Drug treatment of osteoarthritis

Drugs used to treat arthritis can be divided into two categories: symptom-modifying and disease-modifying agents (Edmonds et al 1993). In patients with symptomatic osteoarthritis (OA) drug treatment has been hindered by two factors: first, the widespread and often unjustifiable use of symptom-modifying agents designed for patients with rheumatoid arthritis and, secondly, the lack of data to justify the use of putative disease-modifying drugs.

Symptom-modifying agents. The main symptom of osteoarthritis is pain on activity. Many patients also complain of pain at rest and at night, and of stiffness of the affected joints (Dieppe, Cushnaghan and McCarthy 1993). The cause of these symptoms remains obscure. Community-based surveys have shown that many patients with radiological evidence of advanced OA are, nevertheless, symptom-free (Lawrence, Bremner and Bier 1966; Hochberg et al 1989); the joint pathology that defines the condition is not therefore a sufficient explanation for the pain. Possible causes include raised intra-articular or intraosseous pressure, synovitis, capsular disorders and secondary extra-articular lesions (Dieppe and McCrae 1987). Recent studies suggest that psychosocial factors, such as anxiety and depression, are important determinants of the severity of pain (Summers et al 1988; Davis et al 1992).

It is difficult to rationalise the use of symptom-modifying drugs for OA while the pathogenesis of the symptoms remains unknown. Until recently simple analgesics, such as paracetamol, were the only resource but non-steroidal anti-inflammatory drugs (NSAIDs) have now become popular, largely by default (Dieppe, Frankel and Toth 1993a). The use of NSAIDs in OA is a controversial issue (McAlindon and Dieppe 1990; Dieppe et al 1993a). They do provide significant symptomatic benefit when compared with placebo, but it is not clear that they are superior to simple analgesics. A recent study comparing paracetamol with ibuprofen in patients with knee OA failed to show any advantage of the NSAID (Bradley et al 1991). A two-year placebo-

controlled trial of diclofenac, in which the use of paracetamol was permitted for escape analgesia, showed that about 40% of these patients with advanced OA could manage just as well with placebo as with the NSAID (Dieppe et al 1993b). There have, however, been very few studies comparing analgesics with NSAIDs (Dieppe et al 1993a) and no way has been found to identify possible 'NSAID responders'.

The dispute about the use of NSAIDs is not due only to the lack of evidence that they are better than analgesics; there are two other reasons. First, NSAIDs can cause serious side-effects, particularly in elderly women (Greene and Winickoff 1992), and it is the older woman who is most likely to be in need of symptom relief for OA. Secondly, it has been suggested that NSAIDs may cause joint damage (Doherty 1989). Both in vitro and in animal models of OA, NSAIDs have been shown to affect chondrocytes and cartilage although it may be unwise to extrapolate from these experiments to human OA. Human cartilage does not respond to stimuli in the same way as animal cartilage, and the disease processes and drug metabolism of old people with established OA are extremely complex. Retrospective studies of patients with advanced hip OA have suggested that indomethacin may accelerate bone damage (Newman and Ling 1985; Rashad et al 1989), but no well-designed prospective studies of the potential of NSAIDs to modify the disease have been published. Nor is there any justification for claims that some NSAIDs are better than others for patients with OA. If they are used, the simple, safer, cheaper agents should be prescribed.

What alternatives are there? It is clear that education of the patient, the prescription of suitable footwear and walking aids, and physiotherapy and exercise therapy are all valuable and often underused (Dieppe 1993). There are also other drug options. Rubefacients have been popular with patients for many years and the pharmaceutical industry now provides an array of creams, gels, foams and impregnated bandages to apply to painful joints. They work, but just as with the oral NSAIDs, the relative value of an expensive preparation containing a fancy drug, when compared with cheap old favourites, has not yet been established. Capsaicin may be an interesting option for the future. This extract from peppers, which depletes nerve endings of substance P, has shown some promise as a local pain-relieving agent (Deal et al 1991; McCarthy and McCarty 1992). An alternative approach is to consider the use of centrally-acting agents, such as low-dose amitriptyline at night.

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Psychogenic factors are important determinants of pain in OA (Summers et al 1988; Davis et al 1992) and pain amplification (fibromyalgia) is a common complication (Doherty 1993).

Disease-modifying agents. A variety of systemic drugs, such as Arteparon and Rumalon, has been used to treat patients with OA in several European countries for many years. In addition to relieving symptoms, it is claimed that they are 'chondroprotectives'. There is some published evidence to support this (Rezholec 1987) and they are effective in animal models of OA (Ghosh 1988), but there are no long-term trial data to substantiate the claim of chondroprotection in man. Several of these agents have recently been withdrawn from the market.

Intra-articular agents are also available. For example, several derivatives of hyaluronic acid have been injected into OA joints of various animals, including man (Philipps 1989). One study suggested that synovial ablation by the intra-articular injection of radioactive colloids may be of value (Doherty and Dieppe 1981) but more work is needed before the place of these agents in OA can be accepted.

Many other drugs are now available which may have beneficial disease-modifying activity in OA. Protease inhibitors, cytokines and their inhibitors, sulphated glycosaminoglycans, etc, could arrest or slow the progression of the disease and one of the looming challenges is

to design and complete studies to establish the efficacy (or inefficacy) of such agents.

Conclusions. Patients with symptomatic OA should initially be treated without drugs. If pain remains a problem, the physician should look for the reason. Central causes such as depression or fibromyalgia should be considered, as well as local causes, such as secondary periarticular problems. Local drug therapy is safer than using systemic drugs and rubefacients have the advantage of giving the patient control of the treatment. The relative efficacy, however, of the wide variety of preparations, many of which are very expensive, is not known.

Simple analgesics are the first option for oral drug therapy. Paracetamol, or a combination of paracetamol and dextropropoxyphene, are the most commonly used agents. NSAIDs should be avoided, particularly in patients with a high risk of side-effects, such as elderly women, and those with peptic ulceration or reduced renal function. In patients who are not in these high-risk categories NSAIDs are worth trying if symptoms persist in spite of other measures. Indomethacin should probably be avoided, but there is no good evidence to favour any particular NSAID; safety should dominate decisions about their use. It is likely that disease-modifying agents will be available in the future, but there is none of proven value at this time.

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