EQUINE OSTEOARTHRITIS: MANAGEMENT OVER VIEW, OPTIONS AND TREATMENTS

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Shelley Down presents a two-part article that provides an overview of the management of equine osteoarthritis, including analysis and treatment.

Equine osteoarthritis (OA) is also commonly known as degenerative joint disease (DJD). Lameness due to joint injury and disease in the horse is the most common cause of reduced athletic function and wastage (Rossdale et al, 1985). This two-part article gives an overview of management options for equine OA.

Part one presents the synovial articulation and pathophysiology of OA and the commonly used treatments including intraarticular (IA) corticosteroids (CS), hyaluronan (HA) and polysulphated glycosaminoglycans, in addition to the use of non-steroidal anti-inflammatory drugs (NSAIDs).

Affected area: the synovial articulation

Synovial joints consist of opposed, hyaline cartilage-covered surfaces. The hyaline cartilage rests on subchondral bone plates, beneath which is predominantly cancellous bone. Hyaline cartilage is made up of water (75 per cent), type-2 collagen (15 per cent), proteoglycans (10 per cent) and chondrocytes (two per cent), (Poole, 2001).

The proteoglycans are highly negatively charged, attracting water molecules into the extracellular matrix, providing compressive stiffness (Goodrich and Nixon, 2006). The main proteoglycans are polysulphated glycosaminoglycans. The orientation of the collagen fibrils within the cartilage
provides tensile stiffness (Goodrich and Nixon, 2006).

The function of the joint cartilage is to provide a congruent joint, reducing friction and bone trauma during movement.

The subchondral bone plates are thinner than standard cortical bone, and the haversian system is orientated parallel to the joint surface rather than the long axis of the bone. The deformation of the subchondral bone exceeds that of diaphyseal bone by many times, attenuating forces acting upon it. The synovial membrane lines the inner surface of the joint capsule. It is a vascular connective tissue, and filters blood to create a protein-rich synovial fluid. The synovial capillaries have a “sieve-like” function, allowing only small molecules into the synovial fluid.

The synoviocytes produce HA (Walsh et al, 1997), as well as mediators such as interleukin-1 (IL-1), prostaglandins (PG) and proteases (Mankin and Brand, 1984); synoviocytes are also responsible for phagocytosis. The synovial fluid also contains lubricin (Trotter and McIlwraith, 1996), which in conjunction with HA provides boundary lubrication and steric hindrance (Cohen, 1967).

The subsynovial region contains a rich blood supply, facilitating nutrition to, and removal of waste products from, the synovium. This blood supply is essential for the production of synovial fluid and provides nutrition to the adult articular cartilage via diffusion through the synovial fluid. The joint capsule has a strong outer layer, inserting on to the bone ends at the articular margins. The inner layer supports the synovial membrane.

What is osteoarthritis?

There are multiple causes of OA, including trauma (Figure 1a and b), sepsis (Figure 2), age-related degeneration and osteochondrosis (Figure 3). An abnormal load on normal cartilage (Figure 4) or normal load on abnormal cartilage can induce the inflammatory cascade that results in OA. The inflammatory process can start in any of the synovial tissues, resulting in inflammatory mediator production. These then affect other tissues within the synovial articulation, which in turn produce inflammatory mediators resulting in a “domino” effect.

The inflammatory process involves the release of metabolites of arachidonic acid, which via PG E (PGE2) and I (PGI2), initiates pain (Todhunter and Lust, 1990). Release of freeradicals from neutrophils and macrophages, enzymes from injured synoviocytes and lysosomal enzymes results in degradation of HA. Synovitis leads to abnormal synoviocyte metabolism, resulting in a decrease in HA size. Change in HA levels or size results in reduced viscosity and lubrication leading to further cartilage breakdown. Breakdown of collagen and loss of proteoglycans results in increased cartilage water uptake. This results in softer cartilage that is more easily damaged with mechanical forces (Figure 5). Sclerosis of the subchondral bone secondary to increased stress can reduce deformation and hence force attenuation, contributing to the progression of OA (Kawkak et al,
2000). The synovium is also affected, becoming thickened and congested.

Medical management

Currently, treatment of early OA aims to inhibit the progressive changes described above. In many cases, the clinician is not presented with the horse until a later stage. In these cases, treatment protocols are used to maintain the already damaged cartilage and prevent further degradation. Ideally, cases are identified at an early stage when treatment will have a greater efficacy. Future therapies, such as stem cell therapy, aim to regenerate and/or repair damaged cartilage and synovium.

• Intra-articular corticosteroids (CS)

Corticosteroids are extremely powerful anti-inflammatory drugs that can be highly effective in the management of OA. Normally injected directly into joints, they inhibit PG production by inhibition of phospholipase A2 preventing phospholipid hydrolysis and therefore preventing mobilisation of arachidonic acid. The result is a rapid and significant reduction in pain.

Corticosteroids also inhibit inflammatory effects such as capillary dilation, migration of inflammatory cells and the production and release of degradative enzymes. Controversy has long surrounded the use of CS for fear of over-use of a pain free joint resulting in further degradation. Negative effects on chondrocyte metabolism have also been noted, particularly when CS are used at high concentrations (Chunekamrai et al, 1989), although other studies have found chondroprotective properties of triamcinolone acetonide (TCA), (Frisbie et al, 1997).

Commonly used intra-articular CS, dosages and withdrawal times are presented in Table 1. Type, dose and frequency of CS administration is subjective. The most commonly used IA CS in the horse are methylprednisolone acetate (MPA, 40-120mg/joint) and TCA (6-18 mg/joint). Low dose treatment is mostly used, due to recognition of dose-dependent deleterious effects, and the potency of CS. Co-administration with hyaluronan is often undertaken due to the synergistic effect found in humans (Leardini et al, 1991).

Medication must be undertaken under aseptic conditions. A small risk of infection will always exist and, due to the potent anti-inflammatory effect, signs of infection can be delayed in the presence of CS (Tulamo et al, 1989). Where multiple joints are being injected, the maximum dose that can be administered systemically must not be exceeded. Laminitis secondary to CS administration has been suggested by some authors (Ryu et al, 2004), although the mechanism of such action is unproven. Anecdotally, TCA is considered more frequently associated with laminitis when used intra-articularly. Another rare side effect is steroid arthropathy, where there is rapid advancement of OA and post-injection inflammation.

TCA reportedly has less degradation effect on cartilage than MPA (Frisbie et al, 1998). However,
the studies investigating the effect of MPA on chondrocyte metabolism used high doses that are rarely used clinically. There may also be less effect on chondrocyte metabolism in inflamed joints when compared to normal joints (Todhunter et al, 1998).

There are many indications for the use of CS. Ideally, a full clinical examination and radiographic examination of the joint is undertaken first. This allows the clinician to identify and assess any pathology. If, for example, an osteochondral fragment is present, this should be removed rather than medicate the joint with CS, or further progression of OA may ensue. A short to medium-acting CS can be used in a high-motion joint with synovitis to bring about rapid resolution of inflammation.

Long-acting steroids can be used to relieve pain in horses with end-stage OA and also in low-motion joints at regular intervals to help maintain a horse in work. There is considerable variation in the clearance of CS suspensions. The magnitude and duration of clinical effects vary widely and, therefore, frequency of dosing will depend on the clinician, degree of OA and response to medication.

**Hyaluronan**

Hyaluronan can be used alone or in combination with CS. The specific mode of action is unknown. However, HA also has an anti-inflammatory effect, in addition to viscoelasticity, boundary lubrication of the intraarticular soft tissues and steric hindrance of leukocytes and active plasma components from the joint cavity.

HA is an important part of proteoglycan aggregates in the extracellular matrix. Exogenously administered sodium HA is thought to add to, or replace, the effect of depleted or depolymerised endogenous HA, respectively (Goodrich and Nixon, 2006). Many potentially beneficial effects in vitro are related to the molecular weight, with that above $1 \times 10^6$ possibly providing better chondroprotection, although this is unproven in vivo. The dose in small joints is usually 20mg; in large joints it is 40mg. The frequency of medication differs between reports, but generally it is standard to treat at weekly intervals until no further improvement is seen.

HA should be injected under aseptic conditions. HA can be administered IA or intravenously (IV), (Hyonate injection, Bayer). Again, the precise mechanism of action of IV HA is unknown, but clinical and biochemical beneficial effects have been found (Kawcak et al, 1997). It is common to use the IV product at weekly intervals until no further improvement is seen, or as a “management tool”. This preparation may be useful when there are multiple joints to treat, and is generally used for acute synovitis; there is little value in using the IV preparation for established OA. The main use for HA is acute synovitis, with obvious joint inflammation and effusion with no recognisable changes to bone or cartilage. A synergistic effect of use of CS and HA in combination has been found (Liardini et al, 1999), resulting in a decreased proteoglycan loss. Characteristics of HA formulations are summarised in Table 2.
• Polysulphated glycosaminoglycans (PSGAGs)

Polysulphated glycosaminoglycans are disease-modifying drugs that inhibit the effects of cytokines or PG on cartilage and promote chondrocyte metabolic activity. This alters the progression of OA. Anti-inflammatory effects on other tissues such as the synovium have also been noted. Intra-articular and intramuscular (IM) preparations are available (Adequan, Janssen Animal Health). For IA administration, joints are medicated with 250mg every eight days for five treatments. For IM use, 500mg are injected every four days for seven treatments. Intra-articular administration has been shown to increase the risk of iatrogenic infection, by potentiating the infectivity of *Staphylococcus aureus*. It is, therefore, common to combine IA medication with 125mg of Amikacin or 250mg of gentamicin, although it has been shown safe to use without concurrent IA antibiotics (Kristiansen and Kold, 2007). Intra-articular administration is also associated with acute haemarthroses due to the heparinoid effect of PSGAG. It is contraindicated to use in the face of acute inflammation. Many practitioners often choose to use the IM preparation due to these potential side effects.

Intra-muscular administration does result in therapeutic levels within the articular cartilage, but it is unknown how long these levels are maintained. Some clinicians value its use following arthroscopic removal of chip fragments, where there is OA and cartilage erosion seen. Otherwise, the main indication for PSGAG use is cases of mild, chronic OA, but it is difficult to predict which cases will respond to treatment.

• Pentosan polysulphate

Pentosan polysulphate (Cartrophen vet, Arthropharm [Europe] Limited) is prepared by sulphation of beechwood hemicellulose. Its effects are similar to PSGAG, with promotion of anabolic chondrocyte activity and inhibition of degradative enzymes resulting in chondroprotective effects (Little and Ghosh, 1996). It has been found to provide symptomatic treatment in horses with chronic OA (Little and Ghosh, 1996). The recommended dose is 2-3mg/ kg IM every seven days for 28 days. This can be repeated every three months as required. Further research is required into the efficacy and indications for its treatment.

Palliative treatment

• NSAIDs

All cells contain arachidonic acid as part of membrane phospholipids. Oxidation of arachidonic acid by cyclooxygenase (COX) or 5-lypooxygenase produces PG and leukotriene formation, respectively. NSAIDs inhibit COX, preventing PG production from arachidonic acid. COX can be further divided into COX-1 (“housekeeping” enzyme, producing PG for normal cellular processes) and COX-2 (producing PG responsible for inflammatory processes). Because of this, different NSAIDs have variable efficacy and toxicity. An ideal NSAID would inhibit COX-2 only.
There is a lack of good clinical evidence to choose one NSAID over another. NSAIDS can be very useful at treating horses with OA, providing appropriate diagnosis, imaging and primary specific treatment (for example, IA medication) has been undertaken and addressed. NSAIDs lead to increased joint mobility due to their analgesic effect. This prevents fibrosis of the joint capsule and synovium, which can occur with underuse of the joint. Although increased loading of a joint with OA may increase cartilage erosion, lack of joint loading can lead to cartilage thinning.

The safety margin for the use of NSAIDs is narrow. High doses can cause signs of severe toxicity after a short period, whereas moderate doses can be tolerated for a long time with no adverse clinical signs. Side effects include anorexia, depression, low-grade colic, gastrointestinal signs (gastric ulceration, right dorsal colitis, caecal perforation and protein-losing enteropathy) and renal damage. Commonly used NSAIDs, dose, frequency and withdrawal times are presented in Table 3.

References


Figure 1a. Flexed dorsal 30° medial-palmarolateral oblique radiographic image of the distal phalanx of a 13-year-old showjumper mare with moderate lameness. There is a nonunion articular medial palmar process fracture of the distal phalanx (yellow arrow). The mare was rendered sound following analgesia of the palmar digital nerves and subsequently improved following analgesia of the distal interphalangeal joint. The mare was treated with a palmar digital neurectomy under general anaesthesia to enable use as a companion.
Figure 1b. Lateromedial radiographic view of the same horse in Figure 1a. There is secondary osteoarthritis of the distal interphalangeal joint noted by osteophyte formation on the dorsoproximal aspect of the distal phalanx (black arrow). There is also new bone formation on the dorsoproximal aspect of the middle phalanx and the distodorsal aspect of the proximal phalanx consistent with osteoarthritis of the proximal interphalangeal joint (yellow arrows). This was an incidental finding. There is also modelling of the proximal aspect of the navicular bone (blue arrow).
Figure 2. Dorsal 45° lateral-palmaromedial oblique radiographic image of the proximal interphalangeal joint of a 15-year-old showjumper gelding with iatrogenic proximal interphalangeal (PIP) joint sepsis secondary to joint medication when show jumping outside.
the UK. There are gentamicin impregnated polymethylmethacrylate beads in the dorsal PIP joint from surgical intervention (blue arrow). There is marked proliferative new bone on the mid to proximal dorsomedial aspect of the middle phalanx, the distal dorsomedial proximal phalanx and the distal palmarolateral aspect of the proximal phalanx indicating secondary osteoarthritis of the PIP joint (yellow arrows). The sepsis could not be effectively treated and the horse was euthanised.
Figure 3. Caudal 15° proximal-craniodistal oblique radiographic image of the left stifle of a 13-year-old thoroughbred-cross gelding. Medial is to the left. There is a large osseous cyst-like lesion in the medial femoral condyle and a large peri-articular osteophyte on the proximomedial aspect of the tibia (yellow arrow) consistent with secondary osteoarthritis. There was a positive response to intraarticular analgesia of the medial and lateral femorotibial and femoropatellar joints undertaken simultaneously. The medial femorotibial joint was medicated with 10mg triamcinolone acetonide and 40mg hyaluronan under aseptic
conditions. The horse was able to resume light work with the use of non-steroidal anti-inflammatory therapy.

Figure 4. Longitudinal ultrasonographic image of the dorsal aspect of a
metacarpophalangeal joint in an eight-year-old thoroughbred-cross gelding. Proximal is to the left, dorsal is to the top of the image. There is a focal area of hyperechogenicity on the dorsoproximal aspect of the proximal phalanx (white arrow) consistent with peri-articular osteophyte formation. This was not noted radiographically, highlighting the use of concurrent ultrasonographic examination; the cartilage can also be assessed in the plane of the ultrasound beam (small yellow arrows). This horse had marked mediolateral foot imbalance and was base narrow, placing an asymmetrical load on the metacarpophalangeal joints, resulting in secondary osteoarthritis. The horse was rendered sound by intra-articular analgesia of the metacarpophalangeal joint. The metacarpophalangeal joint was medicated with 8mg triamcinolone acetonide and 20mg hyaluronan under aseptic conditions. The horse was rendered sound and able to resume full work for a period of eight months until euthanasia was undertaken due to unrelated causes.
Figure 5. Postmortem examination of a six-year-old mare previously used for flat racing. Medial is to the left. The horse partially improved to analgesia of the middle carpal joint and was rendered sound to perineural analgesia of the median and ulnar nerves. The horse was euthanised due to multi-limb lameness and pathology. There is a full thickness cartilage defect on the dorsal aspect of the distal surface of the radial carpal bone (RCB). There is also cartilage thinning on the proximodorsal surface of the radial facet of the third carpal bone (3CB). There is periartricular osteophyte formation on the proximodorsal surface of the 3CB and the distodorsal surface of the RCB (black arrows).
**Table 1.** Commonly used intra-articular corticosteroids

<table>
<thead>
<tr>
<th>Corticosteroid</th>
<th>Trade name</th>
<th>Manufacturer</th>
<th>Concentration</th>
<th>Dose</th>
<th>Withdrawal times***</th>
</tr>
</thead>
<tbody>
<tr>
<td>Betamethasone*</td>
<td></td>
<td></td>
<td></td>
<td>3 - 18</td>
<td>Up to seven days</td>
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<tr>
<td>Dexamethasone</td>
<td>Dexadreson</td>
<td>Intervet UK</td>
<td>2</td>
<td>2 - 10</td>
<td>2 - 7 days</td>
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<tr>
<td>Flumethasone*</td>
<td></td>
<td></td>
<td></td>
<td>1.25 - 2.5</td>
<td>2 - 7 days</td>
</tr>
<tr>
<td>Methyprednisolone acetate</td>
<td>Depomedrone V</td>
<td>Pharmacia and Upjohn</td>
<td>4D</td>
<td>4.0 - 120</td>
<td>23 days (44 if given IM)</td>
</tr>
<tr>
<td>Triamcinolone acetonide*</td>
<td>Adcortyl</td>
<td></td>
<td>1D</td>
<td>6 - 18</td>
<td>7 days (15 if given IM)</td>
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</tbody>
</table>

* Can be used under the regulations of the cascade only, IM = intramuscular administration. ***Withdrawal times of CS vary from horse to horse and are dependent on a variety of factors such as level of training, diet and state of health. Detection times issued by various federations are not necessarily the same as withdrawal times.
<table>
<thead>
<tr>
<th>Trade name</th>
<th>Manufacturer</th>
<th>Concentration</th>
<th>Molecular weight (Daltons)</th>
<th>Recommended intra-articular dose (small joints)</th>
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</thead>
<tbody>
<tr>
<td>Hyalovet</td>
<td>Dechra veterinary products</td>
<td>10mg/mL</td>
<td>$7.7 \times 10^6$</td>
<td>20mg</td>
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<tr>
<td>Hylartil Vet</td>
<td>Pfizer</td>
<td>10mg/mL</td>
<td>$3.5 \times 10^6$</td>
<td>20mg</td>
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<tr>
<td>Hyonate</td>
<td>Bayer PLC</td>
<td>10mg/mL</td>
<td>$3 \times 10^5$</td>
<td>20mg</td>
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<tr>
<td>HY-50</td>
<td>Genix Animal Health and nutrition</td>
<td>17mg/mL</td>
<td>&quot;High&quot;</td>
<td>25.5mg</td>
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Table 2. Characteristics of commonly used hyaluronan preparations
<table>
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<tr>
<th>NSAID</th>
<th>Product</th>
<th>Manufacturer</th>
<th>Route(s) of administration</th>
<th>Dose mg/kg</th>
<th>Frequency</th>
<th>Withdrawal times***</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carprofen</td>
<td>Rimadyl Large animal solution and granules</td>
<td>Pfizer</td>
<td>IV and P0</td>
<td>IV, 0.7</td>
<td>q 24 hours</td>
<td>Up to 11 days</td>
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<td></td>
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<td>PO-1.4</td>
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<tr>
<td>Flunixin meglumine</td>
<td>Finadyne</td>
<td>Schering-Plough</td>
<td>IV and P0</td>
<td>1.1</td>
<td>q 24 hours</td>
<td>6-14 days</td>
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<tr>
<td>Ketoprofen</td>
<td>Ketofen 10%</td>
<td>Merial Animal Health</td>
<td>IV</td>
<td>2.2</td>
<td>q 24 hours</td>
<td>4 days</td>
</tr>
<tr>
<td>Phenylbutazone</td>
<td>Equipalazone</td>
<td>Dechra Animal Health</td>
<td>IV and P0</td>
<td>2.2</td>
<td>q 12 hours</td>
<td>Up to 8 days</td>
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<td></td>
<td></td>
<td>dose)</td>
<td>q 24 hours</td>
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<tr>
<td>Salicylate</td>
<td>Tensolvet</td>
<td>Day, Son and Hewitt</td>
<td>Topical</td>
<td>q 12 hours</td>
<td></td>
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</tbody>
</table>

***Withdrawal times of CS vary from horse to horse and are dependent on a variety of factors such as level of training, diet, and state of health.

**Table 3.** Commonly used NSAIDs in equine practice