OsteoArthritis and Devils Claw

Osteoarthritis (OA) is a common disorder of the joints with the principal underlying process being that of cartilage degradation (Hough, 1997, p1945). There is a general consensus (Beers and Berkow 1999, p449; Kumar and Clark, 1999, p446; Souhami and Moxham 1998, p941, Woolf 1998, p1072) that microscopical changes within the cartilage leads to its deterioration and ability to absorb load and so subsequently OA can be thought of as a physiological disorder. Symptoms and signs

In the early stages these are; pain, due to over vigorous exercise and morning stiffness, due to a long periods of inactivity. As OA progresses a creaking sound in the joint known as creptius can be heard and felt. Joint deformity can be seen by x-ray. Inflammation comes with the usual signs of redness, heat, pain and swelling and is most commonly found in the interphalangeal joints. Instability occurs and in advanced cases there is a loss of function (Beers and Berkow, 1999, p450; Kumar and Clark, 1999, p468, Souhami and Moxham,1998, p492; Woolf, 1998, p1074)

Pathophysiology

When healthy cartilage becomes compressed due to load bearing, fluid is pumped out of the cartilage into the joint space. It then flows into the capillaries and venules. As the joint decompresses the fluid returns back to the cartilage, allowing it to re-expand, re-hydrate and absorb the nutrients it needs (Beers and Berkow 1999, p449).

OA is characterised by fibrillation in the cartilage, which leads to its deterioration. Bone erosion, eburnation and remodelling follows and then the synovium and joint capsule can start to thicken (Stevens and Lowe, 1995, p491;).

In these early stages of OA, chondrocytes undergo mitosis and increase synthesis of proteoglycan and type II collagen, which is the dominant form of collagen in articular cartilage (Woolf 1998, p1071). This causes the cartilage to harden and split. Because of this, the joint space narrows until the two bone surfaces are exposed to each other, causing then to become eburnated. The chondrocytes also stimulate osteoblasts and this causes an increase in subchondral bone formation. However, the new bone is stiffer and has less flexibility leading to micro fractures and the development of calluses. Constant friction causes a thickening of the subchondral bone plate and micro fractures appear here. Osteochondrophytes develop and bony cysts then start to form. Inflammation encourages hyperplasia, which is the cause of the synovium and joint capsule thickening. Atrophy of the muscle can occur due to lack of use of the joint (McGee, Isaacson and Wright, 1992, p2086). Repeated load bearing will also increase proteoglycan synthesis and make cartilage stiffer, but continuous decompression of a joint eventually decreases synthesis and causes necrosis (Arokoski et al, 2000, p186-198). As more and more degradation takes place, the peripheral synovial cells undergo metaplasia leading to the formation of osteochondrophytes (Beers and Berkow 1999, p449 Bony cysts develop as a result of the joint fluid being pushed through the hyaline cartilage in towards the bone

marrow (Beers and Berkow 1999, p449; Mills and Bone, 2000, p248). As OA develops into the later stages, osteochondral bodies provoke the inflammatory response (McGee, Isaacson and Wright, 1992, p2086). The capillaries and venules in the synovium dilate; macrophages and lymphocytes stick to the vessel walls and eventually migrate through the increasingly permeable membrane into the synovium (Brewerton, 1995, p73). The stimulation of inflammatory cytokines within the synovium, most notably Interleukin 1 (IL-1) and Tumour Necrosis Factor (TNF), leads to an increased production of nitric oxide (NO). This occurs because inducible nitric oxide synthases (iNOS), inside chondrocytes, synthesise NO when they come into contact with IL-1 and TNF. Similarly, prostaglandins in the cyclooxygenase (COX) pathway can also be stimulated in this way, COX-2 being the inducible enzyme implicated in inflammation (Clancy, Amin and Abramson, 1998, p1141-1151). It should be noted that these events are really non-specific and are present in numerous chronic inflammatory conditions, not just within joints. Growth factors present within the chondrocytes upregulate iNOS and this leads to increased and continuous amounts of NO and being released. These high and sustained levels help to advance tissue injury by then decreasing synthesis of proteoglycans and typeII collagen, activating metalloproteinases and increasing apoptosis of chondrocytes (Clancy et al, 1998, p1141-1151). Metalloproteinases are enzymes such as stromelysin, collagenase and gelatinase that break down collagen and proteoglycans (Yoshihara et al, 2000, p455-461; Kumar and Clark 1999, p467). Together with the decrease in the synthesis of these molecules, these excessive amounts of NO cause a double assault on the foundations of articular cartilage. Ibuprofen A common treatment for OA is non-steroidal anti-inflammatory drugs (NSAIDS).

Of the many that exist, Ibuprofen is a popular choice as it has fewer side effects than most (Henry, 1994, p302). It has a wide therapeutic index and a low dependency rating (Nishihara and Furst, 1997, p629).

The primary mechanism of ibuprofen is inhibition of cyclooxygenase (COX) in the arachadonic acid cascade. This prevents the conversion of arachadonic acid into prostaglandins, the local hormones partly responsible for inflammation and pain. The result of this is that pain associated with prostaglandins is reduced, fever is moderated and platelet aggregation is decreased. It is now thought that the inhibition of COX 2 enzymes is responsible for the efficacious effects of NSAIDS whereas the inhibition of COX 1 enzymes is responsible for the side effects such as G.I. bleeding and kidney damage. This is because COX 1 enzymes are predominantly found in the vascular endothelial cells, platelets, kidney collecting tubules, stomach and smooth muscles. In contrast, COX 2 enzymes are barely detectable in tissue but they are expressed in high amounts during inflammation (Nishihara and Furst, 1997, p69). Ibuprofen is administered orally in the form of tablets or capsules. It can also be applied topically with cream or gel (Henry, 1994, p302). Ibuprofen is a weak acid with a Pka of 4.4. More than 90% is absorbed from the G.I. tract. Absorption is slowed down by food and this makes the peak concentration lower. It diffuses into the synovial spaces and can remain there after plasma concentration has declined. The half-life of ibuprofen is 2- 2.5 hours if it is taken on a regular basis (Nishihara and Furst, 1997, p629). Devils Claw - Harpagophytum procumbens

Harpagophytum procumbens, also known as 'Devils Claw' is a South African herb. It has been used traditionally as an anti-rheumatic and is predominantly known for this (Hoffman, 1997, p196). Unfortunately, pharmacological and clinical studies on this herb are insufficient. It is similar to pharmaceutical NSAIDS in as much as that it has anti-inflammatory and analgesic properties. The most notable constituents of the herb appear to be harpagoside, procumbide and harpagide. It is possible that harpagide is a breakdown product of harpagoside (Bisset, 2001, p 249). Harpagophytum does not inhibit the COX pathway directly (Mills and Bone, 2000, p346). On the other hand, it is capable of inhibiting TNF (Fiebich et al, 2001, p23-30). This is one of the inflammatory cytokines responsible for the stimulation of COX 2 and NO and subsequently inflammation (Clancy et al, 1998, p1141-1151). The anti-inflammatory affect varies with the route of administration and is thought to be most relevant in sub-acute cases. Harpagoside appears to work synergistically with other constituents to convey peripheral analgesia (Bisset, 2001, p249). A harpagophytum extract containing harpagoside has shown to be effective in relieving mild pain (Chrubasik et al, 1999, p118-129).

Harpagophytum is administered orally. Little is known of the pharmacokinetics and pharmacodynamics. However, it is speculated that the anti-inflammatory properties of the herb may be diminished by the high acidic content of the stomach. If this is the case, Devils Claw is best administered between meals when stomach activity is at its lowest (Mills and Bone, 2000, p347)).

Conclusion

Although Ibuprofen is a relatively safe and efficacious drug it can still cause gastric disturbances (Henry, 1994, p302) and is now known to cause heart disease when used on a long term basis. Consequently, NSAIDS will probably be a better option when they are specifically inhibiting COX 2 enzymes. Harpagophytum is a gentle herb that appears to be efficacious for mild pain and inflammation but it does not seem to work for every case of arthritis (Hoffman, 1996, p196). Interestingly enough it is capable of inhibiting TNF. This cytokine stimulates COX 2 and iNOS, the enzymes that provoke inflammation. No literature can be found on Harpagophytum that states it inhibits COX 1. But Harpagophytum does not appear to have any of the side effects that trouble pharmaceutical NSAIDS.

Research into finding out whether Harpagophytum does inhibit COX 1 is necessary. If it does not, it is well worth considering that Harpagophytum procumbens could provide a basis for the development of the COX 2 inhibitor NSAIDS.