ALTERNATIVE MEDICINE

AN EVIDENCE-BASED APPROACH

Bromelain for Osteoarthritis

History of Use

Bromelain is a proteolytic enzyme present in the stem and fruit of the pineapple plant (*Ananas comosus*), which was encountered by Christopher Columbus in Guadaloupe during his second voyage to the Caribbean in 1493. Pineapple had been used by the aboriginal peoples of Central and South America as both food and medicine; they referred to it as "anana," or excellent fruit. Columbus and other explorers carried the fruit back to Spain, and then to the Philippines and possibly Hawaii. It became a much-desired exotic food, and European horticulturists succeeded in hothouse propagation of the plant early in the 18th century.

In 1605, Charles de Rochefort wrote in his "Histoire Naturelle et Morale des Iles Antilles de l'Amerique" that pineapple juice "admirably recreates and exhilarates the Spirits and comfort[s] the Heart; it also fortifies the Stomack, cureth quesiness and causeth Appetite" (J. Ethnopharmacology 1988;22:191-203).

In 1891, R.H. Chittenden isolated bromelain from the juice of the pineapple, but it was not sold on a commercial scale for pharmaceutical purposes until 1957, when Dr. Ralph Heinecke of the Dole Pineapple Company in Hawaii determined that enzyme's concentration was much higher in the stems than in the fruit.

Several proprietary formulations of bromelain are available, some of which also contain other proteolytic enzymes such as trypsin, chymotrypsin, and pancreatin.

Mechanisms of Action

Proteolytic enzymes demonstrate anti-inflammatory, analgesic, antithrombotic, and antiedematous effects in vitro and in vivo. Among the specific effects of bromelain are inhibition of platelet aggregation, prevention of platelet adhesion to endothelial cells, and induction of secretion of cytokines including interleukin (Il)-1, Il-6, Il-8, and tumor necrosis factor–α.

Analgesic effects may result from influence on pain mediators such as bradykinin. Unlike nonsteroidal anti-inflammatory drugs, bromelain may selectively inhibit proinflammatory thromboxane generation, shifting the ratio of thromboxane to prostacyclin in favor of the anti-inflammatory prostacyclin (Cell Mol. Life Sci. 2001;58:1234-45). The enzyme also inhibits T-cell signal transduction and indirectly blocks the activation of the extracellular regulated kinase–2 signaling pathway, which is involved in mitogenesis, apoptosis, and cytokine production (J. Immunol. 1999;163:2568-75).

The primary focus of research on bromelain today is in the treatment of osteoarthritis, but the enzyme's varied properties have also prompted exploration for multiple other indications, including tumors, thrombosis, and burn debridement.

Clinical Studies

One of the initial clinical trials compared Phlogenzym (Mucos Pharma, Geretsried, Germany), each tablet of which contains 90 mg of bromelain as well as trypsin and rutin, with diclofenac. A total of 73 patients with symptomatic osteoarthritis of the knee and radiographic evidence of joint space narrowing were randomized to receive 50 mg of diclofenac three times daily during the first week and then 50 mg twice daily during weeks 2 and 3, or to receive two Phlogenzym tablets three times daily for 3 weeks. These dosages adhered to the manufacturers' recommendations.

► Bromelain is an enzyme found in extracts of pineapple fruit and stems; it possesses anti-inflammatory and analgesic properties.

► Early studies suggest that extracts of bromelain can be safe and effective in knee osteoarthritis, but the data are preliminary and need to be replicated in larger, blinded trials.

Mean scores on the Lequesne index of pain and function decreased from 13.56 at baseline to 3.10 at the end of 3 weeks of therapy in the Phlogenzym group. Scores decreased further to 2.05 after 4 additional weeks of follow-up. Similar improvements were seen in the diclofenac group, with a decrease from 14.04 at baseline to 3.50 after 3 weeks of treatment and to 2.24 at 7 weeks. Statistical analysis determined that the treatments were equivalent (Clin. Drug Invest. 2000;19:15-23).

Different doses of bromelain, ranging from 540 to 1,890 mg/day, were used in other studies, with mixed results in terms of tolerability. In one study, in which the dose of bromelain was 945 mg/day, more adverse events and dropouts were seen among patients in the enzyme therapy group than in the standard-dose diclofenac group (Wien. Med. Wochenschr. 1996;146:55-8). In another study, doses of 1,890 mg/day were comparable in efficacy to diclofenac 50 mg twice daily, and there were no dropouts or safety issues despite the high dose of bromelain (J. Assoc. Physicians India 2001;49:617-21).

An open dose-ranging study compared 1 month of treatment with bromelain 200 mg/day with 1 month at 400 mg/day (Bromelin, Lichtwer Pharma Ltd., Marlow, England) in a group of 77 patients with mild acute knee pain of less than 3 months' duration. On the primary outcome measure, the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), both groups had highly significant reductions in scores for all dimensions after 1 month of treatment with bromelain. Pain scores decreased by 44.6% and 58.2% and overall WOMAC scores decreased by 41% and 59% in the low- and high-dose groups, respectively (Phytomedicine 2002;9:681-6).

The Psychological General Well-Being Index scores also increased significantly in both groups, but the 19.2% improvement in the high-dose group on this measure was more than twice that seen in the low-dose group. No serious side effects were reported.

On a poststudy questionnaire, 60% and 68% of patients in the low- and high-dose groups reported overall improvement, while 4.8% and 3.9% reported deterioration in symptoms.

The conclusion of a review of the available clinical data was that the use of bromelain for osteoarthritis was promising, but that more definitive studies are needed to clarify the optimal dose and to assess the therapy in a randomized, placebo-controlled design (Evid. Based Complement. Alternat. Med. 2004;1:251-7).

—Nancy Walsh

Irradiated Liner Use Prevents Osteolysis

BY BRUCE K. DIXON

Chicago Bureau

CHICAGO — Highly cross-linked polyethylene bearing surfaces in total hip arthroplasties have passed their first long-term longitudinal trial with flying colors, according to a blue-ribbon poster presented at the annual meeting of the American College of Orthopaedic Surgeons.

"After a minimum of five years follow-up of patients all done at Massachusetts General Hospital, there were no signs of radiographic osteolysis either on the acetabular or femoral sides, and this is the earliest point where you might normally start to see that with conventional polyethylene," Charles R. Bragdon, Ph.D., said in an interview.

Irradiation of the polyethylene increases cross-linking and improves wear characteristics.

DR. BRAGDON

Electron beam irradiated highly cross-linked polyethylene (HXLPE) is created by taking standard high-density polyethylene and irradiating it, which increases cross-linking and improves wear characteristics. The material then goes through "a melting step which allows the free radicals generated during radiation to extinguish themselves and form more cross-linking. With the free radicals gone, there's no long-term oxidation, so the properties you get do not change over time," Dr. Bragdon said explained.

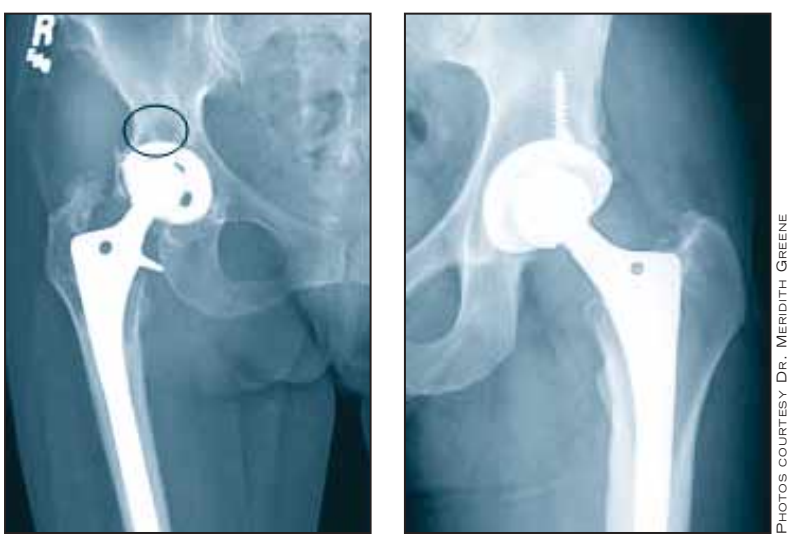
HXLPE has been used as total hip arthroplasty bearing surface for nearly 8 years, according to Dr. Bragdon and his colleagues at the Orthopaedic Biomechanics and Biomaterials Laboratory at Massachusetts General Hospital in Boston. Radiostereometric analysis (RSA) has shown little additional femoral head penetration after the early bedding-in period; however, such studies have been performed on relatively small groups of patients, the authors continued. Using standardized measures, the Boston group studied femoral head penetration in 77 primary total hip replacements in 70 patients with HXLPE liners, with either a 28-mm or 32-mm femoral head.

The average total femoral head penetration was calculated based on the total penetration from the initial postoperative film to the longest follow-up film.

"During the first year following surgery, there was about 100 microns of head penetration into the polyethylene," Dr. Bragdon said. "Thereafter … [there was] no measurable wear of this material at 5 years," he said. In addition, there was no significant difference in the average penetration rate or the steady state wear rates between the 28-mm and 32-mm groups.

"These results are encouraging for lysis in the long term because we've shown in the past that lysis and wear tend to go hand in hand; we think our study bodes well for 7-15 years' follow-up," said Dr. Bragdon, adding that continued follow-up will be necessary to evaluate the material's clinical and radiographic durability.

Dr. Bragdon predicted that these more durable replacements will further reduce the average age of both knee and hip recipients. "Cross-linked polyethylene's introduction has been in hip arthroplasty, but now it's also being used in knees because knee components also suffer from wear and osteolysis." ■



PHOTOS COURTESY DR. MERIDITH GREENE

Osteolysis was seen on x-ray 7 years after placement of a conventional polyethylene liner for total hip arthroplasty (left). No osteolysis was seen 6 years later with a highly cross-linked polyethylene liner (right).

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