The treatment of osteoarthritis

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- 1 The treatment of osteoarthritis is currently purely symptomatic. To enable rational therapy, careful clinical assessment is necessary to identify the origin of symptoms. Often, effective therapy can result from a biomechanical approach such as surgery, orthotics, physiotherapy and dieting. If drugs are required, there is little evidence that the current over-reliance on non-steroidal anti-inflammatory drugs (NSAIDs) is justified. Full dose regular paracetamol should be the first line of analgesic therapy. In the majority of patients, simple analgesics are probably as effective as NSAIDs. If NSAIDs are used it is necessary to review regularly their use and to be aware of potential toxicity.
- 2 Many alternative strategies of pain management such as topical preparations, intra-articular steroid injections, acupuncture, radiosynovectomy, transcutaneous nerve stimulation and anti-depressants, may be effective but their precise place in the armamentarium is not yet fully established.
- 3 The realisation that osteoarthritis is not a passive 'wear and tear' phenomenon but an active process that may be potentially modified, has led to interest in 'chondroprotective' agents, which may beneficially affect the osteoarthritic process. To date there are no convincing data available that such agents are, in fact, chondroprotective in humans.

Keywords osteoarthritis treatment chondroprotection analgesics non-steroidal antiinflammatory drugs

Introduction

Osteoarthritis (OA) is the commonest affliction of synovial joints (Office of Population Censuses and Surveys, 1983) with structural (radiological) joint changes of OA, (Figure 1), present in approximately half of the adult population (Felson *et al.*, 1990; Lawrence *et al.*, 1966). However symptoms are present in a smaller proportion depending on the joint involved (Bagge *et al.*, 1991; Felson *et al.*, 1990; Lawrence *et al.*, 1966). Structural OA may thus be regarded as either symptomatic or asymptomatic and optimal treatment requires identification as to which of many possible mechanisms are responsible for producing symptoms (Figure 2).

The realisation that OA is not simply a passive 'wear and tear' phenomenon but an active process, that has been phylogenetically preserved (Hutton, 1987), and which can be associated with good functional outcome (Mejersjo, 1987; Patrick *et al.*, 1989), has produced the concept of OA as a 'process' rather than a 'disease', representing the normal reparative response to joint insult (Radin & Burr, 1984). Consequently there exists the possibility of manipulating this process towards a favourable outcome. This underlies recent interest in

'chondroprotective' agents (CPAs), which may maintain cartilage and thus possibly, joint function.

Assessment of response to treatment involves three components. Firstly the patient's desire is for symptom relief and thus his/her self-assessment of response is paramount. Secondly there is a need to maintain or improve function: a variety of 'instruments', (predominantly questionnaires), are now available to assess this aspect. Thirdly, if the OA process can be modified, then a sensitive, objective measure of response is required. Currently this involves long-term estimation of gross structural change, but ultimately more sensitive measures of structural change (e.g. microfocal radiography (Buckland-Wright *et al.*, 1990)) or biochemical markers of physiological change (e.g. keratan sulphate (Thonar *et al.*, 1985)) may prove relevant.

Mechanisms of symptoms in OA

The source of symptoms in OA is often unclear and may be multifactorial (Figure 2) (Kantor, 1989; Merritt,

Figure 1 The morphological changes that occur in the osteoarthritic joint.

Figure 2 Possible sources of symptoms in osteoarthritis.

1989). Elucidating those that are important in an individual patient should enable targeted therapy. The usual symptom for which the patient seeks relief is pain. Cartilage is avascular and aneural and it is unlikely that symptoms arise directly from its destruction. However there are associated changes in other joint tissues which may be symptomatic. Alterations in cartilage matrix

may promote crystal formation and shedding, resulting in episodes of inflammation. Pain may be further modulated by the brain and spinal cord (Kantor, 1989; Merritt, 1989).

Other symptoms, e.g. stiffness or loss of function, must also be addressed but their underlying mechanisms are poorly understood. They may however include capsular fibrosis, tendon contracture, muscle atrophy, muscle inhibition and reduced fitness.

Assessment of the OA patient is primarily clinical. Although it has been suggested that the nature of the pain may be of help, i.e. nocturnal pain representing intraosseous hypertension, in practice this is rarely of assistance. Duration is an important consideration since recent deterioration merits consideration of superimposed pathology, e.g. sepsis or avascular necrosis. A marked inflammatory component is suggested by symptoms of prolonged early morning and inactivity stiffness, and signs of warmth, effusion and 'stress' pain. The examination is also directed to determining the precise site of maximal tenderness, eg joint line (probably synovitis) or periarticular. Multiple periarticular and muscular tender sites should prompt consideration of the fibromyalgia syndrome (Goldenberg, 1987) particularly if associated with sleep disturbance. Finally consideration should be made of the patient's affect since this may be as important as structural damage in influencing the degree of disability and pain experienced by the patient.

Biomechanics

Symptoms arising from adverse biomechanical factors, (e.g. obesity, malalignment, instability) are best treated biomechanically, utilising the expertise of the dietician, physiotherapist, occupational therapist, orthotist and surgeon. It is important to identify such factors since appropriate therapy is often effective and probably less hazardous than inappropriate medication.

Analgesia

The optimal management of pain in OA requires identification of its source (Figure 2). For example, much pain in OA appears to be periarticular and appropriate local measures, e.g. periarticular steroid injections, may be effective. If analgesia is required, paracetamol should be used at maximum dosage before progressing to non-steroidal anti-inflammatory drugs (NSAIDs). Nefopam, codeine phosphate, dihydrocodeine or combination preparations (e.g. coproxamol) are often used though any increase in efficacy may be offset by greater toxicity (Kjaersgaard-Andersen *et al.*, 1990; Parr *et al.*, 1985; Stamp *et al.*, 1989). Indeed evidence for improved efficacy in OA over paracetamol is scanty (Brooks *et al.*, 1982; Kjaersgaard-Andersen *et al.*, 1990). Stronger opioids should not be used; uncontrolled pain requires re-evaluation or an alternative approach such as a regional nerve block (Pybus, 1987) or surgery.

Local heat, such as provided by rubifacients, may be beneficial. Similarly acupuncture, and transcutaneous nerve stimulation (Lewis & Lewis, 1985) may be beneficial, though convincing evidence for either is sparse. All may act by modulating pain 'gating' (Wall, 1984) (Figure 2).

Depression is often a feature of chronic pain (Gershon, 1986) and in addition many anti-depressants have analgesic properties (Gershon, 1986). Surprisingly little is known of the incidence of depression and anxiety in OA (Summers *et al.*, 1988) nor of the efficacy of anti-depressants.

Non-steroidal anti inflammatory drugs

NSAIDs are widely used, but although inflammation may be a feature of OA (Altman & Gray, 1985; Huskisson *et al.*, 1979), there is little evidence that NSAIDs are acting other than as analgesics. Their superiority over simple analgesics is poorly documented (Doyle *et al.*, 1981; Parr *et al.*, 1985). A recent large, double-blind, placebo-controlled study of paracetamol (4 g daily) vs ibuprofen at either analgesic (1.2 g daily) or antiinflammatory (2.4 g daily) doses, failed to demonstrate any increased benefit from the NSAID (Bradley *et al.*, 1991).

However NSAIDs are responsible for 25% of all 'yellow card' reports (Committee for the Safety of Medicines, 1986). Whilst individuals are at low risk, the total associated morbidity and mortality from NSAIDs is high (Bloom 1988; Somerville *et al.*, 1986). Furthermore NSAIDs may not always be used appropriately (Jones *et al.*, 1992; Steele *et al.*, 1987); careful,

regular re-evaluation of use is required by both prescriber and patient.

For the minority in whom NSAIDs cannot be substituted by simple analgesics (Bradley *et al.*, 1991; Dieppe *et al.*, 1990; Jones *et al.*, 1992) it would seem wise, particularly in elderly females who may be at increased risk (Blackshear *et al.*, 1985; Somerville *et al.*, 1986), to monitor for adverse effects (Blackshear *et al.*, 1985; Paulus, 1985). Although such monitoring has been widely recommended both by manufacturers and others (Blackshear *et al.*, 1985; Paulus, 1985), the optimum method has not been specified.

Ideally, since acute deterioration in renal and hepatic function may occur in patients recently commenced on NSAIDs (Blackshear *et al.*, 1985), renal and liver function should be measured prior to, and 2–4 weeks after, starting the drug. Iron deficiency anaemia may result without evidence of overt gastrointestinal bleeding and six monthly full blood count might be appropriate.

Differences in the safety profiles of different NSAIDs have yet to be established (Carson *et al.*, 1987; Caruso & Biandu Porro, 1980; Coles *et al.*, 1983; Committee for the Safety of Medicines, 1986; Griffin *et al.*, 1991; Paulus, 1985). There are many methodological difficulties including: the difficulty of establishing equipotent doses; self-selection of patients in non-randomised surveys; and bias in retrospective surveys. Since NSAIDs are given for symptom relief only, the smallest dose that provides this should be used.

Alternative methods of administering NSAIDs have been developed in an attempt to reduce side effects, particularly gastropathy. However adverse effects on the stomach result primarily from systemic absorption, and a reduction in clinically important adverse effects from rectal administration, pro-drugs, enteric-coating or the use of prophylaxis is uncertain (Caruso *et al.*, 1985). Transcutaneous administration may however produce equivalent symptomatic relief to oral preparations (Doogan, 1989; Golden, 1978; Shamzad *et al.*, 1986) but whether they are more effective than simple rubifacients is unclear.

Other approaches to inflammation

Intra-articular steroid injections are simple to administer and safe; the incidence of the main feared side-effect, sepsis, is estimated at only 1:14000–50000 injections (Gray *et al.*, 1981). Intra-articular steroids undoubtedly provide symptomatic relief, but this is transient and there is a significant 'placebo' response (Dieppe *et al.*, 1980; Friedman & Moore, 1980). Longer acting preparations (e.g. triamcinolone hexacetonide) are more effective (Valtonen, 1981) and it may be that different joints show different responses to steroids (Flanagan *et al.*, 1988; Mayer, 1970). In spite of fears to the contrary, repeated injections do not appear harmful (Keagy & Keim, 1967). Indeed animal work suggests that corticosteroids may even be chondroprotective (Pelletier & Martel-Pelletier, 1989). However the role of intra-articular steroids in OA remains controversial (Gray *et al.*, 1981; MacAlindon & Dieppe, 1990).

Hypoxic reperfusion injury may be a mechanism whereby damage occurs in inflamed joints (Blake *et al.*, 1989). Intra-articular orgotein, a bovine super-oxide

dismutase, could theoretically limit this damage. A placebo-controlled, double-blind study of 139 inflammatory OA knee patients demonstrated that those who received orgotein were less likely to withdraw during the study and had statistically significant improvement in all parameters (McIlwain *et al.*, 1989). A less immediate but more sustained symptomatic relief has been demonstrated with orgotein compared with intraarticular injections of either methyl-prednisolone (Gammer & Broback, 1984) or betamethasone (Mazieres *et al.*, 1991). These early results do suggest that orgotein is superior to both saline and steroid injections though whether this will prove to be an acceptable form of treatment for significant numbers of patients, in particular for those without inflammatory symptoms, remains to be demonstrated.

Radio-synovectomy with external-beam therapy (Gibson *et al.*, 1973) or intra-articular yttrium (Doherty & Dieppe, 1981) may be beneficial, but its role is unclear. The published length of follow-up is too short to eliminate potential long-term adverse effects on the OA process.

Chondroprotective agent

It has long been suggested that NSAIDs may hasten joint destruction (Coke, 1967). However since first described the existence of 'Indocid' or 'analgesic' hip as a specific entity has been doubted (Coke, 1967): identical, rapidly progressive changes can certainly be observed in patients not taking NSAIDs (Doherty *et al.*, 1986). Although two studies have demonstrated increased NSAID usage in patients with accelerated hip destruction (Newman & Ling, 1985; Ronningen & Langeland, 1979) their retrospective nature makes accurate interpretation difficult. A 2-year prospective, placebo-controlled study of 89 patients with knee OA failed to demonstrate increased progression in those taking diclofenac (Dieppe *et al.*, 1990).

In an attempt to determine if there are clinically important differences between NSAIDs, the rate of loss of cartilage and time to operation of patients maintained on either indomethacin or azapropazone was assessed prospectively (Rashad *et al.*, 1989). Although a better outcome in terms of longer time to hip replacement and decreased rate of joint space loss was demonstrated in the azapropazone group, this study is readily criticised, for example, in terms of the method of radiographic assessment, lack of blinding, and imprecise criteria for deciding the time of surgery. Indeed patients on indomethacin had less pain, possibly a more important outcome measure, particularly as all patients ultimately underwent surgery (Mann & Young, 1989). To date there is no good evidence that one NSAID is preferable as regards OA progression.

However, this interest in possible actions of drugs on the OA process has encouraged investigation of the effects of drugs on joint metabolism although there may currently be an overemphasis on cartilage. It should be remembered that agents such as NSAIDs, may also affect other tissues, such as bone. For example, it is well demonstrated that NSAIDs at standard pharmacological doses may inhibit the formation of heterotopic new bone following hip replacement surgery (Ritter & Gioe, 1982).

Extrapolations to the clinical situation are difficult if only single tissues are considered.

Notwithstanding this, much *in vitro* experimental work suggests that NSAIDs and other agents may affect parameters thought to represent the OA process, such as enzymatic activity, cytokine production and cartilage biochemistry (Burkhardt & Ghosh, 1987). The relevance of this to human OA, however, is questionable (Doherty, 1989).

Animal models of OA may be of more value and a number have been used (Burkhardt & Ghosh, 1987; Troyer, 1982). For example various agents which may ameliorate or aggravate the OA process have been used in the Pond-Nuki dog model of OA which involves the response to anterior cruciate ligament section (Pond & Nuki, 1973). These include potential CPAs such as tiaprofenic acid (TA), glycosaminoglycans polysulphate (GAG-PS), glycosaminoglycan-peptide complex (GP-C) and hyaluronic acid. Corticosteroid is also chondroprotective in this model (Pelletier & Martel-Pelletier, 1989), whereas indomethacin and salicylates are deleterious. Although animal models of OA may not be relevant to human OA (Troyer, 1982) they all tend to give broadly similar results for various putative CPAs (Burkhardt & Ghosh, 1987).

Human studies of chondroprotection

Ultimately only long-term studies in humans can demonstrate whether CPAs are beneficial. The many difficulties encountered with such trials relate to problems of long-term compliance, assessment and definition (Altman, 1990). Human OA presents when symptomatic and is diagnosed as OA only when structural change is evident. In animal models the time of onset of the OA process is pre-determined and early or prophylactic treatment can be employed. Meniscectomy results in premature OA in predisposed individuals (Doherty *et al.*, 1982) and this may be one suitable human model in which to assess CPAs. Alternatively patients with OA at one site may, in the relative short-term, develop OA in other sites (Massardo *et al.*, 1989) and this rate of acquisition of new sites might be a useful marker of chondroprotection (Dieppe, 1990). In spite of all the difficulties a number of attempts to study CPAs have been made.

Glycosaminoglycans polysulphate

This is an artificially polysulphated extract of bovine trachea and lung which can be given intra-muscularly, intra-articularly or peri-articularly. Its mechanism of action is largely unknown though laboratory data suggest it stimulates synthesis of a large number of cartilage matrix molecules as well as inhibiting a broad spectrum of degradative enzymes. There is evidence in humans that GAG-PS is readily absorbed into synovial fluid following intra-muscular injection and indeed may be concentrated by damaged or inflamed cartilage to which it may bind (for review see Burkhardt & Ghosh, 1987).

The clinical use of this agent has been reviewed

(Rejholec, 1987) but although there are many open studies of its use, blinded controlled studies are less frequent. Several placebo-controlled, double-blind studies have demonstrated symptomatic benefit from GAG-PS in OA (Anderson, 1982; Kerzberg *et al.*, 1987; Pastinen *et al.*, 1988; Siegmeth & Radi, 1983) although there has been an exception (Chamchan *et al.*, 1989). The basis of any improvements seen in these short-term studies, the longest was one year, is unclear; none provide evidence of chondroprotection.

However one long-term (5 year), single-blind placebo-controlled study has suggested both symptomatic improvement and more importantly a slowing of joint destruction (chondroprotection) in patients treated with GAG-PS (Rejholec, 1987).

Glycosaminoglycan-peptide complex

GP-C is a complex derived from bovine cartilage and bone marrow which has potential chondroprotective activity (Burkhardt & Ghosh, 1987). Its use in humans, as an intra-muscular injection has been reviewed (Rejholec, 1987). Again its method of action is largely unknown, though like GAG-PS it appears to inhibit both catabolic enzyme degradation and promote cartilage matrix synthesis (see Burkhardt & Ghosh, 1987). Its complex nature has made isolation of its active components difficult.

As with GAG-PS, although the agent is available in Europe controlled trials of its efficacy are limited. A 2 year single-blind study of intra-muscular GP-C in hip and knee OA demonstrated a symptomatic response to GP-C but no evidence of chondroprotection was provided (Gramajo *et al.*, 1989).

A long-term (13 year) study of GP-C in patients with hip OA has demonstrated both symptomatic benefit and a slowing of radiographic progression (Rejholec, 1987). Similar results were obtained in a 5-year, placebo-controlled single-blind study of knee and hip OA patients for both GAG-PS and GP-C (Rejholec, 1987). These studies by Rejholec and co-workers do suggest that both GAG-PS and GP-C have chondroprotective potential in humans. However, the results need to be replicated in other centres and reservations concerning the blinding techniques and radiographic assessments addressed before the drugs can be confirmed as CPAs.

Tiaprofenic acid (TA)

Although much *in vitro* and animal work suggests TA is chondroprotective, human data is lacking. Two small studies demonstrate theoretically beneficial effects of TA on proteoglycans (Reginister *et al.*, 1985) and stromelysin (Vignon *et al.*, 1990), but the clinical relevance of these observations is unclear.

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Diclofenac

Although designed as a feasibility study of placebo-controlled trials in OA, no increase in the rate of radiographic progression was seen in patients treated with diclofenac slow-release 100 mg (Dieppe *et al.*, 1990), compared with those on placebo. However only 51/89 patients completed 2 years therapy, with withdrawals mainly due to toxicity (5 placebo: 6 diclofenac) or lack of efficacy (3 diclofenac: 12 placebo).

Hyaluronic acid

Hyaluronic acid has been suggested to be a CPA but although it may produce symptomatic relief in double-blind, placebo-controlled studies (Dixon *et al.*, 1988; Grecomoro *et al.*, 1987), no evidence of a chondroprotective effect in humans has been demonstrated.

Conclusions

The current therapy of OA depends on a careful approach to eliciting the source of symptoms. This relies on a careful clinical examination to localise tenderness to joint-line or periarticular sites, and to determine if a more widespread soft-tissue pain problem is present. Biomechanical factors, producing periarticular pain or malalignment may respond well to biomechanical treatments. In particular muscle strengthening exercises and weight reduction are often beneficial.

Local periarticular tender sites arising from bursitis or enthesopathy may respond to local corticosteroid injection. More widespread pain resulting in the fibromyalgia syndrome should be approached with regard to improving aerobic fitness and consideration of a trial of antidepressants.

Pain, the predominant symptom should initially be treated by simple analgesics and regular and full dose paracetamol may be sufficient. If there is marked synovitis, local therapy in the form of corticosteroid injections can also be effective and should be considered, though benefit may only be temporary.

NSAIDs should only be used after careful assessment of risk, and consideration of the alternatives. Regular critical reassessments of continued use should be made and repeat prescribing avoided. There is currently little rational basis for preferring particular NSAIDs, but topical administration is attractive.

Antidepressants may have a place in the treatment of chronic pain and CPAs may be important drugs for the future.

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