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REPORT

ARTHRITIS UPDATE

Drugs That Inhibit COX-2 May Cause Tissue Damage

by: William Faloon

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The Scales Tilt on the Side of Nature

Drugs that inhibit the cyclooxygenase-2 (COX-2) enzyme have shown efficacy in alleviating inflammation and pain caused by arthritis. Celebrex and Vioxx are two popular COX-2 inhibitors that are being aggressively marketed to arthritis patients by drug companies.

A new study published in the Journal of Immunology(1) acknowledges the temporary benefits of COX-2 inhibitors, but identifies a potential long-term problem that could lead to cartilage and other tissue degeneration if these drugs are taken over an extended time period.

The authors of this study found that COX-2 inhibitors cause metabolic imbalances that can result in the over production of two toxic cytokines, tumor necrosis factor alpha (TNF-a) and interleukin one beta (IL1B). Both TNF-a and IL-1B have been shown to play a role in the cartilage destruction and the inflammation process.(2-4) TNF-a and IL-1B have been found to be elevated in the synovial fluid and the cartilage of osteoarthritis patients.(2,5) Thus, the short term beneficial effects of these agents on arthritic pain and inflammation may be achieved at the cost of an increased propensity to long term tissue damage caused by TNF-a and IL1B.

Too much TNF-a results in a host of aging-related disorders including autoimmune disease, congestive heart failure, insulin resistance and catabolic wasting.(6-10) When TNF-a attacks the linings of the joints, the result is inflammation, pain and eventual immobility.(11-13)

Over expression of the destructive cytokines TNF-a and IL-1B are not the only problem that COX-2 inhibitors may induce. While COX-2 inhibitors suppress an inflammatory fatty-acid called prostaglandin E2, they fail to block the formation of a joint-destroying cytokine called leukotriene B4.(14) This all helps explain why COX-2 inhibitors do not always provide complete relief from arthritis symptoms.

Natural solutions

The problem with most drugs is that they function via only one specific mechanism. By affecting just one metabolic pathway, biochemical imbalances can develop in the body that often result in the dangerous side effects characteristic of prescription drugs.

One approach to lowering both prostaglandin E2 (PGE2) and leukotriene B(4) is to eat cold-water fish and/or take fish oil supplements. The oil found in cold-water fish interferes with the production of leukotriene B(4) and PGE2 by suppressing their common precursor, arachidonic acid.(15-21) In one study, fish oil supplements given to rheumatoid arthritis patients reduced arachidonic acid levels by 33% compared to presupplement values.(22) Another human study showed fish oil lowering arachidonic acid levels by 26%.(23)

Fish oil also suppresses the joint-tissue destructive TNF-a and IL-1B cytokines, which helps explain why so many published studies demonstrate that fish oil is an effective arthritis therapy.(24-29) Studies on healthy volunteers and rheumatoid arthritis patients show that fish oil supplementation significantly inhibited production of proinflammatory cytokines!(30) On the other hand, the most recent study shows that COX-2 inhibiting drugs may boost destructive TNF-a and IL1B levels.(1)



How COX-2 inhibiting drugs work

Prostaglandins are hormone-like fatty acids that participate in many life functions. Not all prostaglandins are beneficial. Excess levels of prostaglandin E2 (PGE2) can cause inflammation. COX-2 inhibiting drugs (such as Celebrex and Vioxx) suppress production of PGE2 and are approved by the FDA as effective arthritis therapies.

Celebrex and Vioxx function specifically by inhibiting the enzyme cyclooxygenase-2 (COX-2). COX-2 is required to convert arachidonic acid into a destructive fatty-acid called prostaglandin E2 (PGE2).

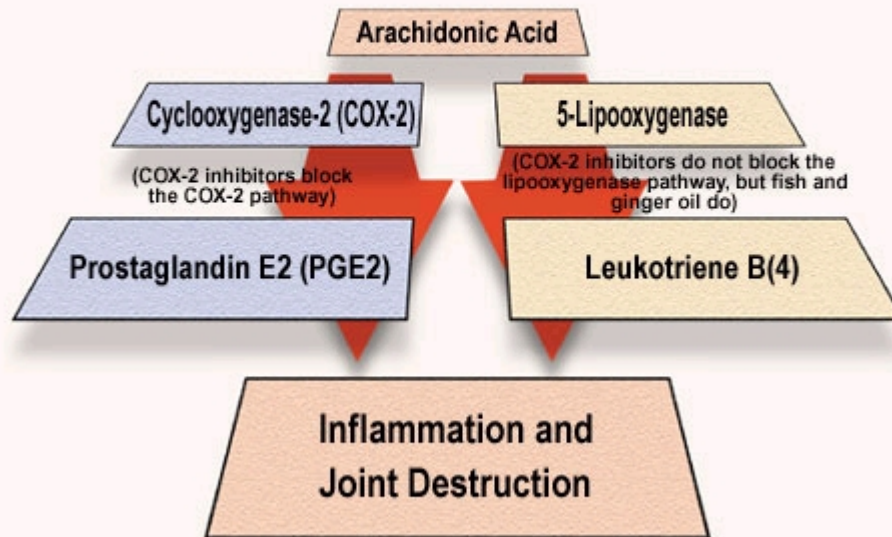
The drugs Celebrex and Vioxx function as COX-2 inhibitors, but as you can see from the chart below, that still leaves the lipoxygenase pathway open to produce joint-destroying leukotriene B(4).

In experimental studies, the pharmacologically active components of the ginger root (gingerols) have been shown to inhibit both the cyclooxygenase and lipoxygenase pathways and the production of prostaglandin E2 and leukotrienes. No significant side effects have been reported using gingerols.(35-37)

Ginger oil is obtained by steam distillation of dried ginger root. In a study on rats,(38) arthritis was induced in the knee and paw by injection of bacilli, leading to inflammation. One group of rats was also given ginger oil by mouth for 28 days starting the day before the injection. The rats given ginger oil had less than half the knee and paw inflammation compared to the controls.

The toxic metabolic cascade of arachidonic acid

(Note that two pathways by which arachidonic acid can cause arthritic conditions)



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Safely reducing TNF-a levels

Tumor necrosis factor (TNF-a) and other cytokines have been implicated in tissue destruction that results in both rheumatoid and osteoarthritis. TNF-a also attacks other tissues that can result in the manifestation of a wide variety of aging-related diseases.

There are nutritional approaches to suppressing TNF-a and other inflammatory factors. While nutritional therapies work slower than drugs, they have the benefit of being less costly and virtually free of side effects. In fact, these nutritional approaches provide potential side benefits such as cartilage regeneration and reductions in cardiovascular disease risk.

Nettle leaf is an herb that has a long tradition of use as an adjuvant remedy in the treatment of arthritis in Germany. Nettle leaf extract contains active compounds that reduce TNF-a and other inflammatory cytokines.(31,32)

Not only does nettle leaf lower TNF-a levels, but it has been demonstrated that it does so by potentially inhibiting the genetic transcription factor that activates TNF-a and IL-1B in the synovial tissue that lines the joint.(33)

A study on healthy volunteers demonstrated the anti-inflammatory potential of nettle.(32) In this study, nettle extract significantly reduced TNF-a and IL-1B concentration in response to stimulation by these pro-inflammatory cytokines.

Another study conducted on forty patients suffering from acute arthritis compared the effects of 200 mg of an anti-inflammatory drug (diclofenac) with only 50 mg of the same drug in combination with stewed nettle leaf.(34) Total joint scores improved significantly in both groups by approximately 70%. The addition of nettle extract made possible a 75% dose reduction of the toxic drug, while still retaining the same anti-inflammatory benefits with reduced side effects. This study implies that people taking nettle extract could possibly reduce their dose of a COX-2 inhibiting drug, while at the same time protecting against the recently discovered potential adverse of effects of COX-2 inhibitors, i.e. elevated TNF-a and IL-1B.



Nettle leaf is an herb that has a long tradition of use as an adjuvant remedy in the treatment of arthritis in Germany.

Please note that an extract from the nettle root (*Urtica dioica*) is used to alleviate symptoms of benign prostate enlargement. Nettle leaf extract, on the other hand, is what has been shown to reduce the pro-inflammatory cytokines TNF-a and IL-1B.

Cartilage regeneration

According to the March 15, 2000 issue of the Journal of the American Medical Association (JAMA), a review of all known studies on glucosamine and chondroitin in the treatment of arthritis showed a mean improvement in quality scores of 35.5%. The conclusions of the authors were:



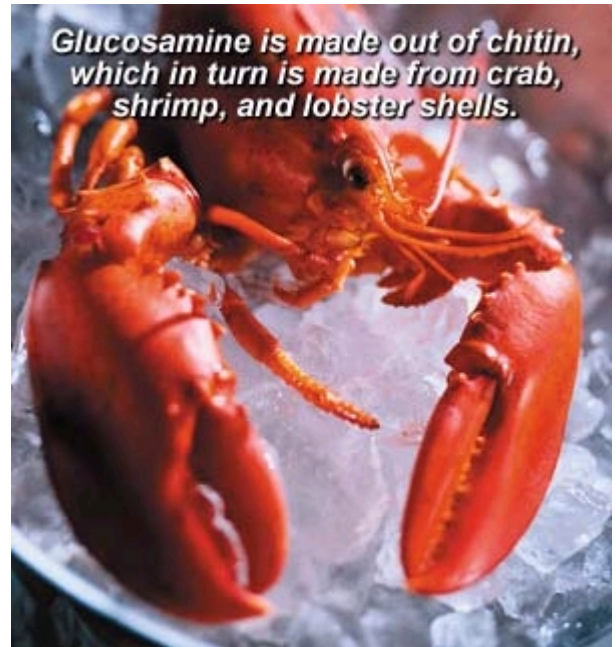
“Trials of glucosamine and chondroitin preparations for osteoarthritis symptoms demonstrate moderate to large effects, but quality issues and likely publication bias suggest that these effects are exaggerated. Nevertheless, some degree of efficacy appears probable for these preparations.”

This rather pessimistic conclusion may be warranted based on the knowledge that to adequately treat arthritis, it is crucial to suppress cartilage-destroying cytokines like TNF-a and pro-inflammatory fatty acid-derivatives such as PGE2. This is where a holistic approach to treating arthritis starts to make sense even in the world of conventional medicine. Since glucosamine and chondroitin preparations obviously provide some benefit, it makes sense to combine them with nutritional and/or drug

therapies that suppress inflammatory damage to the lining of the joint.

Among the natural therapies for osteoarthritis, glucosamine sulfate is probably the best known. It is extensively used as a drug for osteoarthritis in Europe, and it has been readily available in health food stores in the United States in recent years.

Glucosamine is a naturally occurring substance in the body, synthesized in the chondrocytes. The body uses supplemented glucosamine to synthesize the proteoglycans and the water-binding glycosaminoglycans (GAGs) in the cartilage matrix. In addition to providing raw material, the presence of glucosamine seems to stimulate the chondrocytes in their production of these substances. Glucosamine also inhibits certain enzymes, which destroy the cartilage, e.g. collagenase and phospholipase. By blocking pathogenic mechanisms that lead to articular degeneration, glucosamine delays the progression of the disease and relieves symptoms even for weeks after termination of the treatment.(39)



Chondroitin sulfate is a major component of cartilage. It is a very large molecule, composed of repeated units of glucosamine sulfate. Like glucosamine, chondroitin sulphate attracts water into the cartilage matrix and stimulates the production of cartilage. Likewise it has the ability to prevent enzymes from dissolving cartilage. Although the absorption of chondroitin sulfate is much lower than that of glucosamine (10% to 15% versus 90% to 98%), recent studies have shown good results from long-term treatment with chondroitin sulfate, reducing pain and increasing range of motion.

Conclusions

Tumor necrosis factor alpha (TNF-a) contributes to many diseases associated with normal aging such as arthritis, congestive heart failure, Type II diabetes and immune dysfunction.

TNF-a may be suppressed with an expensive prescription drug called Enbrel, or by using nutrients such as nettle leaf extract and fish oil supplements. COX-2 inhibiting drugs, on the other hand, may increase destructive TNF-a and IL-1B levels. If you are using COX-2 inhibiting drugs, you may want to also consider fish oil and nettle leaf extract supplements to reduce excessive formation of the dangerous cytokines TNF-a and IL1B.

Fish oil also helps to block the formation of joint-destroying cytokine called leukotriene B(4), as do certain ginger oil extracts.

Glucosamine and chondroitin have shown modest cartilage protecting and restoring effects. When combined with nettle leaf extract and fish and ginger oil extracts, the anti-arthritic effects of glucosamine and chondroitin may be considerably enhanced.

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