Scientists find link between arthritis pain reliever and cardiovascular events

September 13 2010

A research team from the University of California, Davis and Peking University, China, has discovered a novel mechanism as to why the long-term, high-dosage use of the well-known arthritis pain medication, Vioxx, led to heart attacks and strokes. Their groundbreaking research may pave the way for a safer drug for millions of arthritis patients who suffer acute and chronic pain.

Using metabolomic profiling to analyze murine (rodent) plasma, the scientists discovered that Vioxx causes a dramatic increase in a regulatory lipid that could be a major contributor to the heart attacks and strokes associated with high levels of the drug and other selective COX-2 inhibitors, known as "coxibs."

"This is a major breakthrough that can lead to a better medication for people suffering from acute pain," said entomologist-chemist Bruce Hammock, a distinguished professor of entomology with a joint appointment at the UC Davis Cancer Center. The research took place in the laboratories of Hammock, cell biologist Nipavan Chiamvimonvat, UC Davis Division of Cardiovascular Medicine; and physiologist Yi Zhu, Peking University.

The research is to be published the week of Sept. 13 in the Proceedings of the National Academy of Sciences.

"Our metabolomics study discovered that 20-hydroxyeicosatetrasanoic acid, also known as 20-HETE, contributes to the Vioxx-mediated

cardiovascular events," said UC Davis bioanalytical chemist Jun-Yan Liu, the senior author of the paper and a five-year member of the Bruce Hammock laboratory.

Millions of arthritis patients took Vioxx before its withdrawal from the global market in 2004. Vioxx, a nonsteroidal anti-inflammatory drug (NSAID) and coxib for acute and chronic pain, particularly for arthritis and osteoarthritis, was on the market for five years. Merck & Co. voluntarily withdrew it in September 2004 due to concerns about the increased risk of heart attacks and strokes.

The chronic administration of high levels of selective COX-2 inhibitors, particularly rofecoxib, and valdecoxib, increases the risk for cardiovascular disease, Liu said.

Cardiology expert Garrett J. Gross, professor in the Department of Pharmacology and Toxicology at the Medical College of Wisconsin, Milwaukee, who is not associated with the research, described the UC Davis-based research as "a highly significant finding."

"The recent discovery of Hammock and co-workers at UC Davis that murine plasma concentrations of 20-HETE may be a significant biomarker which may predict the susceptibility of patients to having an unfavorable cardiovascular event while taking selective COX-2 inhibitors such as rofecoxib is an important and novel finding," Gross said. "This discovery may help to unravel the unexpected occurrence and potential mechanism responsible for sudden cardiac death in a number of patients taking COX-2 inhibitors for inflammatory disorders such as arthritis. This a highly significant finding which may lead to a safer use of these drugs in selective patients with disabling inflammatory disorders and may lead to the development of more selective drugs for use in these types of patients."

Urologist Ralph devere White, professor of urology at the UC Davis School of Medicine and director of the UC Davis Cancer Center, described the research as "extremely exciting."

"Vioxx and other drugs in this class were looked on as extremely promising in moderation," devere White said. "The fact that the Hammock lab discovered why the drug could lead to heart attacks and strokes and is able to quantify the deleterious facts is extremely exciting. I hope that patients can safely use this drug in the future or block the deleterious effects so it will have all of the benefits and none of the adverse side effects."

When asked to comment on the research, Richard Roman, professor and chair of the Department of Pharmacology and Toxicology, University of Mississippi Medical Center, with expertise in 20-HETE and cardiology, said: "Rofecoxib (Vioxx) a COX2 inhibitor that was widely used for pain relief was recently withdrawn from the market because it increased the risk of heart attack and stroke. The mechanism of the adverse effects of has not been determined. The study of Hammock et al is important breakthrough because it indicates that Rofecoxib raises the blood levels of 20-HETE which is a potent constrictor of vessels in the heart and brain and they showed it also increases platelet aggregation and clot formation."

"They further demonstrated," Roman said, "that this adverse effect was due to the ability of the compound to inhibit the enzyme COX2 which appears to play a major role in metabolizing and inactivating 20-HETE in the body. Overall this study suggests that the cardiovascular risk associated with Vioxx is not unique to this drug but is likely shared by all members of this class of drugs. It also indicates that one might be able to predict patients that are at risk for a potential cardiovascular event by monitoring serum 20-HETE levels."

"Obviously, more studies are now needed to measure 20-HETE levels in patients treated with COX2 inhibitors because the current study was done in mice and the relative importance of COX2 enzymes in the metabolism of 20-HETE may differ substantially in man versus the mouse."

Nationally, some 46 million individuals suffer from arthritis. "And almost one million patients are admitted to hospitals every year because of their arthritis," Hammock said. "They do need effective and safer drugs to relieve their pain."

The UC Davis scientists predicted their research will open up new strategies to develop safer coxibs. For example, inhibiting the regulation of the enzymes CYP4A and CYP4F could lower the circulation level of 20-HETE and that may reduce the cardiovascular events of coxibs.

More information: The paper, "Metabolic Profiling of Murine Plasma Reveals an Unexpected Biomarker in Rofecoxib-Mediated Cardiovascular Events," is co-authored by Jun-Yan Liu, Ning Li, Jun Yang, Nan Li, Hong Qiu, Ding Ai, Nipavan Chiamvimonvat, Yi Zhu and Bruce Hammock. All are from UC Davis except Nan Li and Yi Zhu, from Peking, while Ding Ai is associated with both Peking University and UC Davis.

Provided by University of California - Davis