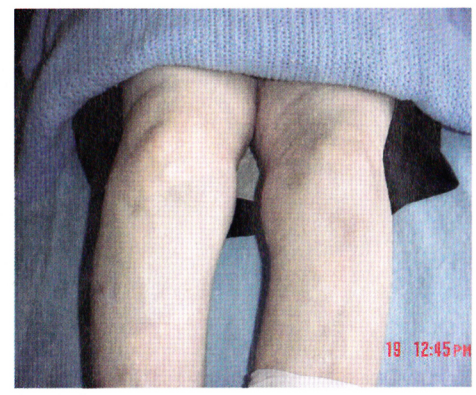
Interest quickens in use of disease modifying drugs for osteoarthritis

Dr Fahim Khan* writes about drugs that may prevent or retard progression of articular cartilage breakdown in OA.



Knees affected by osteoarthritis.

Osteoarthritis can lead to disability.

Osteoarthritis is a disease of an organ (the synovial joint) and not of only a single tissue, such as articular cartilage. In osteoarthritis, all of the tissues of the joint are involved - the subchondral bone, synovium, ligaments, periarticular muscle and articular nerves – not only the cartilage.

For many patients with osteoarthritis (OA), symptomatic treatment with an NSAID or analgesic may achieve some reduction in joint pain but, because of limitations in efficacy, cost and/or side effects, it is by no means satisfactory.

Interest has arisen, therefore, in the possibility of modifying the disease process in OA pharmacologically. Drugs that may prevent or retard progression of articular cartilage breakdown in OA are now receiving increasing attention.

In animal models of osteoarthritis (OA), pharmacological and biological agents have been identified whose primary action is not the reduction of joint pain or inflammation (as with first-line therapy), but which can prevent structural damage in a joint at high risk for developing OA and/or slow the progression of tissue damage in a joint in which OA is already established.

A number of pharmacologic agents have been shown to reduce proteolytic breakdown of articular cartilage and/or to stimulate matrix repair in animal models of OA.

Such agents, which are viewed as potential second-line therapy for OA, have been designated disease-modifying OA drugs (DMOADs).

Disease-modifying OA drugs range from empirical compounds, e.g., tissue extracts, to site-specific collagenase inhibitors designed by structural analysis to fit precisely into the catalytic site of the enzyme.

Most DMOADs decrease articular cartilage levels of matrix metalloproteinases (MMPs) (e.g. collagenase, gelatinase, stromelysin) which have been implicated in damage of the cartilage in OA. Some DMOADs have broad specificity against MMPs, while others have relatively high specificity against one MMP.

Disease Modifying OA Drugs

Doxycycline

Based on prior observations that activities of matrix metalloproteinases (e.g., collagenase, gelatinase or stromelysin) are increased in articular cartilage from humans with OA and from animal models of the disease. Tetracyclines inhibit metalloproteinases, inhibiting the activities of both gelatinase and collagenase in a concentration-dependent fashion.

Doxycycline initially generated interest as a possible DMOAD when it was shown to inhibit in vitro the 92 kDa gelatinase which degrades type XI collagen in articular cartilage, and that this inhibition could be reversed by addition of small amounts of the divalent cations, calcium or zinc.

These observations led to in vivo studies in canine cruciate-deficiency models of OA, in which Doxycycline was shown to possess DMOAD activity regardless of whether it was administered prophylactically (i.e. promptly after the induction of joint instability) or therapeutically (i.e. after joint damage has already been established).

Evidence supporting these observations was subsequently obtained with other animal models of OA and with chemically modified tetracyclines.

Further work aimed at elucidating the underlying mechanism of action has been indicated that doxycycline may inhibit transcription of mRNA involved in MMP synthesis and of mRNA for inducible nitric oxide synthase (iNOS) – an enzyme whose action results in the generation within cartilage of nitric oxide, a powerful stimulant of the production and release of MMPs by chondrocytes11.

Other work has shown that doxycycline may inhibit the translation of MMPs.

Anthraquinones

There is also interest currently in the anthraquinone, diacerhein, as a potential DMOAD.

This drug has been shown to slow the development of chondropathy in a canine cruciate-deficiency model.

Glucosamine & Chondroitin

Glucosamine & Chondroitin are approved drugs in many European countries for treatment of OA. There are many randomised clinical trials favouring these drugs in the treatment of OA and most data suggests these compounds are modestly efficacious.

Pharmakokinetic studies suggest that they do get absorbed and in vitro and ex vivo cartilage studies, both have modest anti inflammatory effects in animal models of induced inflammation.

Glucosamine Sulphate slows the progression of joint damage in patients with knee OA.

There is modest mechanism of action work that suggest the most likely mechanism for Glucosamine and Chondroitin compounds is anti inflammatory and there may be an additional cartilage repair mechanism of Glucosamine.

Side effects

Side effects of Glucosamine and Chondroitin are remarkably benign. None of the studies has shown any adverse side effects and in any degree greater than in placebo patients. Whether these compounds are benign in any specific subgroups like Diabetics or patients on anticoagulants is not entirely clear at this point.

There are many different brands of Glucosamine in the market. In the US, rheumatologists have an approved list of preparations; choice depends upon the low cost of drug and availability in local pharmacy.

In Ireland, recently DONA (Glucosamine Sulphate) has been introduced by Helsinn Bisrex for the treatment of OA, although many other preparations with Glucosamine & Chondroitin are available in the pharmacies.

Conclusions

The great gains achieved recently in our understanding of the pathobiology and pathobiochemistry of cartilage damage in OA have led to efforts within the pharmaceutical industry and in academia to develop agents which inhibit cartilage MMPs.

It remains to be seen whether any of these will prove to be clinically useful DMOADs. Even if this should prove to be the case, it is uncertain whether DMOADs will have a beneficial effect on symptoms of disability.

Even if a therapeutic agent is shown convincingly to slow the progression of cartilage damage in an osteoarthritic joint, it is unclear whether this "chondroprotection" will be accompanied by improvement in clinically important outcomes, such as an increase in the time to disability or decrease in the frequency of total joint arthroplasty.

References are available on request.

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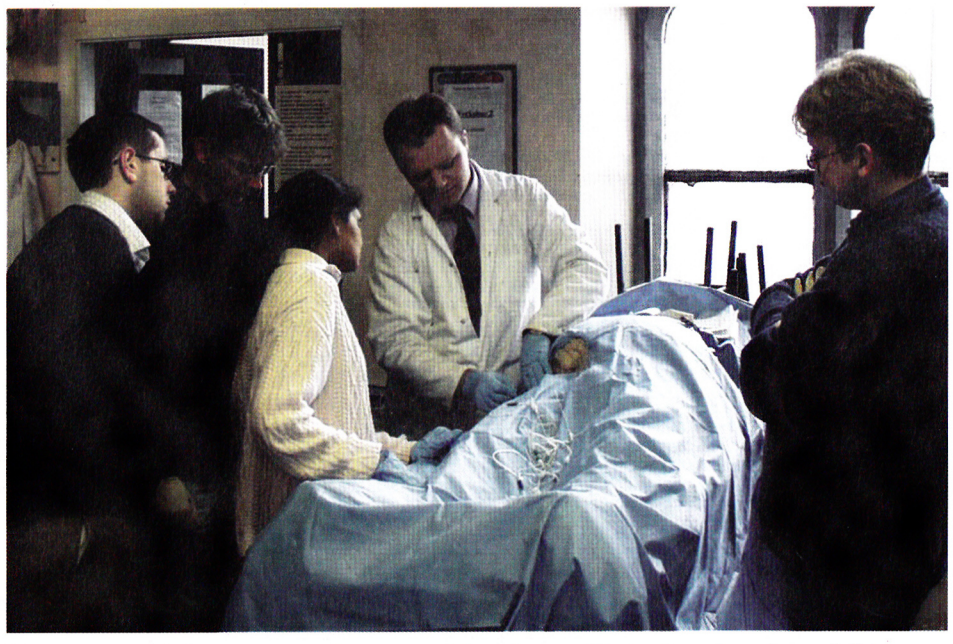
Cork course 'best educational experience'



Instructor and delegates at continuous peripheral nerve blockade cadaveric workshop.

The popularity and importance of regional anaesthesia, and especially peripheral nerve blockade, have increased dramatically worldwide in the last two decades.

International Regional Anaesthesia Societies have promoted postgraduate training opportunities, including dedicated interactive courses.

Blockade techniques

The content of these courses includes knowledge of applied anatomy, electrophysiological principles of peripheral nerve electrical stimulation and blockade techniques.

In a new, educational venture in Ireland, a Peripheral Nerve Blockade Course was recently held in University College Cork. This course was organised under the auspices of the department of Anaesthesia and Intensive Care Medicine, Cork University Hospital and the College of Anaesthetists, RCSI and held in the Department of Anatomy, University College Cork.

Cadaver demonstrations

The course compromised didactic lectures, workshops (including surface anatomy of live models) and cadaver demonstrations of block anatomy and techniques.

Invited national and local expert instructors participated. Delegates, both consultant and non-consultant, throughout Ireland attended.

Demand for the course far exceeded expectation, with 160 applicants for 24 places.

Participants completed assessment questionnaires, which demonstrated an overwhelming approval of the course content and organisation.

Educational experience

One delegate described the course as "the best educational experience I have had". It is planned that this course, following a most successful start, will continue on an annual basis.

The course was kindly sponsored by B. Braun and Abbott Laboratories Ltd.

Course Co-ordinator was **Dr Dominic Harmon,** Clinical Lecturer, Department of Anaesthesia and Intensive Care Medicine, Cork University Hospital and University College Cork.