Leader

‘Chondroprotection’ by non-steroidal anti-inflammatory drugs

The last decade has witnessed increasing interest in the possibility that available non-steroidal anti-inflammatory drugs (NSAIDs) may influence the osteoarthritis process. This interest has been spurred by major advances in cartilage biochemistry,^{1–4} but also by an altered perception of the osteoarthritis process itself. Previously considered a ‘wear and tear’, ‘degenerative’ disease that inevitably leads to joint failure, osteoarthritis is now regarded as a dynamic, metabolically active remodelling process with potential to compensate for a variety of triggering insults.^{5–8} Animal and in vitro studies have shown that this process may be open to therapeutic manipulation,^{9–10} and encouraged by relative success in more inflammatory joint conditions, the search for ‘process modifying’ drugs in osteoarthritis is underway.

There is considerable in vitro evidence that different NSAIDs may variably influence several aspects of cartilage metabolism: for example, synthesis and degradation of proteoglycan and collagen; cytokine mediated cartilage resorption; inhibition or release of neutral proteases; and free radical depolymerisation of hyaluronic acid.^{9–22} In vivo studies of spontaneous or induced animal models of ‘osteoarthritis’ also show detrimental or protective effects on cartilage from different NSAIDs.^{9–13–14–16–19–22} The mechanisms of such actions remain unexplained but appear independent of prostaglandin inhibition.^{9–12} Interestingly, susceptibility to influence by NSAIDs appears greater for osteoarthritic than normal cartilage.²³ This could relate to (a) increased drug delivery from hypervascular synovium and breaching of the calcified zone by subchondral vessels; (b) enhanced drug penetration owing to increased surface area of fissured cartilage and altered charge characteristics; or (c) increased susceptibility of stimulated chondrocytes.^{23–24}

In vitro and in vivo experimental data relating to NSAID effects on cartilage must, of course, be interpreted with caution. For example, reported effects from individual NSAIDs are not always consistent⁹; intersample variability in the same study (even for cartilage from different areas of the same femoral head) may be marked¹¹; appropriate tissue concentrations of NSAID or relevant metabolite are

problematic^{9–19}; the chondrocyte metabolism of non-human cartilage may differ²⁵; and many animal models are of joint injury rather than osteoarthritis, with a different time scale from that in man. Nevertheless, notwithstanding such problems it appears that many NSAIDs have suppressive effects on glycosaminoglycan synthesis and other aspects of cartilage metabolism that may be considered potentially detrimental. Equally, certain NSAIDs, notably tiaprofenic acid, diclofenac, and piroxicam, appear to have no suppressive effect on glycosaminoglycan or proteoglycan biosynthesis at concentrations normally attained in man.^{9–19} In the face of such data what evidence is there for modifying effects (detrimental or beneficial) from NSAIDs in patients with osteoarthritis.

After their widespread introduction it was initially suggested that NSAIDs, particularly indomethacin, might cause *specific* arthropathy (‘analgesic’ or ‘indomethacin hip’) characterised by extensive cartilage and bone attrition, paucity of osteophyte, and apparent retention of joint space.^{26–27} Suggested mechanisms included overuse of compromised joints rendered less painful by NSAIDs (‘iatrogenic Charcot arthropathy’) or direct cartilage and bone toxicity. It is now apparent, however, that such rapidly destructive large joint osteoarthritis is not specific to NSAID users,²⁸ and prominence of pain in affected (mainly elderly female) patients discounts overuse as a plausible mechanism.²⁸ Nevertheless, the possibility that NSAIDs cause direct toxicity to osteoarthritic joints is supported by two studies reporting greater radiographic destructive change in osteoarthritic hips of patients taking indomethacin²⁹ or regular NSAIDs³⁰ than in those receiving no indomethacin or infrequent NSAIDs. Both studies, however, can be criticised in terms of retrospective design, small numbers, questionable radiographic assessment, and lack of control for other factors that may influence progression—for example, pattern of hip osteoarthritis, chondrocalcinosis, or osteoarthritis at other sites.³¹ Different conclusions were reached in a prospective study of osteoarthritis and rheumatoid hips, which implicated obesity (uncontrolled in the previous two studies) but not NSAIDs in rate of femoral head height loss.³² A pathologic

study of resected osteoarthritic femoral heads also found no difference in gross osteoarthritic changes between patients receiving indomethacin, salicylate, or no NSAIDs (Robinson H J Jr, 26th annual meeting of the ORS, Atlanta, Georgia, 1980). Few other clinical studies have addressed the NSAID issue, and to date none has claimed a beneficial modifying effect in osteoarthritis.

Notwithstanding the paucity of clinical evidence, terms such as 'chondroprotection', 'arthroprotection', and 'shielding of cartilage' are increasingly prominent in NSAID marketing publications (advertisements for Naprosyn and Feldene, for example). Even though described and referenced correctly, implicit in the mention of in vitro and animal data in this context is extrapolation of such results to the clinical situation in man. Existing experimental evidence is certainly sufficient to demand investigation of possible beneficial (or detrimental) effects from NSAIDs in patients with osteoarthritis, but we must be careful to guard against too narrow a perspective. Terms such as chondroprotection are unhelpful in reflecting the common, though possibly unwarranted, focused emphasis on cartilage. Yet we know the discordance between radiographic joint damage and symptoms,³³ and that despite gross cartilage loss most osteoarthritic joints (especially in the hand) function normally with minimal or only periodic symptoms.³⁴ Furthermore, a readily demonstrable in vivo effect of several NSAIDs is inhibition of heterotopic new bone following hip replacement^{35, 36}—hardly an effect one would imagine to be of benefit to remodelling osteoarthritic joints. It is apparent, therefore, that though cartilage may be the best understood component, other joint tissues—for example, bone, capsule, ligaments, muscle, may also influence progression of osteoarthritis and be equally amenable to modification (good or bad) by NSAIDs. Clinical studies underway to test whether NSAIDs influence osteoarthritis will need to assess global outcome (symptoms, function, balance between benefit and side effects) before attaching undue importance to changes in isolated features of interest—for example, cartilage thickness. The gold standard for improvement has to be long term symptom and functional outcome rather than individual biochemical or structural characteristics (correlation between these has yet to be determined). While awaiting results of well conducted studies it seems reasonable for pharmaceutical companies to promote NSAIDs for their proved symptom relieving effects but to curb speculation on 'process modification' until the human in vivo data are at hand. If differential process modification is truly demonstrated an exciting possibility is that 'good' and 'bad'

NSAIDs could be used as probes to unravel mechanisms of joint injury and repair, thus extricating us from the confusing situation of having numerous biochemical mechanisms and mediators whose relevance to in vivo human osteoarthritis are uncertain. Results of 'osteoarthritis modifying' trials are therefore eagerly awaited by patients, pharmaceutical companies, and experimenters alike.

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