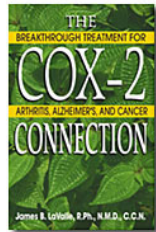




NEXRUTINE™: A BREAKTHROUGH IN NATURAL PAIN MANAGEMENT



Dr. Jim LaValale
R.Ph., N.M.D., C.C.N.
*Appearing in the August 2001
issue of Total Health Magazine*

*Author of "The Cox-2 Connection:
Breakthrough Treatment of Arthritis, Alzheimer's, & Cancer"*

If you live long enough, chances are that by age 50 you are going to have some arthritic condition. In fact 80% of people over the age of 50 suffer from arthritis. Plus, more people are living active lifestyles and sometimes the pain and strain from exercise can make recovery difficult. Traditionally people turn to a vast number of over-the-counter (OTC) solutions such as aspirin, ibuprofen and acetaminophen. But many people today are looking for natural options that are safer, offer less long-term risk, and provide solutions to common pain, inflammation, and arthritis. But consumer confidence in natural products isn't as strong as it should be. This may be due to lack of information, inconsistent product quality, or just being confused on what to choose. Finding a natural supplement proven safe and effective for pain management has remained elusive until recently. Over the last few years there has been a great deal of research in the herbal and nutraceutical arena in these areas. One such example of the emerging science in natural medicine is Nexrutine. This new patent-pending natural ingredient combines the wisdom of traditional botanical knowledge with the latest in pharmaceutical science. With the development of Nexrutine, by Irvine, California based Next Pharmaceuticals, Inc., consumers truly have an all-natural choice when dealing with pain.

What is Nexrutine and Where does it Come From?

Nexrutine is an exciting new patent-pending dietary supplement that has potent anti-inflammatory action. A rapidly acting ingredient, Nexrutine alleviates the pain associated with arthritis as well as the joint and muscle soreness associated with over-exertion or physical activity. Significantly, test subjects report that Nexrutine not only eases general aches and pains but also helps make everyday activity more comfortable.

Nexrutine is a proprietary extract from a plant that is new to Western Medicine but has a long history of successful medical use in other cultures. Nexrutine is derived from the Phellodendron tree, a member of the Rutaceae plant family. This family of plants has played a significant role in Chinese Medicine and teas made from the Phellodendron tree itself have been used for centuries to treat inflammation, abdominal pain, and gastrointestinal discomforts. Considering the historical use of Nexrutine's natural source, it should come as no surprise that the supplement is safe, gentle on the stomach, and free of side effects. Some studies have even reported

that certain compounds in Nexrutine actually protect the gastrointestinal tract against ulceration. A large number of Americans will be welcoming this new remedy to their medicine cabinets. Nexrutine may provide significant benefits to those who have experienced the unwanted and sometimes severe side effects produced by popular prescription and OTC pain medicines. And it will work for those who simply seek safe, natural pain relief.

Nexrutine as Cox-2 Inhibitor

The lack of side effects is but one advantage Nexrutine has over other painkillers like ibuprofen, naproxen and other non-steroidal anti-inflammatory drugs (NSAIDs). Nexrutine's unique mechanism of action is an even more compelling attribute. A comparison with other anti-inflammatory drugs serves as a good illustration. First, Nexrutine inhibits the COX-2 enzyme, a chemical in the body that causes inflammation. Unlike other COX-2 inhibitors, Nexrutine does not act directly on the enzyme itself. Instead, Nexrutine's true strength resides in its ability to inhibit the actual production of the enzyme that leads to inflammation so it shuts off the problem at the source.

Another unique quality of Nexrutine is that it selectively inhibits the COX-2 enzyme. This means that it does not interfere with another related enzyme in the body, the COX-1 enzyme. This "good" Cox enzyme is involved in maintaining the lining of the stomach and also promotes kidney function. Nexrutine leaves the COX-1 alone to do its work. Yet the same cannot be said of other NSAIDs. Many such over-the-counter painkillers block both COX enzymes. And over-use of these medicines can prove dangerous. Indeed, drugs that block the good COX-1 enzyme have been associated with kidney and liver damage, and over 100,000 deaths a year!

Selective Cox-2 inhibitors are now some of the most prescribed pharmaceutical drugs on the market. Recent reports show that Celebrex™, a proprietary COX-2 drug, has surpassed the anti-impotence medication Viagra™ as the fastest selling new prescription drug in history. According to IMS Health, Celebrex sold 6.86 million prescriptions during its first six months on the market, compared with about 5.3 million for the anti-impotence drug Viagra. The amazing number of prescriptions for COX-2 inhibiting drugs, coupled with the fact that Nexrutine is the first all-natural selective COX-2 inhibitor, suggests that Nexrutine has the potential to become the single major selective COX-2 pain reliever available without a prescription.

It should be noted that all NSAIDs and COX-2 drugs can reduce renal function. Patients on these drugs are at risk for edema and increased blood pressure. Therefore, even though Nexrutine is gentle and comes from a plant with a long history of safety, it is a COX-2 inhibitor and should be used with caution and under a physician's guidance in patients who have impaired renal function, hypertension, or heart failure.

The Development of Nexrutine

One of the major obstacles facing consumers who wish to use natural remedies is finding products that are made with materials that are consistently effective and safe. Next Pharmaceuticals, the company credited with bringing us Nexrutine, has proven itself in this arena by producing new ingredients that the consumer can trust with confidence. Next Pharmaceutical's natural ingredients are designed for nutritional supplements, functional foods, and other natural alternatives to the OTC drug markets. The company has several areas of strength and expertise that are especially important, including science-based new proprietary product development and a strong consumer education program. Such education is essential for those who want and deserve to know how a given product works in our bodies.

There are a number of herbs and spices, such as feverfew, holy basil, turmeric, and ginger that are purported to have COX-2 inhibition properties. But these have not been as systematically studied to observe the level of COX-2 versus COX-1 inhibition. The extensive and complex process that was undertaken before testing Nexrutine on human subjects began with selecting the appropriate plants for screening in appropriate pharmaceutical models. A worldwide literature search of the plants used in traditional medical practices was conducted. The literature was evaluated in terms of method of preparation, chemical compounds and reported results for each botanical. In addition, the structure-activity relationship between the chemicals found to be present and the pharmacological activity claimed for the product were analyzed. Investigations focused on plants that had purported effectiveness as traditional medicinals in other countries for alleviating inflammation and pain.

Using its in-depth knowledge of phytochemistry, pharmacology, bioavailability, toxicology and chemistry, the company narrowed the vast number of possible candidates to a few plants that promised to be effective and safe. This research process led to the study of the Rutaceae plant family as a source of an extract to treat inflammation. An exhaustive literature review revealed that material from the Phellodendron tree and an isoquinoline alkaloid in Phellodendron had been used to treat inflammation and arthritis in China. To make an effective plant-based remedy to treat any specific condition, it is necessary to create the ideal extract by removing unwanted compounds and concentrating the key active compounds. This lengthy process was applied to Phellodendron in order to have a safe anti-inflammatory/pain reliever that would be standardized for uniformity and consistent efficacy.

Plants contain a wide variety of active constituents and it's important to determine the best way to concentrate the largest number of these actives while eliminating unwanted compounds. Once different fractions of the Phellodendron tree were prepared, those that met the desirable criteria and would eventually become Nexrutine were tested by a variety of methods to see which one demonstrated the greatest biological activity in the therapeutic area for which it was being considered. As with other botanical-based medicines, the extracts were sent to well-established laboratories in order to undergo rigorous pharmacological screening in order to gain insight on Nexrutine's mechanism of action.

In the next phase, the fractions were tested in various animal models. These models, widely used throughout the world in commercial laboratories and universities, are helpful in predicting how the agent under study will affect human beings. During this phase, Nexrutine was compared to well known anti-inflammatory drugs, such as naproxen. A comparison of the analgesic properties of Nexrutine and naproxen is shown in Figure 1. Nexrutine and naproxen's analgesic properties in this rat model were similar.

Even though the parent plant has a long history of safe use, toxicity tests were still performed to make sure that Nexrutine is safe for human beings. No toxicity was noted in the animals at 5 grams per kilogram, an extremely large dose that is way beyond the therapeutic dose. The overall results obtained through testing were very exciting and indicated great promise for this natural remedy in the fight against inflammation and pain.

Human Study

The company then retained the services of a contract research organization that tested 53 human subjects who took the product for two weeks, receiving a dosage of 250 mg three times daily. The product was tested and found to be safe and effective. An analysis of the results of the trial showed that 72% of the patients involved found the remedy to be effective. Two out of three subjects reported that Nexrutine not only eases general aches and pains but also helps make everyday activity more comfortable. All the subjects involved were comfortable using the product and no significant side

effects were reported. Since gastrointestinal side effects are common with other anti-inflammatory products, it is quite significant that 86% of those taking Nexrutine found it to be gentle on the stomach.

Because of its unique properties, Nexrutine seems to be the only one of the plants with COX-2 inhibiting properties that will receive patent protection. Why? Nexrutine is the only plant extract for which both COX-1 and COX-2 activities have been quantitatively measured and that exerts its pain relieving properties.

It is expected that dietary supplement companies with brand development expertise will see the value of Nexrutine, and that consumers will soon find Nexrutine on the shelves in drug and health food stores. FlexAnew™ with Nexrutine from Natrol is on drug store shelves now. Both the manufacturers of products containing Nexrutine and consumers who use these products will be able to do so with the highest degree of assurance that they are using a product that is everything it claims to be.

Other Potential Benefits of Nexrutine

As a COX-2 inhibitor, Nexrutine joins some exciting news that has recently surfaced about other uses for these drugs. Because the pro-inflammatory COX-2 enzyme is also produced in human colon cancer cells, COX-2 inhibiting compounds like Nexrutine could provide a promising role in an overall cancer prevention plan. Furthermore, the risk of developing Alzheimer's disease, which is thought to involve an inflammatory component, may also be reduced by use of NSAIDs. Lastly, the Phellodendron tree from which Nexrutine is derived has been shown to have an effect on the central nervous system and the potential to help control mild anxiety.