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REPORT

Arthritis Victims Suffered...
Cancer Patients Died,
While An Effective Therapy Already Existed

When Celebrex was approved in the United States, most people thought a breakthrough in the treatment of arthritis had been discovered. Celebrex alleviates inflammation and pain by inhibiting an enzyme called cyclooxygenase-2 (COX-2).

The truth, however, is that Celebrex was not the first COX-2 inhibiting drug. Way back in 1971, a COX-2 inhibitor called nimesulid was developed and subsequently sold in most countries around the world...except the United States.

Americans suffered inflammatory pain while those living outside of the U.S. benefitted from the COX-2 inhibiting effects of nimesulid. In addition, nimesulid inhibits the growth of certain cancer cells.

In this article, we discuss the role of COX-2 inhibition therapy in the adjuvant treatment of arthritis and cancer.

Before COX-2 inhibitors were approved, Americans had to rely on toxic NSAIDs (non-steroidal anti-inflammatory drugs). Some commonly used NSAIDs were Indocin, Volteran and high-dose aspirin therapy. While these drugs were partially effective in treating arthritic pain and inflammation, side effects such as stomach irritation-bleeding and kidney toxicity made them less appealing for long-term use. NSAIDs also cause peptic ulcers, requiring 100,000 hospitalizations and 7,500 deaths per year in the U.S.

NSAIDs work by inhibiting both the COX-1 and COX-2 enzymes. The advantage of selective COX-2 inhibiting drugs like Celebrex or nimesulid is that they primarily inhibit COX-2, thus sparing the body the toxic effects of over-suppression of COX-1.

Over-inhibition of COX-1 is a primary cause of NSAID toxicity. COX-1 is naturally and consistently present in many cells throughout the body. It plays a benevolent role in overseeing a number of physiological processes, such as modulating the release of beneficial prostaglandins, whose job it is to protect the mucosal lining of the stomach. The COX-2 form, dwelling mainly in inflammatory and immune cells, has a more evil role to play, causing excess production of the pro-inflammatory prostaglandin E2. Thus, COX-2 inhibiting drugs can play an important adjuvant role in suppressing arthritic pain and inflammation.

It is unfortunate that American arthritis sufferers had to wait until 1999 to obtain this class of drug. This same class of drug (COX-2 inhibitor) was approved in Europe way back in 1985. Hundreds of thousands of Americans died from NSAID-induced side effects while the safer nimesulid drug could have been used to reduce these lethal side effects.

COX-2 and cancer

COX-2 is involved in regulating cell growth, which might suggest why it's expressed in human colon cancer cells and seems to spur on tumor growth. That also helps to explain why we've been hearing lately about how NSAID drugs can help to retard tumor growth in colon cancer, conceivably through apoptosis (programmed cell death) of malignant cells.



In fact, regular aspirin users have between a 40% to 50% reduction in the incidence of colorectal polyps in women.(1) In addition, aspirin and NSAIDs are associated with a 50% decrease in the cancer mortality. In a randomized clinical trial, the drug sulindac (a NSAID) reduced colon polyps both in patients with familial adenomatous polyposis. One theory is that these are the results of COX enzyme inhibition.

Likewise, studies are also suggesting that chronic long-term use of NSAIDs may help reduce the risk of developing Alzheimer's disease.

Unfortunately, high doses of aspirin, ibuprofen and other NSAIDs act by suppressing both forms of the COX enzyme, thereby inhibiting the body's ability to synthesize beneficial prostaglandins. Hence, the nasty side effects make long-term, heavy use of NSAIDs a mixed proposition. Thankfully, COX-2 inhibitors are more selective in that they target primarily the COX-2 form, thus sparing the protective COX-1 and leaving it enabled to do its work. In addition, researchers have also noted that COX-2 inhibitors have demonstrated enhanced tumor inhibition in a variety of animal models. The COX-2 inhibitor, Celebrex—the main COX-2 inhibitor approved in the U.S.—actually inhibited xenografted tumor cells by as much as 90%.

Using COX-2 inhibitors to prevent cancer

A number of scientists are actively investigating COX-2 inhibitors as a potential drug therapy for the prevention and/or treatment of different forms of cancers. As early human studies of familial adenomatous polyposis have shown, virtually all patients with this genetic disease will develop colorectal cancer before 50, and the average life expectancy is only 42. The COX-2 inhibitor, Celebrex, which has been studied in three controlled studies, has demonstrated up to a 30% decrease in polyp burden. While these studies are too recent to assess long-term survival implications, the results were encouraging enough for the FDA to approve Celebrex for the treatment of familial adenomatous polyposis.

Being a rare cancer, however, researchers have turned their attention to other forms of the disease. In particular, since COX can activate carcinogens and inhibit apoptosis, inhibiting COX-2 has the potential in a variety of settings. Due to COX-2 overexpression in Barrett's esophagus and related cancers, a clinical trial has just been initiated at Johns Hopkins to examine the potential of Celebrex. With a 150-fold increase in COX-2 in squamous cell carcinoma patients, a clinical trial is also being planned to evaluate Celebrex for pre-malignant and malignant head and neck cancers. Recurrent bladder cancer is also the target of a clinical trial, and cervical and breast cancer have also been implicated through animal experimentation as potential targets, and the same is true of liver cancer and non-small cell lung cancer. It may also prove useful in combined protocols with paclitaxel, a chemotherapeutic agent that induces COX-2 expression and has, as a common toxicity, muscle and joint pain.

The mechanism for tumor inhibition, while not totally understood, appears to be related to starving tumor cells rather than directly killing off cancerous cells. That is, COX-2 inhibitors seem to retard and decrease tumor growth by disrupting formation of new tumor blood supplies (angiogenesis). Apparently, various cancers rely on large amounts of the COX-2 to proliferate and fuel malignant cell growth.

Using COX-2 inhibitors as an adjuvant cancer therapy

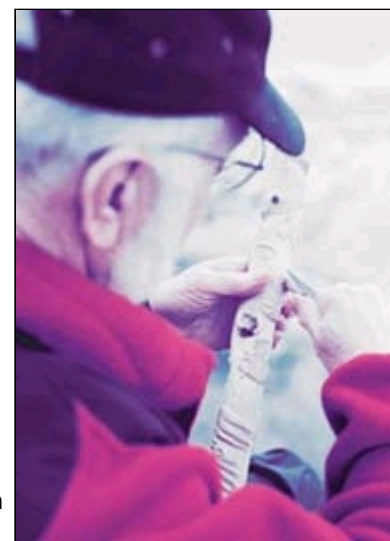
Most oncologists continue to overlook the value of COX-2 inhibiting drugs in the treatment of cancer. Many types of cancer cells use COX-2 to propagate and metastasize. This includes cancers of the colon, pancreas, breast, prostate, bladder, lung, head and neck, to name a few.

Several years ago, The Life Extension Foundation reported that European doctors were using nimesulid as an adjuvant cancer therapy. A protocol for using COX-2 inhibiting drugs was published so that Foundation members could provide their oncologist with guidelines for using COX-2 inhibitors to treat cancer.

New findings continue to show that COX-2 inhibitors suppress cancer cell growth. The December 1999 issue of the British Journal of Cancer showed that a COX-2 inhibiting drug significantly reduced the metastasis of colon cancer cells to the lungs of mice. The scientists concluded that COX-2 inhibitors may be a novel class of therapeutic agents to prevent colon cancer metastasis (which is how colon cancer kills).

A study published in the January 2000 issue of Carcinogenesis shows that human colorectal cancer cells can be made more sensitive to butyrate (a European cancer therapy) when the butyrate is combined with a COX-2 inhibiting drug. Butyrate helps to induce the differentiation and death (apoptosis) of colorectal tumor cells, but is not readily available in the United States. The doctors conducting this study stated that dietary modification (using therapies such as butyrate) along with COX-2 inhibiting drugs could be considered in the treatment of colon cancer.

In the January 1, 2000 issue of the Journal of Immunology, COX-2 inhibition in human lung cancer cells led to marked immune cell



COX-2 inhibiting drugs can play an important adjuvant role in suppressing arthritic pain and inflammation.

infiltration of the tumor and reduced tumor growth. COX-2 inhibition was accompanied by a significant decrease in the immunosuppressive cytokine IL-10 and a restoration of the more beneficial IL-12. The doctors conducting this study concluded that COX-2 inhibition suppresses tumor activity by restoring the balance of IL-10 and IL-12 in vivo.

Many types of cancer cells produce excess amounts of COX-2 and use this as biologic fuel to stimulate their rapid division. The theory behind cancer patients using COX-2 inhibitors is to deny the COX-2 enzyme to cancer cells. In a study published in Nature Medicine (1999;5:1348-1349), doctors found that blocking the COX-2 enzyme interferes with the formation of new blood vessels (angiogenesis). Since tumors require large amounts of blood to sustain their growth and to establish metastatic colonies, inhibiting the formation of new blood vessels is a desirable effect. COX-2 inhibitors appear to do just that. The doctors who conducted this study pointed out that new blood vessel growth is necessary for wound and ulcer healing and expressed concern that COX-2 inhibitors could produce gastric ulcer complications in some people. This is why it is so important for cancer patients to work closely with their oncologist if they plan to combine a COX-2 inhibiting drug with chemotherapy regimens. The rationale for using a COX-2 inhibitor with other cancer therapies is to increase the chances of a cure by attacking the tumor at multiple points in its division cycle.

One of the most exciting new therapies to treat cancer is the combined use of a COX-2 inhibiting drug along with a "statin" drug. The "statin" class of drugs are used to lower cholesterol, but they also suppress the propagation of certain cancer cells. When used together, these two drugs (a statin and COX-2 inhibitor) may provide the necessary one-two punch needed to control or eradicate the malignancy.

Cancer patients normally take one 100 mg tablet of nimesulid, twice a day. When using the drug Celebrex, cancer patients usually take 400 mg a day. If a cancer patient is on alpha interferon, COX-2 inhibitors should be avoided or reduced to a limited dosing schedule.

In order to help those with cancer to convince their doctors to prescribe COX-2 inhibitors and statin drugs, we have prepared a letter that cancer patients can present to their oncologist for consideration. This letter provides a scientific basis for an oncologist to prescribe these potentially life-saving drugs to cancer patients now! Access a free copy of this letter.

Unique properties of nimesulid

While we know nimesulid as a COX-2 inhibitor, it additionally boasts other actions. For example, one recent study(2) discusses its in vitro role in the antioxidant system of erythrocytes (red blood cells). The investigative team reports that there are approximately 150 NSAIDs, and that typically, these drugs have other properties, including the inhibition of superoxide generation in neutrophils, and other pathways related to free radical formation. It has been suggested for more than a decade that part of the pharmaceutical action of the NSAIDs have to do with free radical scavenging.

Nimesulid is a selective COX-2 inhibitor. As such, nimesulid targets COX-2 mediated prostaglandins, free radicals, proteolytic enzymes and histamine, while generally sparing the protective COX-1.

American cancer patients do not have ready access to nimesulid. Celebrex has proven benefits in fighting cancer, whereas another FDA-approved COX-2 inhibitor called Vioxx does not.

Americans suffered too long

Nimesulid is a drug that should have been approved by the FDA more than an decade ago. Americans suffered from arthritis pain and the lethal side effects from more toxic NSAIDs, while nimesulid was already approved throughout the world.

The price for a month's supply of Celebrex is \$125, yet nimesulid can be obtained in Europe for only \$22.00 per month. Americans pay for the FDA's drug lag with their pocketbooks and their lives.

Not only does nimesulid inhibit the activity of COX-2 enzyme, but it also reduces its genetic expression. It's the first COX-2 preferential inhibitor to be marketed worldwide and is available in 40 countries. In 1999, about 40 million patients were treated with nimesulid. Nimesulid trademarks include Aulin, Mesulid, Nimed, Nexen, Guaxan, Donulide, Nisulid, Ainex, Scaflam, Scaflan, Nimedex, Eskafam, Antifloxil, Plaurium, Restasis and Edrygil.



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Side effects of nimesulid and other COX-2 inhibitors

According to the World Health Organization, nimesulid's "pharmacodynamic profile is compatible with a lower incidence of adverse GI reactions in comparison with other NSAIDs, although this has not been clearly demonstrated."

In a recent ADR newsletter edition, the World Health Organization (WHO)(3) wrote that, "Some studies show that the incidence of this type of ADR (adverse drug report) with nimesulid is similar to that of patients treated with control NSAID. Furthermore, there may appear endoscopically visible lesions of the gastric mucosa with nimesulid, and the selectivity of COX-2 inhibition may be lost at higher doses." That last statement is of particular note, as it suggests that, in high enough doses, nimesulid also shows evidence of inhibiting COX-1 and causing gastrointestinal problems. Even with Celebrex—the first U.S. approved COX-2 inhibitor—while it is supposedly 325 times more selective for COX-2 at doses only twice to four times the therapeutic dose, it significantly inhibits COX-1.(4)

Adverse drug reports attributed to nimesulid include skin, liver, peripheral oedema, stomatitis, paresthesia, thrombocytopaenic purpura, irritability and headaches/reduced visual acuity. At least one of the skin reactions was fatal. Of the adverse effects on the liver, some were compatible with Reye's syndrome and were fatal, and another of cholestasis, coagulopathy and liver enzyme elevation was also fatal. There also seems to be an association between higher toxicity and the combined use of nimesulid with other drugs, in particular, lisine salicylate and amoxicillin and clavulanate. It's possible that these don't mix well with nimesulid, although that hasn't been confirmed or denied by scientific research yet. However, one study found(5) that patients who were intolerant of NSAIDs had a much higher reactivity to nimesulid and acetaminophen. Patients that were intolerant of NSAIDs, and had a history of reactions to antimicrobial drugs, had a very high reaction rate with the Tylenol and nimesulid (24%).

Studies that do exist include a paper that discusses kidney toxicity of nimesulid, whereby there were 120 reports between 1988 and 1997 in the Northern Italian Regional Database.(6) Eleven of these were kidney adverse reactions, six requiring hospitalization. Another note in the WHO literature suggests that, "This drug is contraindicated in patients with hepatic [liver] failure and gastrointestinal bleeding."(7)

Finally, with typical NSAIDs (non-specific COX inhibitors), H2- receptor blockers are often employed to prevent gastric toxicity. In a recent poster at the 6th Internet World Congress for Biomedical Sciences, a team of Indian scientists who reported using an animal model argued that such protection isn't needed in patients taking nimesulid. Typically, with Vioxx or Celebrex, in the U.S., physicians haven't been prescribing such agents in conjunction with the drug. This certainly speaks to nimesulid's safety profile, relatively speaking.

When using COX-2 inhibitors, it is important to look out for NSAID-like side effects. Many doctors think COX-2 inhibitors are safe, but studies show that taking too high a dose can have the potential to create the same side effects of old-line NSAID drugs. In other words, if too much nimesulid or Celebrex is taken, toxic suppression of the beneficial COX-1 enzyme can occur.

To help guard against the risk that a COX-2 inhibitor (like Celebrex or nimesulid) or NSAID drug (like ibuprofen) might cause gastric irritation, the consumption of 1800 mg a day of polyenylphosphatidylcholine is suggested. This potency can be obtained in two capsules a day of a dietary supplement called HepatoPro (formerly GastroPro) that is offered by The Life Extension Buyers Club.

References

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