

Inflamação. Antiinflamatório Serrapeptase, derivado de enzima do bicho da seda, é mais eficaz que os antiinflamatórios não hormonais e desprovido de efeitos colaterais. Acresce possível efeito anti placa de ateroma

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Insect-Derived Enzyme Fights Inflammation

By Kimberly Pryor

Our bodies have a love-hate relationship with inflammation. On the one hand, inflammation is a natural response, necessary to protect the body from invading organisms. On the other hand, inflammation can limit joint function, and destroy bone, cartilage and other articular structures.

An elusive goal of scientists and physicians has been to find a side-effect-free substance to reduce the pain and inflammation associated with fibrocystic breast disease, rheumatoid arthritis, idiopathic edema, carpal tunnel syndrome and post-operative swelling. It appears that the search may be nearing an end, thanks to an enzyme produced by the larval form of the silk moth.

Serrapeptase is an enzyme that is produced in the intestines of silk worms to break down cocoon walls. This enzyme is proving to be an alternative to the non-steroidal anti-inflammatory agents (NSAIDs) traditionally used to treat rheumatoid arthritis and osteoarthritis. Its uses have also been extended to the treatment of chronic sinusitis and postoperative inflammation, and some researchers believe the substance can play an important role in arterial plaque prevention and removal.

Harmful Effects of NSAIDs

NSAIDs, which include aspirin, ibuprofen, salicylates, and naproxen, are among the most commonly prescribed medications for inflammation resulting from rheumatoid arthritis, joint conditions, osteoarthritis, gouty arthritis, joint and muscle discomfort associated with systemic lupus erythematosus, and other musculoskeletal disorders.(1) In some cases, this overreliance on NSAIDs has proved deadly. Annually, 76,000 people are hospitalized from NSAID-induced gastrointestinal complications. The American Medical Association estimates that from 50-80 percent of those hospitalized for gastrointestinal bleeding are taking some form of NSAIDs. At this stage in the medication-induced bleeding, there is a ten percent chance of fatality.(2)

NSAIDs lethal effects result from the inhibition of the biosynthesis of prostaglandins. NSAIDs block cyclo-oxygenase, the enzyme responsible for catalyzing the reactions of arachidonic acid to endoperoxide compounds. This process results in the inhibition of gastric prostaglandin E, a hormone which protects the lining of the stomach from acid. After prolonged and frequent ingestion of NSAIDs, the stomach remains defenseless and at increased susceptibility to ulcers.(3-4) If an ulcer erodes into a blood vessel, bleeding results. An ulcer can destroy part of the stomach and duodenal walls, leaving a gap that requires immediate surgery.

In one study, 1,826 osteoarthritis or rheumatoid arthritis patients who had been taking NSAIDs for six months or more and who had been unable to tolerate continuous NSAID use because of adverse gastrointestinal symptoms were examined endoscopically for gastroduodenal lesions and ulcers. Clinically significant gastroduodenal lesions were found in 37.1 percent of the patients. Of those, 24 percent had ulcers. The prevalence of gastroduodenal ulcers increased with age, duration of osteoarthritis, and duration of current NSAID use. The authors of the study wrote: These results provide further endoscopic confirmation of the association between NSAID use and gastroduodenal lesions and ulcers and support the contention that safer treatment alternatives to conventional NSAIDs are required.(5)

That advice is particularly wise in light of the other effects NSAIDs have on the gastrointestinal tract. In one group of 312 NSAID takers, 20 percent had levels of inflammation comparable to that previously reported in patients with inflammatory bowel disease.(6) Besides damaging the gastrointestinal tract, NSAIDs also interfere with and suppress bone repair and remodeling. One paper presented data obtained over a 12-year period, and outlined the effects of NSAIDs on the matrix synthesis and turnover in 650 arthritic and 180 non-arthritic human cartilages. The study showed that one category of NSAIDs that includes Naproxen, ibuprofen, indomethacin, and nimesulide significantly inhibited matrix synthesis and had toxic effects on cartilage metabolism.(7) Thus, it appears that the drugs many patients take to relieve their arthritic pains actually contributes to further destruction of their joints!

Additionally, NSAIDs have been shown to interfere with patients sleep patterns. One study of 37 male and female subjects at the sleep laboratory at Bowling Green State University in Ohio demonstrated that aspirin and ibuprofen, in comparison to a placebo, increased the number of awakenings and the percentage of time spent awake. The drugs also decreased sleep efficiency, and delayed the onset of the deeper stages of sleep.(8)

Even insulin secretion is affected by NSAIDs. Neonatal rat pancreatic cells were examined partly to determine the effects of insulin secretion caused by prostaglandin E (PGE) and drugs that inhibit its synthesis—i.e. NSAIDs. Two NSAIDs, sodium salicylate (aspirin) and ibuprofen, at drug concentrations similar to those achieved therapeutically in humans, inhibited PGE synthesis up to 70-80 percent. Augmented insulin secretion accompanied the PGE inhibition. Both drugs shifted the glucose-insulin response curves to the left at low glucose concentrations and augmented maximal insulin release at high glucose concentrations.(9)

Other NSAID-induced side effects include kidney damage, blood dyscrasias and cardiovascular effects, complication of antihypertensive therapies involving diuretics or beta-adrenoceptor blockade, and adverse effects in patients with heart failure and cirrhosis.(10) In one instance, a woman treated for rheumatoid arthritis with the NSAID sulindac developed gallstones composed of sulindac metabolites.(11)

Interestingly, NSAIDs have also induced adverse psychiatric reactions. Five psychiatric outpatients—two with major depressive disorders, one with a bipolar disorder, one with a schizophrenic disorder and one with an anxiety disorder—were treated with NSAIDs due to rheumatoid arthritis, osteoarthritis, or other painful neuromuscular conditions. All five patients developed moderate to severe depression. Three patients became paranoid, and four either attempted or considered suicide. These psychiatric symptoms disappeared once the patients stopped taking NSAIDs. When the patients re-started the drugs, the symptoms returned.(12)

NSAIDs Roulette

Due to the detrimental effects of NSAIDs on the body, most physicians resort to a game of NSAID musical-chairs, taking a patient off one NSAID as soon as side effects become evident or the drug stops working, then treating the patient with another of the 10 most widely prescribed propionic acid-derived NSAIDs.

To provide a more consistent form of treatment, researchers have long searched for a side-effect free anti-inflammatory agent. Researchers have recently focused on selective cyclo-oxygenase (COX-2) inhibitors, more precise versions of NSAIDs. Whereas previous NSAIDs reduced inflammation by inhibiting all cyclo-oxygenase activity, these new selective COX-2 inhibitors differentiate between the two forms of COX: COX-1 appears to regulate many normal physiologic functions and COX-2 mediates the inflammatory response. These selective inhibitors are believed to reduce inflammation without influencing normal physiologic functions by inhibiting

only COX-2. By leaving COX-1 alone, the selective inhibitors result in fewer gastrointestinal side effects.

At first glance, these COX-2 inhibitors look like the solution to NSAID complications. Upon further inspection, however, celecoxib, a highly selective COX-2 inhibitor, can cause headaches, change in bowel habits, abdominal discomfort and dizziness in osteoarthritis patients. Fewer adverse effects are reported in rheumatoid arthritis patients, but because the drug is metabolized in the liver by cytochrome P-450 isozyme CYP2C9, serious drug interactions are possible. Fung and colleagues pointed out that more clinical studies are needed before the selective COX-2 inhibitors are put into widespread use.(13)

Another new drug, Enbrel, initially showed promise of treating the pain associated with rheumatoid arthritis. Currently, however, the FDA is advising physicians about safety concerns of the new drug. Thirty of the 25,000 patients treated with Enbrel since the drug's approval have developed serious infections, including sepsis. Several of those patients died as a result of the infections. Those at greatest risk when taking Enbrel appear to be patients with a history of chronic or recurrent infections, pre-existing infections, diabetes, or other conditions making them more susceptible to infection.(14)

The potentially lethal side effects associated with NSAIDs and other drugs indicate that a superior anti-inflammatory substance is needed.

A Natural Anti-Inflammatory

Serrapeptase, also known as Serratia peptidase, is a proteolytic enzyme isolated from the non-pathogenic enterobacteria *Serratia E15*. When consumed unprotected, in tablets or capsules, the enzyme can be destroyed by acid in the stomach. However, when Serrapeptase is microencapsulated within a capsule, the raw material is protected, enabling the enzyme to pass through the stomach intact, and to be absorbed in the intestine. Serrapeptase is found in negligible amounts in the urine, suggesting that it is transported intact from the intestine into the bloodstream.(15,16)

Clinical studies show that serrapeptase induces fibrinolytic, anti-inflammatory and anti-edemic (prevents swelling and fluid retention) activity in a number of tissues, and that its anti-inflammatory effects are superior to other proteolytic enzymes.(17)

Besides reducing inflammation, one of serrapeptase's most profound benefits is reduction of pain, due to its ability to block the release of pain-inducing amines from inflamed tissues.(18) Physicians throughout Europe and Asia have recognized the anti-inflammatory and pain-blocking benefits of this naturally occurring substance and are using it in treatment as an alternative to salicylates, ibuprofen and other NSAIDs.(19)

In Germany and other European countries, serrapeptase is a common treatment for inflammatory and traumatic swellings, and much of the research that exists on this substance is of European origin. One double-blind study was conducted by German researchers to determine the effect of serrapeptase on post-operative swelling and pain. This study involved sixty-six patients who were treated surgically for fresh rupture of the lateral collateral ligament of the knee. On the third post-operative day, the group receiving serrapeptase exhibited a 50 percent reduction of swelling, compared to the controls. The patients receiving serrapeptase also became more rapidly pain-free than the controls, and by the tenth day, the pain had disappeared completely.(20)

Cystic Breast Disease

Serrapeptase has also been used in the successful treatment of fibrocystic breast disease. In a double-blind study, 70 patients complaining of breast engorgement randomly were divided into a treatment group and a placebo group. Serrapeptase was superior to the placebo for improvement of breast pain, breast swelling and induration (firmness). Nearly eighty-six percent of the patients receiving serrapeptase reported moderate to marked improvement. No adverse reactions to serrapeptase were reported and the researchers concluded that serrapeptase is a safe and effective method for the treatment of breast engorgement.(21,22)

Serrapeptase and Sinusitis

Due to its anti-inflammatory properties, serrapeptase has been shown in clinical studies to benefit chronic sinusitis sufferers. In this condition, the mucus in patients' nasal cavities is thickened and hypersecreted. This thickening causes mucus to be expelled less frequently. Japanese researchers evaluated the effects of serratiopeptidase (30 mg/day orally for four weeks) on the elasticity and viscosity of the nasal mucus in adult patients with chronic sinusitis. Serratiopeptidase reduced the viscosity of the mucus, improving the elimination of bronchopulmonary secretions.(23)

Other clinical trials support serrapeptase's ability to relieve the problems associated with chronic sinusitis. In one study, 140 patients with acute or chronic ear, nose and throat pathologies were evaluated with either a placebo or the active *Serratia peptidase*. Patients taking the serrapeptase experienced a significant reduction in severity of pain, amount of secretion, purulence of secretions, difficulty in swallowing, nasal dysphonia, nasal obstruction, anosmia, and body temperature after three to four days and at the end of treatment. Patients suffering from laryngitis, catarrhal rhinopharyngitis and sinusitis who were treated with serrapeptase experienced a significant and rapid improvement of symptoms after 3-4 days. Physicians assessed efficacy of treatment as excellent or good for 97.3 percent of patients treated with serrapeptase compared with only 21.9 percent of those treated with a placebo.(24)

Respiratory diseases are characterized by increased production of a more dense mucus modified in viscosity and elasticity. Traditionally, in respiratory diseases, muco-active drugs are prescribed to reestablish the physicochemical characteristics of the mucus in order to restore respiratory function. Some of these drugs, however, cause a functional depletion of mucus, whereas serrapeptase alters the elasticity of mucus without depleting it.(25,27)

A powerful agent by itself, serrapeptase teamed with antibiotics delivers increased concentrations of the antimicrobial agent to the site of the infection. Bacteria often endure a process called biofilm formation, which results in resistance to antimicrobial agents. In an attempt to prevent this bacterial immunity, researchers have experimented with various means of inhibiting biofilm-embedded bacteria. Their search may have ended with serrapeptase. One study conducted by Italian researchers suggests that proteolytic enzymes could significantly enhance the activities of antibiotics against biofilms. Antibiotic susceptibility tests showed that serratiopeptidase greatly enhances the activity of the antibiotic, ofloxacin, and that it can inhibit biofilm formation.(28)

Another double-blind randomized study evaluated the effects of administering the antibiotic cephalexin in conjunction with serrapeptase or a placebo to 93 patients suffering from either perennial rhinitis, chronic rhinitis with sinusitis or chronic relapsing bronchitis. The serratiopeptidase-treated group experienced significant improvement in rhinorrhea, nasal stuffiness, coryza and improvement of the para-nasal sinus shadows.(29)

Researchers witnessed equally impressive results in the treatment of infections in lung cancer patients undergoing thoracotomy. Serrapeptase and cefotiam, an antibiotic with a broad spectrum of activity against both Gram-positive and Gram-negative microorganisms, were administered to 35 thoracotomy patients with lung cancer. The patients were divided into two groups. A single dose of cefotiam was administered to the 17 subjects in Group I. The 18 subjects in Group II received a combination of Cefotiam and serrapeptase. The level of the antibiotic in the tissues versus the blood was significantly higher in the serrapeptase group than the single dose group.(30)

Cardiovascular Implications

Hans A. Nieper, M.D., an internist from Hannover, Germany, studied the effects of serrapeptase on plaque accumulations in the arteries. The formation of plaque involves deposits of fatty substances, cholesterol, cellular waste products, calcium and fibrin (a clotting material in the blood) on the inner lining of the arteries. Excessive plaque results in partial or complete blockage of the blood's flow through an artery, resulting in arteriosclerosis, or hardening of the arteries, and an ensuing stroke or heart attack. The evidence to support serrapeptase's role in preventing plaque build-up is anecdotal. Still, further studies are called for in this area as Nieper's research indicated that the protein-dissolving action of serrapeptase will gradually break down atherosclerotic plaques.(31)

Conclusion

Regardless of whether serrapeptase is used for inflammatory diseases or to prevent plaque build-up on the arteries, it is well-tolerated. Due to its lack of side effects and anti-inflammatory capabilities, serrapeptase is a logical choice to replace harmful NSAIDs. Thanks to the tiny larvae of the silk moth, researchers have taken a large step toward finding relief for inflammatory disease sufferers.

References:

1. Raskin JB. Gastrointestinal effects of nonsteroidal anti-inflammatory therapy. *Am J Med.* 1999; 106 (5B):3S-12S.
2. No author listed. Regular Use of Pain Relievers Can Have Dangerous Results. *Kaleidoscope Interactive News*, American Medical

Association media briefing. July 24, 1997.

3. Fung HB, Kirschenbaum, HL. Selective cyclooxygenase-2 inhibitors for the treatment of arthritis. *Clin Ther.* 1999; 21(7):1131-57.
4. Geis GS. Update on clinical developments with celecoxib, a new specific COX-2 inhibitor: what can we expect? *Scand J Rheumatol Suppl.* 1999; 109:31-7.
5. Cheatum DE, Arvanitakis C, Gumpel M, Stead H, Geis GS. An endoscopic study of gastroduodenal lesions induced by nonsteroidal anti-inflammatory drugs. *Clin Ther.* 1999; 21(6):992-1003.
6. Tibble JA, Sigthorsson G, Foster R, Scott D, Fagerhol MK, Roseth A, Bjarnason I. High prevalence of NSAID enteropathy as shown by a simple faecal test. *Gut.* 1999; 45(3):362-6.
7. Dingle JT. The effects of NSAID on the matrix of human articular cartilages. *Z Rheumatol.* 1999; 58(3):125-9.
8. Murphy PJ, Badia P, Myers BL, Boecker MR, Wright KP Jr. Nonsteroidal anti-inflammatory drugs affect normal sleep patterns in humans. *Physiol Behav.* 1994; 55(6):1063-6.
9. Metz SA, Robertson RP, Fujimoto WY. Inhibition of prostaglandin E synthesis augments glucose-induced insulin secretion in cultured pancreas. *Diabetes.* 1981; 30(7):551-7.
10. Raskin JB. Gastrointestinal effects of nonsteroidal anti-inflammatory therapy. *Am J Med.* 1999; 106 (5B):3S-12S.
11. Tokumine F, Sunagawa T, Shiohira Y, Nakamoto T, Miyazato F, Muto Y. Drug-associated cholelithiasis: a case of sulindac stone formation and the incorporation of sulindac metabolites into the gallstones. *Am J Gastroenterol.* 1999;94(8):2285-8.
12. Jiang HK, Chang DM. Non-steroidal anti-inflammatory drugs with adverse psychiatric reactions: five case reports. *Clin Rheumatol.* 1999;18(4):339-45.
13. Fung HB, Kirschenbaum, HL. Selective cyclooxygenase-2 inhibitors for the treatment of arthritis. *Clin Ther.* 1999; 21(7):1131-57.
14. FDA MedWatch: The FDA Medical Products Reporting Program. May 12, 1999. FDA Talk Paper.
15. Moriya N, Nakata M, Nakamura M, Takaoka M, Iwasa S, Kato K, Kakinuma A. Intestinal absorption of serrapeptase (TSP) in rats. *Biotechnol Appl Biochem.* 1994; 20(Pt1):101-8.
16. Miyata, K. Intestinal absorption of Serratia Peptidase. *J Appl Biochem.* 1980;2:111-16.
17. Mazzone A, Catalani M, Costanzo M, Drusian A, Mandoli A, Russo S, Guarini E, Vesperini G. Evaluation of Serratia peptidase in acute or chronic inflammation of otorhinolaryngology pathology: a multicentre, double-blind, randomized trial versus placebo. *J Int Med Res.* 1990; 18(5):379-88.
18. Mazzone A, et al. Evaluation of Serratia peptidase in acute or chronic inflammation of otorhinolaryngology pathology: a multicentre, double-blind, randomized trial versus placebo. *J Int Med Res.* 1990; 18(5):379-88.
19. Aso T et al. Breast engorgement and its treatment: Clinical effects of Danzen an anti-inflammatory enzyme preparation. *The world of Obstetrics and Gynecology (Japanese).* 1981; 33:371-9.
20. Esch PM, Gerngross H, Fabian A. Reduction of postoperative swelling. Objective measurement of swelling of the upper ankle joint in treatment with serrapeptase-a prospective study (German). *Fortschr Med.* 1989;107(4):67-8, 71-2.
21. Kee WH, Tan SL, Lee V, Salmon YM. The treatment of breast engorgement with Serrapeptase (Danzen): a randomized double-blind controlled trial. *Singapore Med J.* 1989;30(1):48-54.
22. Aso T et al. Breast engorgement and its treatment: Clinical effects of Danzen an anti-inflammatory enzyme preparation. *The world of Obstetrics and Gynecology (Japanese).* 1981; 33:371-9.
23. Majima Y, Inagaki M, Hirata K, Takeuchi K, Morishita A, Sakakura Y. The effect of an orally administered proteolytic enzyme on the elasticity and viscosity of nasal mucus. *Arch Otorhinolaryngol.* 1988;244(6):355-9.
24. Mazzone A, et al. Evaluation of Serratia peptidase in acute or chronic inflammation of otorhinolaryngology pathology: a multicentre, double-blind, randomized trial versus placebo. *J Int Med Res.* 1990; 18(5):379-88.
25. Tomoda K, and Miyatam K. Some information on the composition of tracheal secretions before and after the administration of Danzen. *Exper Ther.* 1972; 477:9-16.
26. Kase Y, et al. A new method for evaluating mucolytic expectorant activity and its application to two proteolytic enzymes, serratiopeptidase and seaprose. *Arzneimittelforschung.* 1982; 32:374-378.
27. Marriott C. Modification in the rheological properties of mucus by drugs. *Adv Exp Med Biol.* 1982; 144:75-84.
28. Selan L, Berlutti F, Passariello C, Comodi-Ballanti MR, Thaller MC. Proteolytic enzymes: a new treatment strategy for prosthetic infections? *Antimicrob Agents Chemother.* 1993; 37(12):2618-21.
29. Perna L. Osservazioni Cliniche sui trattamenti in ospicio cleco con Serratia peptidasi nella neifre perenna naila ninite cronica nacutizzata con sinusopattia, nella bronchia cronica nacutizzata. *Riv Pat Clin Tuberc Penumol.* 1985; 56:509-516.
30. Koyama A, Mori J, Tokuda H, Waku M, Anno H, Katayama T, Murakami K, Komatsu H, Hirata M, Arai T, et al. Augmentation by serrapeptase of tissue permeation by cefotiam (Japanese). *Jpn J Antibiot.* 1986; 39(3):761-71.
31. Brewer Science Library website. 1999.