis.

**Post mortem findings.**
Post-mortem examination of the elbow joint revealed a good fracture healing and no macroscopic signs of joint sepsis.

**Discussion**

Treatment of synovial sepsis was a challenge in all the four patients described above despite systemic broad-spectrum antimicrobial administration, early and frequent repeated synovial lavages and local antimicrobial delivery with intra-articular antibiotic injections and regional limb perfusions. Concerns about the development of future resistance (Prescott et al., 2002) and the lack of previous information published on the dose and the unknown effects on synovia and cartilage after intra-synovial imipenem injection were the main reasons for leaving it as a last resource.

Isolation of bacteria from infected synovial fluid is frequently disappointing, and for agar culture, isolates were recovered in only 37.5% of horses with a clinical diagnosis of synovial infection (Pille et al., 2007). The use of blood culture media (Dumoulin et al., 2010) to culture synovial fluid samples probably favoured that in our cases all synovial fluid cultures resulted positive, further revealing sensitivity to imipenem.

Intra-articular administration of antibiotics is a routine treatment in horses with septic arthritis. Antibiotics such as gentamicin (Lloyd et al., 1998), amikacin (Moore et al., 1992), and ceftiofur (Mills et al., 2000) have been currently used over the last years. Several other antibiotics have been used intra-synovially, however, there are no published references on their experimental or clinical experiences. There is only a short communication on a foal with Rhodococcus equi septic physis/arthritis (Kelmer and Hayes, 2009) in which they mention that the use of intra-articular imipenem (250 mg) was not effective for treating septic arthritis, even with regional
perfusions (500 mg in 40 mL of saline). This might be explained by an imipenem resistant *Rhodococcus equi* strain related to an altered penicillin-binding protein pattern of the bacteria (Nordmann et al., 1993). In the latter report, in order to deliver 250 mg concentration of imipenem in a volume small enough for intra-articular injection, the solute was dissolved in 10 mL of saline instead of the 100 mL recommended by the commercial product (Primaxin IV). In our cases, however, we decided to inject a lower dose of imipenem into the joint instead of over-concentrating the antibiotic against product recommendations.

Antimicrobial intra-articular administration is known to achieve a greater concentration that is maintained in the synovial fluid for a longer period of time compared with parenteral administration (Schneider, 2006); therefore, systemic imipenem was initially not contemplated as a therapeutic option in any of our patients. However, systemic imipenem was finally tested in the polyarthritic septic foal as the blood culture results were only susceptible to imipenem and the owner accepted the systemic imipenem administration costs and possible unknown risks. Although intra-articular administration of imipenem showed quick clinical and laboratory signs of polyarthritis improvement, systemic imipenem failed to combat the final fatal septic meningitis of the foal. This was not surprising as imipenem is unable to cross the haematocoeplhalic barrier.

Our initial goal was to inject a dose of 250-500 mg of imipenem per joint, by extrapolation from the routine clinical intra-synovial dose of other antibiotics such as amikacin. The biggest limiting factor was that the recommended saline volume for reconstitution for both the 250 and 500 mg imipenem vials was of 100 mL. This made it difficult to achieve a small enough concentrated volume of imipenem without ignoring commercial product recommendations. Consequently, the intra-articular volume of imipenem was subjectively and experimentally adjusted to each case based on the size of the affected joints/sheath (aiming to fill the whole synovial cavity), on initial response to treatment and on the severity of the local infection.

The objective of this clinical report is purely descriptive and does not intend to demonstrate the efficacy of the antibiotic, or report intra-synovial imipenem dosing in horses with septic arthritis/tenosynovitis or encourage the use unreasonably. The aim is to report our positive clinical experience after injecting imipenem intra-synovially of 4 equine patients with septic arthritis/tenosynovitis that were not responding to any of the other conventional treatments. However, highlight the need for further studies to be carried out in a larger number of horses on the pharmacokinetics, dosage, and efficacy of this antimicrobial when injected intra-synovially.

One must keep in mind that imipenem should always be the last treatment resort and never the first choice antibiotic, even after a positive culture sensitivity result, and should be used only when other systemic and local treatment possibilities have previously failed.

References


