

LE Magazine October 2002

REPORT

Topical Pain Relief Using A Novel Anti-Inflammatory Agent

The estimated 43 million Americans who suffer from arthritis and other rheumatic conditions endure chronic and sometimes disabling pain and inflammation. This crippling joint disease will afflict an estimated 60 million people by the year 2020.[1]

The nationwide economic impact of arthritis and its associated conditions has been compared to a moderate recession, according to Edward Yelin, Ph.D., a researcher at the University of California, San Francisco.

Over the past decade, a remarkable amount of knowledge has been garnered that explains the underlying causes of chronic inflammation. In this article, we introduce a discovery that inhibits the inflammatory cascade in its earliest stages.

Great strides have been made toward understanding the mechanisms involved in chronic inflammatory disorders such as arthritis. One culprit is the excess accumulation of arachidonic acid that cascades down into pro-inflammatory agents such as prostaglandin E2, leukotrienes and thromboxanes.

Drugs like Celebrex suppress the COX-2 enzyme, which inhibits arachidonic acid from breaking down into prostaglandin E2. The problem is that arachidonic acid can cascade down via other pathways to produce equally damaging leukotrienes and thromboxanes. In order to block the formation of prostaglandin E2, leukotrienes and thromboxanes, it is critical to reduce arachidonic acid levels.

Dietary factors can influence how much arachidonic acid is produced in the body. An enzyme that is needed to convert dietary factors into arachidonic acid is phospholipase A2 (PLA2). Arthritic pain and inflammation are the end results of a pathway known as the "arachidonic acid cascade."

Blocking PLA2

Researchers have been seeking agents that block the PLA2 enzyme in order to reduce the amount of arachidonic acid produced in the body. By suppressing PLA2 enzyme activity, arachidonic levels are reduced along with the pro-inflammatory compounds it generates, like leukotrienes, thromboxanes and prostaglandin E2. Suppressing PLA2 enzyme activity interferes with the arachidonic acid cascade that is responsible for the chronic pain and tissue destruction seen in so many age-related diseases. High levels of PLA2 enzyme activity have been found in synovial tissue in the joint, and scientists have linked elevated levels of serum PLA2 to activity associated with rheumatoid arthritis.[2] In fact, PLA2 has been found in a variety of human tissues, including platelets, cartilage cells known as chondrocytes, placenta, cartilage, peritoneal cells and peritoneal fluid and spleen.[3]

Scientific studies have shown that inflammation that accompanies arthritis is directly linked to enzymatic actions. In other words, the PLA2 enzyme increases arachidonic acid, which is then converted by enzymatic actions (COX-2, lipooxygenase, COX-1) into prostaglandin E2, leukotrienes and thromboxanes. In fact, the evidence has demonstrated that excessive concentrations of extra-cellular PLA2 may initiate and spread inflammation and cause cellular damage. High activities of PLA2 have been identified in several inflammatory diseases, including rheumatoid arthritis and osteoarthritis.[2]

The revelation that enzymes such as PLA2 are directly related to the chronic pain



Two Common Types of Arthritis

Osteoarthritis is the most common form, targeting mostly older people. It attacks the cartilage, the slippery tissue that covers the ends of bones that make up the joint. Over time, the surface layer of healthy cartilage wears away, allowing bones underneath to rub together, resulting in pain, limited movement and joint swelling. Over time, bone spurs known as osteophytes may develop on ends of the joints. As a result, bits of bone may break off and invade the joint space, causing even more pain and swelling.*

Rheumatoid arthritis is the second most common form of this debilitating

associated with arthritis has led to the development of a topical treatment uniquely designed to target these underlying causes of chronic inflammation.

The development of Inflacin™

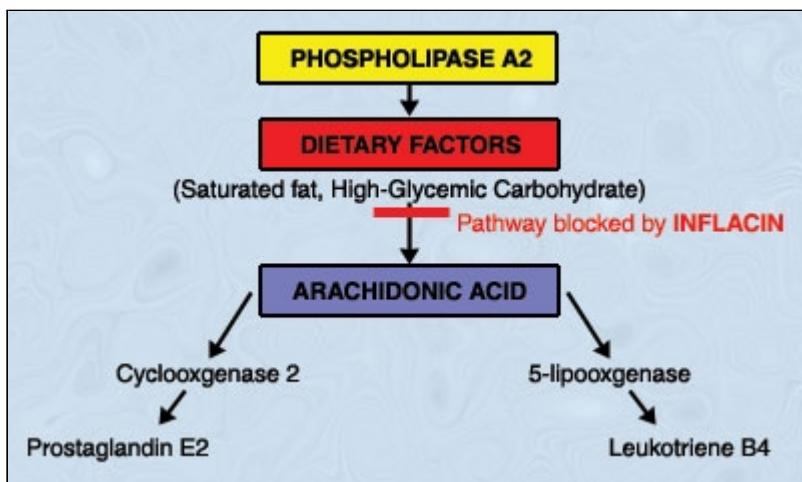
In their quest for PLA2 inhibitors, scientists at BioZone Laboratories, Inc. have discovered a new group of compounds called Inflacin™. When tested, these topically applied compounds alleviated pain associated with arthritis and increased joint mobility.

disease, but it affects other parts of the body in addition to the joints. It typically manifests itself earlier than osteoarthritis, and can make its victims sometimes feel sick, tired and even feverish.*

*National Institute of Arthritis and Musculoskeletal and Skin Diseases. Handout on Health. Osteoarthritis.

Inflammatory Cascade

This chart depicts how phospholipase A2 causes dietary factors to cascade into arachidonic acid, which is then converted by COX-2 and 5-LOX into pro-inflammatory prostaglandin E2 and leukotriene B4. Blocking phospholipase A2 enzyme activity inhibits conversion into arachidonic acid, thus reducing the formation of the pro-inflammatory factors from both COX-2 and 5-LOX. COX-2 inhibiting drugs only suppress the formation of prostaglandin E2, whereas suppression of arachidonic acid blocks formation of leukotriene B4, in addition to prostaglandin E2.



In a double blind, patient randomized, placebo-controlled crossover clinical trial enrolling 30 participants, Inflacin™ was tested to evaluate its analgesic benefit when applying the topical cream to areas of the body affected by stiffness, soreness and pain. These included: hands, feet, knees and shoulders and muscles of the neck, arms, legs and back. Assessment tools used to measure changes in pain and handgrip strength included a visual analog scale (VAS) that recorded pain levels, and a hydraulic hand dynamometer that evaluated changes in handgrip strength. The visual analog scale is a common assessment tool that accurately evaluates pain and stiffness based on a ranking recorded on a scale from zero to 10; zero being no pain, and 10, very severe pain. Each assessment in the study was conducted three times using this method, and an average of three rankings was recorded as the value for that time point.

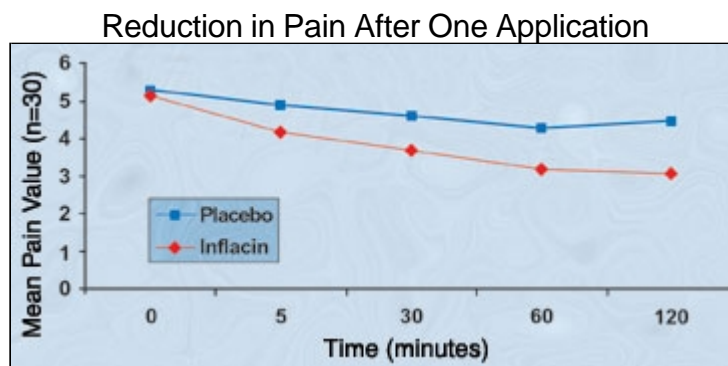
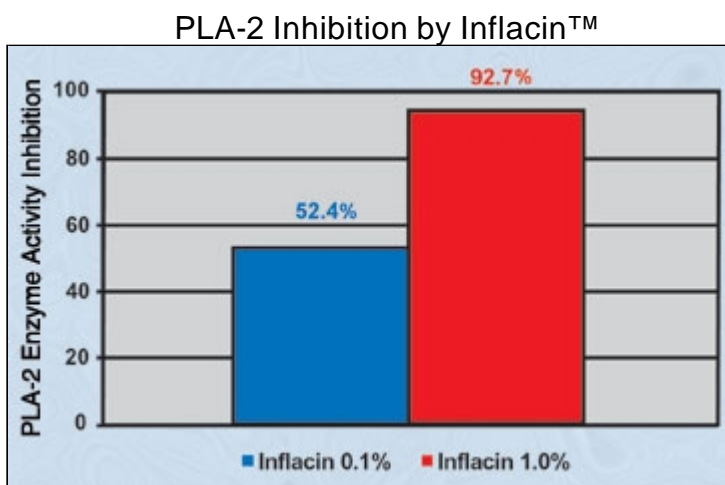


Figure 1

Assessments using the hydraulic hand dynamometer were recorded three times with each hand, by holding the device at arm's length vertically. After initial assessments, the blinded investigator applied measured amounts of either Inflacin™ or placebo to affected areas. Subsequent assessments were then recorded at intervals of five minutes, 60 minutes and 120 minutes. Results of the study showed that Inflacin™ significantly reduced pain and stiffness after just one application of 2 grams. On average, Inflacin™ reduced pain by 45% (as compared to 15% in the placebo group) after one dose in the first 60 minutes of application. In several test subjects, researchers recorded a dramatic reduction of pain. In some, a complete eradication of pain and almost total loss of stiffness occurred. Over the next 60 minutes, pain and stiffness returned among those in the placebo group, while subjects in the Inflacin™ group continued to experience a decrease in pain and stiffness. Moreover, subjects in the Inflacin™ group experienced average increase in grip strength of 10% in both hands; grip strength did not improve in subjects using the placebo (see Figure 1).



In the clinical test, Inflacin™ showed an immediate effect (within five minutes) of statistically reducing pain and stiffness (by as much as 72%, compared to 15% for the placebo in one subject). Inflacin™ was also shown to improve handgrip strength within five minutes, whereas the same improvements were not demonstrated among those using the placebo.

Data indicated that at every time point in the trial-at 5, 30, 60 and 120 minutes-Inflacin™ improved the pain score and performed better than the placebo in decreasing pain.

The overall conclusions drawn from the study indicate that in subjects with mild to moderate pain, Inflacin™ is an effective compound for reducing pain and stiffness and improving grip strength when applied topically. Despite some relief of pain and stiffness noted within the first 60 minutes among those in the placebo group, symptoms ultimately began to return. Additionally, subjects who used the placebo cream reported no improvement in handgrip strength.[4]

Why Inflacin™ works

BioZone Laboratories, Inc., of Pittsburg, California, was granted a U.S. Patent entitled Compounds and Methods for Inhibition of Phospholipase A2 and Cyclooxygenase 2. BioZone then trademarked the technology and compound as Inflacin™. In addition to arthritis, BioZone's patent addresses other diseases caused by excessive phospholipase A2. Listed below are examples referenced in the patent:

- Psoriasis Fibromyalgia
- Shingle Gout
- Pancreatitis Sepsis and shock
- Eczema Peritonitis
- Collagen vascular disease

Inflacin's™ combination of active ingredients and unique delivery system makes it an effective anti-inflammatory topical analgesic. The patent-pending ingredient that developers at BioZone Laboratories used to make Inflacin™ specifically inhibits certain enzyme systems that mediate a variety of physiological responses, including a cascade of biochemical reactions that help facilitate pain, fever, inflammation and other functions. The resulting anti-inflammatory action is much more effective than that used in other marketed topical products, which have a counter irritant mode of action but are only marginally effective at disguising the pain.

In addition to Infracin's™ effective anti-inflammatory ingredients targeting PLA2 activity, the product's unique QuSome™ delivery system ensures a strong effect on pain and inflammation. This unique anti-inflammatory therapy can be administered topically, though in its present commercial form, it can only be used for alleviating muscular, joint and skeletal pain. An intravenous version is being developed to treat pancreatitis, peritonitis, sepsis and other internal inflammatory disorders.

Although the market is flooded with products containing topically active ingredients, the vehicles of topical delivery have remained relatively unchanged over the past 200 years. That's why the advent of BioZone Laboratories' QuSomes™, a method of reformulating topical products, is such an exciting development.



Infracin™ contains QuSome™ liposomes (microscopic vesicles composed of membrane like lipid bilayers separated by an aqueous layer with an aqueous center) within a multiphase system. Each phase contains an active ingredient. What's more, these active ingredients are encapsulated, thereby enhancing the delivery and improving product performance.

Why is this unique form of encapsulation so effective? Because rather than flooding or bombarding the skin and causing irritation, encapsulation serves to protect the active ingredients until they are absorbed into the lower layers of skin, where they can be released over a prolonged period of time.

The liposomes form a bubble-like "packet" that contains the active ingredients. The drugs are shielded and protected inside the liposomes, which help carry these drugs through the upper layers of the skin until they are released into the lower layers of skin, explains Dr. Sangita Ghosh, chief scientist at BioZone Laboratories.

Benefits of QuSome Infracin™ over other analgesics

QuSome Infracin™ provides several advantages over "free active" topicals (those in which the ingredients are not encapsulated). Liposomal encapsulation increases permeation of the active ingredients. Because they are encapsulated as they pass through the upper layers of skin, QuSomes™ eliminate irritation and optimize dosage levels. Their greater concentration and residence time in the epidermis and dermis allow for prolonged release. Encapsulation also protects the drug from metabolic degradation. And finally, this mode of delivery reduces systemic absorption.

When it comes to analgesic drugs designed to reduce inflammation and pain due to arthritis and related conditions, topicals are not the only option. Internal analgesics are also available. And while they do not irritate the upper layers of the skin, many users complain of irritation to the stomach. Because it is topical, Infracin™ has no risk of irritating the stomach.

In essence, Infracin™ provides a partial solution to those who suffer from mild to moderate pain and inflammation due to arthritis and related conditions. It offers long-lasting and fast pain relief that won't irritate the stomach, has no offensive odor and doesn't leave a greasy residue on the skin.

[Find out more about Infracin](#)

References

1. University of California, San Francisco. National Arthritis Action Plan: A Public Health Strategy, 1999.
2. Vades P, et al. 1985 Characterization of extra cellular phospholipase A2 in human synovial fluids. Life Sci 36:579.
3. Vades P, et al. 1990 Soluble phospholipase A2 in human pathology: clinical-laboratory interface. Biochemistry, molecular biology, and physiology of phospholipase A2 and its regulatory factors. Ed. AB Mukherjee, Plenum Press, New York.
4. Keller, Brian C. Topical Treatment for Arthritis Clinical Study, 2002.

[Back to the Magazine Forum](#)

All Contents Copyright © 1995-2009 Life Extension Foundation All rights reserved.

LifeExtension[®]

These statements have not been evaluated by the FDA. These products are not intended to diagnose, treat, cure or prevent any disease. The information provided on this site is for informational purposes only and is not intended as a substitute for advice from your physician or other health care professional or any information contained on or in any product label or packaging. You should not use the information on this site for diagnosis or treatment of any health problem or for prescription of any medication or other treatment. You should consult with a healthcare professional before starting any diet, exercise or supplementation program, before taking any medication, or if you have or suspect you might have a health problem. You should not stop taking any medication without first consulting your physician.