Pain in Osteoarthritis

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- Osteoarthritis • Joint pain • Articular cartilage
- Pharmacologic management of joint pain

Osteoarthritis (OA), also known as osteoarthrosis or degenerative joint disease, is the most important chronic musculoskeletal disorder in both humans and horses. Although not a life-threatening disease, OA is considered one of the major concerns in human health care because of the vast number of people involved and the severe impact this literally crippling disease can have on quality of life. In the United States alone, total costs of OA were estimated at $89.1 billion in 2001[1] and a more recent article estimates that, compared with 2005, total hip replacements will have gone up by 673% in 2030 to a total of 3.5 million surgeries per year.[2] In France, direct costs of OA exceeded $2 billion in 2002 and accounted for 13 million physician visits. That year's figures represented a 156% increase in costs over 1993, which was for more than 90% because of an increase in the number of patients, rather than because of the increase of costs per patient.[3] The substantial direct and indirect costs of OA make this disease a major economic burden, in addition to a cause of loss of quality of life for hundreds of millions of people. In horses, articular disorders, most of which are related to osteoarthritic pain, account for the greatest single economic loss to the equine industry,[4] and likewise form a major animal welfare concern.

This article focuses on pain associated with OA. It first describes the basic biology of articular cartilage and other joint structures and the defining features of the osteoarthritic disease process. Subsequently, the possible origins of pain in OA are discussed before embarking on how to manage this clinical entity. The emphasis is on the pharmacologic management of joint pain, and attention is paid to systemic therapeutic strategies as well as to local (intra-articular [IA]) treatment modalities. Nonmedical ways of modulating joint pain are briefly mentioned, but not extensively discussed, as these are outside the scope of this article.

BIOLOGY OF THE DIARTHRODIAL JOINT AND CHARACTERISTICS OF OA

The fluid-filled cavity of the diarthrodial joint is surrounded by a limited number of tissues. These always include articular cartilage and the synovial membrane, in some cases supplemented by IA structures such as ligaments and menisci. Of these

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tissues, articular cartilage has been studied most extensively, probably followed by subchondral bone, a tissue that is not normally in direct contact with the joint cavity but may become exposed to it in severe cases of OA or in other joint disorders like IA fractures or osteochondrosis. Notwithstanding the historical focus of research interest on articular cartilage and subchondral bone, it is increasingly being recognized that synovial joints should be regarded more comprehensively as complex organs in which all constituent tissues play an important role: IA homeostasis is key to maintaining joint health, and impaired homeostasis is central to the pathogenesis and progression of joint degeneration.[5,6]

Biology of the Diarthrodial Joint

The main function of diarthrodial joints is to enable smooth articulation of 2 adjoining bone ends, at the same time providing both strength to accommodate the forces generated by the combined influences of gravity, locomotion, and inertia, and resilience necessary to attenuate the shocks generated by locomotion. All articular tissues participate in accomplishing this complex task that poses severe biomechanical challenges to some of them, as opposing requirements like the need for simultaneous resilience and strength are hard to reconcile.

The joint capsule is a stiff fibrous tissue that offers structural support. It is often functionally and anatomically reinforced by other supporting structures, such as collateral ligaments. The inner lining of the joint capsule, the synovial membrane, consists of an inner thin (1–3 cells thick) cellular layer, variably supported by an outer stromal layer consisting of adipose and fibrous tissue that is well innervated and vascularized and that becomes continuous with the outer fibrous joint capsule. Owing to the lack of a basement membrane, the gaps between adjacent synoviocytes, and the close proximity of subsynovial blood vessels, there is ample possibility of exchange of all components but macromolecules between plasma and synovial fluid, and the latter can hence be considered an ultrafiltrate of the former.[7] The synovial membrane is populated by 3 types of cells. Synovial type A cells are mainly phagocytic, B cells are active paracrine secretors and produce hyaluronic acid (HA), and C cells are believed to be intermediate between the two. The high degree of vascularization of the subsynovial tissue and the capacity of the synovial cells to produce a wide variety of inflammatory mediators and catabolic enzymes make the synovial membrane a key player in all forms of joint inflammation or arthritis.

The hyaline cartilage that covers the articular surfaces of bones is a highly specialized connective tissue with biomechanical characteristics that make it particularly suitable for load bearing and shock absorption.[8] A sparse population of chondrocytes (1%–2% of articular cartilage volume) is distributed throughout the extracellular matrix, which consists mainly of type II collagen, proteoglycans, glycoproteins, and water. The physical properties of the tissue depend on the structure and organization of the macromolecules in the extracellular matrix.[9,10] The collagen molecules are organized in a dense cross-linked fibrillar network that is packed with proteoglycans, which are strongly negatively charged as a result of their polyanionic glycosaminoglycan sidechains. This creates a large osmotic swelling pressure, drawing water into the tissue and expanding the collagen network. It is this balance within the extracellular matrix between the tension in the collagen network and the osmotic swelling pressure of the proteoglycans that gives articular cartilage its unique biomechanical characteristics, as it provides a combination of high compressive stiffness and resilience. These properties are critically dependent on both the integrity of the collagen network and the synthesis and retention of proteoglycans.[9,11,12]

Articular cartilage is connected to the underlying subchondral bone via the calcified cartilage layer. The subchondral bone consists of a so-called subchondral plate of dense cortical bone that is supported by trabecular bone with a more open structure. The thickness of the subchondral bone plate may vary and can be heavily influenced by pathology. Distal tarsal subchondral bone plate thickness has been measured at 2 to 4 mm in normal horses[13] and is in the same order of magnitude in other joints. The subchondral bone provides structural support for the overlying cartilage; its mechanical properties are therefore vital to the accommodation of forces of locomotion by the articular cartilage.

The joint cavity is filled with synovial fluid (SF), which as discussed can be considered an ultrafiltrate of blood plasma, with molecules smaller than 10 KDa existing in full equilibrium between plasma and SF.[14] Synovial fluid is highly viscous, mainly because of its high concentration of HA. Synovial fluid is a key component in joint homeostasis, as it acts both as a lubricant to allow nearly frictionless joint motion and as the medium for transport of nutrients and waste products to and from the avascular articular cartilage. From a research point of view, it is also uniquely suited to monitor IA events, as all changes evoked by a disturbance of joint homeostasis, such as influx of cells or locally produced inflammatory mediators and cytokines but also by-products of tissue turnover, which all have the potential to be used as biomarkers of disease, can be detected in the SF.[15]

Osteoarthritis

Recently, 3 of the world's most prominent OA researchers agreed on the following definition of OA: *"Osteoarthritis can be described as the failed repair of damage that has been caused by excessive mechanical stress (defined as force/unit area) on joint tissues."*[16] This implies that although multiple factors may lead to OA, mechanical impact (either as a major single event or as repetitive microtrauma) is central to all of these, and that the sequence of events that ensues represents the intrinsic repair process, which may either fail or be successful in restoring joint function.

The focus on biomechanical influences as the sole primary etiological factor in OA is not uncontested. In the horse, synovitis is also regarded as an important primary, or at least concomitant, event.[17] Irrespective of whether there are only single or multiple primary factors, there is general consensus that after this primary event a vicious cycle may ensue that comprises both inflammatory and degradative components. There is no doubt that inflammation in OA is much less prominent than in rheumatoid arthritis (RA), and OA has even long been considered a noninflammatory degenerative disorder. However, in the genomic era of molecular biology, this view can no longer be maintained[18] and it is now widely recognized that synovial inflammation is an important component of OA, contributing to the dysregulation of chondrocyte catabolic and anabolic activities (**Fig. 1**).[19] In OA, bouts of more intense inflammatory activity typically alternate with (often long) quiescent spells in which joint abnormalities are minimal. This slow and insidious progression of the disease is reflected by the intermittent occurrence of clinical symptoms, with "flare-ups" and overt lameness often alternating with periods in which the joint may be largely asymptomatic.[20] Although OA can be managed relatively well for prolonged periods if loading can be adapted to the (reduced) carrying capacity of the joint, often this is not the case and instead the joint enters a vicious cycle of inflammation, structural damage, further loss of resistance to loading, aggravated inflammatory response, and so forth. In this respect, it is important to realize that articular cartilage is not able to fully repair itself because of the extremely long turnover time of collagen type II (half-life of human collagen type II has been calculated at 117 years[21]). Instead, cartilage damage will be

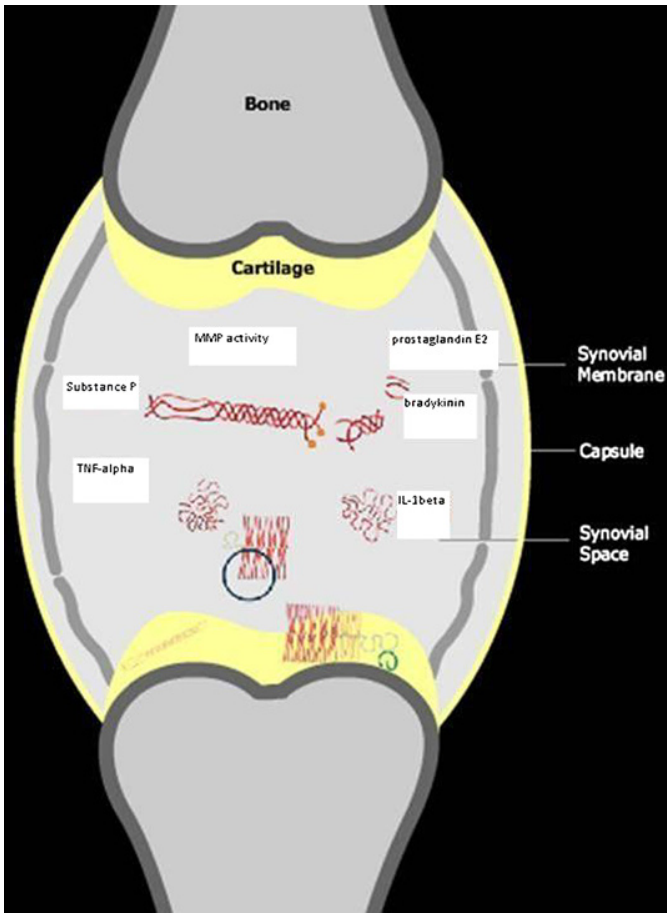

Fig. 1. Simplified, schematic view of a joint with active synovitis. The fluid-filled synovial cavity contains a plethora of mediators and activated catabolic enzymes released by the synovial membrane as well as by chondrocytes, which will in turn affect the cleavage as well as synthesis of articular cartilage matrix components like collagen type II and proteoglycans.

repaired by fibrocartilage that is mainly composed of collagen type I and that has inferior biomechanical qualities compared with the original tissue.

The cumulative damage will eventually lead to softening, fibrillation, ulceration, and loss of articular cartilage (**Fig. 2**); hypertrophy and fibrosis of the synovial membrane and joint capsule; sclerosis and eburnation of subchondral bone; and formation of

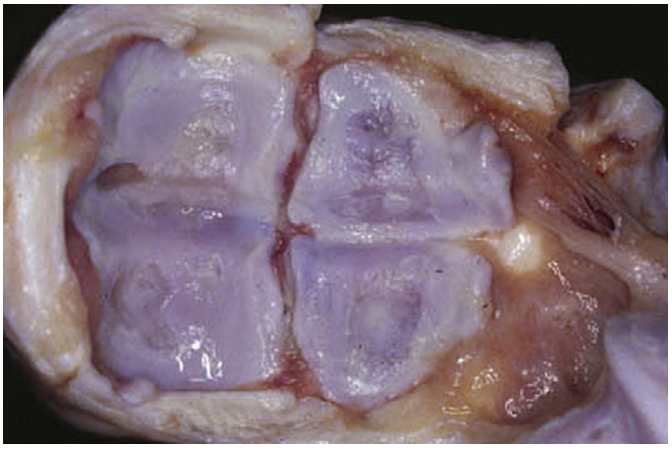

Fig. 2. View of the proximal articular surface of the first phalanx and of the articular side of the sesamoid bones from a metacarpophalangeal joint that was heavily affected by late-stage OA.

osteophytes and/or subchondral cysts.[22] Both at this end stage and at each intermediate stage of the disease process, there are many potential sources of joint pain.

PAIN IN OA

Joint pain (often intermittent) is one of the hallmarks of OA and the major cause of lameness associated with the disease. It has been described as "the most prominent but least well-studied feature of OA."[23]

The Origin of Pain

For the perception of pain, 2 general conditions need to be met: first, a pain stimulus must be generated, and second this stimulus must be detected, transduced, and transmitted by the nervous system to the brain where pain perception can take place. Two general types of pain stimuli in synovial joints can be distinguished: mechanical stimuli, generated by (severe) mechanical changes in the environment of the joint (eg, by direct trauma), and chemical stimuli resulting from tissue inflammation. These stimuli are detected and forwarded by different types of receptors, mechanoreceptors, and nociceptors, the distribution and relative abundance of which differ in various joint tissues. The signal is then carried by Aδ or C-nerve fibers in peripheral nerves to the dorsal horn of the spinal cord, where neuromodulators and neurotransmitters are located within synapses between primary and secondary neurons. The latter decussate within the spinal cord and travel to the brain where the signal is further processed, modulated, and finally perceived.[24]

Innervation of Articular Tissues

Articular cartilage is unique in that it is both aneural and avascular (at least in mature individuals). As a result, damage limited to the cartilage layer will not immediately be detected, and this may explain how cartilage erosion as seen in OA can silently progress for a long time before becoming clinically manifest. Of the other articular tissues, both subchondral bone and the joint capsule are innervated, the latter quite densely. This is also the case for IA ligaments and menisci. In articular tissues, 4 types of afferent receptors can be discerned.[25] Type 1 receptors are low-threshold mechanoreceptors, consisting of thinly encapsulated end organs of medium size (80–100 μm) connected to medium-sized myelinated nerve fibers. They can be found in the joint capsule, but not in the synovial membrane, and serve mainly a proprioceptive function. Type 2 receptors are large encapsulated end organs (280–300 μm), connected to 9- to 12-μm myelinated nerve fibers. They are low-threshold mechanoreceptors and can be found typically at the junction of the fibrous joint capsule and the subsynovial adipose tissue, hence in closer proximity to the joint cavity. These receptors are rapidly adapting and are activated only when the joint is in motion, acting as dynamic proprioceptive sensors. Type 3 receptors are relatively large (150 × 600 μm), thinly encapsulated end organs located near the bony insertions of IA and peri-articular ligaments. They have a high threshold and are inactive in static conditions and during limited passive movement. These receptors are activated when joint motion reaches its physiologic limits; they have both mechanoreceptive and nociceptive potential and can be seen as safety mechanisms. They are connected to very rapidly conducting myelinated fibers. Type 4 receptors, also known as polymodal nociceptors, are not really anatomically discernible as receptors, but rather consist of free nerve endings of afferent nonmyelinated C-fibers or small myelinated Aδ fibers. They are abundant in the entire joint capsule and can even be found in limited numbers within the synovial membrane. Also, the periosteum directly adjacent to the joint

margins has a dense supply of these receptors. Type 4 receptors are high-threshold nociceptors that respond to thermal and chemical, but also mechanical, stimuli, whereby chemical stimuli (like those evoked by inflammatory mediators) may augment the responsiveness to mechanical stimuli, hence sensitizing the joint to these and causing hyperalgesia as well as allodynia.

Pain transmission through afferent fibers is not the simple one-way procedure it may appear to be. Peripheral sensory neurons function as afferent conductors, but they also exert important efferent functions mediated by neuropeptides.[26] Neuropeptides are small molecules that are synthesized in the dorsal root and autonomic ganglion neurons and from there are transported via the axon to peripheral nerve terminals. They are potent bioactive substances that can induce the release of other mediators, such as cytokines, prostaglandins, and nitric oxide (NO). Their active range is usually limited, both in space and time, owing to their chemically labile character. In healthy or regenerating tissue, they may have growth factorlike functions[27] and thus they do not only play a role during inflammation but also in the maintenance of joint homeostasis. Well-known neuropeptides include substance P (SP), calcitonin gene–related peptide (CGRP), vasoactive intestinal polypeptide (VIP), neuropeptide Y (NPY), and somatostatin (SOM).[26] Neuropeptides play an important role in the complex mechanisms that modulate and mitigate nociceptive input; for instance, VIP is thought to be instrumental in the augmentation of the responsiveness to mechanical stimuli in case of joint inflammation.[28]

Pathophysiological Sources of Pain in OA

Numerous processes in the course of OA can contribute to the joint pain experienced by affected subjects, and very rarely can the precise tissue origin of pain be identified in the individual patient (**Fig. 3**). The previously described sensory innervation patterns of the subchondral bone, marginal periosteum, synovial membrane, and joint capsule will contribute to a variable extent to OA pain and loss of function, depending on individual disease stage and activity. In addition, alterations of central nervous system pathways associated with chronic pain states (central sensitization or “wind-up”)

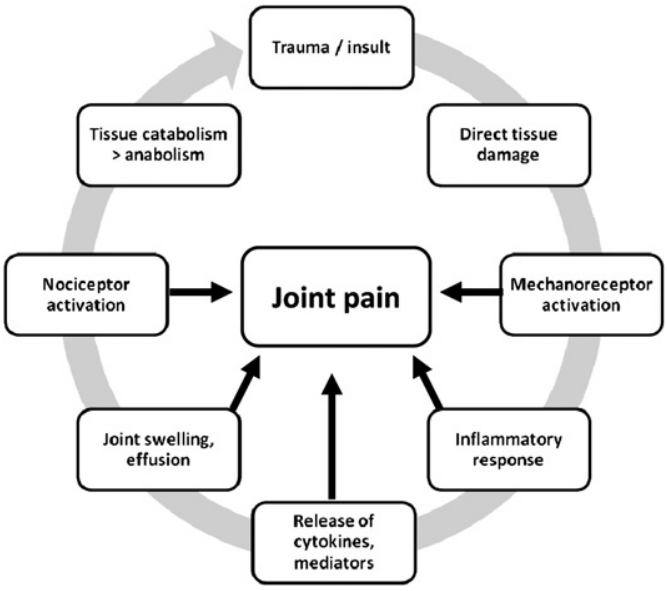

Fig. 3. Simplified schematic diagram of the vicious cycle of osteochondral damage and cartilage degeneration in OA, showing key processes that may contribute to joint pain associated with the disease.

have also been identified in human patients with OA and may partially explain the difficulty in long-term management of OA pain.[29] Within the joint tissues, subchondral bone exposure, remodeling, and/or marrow edema (causing a rise in intraosseous pressure), as well as marginal periosteal activation associated with osteophyte formation, have been implicated as sources of pain in more advanced stages of OA.[25] Synovitis is an important factor that contributes to pain in OA both through joint effusion, swelling, and/or fibrosis that in turn will activate mechanoreceptors in the joint capsule, and through direct chemical stimulation of nociceptors.

Pathways of Inflammatory Pain

Whereas the stimulation of mechanoreceptors by mechanical influences is relatively straightforward, nociception will in most cases be stimulated or enhanced by inflammation. In this context, the interrelationship between the 2 receptor types needs to be pointed out: not only can mechanoreceptors become sensitized by chemical stimuli released during inflammatory processes, as alluded to previously, but mechanical stimulation itself may, through tissue damage, elicit an inflammatory response with release of pro-nociceptive mediators.

Pain is 1 of the 5 classic characteristics of inflammation (rubor, tumor, dolor, calor, and functio laesa), as already formulated in Antiquity by Celsus (30BC–38AD). In inflammation, pain originates from the chemical stimulation of nerve afferents by a variety of endogenous mediators. It is commonly accepted that interleukin-1 (IL-1) and tumor necrosis factor alpha (TNF-α) are the 2 major cytokine players in the pathogenesis of OA.[30] IL-1 and TNF-α increase the synthesis of prostaglandin E_2 (PGE_2) by stimulating cyclooxygenase (COX)-2, microsomal PGE synthase-1 (MPES-1), and soluble phospholipase A_2 ($SPLA_2$), and they upregulate the production of nitric oxide via inducible nitric oxide synthetase (iNOS).[23] IL-1β is known to induce the production of other proinflammatory cytokines also, including IL-6, -17, and -18 (for a review, see Goldring and Goldring[31]). Relatively little work has been devoted to the exact identification of pain-related mediators in joint disease, which supports the earlier quoted statement that pain is one of the principal but least researched symptoms of OA.[23] Prostaglandins have always been incriminated as the major pain mediators in arthritis,[32] but this key role is not as clear-cut and unambiguous as it may seem. In a dog study, significant positive correlations were established between PGE_2 levels in SF and subjective lameness score,[33] but in another dog study comparing normal and osteoarthritic tissues, a significant increase in COX-2 protein was found in OA specimens without an increase in PGE_2 concentration.[34] In a study using human synovial tissue and comparing early and established OA, COX-2 expression was higher in early OA, but cytokine-induced PGE_2 production in culture was similar.[35] In a horse study where PGE_2 levels in SF were compared in lame horses that did or did not respond to IA analgesia, no significant difference was found. Interestingly, however, when comparing the SF PGE_2 levels of these lame horses (blocking to a low 4-point or 6-point perineural nerve block) to those of sound horses, the lame horses had significantly higher and more variable PGE_2 levels than the sound controls.[36] There are indications that the other branch of the arachidonic acid cascade, the pathway that leads via 5-lipoxygenase (LOX) to the formation of leukotrienes, may play a role in articular nociception too. In the previously mentioned dog study,[34] there was a trend ($P = .069$) toward upregulation of LOX in OA-affected animals. Further, leukotriene B_4 (LTB_4) has been shown to be implicated in hyperalgesia in joints of mice.[37] In the horse, LTB_4 levels have been shown to be increased in animals suffering from osteochondrosis (OC) and may be involved in the extensive joint distension that is seen in many of these

cases.[38] However, lameness in these patients is uncommon and thus far no link between LTB_4 and joint pain in the horse has been established.

Various neuropeptides have been identified as direct pain mediators in joint disease in humans. These include neuropeptide Y, serotonin, and calcitonin gene–related peptide.[39,40] In the horse, substance P has been suggested to play a role in the signaling and maintenance of pain associated with OA,[41] but could not be related to radiographic OA status of a joint.[42] However, substance P was the only mediator from a panel of possible mediators that could be directly linked to outcome of IA analgesia in the study by De Grauw and colleagues.[36] Kinins, with bradykinin as the main representative,[43,44] the major inflammatory cytokines themselves, and chemokines, a rather novel family of cytokines that now has been linked to the induction and maintenance of chronic pain,[45] have all been implicated in the generation of joint pain and are involved in the regulation of sensory neuron function (for an overview see Miller and colleagues[46]). None of these pain mediators have yet been investigated in the horse, with the exception of bradykinin, the concentration of which was not related to the outcome of IA analgesia,[36] but did show a strong correlation with lameness and joint hyperalgesia in chemically induced synovitis.[47]

MANAGEMENT OF JOINT PAIN

Pain is the most salient clinical feature of OA and has the biggest impact on both welfare and performance. Pain management is therefore of great importance when managing osteoarthritis; however, it should be realized that treatment aimed at pain reduction does not necessarily treat the underlying primary disease process and may even interfere negatively with it. In fact, it has been suggested that long-term use of nonsteroidal anti-inflammatory drugs might enhance the pathologic process of cartilage degeneration by removing the regulatory role of PGE_2 on IL-1 synthesis.[48] On the other hand, treatment aimed primarily at pain relief may, through anti-inflammatory actions, also positively affect the articular cartilage by means of inhibition of release of catabolic factors.[49]

Chronic pain attributable to OA is mostly managed pharmacologically, but other ways of modulating joint pain are available and may prove efficacious. The following section first discusses systemic medical treatment of OA pain, followed by IA or other topical therapies, to conclude with a paragraph on nonpharmacologic modulation of joint pain.

Systemic Treatment of Joint Pain

The nonsteroidal anti-inflammatory drugs (NSAIDs) are by far the most important class of compounds in this category. However, several other systemically administered OA drugs also provide some extent of analgesia, although this is secondary to their influence on the primary process and not the principal *rationale* for their use.

Nonsteroidal anti-inflammatory drugs

NSAIDs inhibit the enzyme cyclooxygenase (COX) in the arachidonic acid cascade, thus inhibiting prostaglandin production. Most of the older NSAIDs indiscriminately inhibit both COX-1 and -2 iso-enzymes, and therefore also affect constitutive prostaglandin production by COX-1 that exerts physiologic functions among which is protection of mucosal barriers in the gastrointestinal tract. Newer generation NSAIDs have been developed that are more selective COX-2 inhibitors and these have demonstrated a superior gastrointestinal safety profile in humans, while providing comparable analgesic and anti-inflammatory potency.[50] Preferential and selective COX-2 inhibitors have also become available for the treatment of OA in the horse, but

traditional nonselective NSAIDs are still routinely used, with phenylbutazone maintaining its prominent place over the past decades. **Table 1** summarizes dosages and ways of administration for the most commonly used NSAIDs, which will be dealt with in somewhat more detail in the following paragraphs.

Phenylbutazone (PBZ), or "bute" as it is sometimes semi-affectively called, is the most widely used drug in equine orthopedic practice and is often cited as the most cost-effective treatment for OA pain.[51] Its use is not entirely uncontested, though, as the drug may have severe adverse health effects on humans. Butazones have been associated with a (slightly) increased risk of aplastic anemia in humans[52] and potential genotoxic and carcinogenic effects were identified in mice and rat studies[53]; for this reason, the drug has been withheld from official registration for equine use in some countries. Recently, concern was expressed about the possible public health effect of PBZ in horse meat exported from the United States. In the United States, horse meat is not regularly sold for human consumption, but many slaughter horses are exported, and eventually enter the food chain.[54] PBZ is mostly used orally in a dose of 2.2 mg/kg twice a day (or tapered to once a day) after an initial loading dose of 4.4 mg/kg twice a day for 2 consecutive days. Intravenous formulations are also available, but carry some risk of perivenous irritation.[51] Most equine clinicians will agree that PBZ is very effective in treating articular pain, and this is indeed supported by literature, but comparative research on clinical efficacy versus other NSAIDs in horses is surprisingly limited.[55–58] The information on the effects of PBZ on cartilage or chondrocytes (ie, on the primary disease process), is even scarcer and stems mainly from in vitro studies that have produced conflicting results. Beluche and colleagues[59] reported detrimental inhibition of proteoglycan synthesis in articular cartilage of horses that were administered PBZ in vivo, whereas Frean and colleagues

Table 1
Overview of the most commonly used NSAIDs with their route of administration and dosage

Name of Drug	Route of Application	Dosage	Remarks
Phenylbutazone	Oral	2.2 mg/kg BID (Initial loading dose often 4.4 mg/kg for 2 days and for long-term use standard dose tapered to SID)	In some countries not permitted because of perceived risks for human health
Flunixin	Oral or IV	1.1 mg/kg SID	IM application possible, but has been associated with myonecrosis
Carprofen	IV or oral	0.7 mg/kg (IV) SID 1.4 mg/kg (oral) SID	
Ketaprofen	IV or IM	2.2 mg/kg SID	In oral form not bioavailable
Vedaprofen	Oral	Initial dose 2 mg/kg BID, maintenance 1 mg/kg BID	
Meloxicam	Oral	0.6 mg/kg SID	A positive effect on cartilage metabolism has been demonstrated in vivo[49]
Naproxen	Oral or IV	10 mg/kg BID or SID	

Abbreviations: BID, twice a day; IM, intramuscular; IV, intravenous; SID, once a day.

and Jolly and colleagues failed to demonstrate any such effect after in vitro exposure of cartilage to PBZ.[60,61] Fradettte and colleagues[62] showed that administration of PBZ increased osteocalcin levels in synovial fluid in healthy equine joints, but found no effects on biomarkers of both collagen and proteoglycan metabolism. PBZ has a narrower safety margin than most other equine NSAIDs and may have severe toxic side effects when recommended dosages are exceeded and/or in susceptible animals (which include geriatric horses, ponies, foals, and those with vascular, renal, or hepatic compromise[63]). These adverse effects include gastrointestinal ulceration, renal papillary necrosis, and thrombosis and are potentially lethal.

Flunixin has found its widest application in equine practice in the treatment of abdominal pain. It is, however, also effective for the alleviation of lameness[64] and was shown to be equally efficacious to PBZ in horses with navicular disease[58] and to provide longer postoperative analgesia.[57] Flunixin suppresses induced PGE_2 production by synovial membrane in vitro without detrimental effects on function or viability of the tissue,[65] but has been shown to increase IL-6 production by synoviocytes, albeit at very high doses.[48] Other possible effects of the drug on joint homeostasis have not been investigated. Flunixin is generally administered at a dose of 1.1 mg/kg once a day orally or intravenously (IV). Toxicity is low, with adverse effects only becoming apparent at 5 times the recommended daily dose.[66]

Carprofen was shown to be a relatively potent analgesic in horses, with duration of postoperative analgesia intermediate between that of flunixin and PBZ.[57] It is administered at a dose of 0.7 mg/kg IV or 1.4 mg/kg orally in countries where the oral dosage form carries market authorization for horses. Several in vitro studies have focused on the potential influence of the drug on joint homeostasis and indicated possible positive effects. Carprofen, which exists as 2 enantiomers, attenuated lipopolysaccharide (LPS)-induced IL-6 increase in cultured synoviocytes and the S enantiomer did the same in chondrocytes.[67] Also, (S-)carprofen stimulated proteoglycan synthesis in chondrocytes[68] and in cartilage explants.[69] Carprofen is considered a safe NSAID but has a relatively narrow therapeutic index, with adverse effects developing at twice the recommended dose.[70] Because of its potential beneficial effects on articular tissues, it has been suggested that carprofen could become a future NSAID of choice in OA,[51] but thus far the drug has not really challenged the position of PBZ and data on tissue effects in vivo are lacking.

Ketoprofen has been shown to accumulate in inflamed tissues, which has been suggested to result in improved efficacy in inflamed joints[71]; given that most NSAIDs are weak acids, accumulation in an inflamed environment should however not be unique to ketoprofen. In a direct comparison with PBZ in induced synovitis, the drug was found to be inferior to PBZ in treating acute joint inflammation,[56] although it proved equally effective at alleviating hoof pain.[72] The recommended dosage of ketoprofen is 2.2 mg/kg IV once a day. Ketoprofen is a relatively safe NSAID[73] but the main disadvantage of the drug precluding its routine use in chronic joint disease is that it is not orally bioavailable, restricting routes of administration to either intramuscular (IM) or IV.

This restriction does not apply to the related drug vedaprofen that has been registered for oral use (initial dosage 2 mg/kg twice a day, maintenance 1 mg/kg twice a day) in several countries. Vedaprofen seems to have more affinity for COX-1 than COX-2.[74] Nothing is known about its effects on the primary process of OA or about its efficacy against musculoskeletal pain in general. On clinical impression it has been suggested that the analgesic efficacy of vedaprofen for orthopedic pain compares unfavorably with that of PBZ, which may be because of its relatively short-lived reduction of PGE_2,[74] but no well-designed comparative clinical efficacy

studies have been performed. In countries where the use of PBZ is either illegal or restricted, however, meloxicam rather than vedaprofen seems to have become the preferred oral NSAID for orthopedic diseases.

Meloxicam (orally dosed at 0.6 mg/kg once a day) was shown to be a potent anti-inflammatory and analgesic drug in an equine arthritis model.[75] Meloxicam was also shown to be the most selective COX-2 inhibitor of 4 examined NSAIDs (with PBZ, flunixin, and carprofen) when tested in vitro at the level of 50% inhibition (IC50), although at 80% inhibition, COX-2 selectivity was relatively less, whereas that of other NSAIDs increased.[76] Meloxicam is the only NSAID for which data exist regarding the in vivo effects of treatment on cartilage metabolism over the course of acute synovitis. In an LPS-induced arthritis model, De Grauw and colleagues[49] demonstrated a significant clinical effect on lameness and a local anti-inflammatory effect in the joint, as evidenced by suppression of PGE_2, bradykinin, and substance P release in the synovial fluid of the affected joints. Interestingly, matrix metalloproteinase (MMP) activity in synovial fluid was also lower than in placebo-treated joints, as were markers of proteoglycan breakdown and collagen II turnover. This indicated that meloxicam was able to mitigate the catabolic effects of acute joint inflammation on articular cartilage, although it remains to be established whether this also translates into chondroprotection in the longer term.

Naproxen does not seem to find wide application for use in equine musculoskeletal pain given the virtual absence of the drug in samples taken from track fatalities in a recent study, which was in contrast to PBZ and, to a lesser extent, flunixin.[77] Efficacy for treating equine OA has not been compared with other more commonly used drugs; therefore, no reliable data are known.[51] However, naproxen did prove more potent than PBZ in an equine myositis model.[78] Naproxen is administered orally or IV at a dosage of 10 mg/kg twice or once a day and has a wide safety margin.

Other systemic treatments

Horses suffering from OA or other chronic joint disorders are frequently orally treated with so-called "neutraceuticals," which are supposed to have a disease-modifying effect and in most cases contain, among other ingredients, mixtures of chondroitin sulfate and glucosamine. There has been (and still is) much controversy about the potential usefulness and mechanisms of action of these products in horses (for reviews see Trumble,[79] Goodrich and Nixon,[51] and Richardson and Loinaz[80]). Although some of the proposed modes of action include some level of anti-inflammatory activity, implying an indirect analgesic effect, these drugs are not primarily given to alleviate pain and will not be discussed further here.

Tiludronate is a bis-phosphonate that has been reported to be effective in cases of navicular disease or bone spavin characterized by osteolytic lesions.[81] Although tiludronate is not a primary analgesic agent, it was found to be effective against pain caused by osteoarthritic lesions of the thoracolumbar vertebral column.[82] There are no reports on its effects on OA in the appendicular skeleton.

Other systemic treatments for OA in horses include IM polysulfated glycosaminoglycans (PSGAG) and IV or oral sodium hyaluronate (HA). Various modes of action of each of these drugs have been identified in vitro, but precisely which of these contribute(s) most to clinical effects remains to be established. Intramuscular PSGAG was shown to reduce lameness (and hence pain) as well as effusion in an equine carpitis model,[83] but in 2 other in vivo studies using a carpal chip–induced OA model, no clinical (analgesic) benefit and no disease-modifying effect on any of the joint tissues were detected.[84,85]

Hyaluronan (HA; sodium hyaluronate) is available for systemic use in an IV formulation and in some countries also as an oral gel. The in vivo mode of action of intravenous HA on joint pain is thought to be mainly anti-inflammatory, although the way this effect comes about remains uncertain given the very rapid clearance of exogenous HA from the systemic circulation (terminal half-life after IV administration in horses of 43 minutes[86]). Interestingly, HA has been shown to have a direct analgesic effect through interaction with peripheral nerve endings in joints,[87] which could contribute to observed analgesic effects in horses.[88]

LOCAL TREATMENT OF JOINT PAIN

Topical therapies for joint pain in the vast majority of cases comprise IA injection of corticosteroids (for an overview of most commonly used drugs and dosages see **Table 2**). The principal aims of corticosteroid use are attenuation of inflammation and pain relief (ie, mitigation of symptoms). The corticosteroids are discussed to some extent in the following section. In addition, there are a few other intra-articularly applied pharmaceuticals that principally target the primary process of OA, but may have some effect on pain perception and these are also mentioned briefly.

Corticosteroids

Intra-articular corticosteroids were first used in human medicine in the early 1950s.[89] Application in veterinary practice soon followed suit.[90] Corticosteroids inhibit the nuclear factor (NF)-κB signaling pathway, which plays an important role in the sequence of events leading to inflammatory mediator production, thereby acting as a potent upstream inhibitor of inflammation.[91,92] They are known to regulate gene expression levels of not only inflammatory but also matrix genes (eg, collagen type II and aggrecan gene expression) and hence can also affect cartilage turnover and repair.[93]

Corticosteroids inhibit inflammatory mediator production by inhibiting phospholipase A_2 through the production of anti-phospholipase proteins called lipocortins.[94] Because of their mode of action upstream in the arachidonic acid cascade, corticosteroids not only inhibit COX-1/2 derived mediators (including prostaglandins, thromboxanes, and lipoxins), but also the LOX-derived mediators like leukotrienes.

It should be realized that corticosteroids are primarily potent anti-inflammatory agents, exerting their analgesic action indirectly via the suppression of inflammation.

Table 2
Overview of the most commonly used corticosteroids for intra-articular use

Name of Drug	Duration of Action	Dosage	Remarks
Methylprednisolone acetate	Long	40–100 mg	The lower end of the dosage range is recommended for an optimal effect while avoiding damage at a longer term
Bethamethasone acetate	Medium to long	3–18 mg	
Triamcinolone acetonide	Medium	6–18 mg	Most commonly used

In case of a combination of a corticosteroid and hyaluronic acid (HA), the former is commonly used at its normal dosage and HA often at approximately 20 mg/joint (but there are relatively large differences in molecular weight and purity among commercially available HA preparations and recommendations by the manufacturer may differ).

They are not specific analgesics. This explains the differences in analgesic efficacy in various joint disorders. Corticosteroids have been found to be most effective in those conditions where inflammation is the most important hallmark of the joint disorder, such as RA and juvenile idiopathic arthritis in humans.[95] In conditions like OA, where inflammation is less prominent and tissue degradation is at the forefront, they provide less effective pain relief. In humans, corticosteroid use in knee OA produced temporary pain relief for 3 weeks only; in RA this was much longer.[96]

Although first hailed as a more or less magic class of drugs in joint disease, corticosteroid use became controversial after reports on steroid-induced deterioration of articular tissues, which soon became known as "steroid arthropathy."[97,98] The issue has led to decades of debate about the suitability and even the ethical acceptability of IA corticosteroid use in horses, but seems to have settled down in recent years as a result of dedicated research and the publication of more long-term clinical data. In human medicine, IA use of corticosteroids is common practice for many conditions, including RA, juvenile idiopathic arthritis, and OA.[95] Multiple injections of 40 mg of triamcinolone into the knee joint at 3-month intervals for a period of 2 years did not lead to loss of joint space over time[99]; however, frequent repetition of IA injections with corticosteroids (up to 20 injections with half-week intervals) may lead to deleterious effects.[100] In horses, studies that showed negative matrix effects of corticosteroids have generally tended to use relatively high, repeated doses, and/or looked at effects in healthy joints. In a joint with preexistent synovitis, inflammatory gene expression is upregulated and catabolic enzyme activity increased, and the positive inhibitory effects of corticosteroids on these processes exceed the potential negative effects on cartilage matrix.[101,102] There now seems to be common agreement that, if used judiciously with respect to frequency and interval and not excessively dosed, the beneficial effects of IA corticosteroids in joint disease outweigh the disadvantages and possible risks.[51]

Other potential risks of corticosteroid use include an increased risk of joint infection and masking of signs thereof because of the immunosuppressive action of corticosteroids, and occurrence of so-called "flare," a transient but occasionally severe aseptic synovitis. The perceived risk of joint infection is low. A rate of 1:25,000 has been reported in humans.[103] Although the risk is low, the potential consequences of joint infection in the horse may be devastating and strict asepsis is imperative when performing the arthrocentesis. The routine use of antibiotics as practiced by many can be questioned, but is understandable when conditions are less than optimal. Joint flare after IA injection is seen in approximately 2% of cases in human medicine.[104] In the horse, the condition is known too. It is self-limiting, but may require treatment with NSAIDs.

There are several types of corticosteroids that are used in equine practice. They differ mainly in duration of action. Most commonly used are methylprednisolone acetate, betamethasone, and triamcinolone, which are discussed briefly in the following paragraphs.

Methylprednisolone acetate (MPA) is a long-acting corticosteroid with a recommended dose of 40 to 100 mg per joint. However, it is advised to aim for the lower end of this dose range. Doses between 10 and 40 mg have been shown to have a clear anti-inflammatory effect while preserving the normal joint environment.[105,106]

Betamethasone acetate is a medium- to long-acting corticosteroid. It has been used in equine medicine for more than 40 years.[107] The advised dose is 3 to 18 mg per joint. The drug did not have deleterious effects 7 weeks after application in both exercised and unexercised horses in an osteochondral chip model.[108] However, in vitro work showed suppression of proteoglycan synthesis at low to medium doses.[60]

Triamcinolone acetonide is probably the most widely used corticosteroid in equine orthopedics. It has a medium duration of action and was shown to have potent analgesic action in an LPS-induced lameness model in the horse.[109] In vitro studies have indicated that triamcinolone may potentially effectively suppress inflammation without negative effects on the transcription of extracellular matrix genes[110]; work by Frisbie and colleagues[111] even suggested minimization of OA development in an osteochondral chip model. However, as with all corticosteroids, the potential for unintentional alteration of cartilage metabolism is also present with triamcinolone, as evidenced by changes in SF biomarkers in healthy horses after 3 consecutive IA injections with 2-week intervals.[112]

Opioids

Opioids, of which morphine is most widely used for medical purposes, are analgesic drugs par excellence. The IA use of morphine was introduced for postoperative analgesia after arthroscopic knee surgery in human medicine in the early 1990s.[113] Morphine produces analgesia in joints by the interaction with opioid receptors in the synovial membrane, which are upregulated in inflammation. The efficacy of the treatment is not uncontested. An initial meta-analysis of results from multiple clinical trials showed that intra-articularly administered morphine had a definite but small analgesic effect,[114] but a more recent one did not corroborate this.[115] In veterinary medicine, the technique has been adopted quite quickly in small animal practice,[116] but only recently has work been published in the horse. Santos and colleagues[117] compared the effect of IA morphine in horses with experimentally induced synovitis with the local anesthetic ropivacaine and found the analgesic effect of morphine to have a slower onset, but also to be stronger and longer lasting (up to 24 hours). The effects of IA morphine in an LPS-induced synovitis model were also studied recently by Lindegaard and colleagues[118,119] and Van Loon and colleagues[47]; the latter showed a significant effect of IA morphine on lameness, joint effusion, behavioral expression of pain, and on SF inflammatory mediators (PGE_2 and bradykinin). Interestingly, morphine had no effect on biomarkers of cartilage metabolism (De Grauw and colleagues, unpublished results, 2009) or on substance P release. Although IA morphine has been suggested as an alternative treatment for chronic joint pain in humans,[120,121] it is unlikely that the drug will be used in the horse for this purpose because of its relatively short duration of action as well as regulatory issues associated with opiate usage.

Hyaluronic Acid

Hyaluronic acid (HA), also called hyaluronan, is a large unsulphated glycosaminoglycan that consists of repeating units of D-gluronic acid and N-acetylglucosamine. It has been used extensively as IA treatment in horses (for a review, see Caron[122]) initially mainly as visco-supplementation, but later more on the basis of its anti-inflammatory capacities that seem to be more crucial to clinical efficacy.[51] Although HA is supposed to positively affect the primary disease process and its principal use is not to provide analgesia, as is the case with corticosteroids or NSAIDs, HA reportedly also has some analgesic effect itself.[123] In humans there are various reports on the analgesic effects of HA in OA but publication bias and flaws in experimental design may have overestimated the beneficial effects in many studies. A meta-analysis showed only a relatively small positive effect of HA application compared with placebo.[124] In the horse, there are various studies reporting reduction of lameness following IA HA treatment, but many of these suffer from flaws in the experimental design, such as lack of description of randomization and blinding, and absence of a control group or use of an inappropriate control group, which may have affected the trustworthiness of the results.[80] A well-controlled

study comparing the effects of IA polysulphated glycosaminoglycans and IA HA in an osteochondral chip model showed positive effects of HA at the tissue level, but failed to substantiate any clinical effect.[84]

The combination of IA corticosteroids and HA is popular in equine practice, as it permits the reduction of the dose of corticosteroids and, at least intuitively, may counteract the possible deleterious effects of these drugs on the cartilage either through such dose reduction and/or through a possible "chondroprotective" action of HA.[122] Unfortunately, no controlled trials have been reported to date that compare the clinical (analgesic) efficacy and cartilage matrix effects of IA HA, IA steroids, and IA steroid plus HA. Although it can indeed be assumed that the combination will have a substantial analgesic effect, in vitro studies so far have not provided support for the premise that HA might counteract potentially negative steroid effects on the articular cartilage.[125,126]

Other Local Treatments

Topical administration of NSAIDs to specific joints has been investigated in horses, but has not found widespread application in practice thus far, probably because of the convenience of oral administration in practical circumstances. Iontophoric administration of ketoprofen to the middle carpal joint of sound horses has been tried, but was found to have far insufficient delivery efficiency.[127] A study investigating topical application of the NSAID diclofenac in a liposomal cream formulation in an equine-induced OA model was more successful, showing a significant reduction of lameness scores versus untreated controls that was comparable with that produced by PBZ.[55] Interestingly though, diclofenac was detected in the joint fluid only at concentrations far below that needed for effective COX-inhibition, and indeed did not reduce synovial fluid PGE_2 concentration compared with untreated controls, whereas PBZ did. This again highlights the less than simple direct relationship between clinical pain or lameness and SF prostaglandin concentration. Whether the lesser radial carpal bone sclerosis and overall gross cartilage erosion with topical diclofenac versus PBZ was somehow also related to the lack of reduction of SF PGE_2 concentration or was rather because of a COX-independent effect of the cream remained unclear.

Gene therapy has been used in the horse in an experimental setting.[128,129] It proved feasible to elevate expression of the IL-1 receptor antagonist for a prolonged period, thus exerting an anti-inflammatory effect that may indirectly affect pain perception.[128] Although promising and scientifically highly interesting, it cannot be expected that gene therapy will find wide application for alleviation of joint pain in the horse in the foreseeable future.

NONPHARMACEUTICAL WAYS TO MODULATE CHRONIC JOINT PAIN

There are various nonpharmacological ways to influence pain from osteoarthritic joints (for an extensive overview, see Malone[130]). The most radical way is surgical arthrodesis of the affected joint, which eliminates joint motion but consequently also joint pain. For certain joints, particularly the proximal interphalangeal joints and the smaller tarsal joints, this is a viable therapeutic option in the horse, as it does not preclude athletic performance. Performed in other joints such as the metacarpophalangeal, metatarsophalangeal, or carpal joints, arthrodesis usually is a salvage procedure for valuable breeding stock. Most arthrodeses are performed using osteosynthetic techniques,[131,132] but other techniques such as chemical arthrodesis through IA injection of ethyl alcohol[133] have also been described.

A wide variety of complementary therapeutic modalities are available that are of potential utility in the treatment of chronic OA pain in horses. These include, but are

not limited to, physiotherapy, acupuncture, extracorporeal shock wave treatment (ESWT), magnetic field therapy, transcutaneous electric nerve stimulation (TENS), therapeutic ultrasound, and laser therapy.[130] Of these, few have stood (or even have been subjected to) the test of rigorous scientific scrutiny, either in horses or in humans, and much of the "evidence" regarding these therapies is anecdotal at best. Interferential and patterned muscle stimulation has been claimed to be effective in the treatment of pain associated with knee OA in humans,[134] but the overall conclusion with regard to the efficacy of TENS for pain relief in OA is inconclusive, as published trials are small and of questionable quality.[135] In horses, ESWT has been suggested by some to be a viable option for pain relief from OA,[136] but recently it was shown to have no clinical or disease-modifying beneficial effect in a carpal chip model of induced OA,[137] and caution seems warranted as another recent study in rats demonstrated degeneration of articular cartilage caused by ESWT treatment.[138] For most other modalities, no studies that can stand the test of scientific rigor have been performed in horses.

SUMMARY

Pain is the most important clinical hallmark of OA and OA pain management is an important item for the equine practitioner whose caseload on average consists of 67% orthopedic cases, most of them attributable to joint disorders. It is important to repeat here that pain is a symptom generated by the underlying disease process. Pain relief alone may have a favorable (short- to midterm) clinical effect, but could have adverse effects on the underlying disease process and hence on long-term outcome if overall management of the athletic horse is not altered (ie, exercise regimes adjusted accordingly) and/or if analgesia is not combined with other strategies that target the underlying degenerative process. Therefore, any pain treatment that is instituted in patients suffering from OA should be critically evaluated in this context. Progress in pain management in OA will likely come from 2 sources. First, it will stem from research on the disease process itself. The global research effort on human as well as animal OA is tremendous, and rapid progress is being made on both fundamental issues such as the detailed elucidation of pathogenetic mechanisms, and in areas with great therapeutic potential like the exciting field of tissue engineering.[139] Second, progress can be expected in our knowledge of systemic and local nociceptive pathways and pharmacologic modulation thereof. Both sources of progress are related. Knowledge of the molecular events in the pathogenesis of OA will lead to the identification of novel targets for pain therapy, which may include key receptors, ion channels, and neurotrophins.[140]

Progress can be expected to be most rapid in human medicine, given the huge research effort and research funding in this field compared with veterinary medicine. However, basic joint biology and pathogenetic mechanisms of common joint disorders such as OA have proven to be highly conserved among mammalian species and there is no doubt that pain control in the equine orthopedic patient will directly benefit from the research performed on behalf of its human counterpart.

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