Glucosamine for osteoarthritis of the knee

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Summary

Glucosamine is a normal constituent of the proteoglycans found in joint cartilage and synovial fluid. It has been recommended for many years by practitioners of complementary medicine for the treatment of osteoarthritis. Clinical trials have now shown that the use of oral glucosamine sulphate 1.5 g daily in patients with osteoarthritis of the knee results in a significant reduction in joint pain and an improvement in joint function. In addition, glucosamine appears to reduce the loss of cartilage in the knee joint over at least a three-year period, particularly in those with milder radiological osteoarthritis. It would therefore seem reasonable to recommend a trial of glucosamine in patients with symptomatic osteoarthritis of the knee.

Key words: arthritis, complementary medicine.

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Introduction

Osteoarthritis is the commonest form of arthritis and often results in significant disability. The management of osteoarthritis involves both pharmacological and non-pharmacological interventions to control pain and loss of function.[1] The drugs used to treat osteoarthritis can be classified as symptom-modifying (drugs that improve pain and joint function) or structure-modifying (drugs that alter the progression of joint damage, in particular cartilage loss). Symptom-modifying drugs include analgesics such as paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs). It is controversial whether any substance fulfils the criteria for structure-modification, but two randomised controlled trials[2,3] suggest that the first may be glucosamine sulphate.

For more than 20 years, practitioners of complementary medicine have used glucosamine to treat patients with osteoarthritis. Their approach was further popularised by the publication of a book optimistically titled 'The arthritis cure' in the 1990s.[4] This book presented many excellent strategies for arthritis self-management, but several chapters discussing the use of glucosamine and a 'sister' preparation chondroitin were met with considerable scepticism by the traditional medical community.

In the 1990s multiple, small, variable quality studies were performed, mainly in Europe, to test the efficacy of glucosamine and chondroitin in patients with various types of osteoarthritis. These studies were evaluated in a meta-analysis in 2000.[5] The authors of this review of 15 studies concluded that 'trials of glucosamine and chondroitin preparations for osteoarthritis symptoms demonstrate a moderate to large effect, but quality issues and likely publication bias suggest that these effects are exaggerated. Nevertheless, some degree of efficacy appears probable for these preparations.'

Pathophysiology

Glucosamine sulphate is a derivative of the naturally occurring aminomonosaccharide glucosamine, a constituent of the glycosaminoglycans chains in aggrecan and other proteoglycans found in the synovial fluid and cartilage of joints. Aggrecan and other proteoglycans trap water into the matrix of cartilage providing it with the deformable resilience which is necessary for its function. In the early phases of osteoarthritis there is an increase in the production of structural molecules such as aggrecan and collagen, but this appears to be more than matched by an increase in their catabolism by proteases under the influence of cytokines. *In vitro*, the addition of glucosamine to chondrocyte cultures increases aggrecan synthesis. Whether this observation explains the apparent efficacy of glucosamine is currently unknown.

Pharmacology

Although glucosamine has been given parenterally, it is usually taken by mouth. Glucosamine sulphate is well absorbed orally but undergoes substantial first-pass metabolism. The half-life of one preparation of glucosamine (the one used in European clinical trials[2,3]) is 58 hours and it is distributed to liver, kidney and other tissues including the articular cartilage. Pharmacokinetic studies have suggested that glucosamine is generally a substrate for the synthesis of mucopolysaccharides rather than a source of energy. There is a latency of four to eight weeks before the therapeutic effect emerges.

In animal models of diabetes glucosamine increases insulin resistance through a mechanism that is not well understood. A concern with the use of glucosamine in the treatment of patients with osteoarthritis of the knee (a population which statistically has higher body mass indices (BMIs) than the community average) is a further increase in their insulin resistance. In both of the clinical trials of glucosamine patients with a high BMI were excluded.[2,3] It is therefore difficult to conclude that an increase in insulin resistance does not occur in humans.

Efficacy of glucosamine for osteoarthritis of the knee

The European randomised, controlled, double-blind trials took place in Belgium and the Czech Republic. They compared glucosamine sulphate 1.5 g daily to placebo for three years in patients with osteoarthritis of the knee. Both trials are admirable because they evaluated the efficacy of glucosamine in a rigorous way and over a period longer than almost all previous randomised studies of patients with osteoarthritis, particularly studies of NSAIDs which have been notoriously short. The trials are also notable because structure-modification was the primary end-point rather than symptom-modification, which was a secondary end-point. Both trials were sponsored by the Rotta Research Laboratorium and used that company's formulation of glucosamine sulphate. This formulation may differ from those available in Australia.

Belgian trial [2]

This trial screened 355 patients and enrolled 212 (76% women) of whom 106 received placebo and 106 received glucosamine sulphate for three years. Patients with BMIs greater than 30 kg/m^2 were excluded and thus the mean BMI of the group was 27.5 kg/m^2. The majority of the patients (70%) had mild osteoarthritic changes (Kellgren and Lawrence grade II[6]) on baseline X-rays. At the completion of the study, 71 remained in the placebo group and 68 in the glucosamine group. Most withdrawals were due to adverse events or being lost to follow-up.

The primary end-point was change in the joint space width of the narrowest medial tibiofemoral joint compartment. The main symptomatic secondary end-point was the WOMAC (Western Ontario and McMaster Universities Arthritis Index), a validated osteoarthritis outcome measure that evaluates pain, stiffness and limitation of function.

An intent-to-treat analysis, using a last observation carried forward approach, showed a significantly greater decrease in joint space width in the placebo group. After three years the joint space width appeared not to have significantly deteriorated in the patients taking glucosamine. If those patients who completed the study were analysed separately (a per protocol analysis), the mean joint space was reduced by 0.31 mm in the placebo group and increased by 0.07 mm in the glucosamine group. In a subsequent analysis of the data the authors found that those with the least severe osteoarthritis at baseline benefited the most from the use of glucosamine. Glucosamine had little effect in patients with the most severe radiological osteoarthritis.

The symptomatic response to glucosamine was also positive. There was a reduction (improvement) of the total WOMAC by 11.7% in the glucosamine group and an increase (worsening) of 9.8% in the placebo group. The pain and function, but not stiffness, subscales of the WOMAC were also significantly improved by glucosamine. There was a poor correlation between structural and symptomatic responses, with some of the patients with the worst radiological osteoarthritis having a significant symptomatic response.

Czech trial [3]

This study screened 385 patients and enrolled 202 (77% women) of whom 101 received placebo and 101 received glucosamine sulphate for three years. Patients with BMIs greater than 27 kg/m^2 were excluded and this reduced the mean BMI of the study population to a nearly normal level. Nearly 50% of the patients had X-rays showing the more severe Kellgren grade III changes. At the completion of the study 55 remained in the placebo group and 66 in the glucosamine group. Most of the withdrawals were due to adverse events or by 'free choice'.

The primary end-point was change in the joint space width of the narrowest medial tibiofemoral joint compartment after three years. The symptomatic secondary end-points were the Lesquesne index (another validated outcome measure for osteoarthritis of the knee) and the WOMAC. Joint space width remained relatively static during the study in the patients taking glucosamine and worsened in the patients taking placebo. The measures of symptomatic response were improved in both the groups, but the patients who took glucosamine improved significantly more than the placebo group.

Safety of glucosamine

The proportion of patients who dropped out of the trials was similar in the placebo and glucosamine groups. There were no significant differences between the glucosamine and placebo-treated patients in the frequency of adverse events. The most frequently reported adverse effect was abdominal pain or nausea. Rashes were uncommon. Routine blood tests were not affected by treatment. In the Belgian trial fasting blood glucose was not increased in the patients taking glucosamine although it must be remembered that patients with high BMIs were excluded which may have reduced the risk of unmasking diabetes.

Glucosamine for osteoarthritis affecting other joints

Little evidence of good quality supports the use of glucosamine in the treatment of osteoarthritis affecting other joints. Small studies of temporomandibular joint pain and lumbar degenerative joint pain have revealed equivocal efficacy. Although it is tempting to extrapolate the results from the knee to osteoarthritis of other joints, this needs to be done with caution and could only be sanctioned on the grounds of the apparently low toxicity of glucosamine.

Conclusions

The two trials suggest that glucosamine sulphate 1.5 g orally daily has a substantial symptom- and structure-modifying effect in patients with mild to moderate osteoarthritis of the knee

and a relatively normal BMI. Whether glucosamine would be as effective or as safe in patients with higher BMIs is currently unknown. The evidence of effectiveness only extends for three years. It is also unclear whether the long-term structure-modifying effects of glucosamine will translate into more 'real' outcomes such as reduced functional decline or a delayed requirement for total knee replacement surgery. Despite these reservations, it would be reasonable to recommend a trial of glucosamine sulphate for the majority of patients with osteoarthritis of the knee, particularly early in the disease when you would normally consider paracetamol or NSAIDs. Prescribers need to advise patients to expect a latency of a month or two between onset of treatment and symptomatic response. Continuing analgesic therapy may be needed during this period. Caution should be exercised in the use of glucosamine in patients with diabetes mellitus.

References

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Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 79)

1. The benefits of glucosamine are limited to patients with severe osteoarthritis of the knee.
2. Glucosamine has no effect on the radiological progression of osteoarthritis of the knee.

Web site review

AdWatch web site www.healthyskepticism.org/adwatch.asp

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Healthy Skepticism was originally established in Australia in 1982 as the Medical Lobby for Appropriate Marketing (MaLAM). The organisation maintains a web site containing an excellent (and growing) collection of material about the techniques and impact of pharmaceutical promotion.

AdWatch is a new service established by Healthy Skepticism. It aims to critique particular pharmaceutical advertisements, focusing on both the promotional techniques and the information content. AdWatch comments on how well the claims made by the advertisement fit with the evidence and independent expert opinion. The analysis concludes by making general recommendations about the use of the drug promoted. A feedback form is provided for comments on the analysis.

Nexium (esomeprazole) from AstraZeneca was the first advertisement critiqued by AdWatch, in October 2003. Respondents' feedback was published in December 2003.

AdWatch has just commenced and inevitably there is room for improvement. The site could be improved by better linkage of its materials. In particular, the home page, 'Welcome to AdWatch', lacks the links to 'Introduction' contained on subsequent pages which explain the background to AdWatch. In addition, the home and subsequent pages lacked a link to 'Feedback about the AdWatch prototype' (found on the site map) which had useful correspondence with AstraZeneca staff about the prototype Nexium critique. I suggest that every AdWatch critique should offer the pharmaceutical company involved a space for their response, even if this may not always be forthcoming. AdWatch would provide additional value if it was linked to the National Prescribing Service (NPS) information service (RADAR) about drugs newly listed on the Pharmaceutical Benefits Scheme (PBS).[1]

Conclusion

Given the money spent on pharmaceutical promotion and its proven ability to influence drug use, AdWatch (and Healthy Skepticism) provide a unique and valuable corrective service. AdWatch is free and should be part of all health practitioners' continuing education strategies. The NPS should at least add AdWatch to the list of useful links on its web site.

Reference

1. http://www.npsradar.org.au