SR Home

News

People

Events

For the Record

Opinion

Classifieds

Contact Stanford Report

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COX-2 inhibitors may interfere with bone growth, healing

By SARA SELIS

Researchers at the medical center have found that selective COX-2 inhibitors — a class of medications widely prescribed for painful inflammatory conditions such as osteoarthritis and rheumatoid arthritis — interfere with the healing process after a bone fracture or cementless joint implant surgery.

Their findings, published in the November issue of the *Journal of Orthopaedic Research*, suggests that patients who regularly take COX-2 inhibitors should switch to a different medication, such as acetaminophen or codeine derivatives, for a period of time following a bone fracture or cementless implant.

The results also suggest that physicians should consider changing prescribing patterns since many doctors commonly prescribe anti-inflammatory drugs including COX-2 inhibitors under the very circumstances in which they should be avoided.

"It's very common. You break a bone and go to the ER. The doctor sets it in a splint and prescribes one of these anti-inflammatory drugs (including COX-2 inhibitors) for pain," said Stuart Goodman, MD, professor of orthopedic surgery at the medical school and lead author of the study. "We now know that could actually delay healing."

The enzyme Cyclooxygenase-2, or COX-2, is produced by the body in response to injury or inflammation. COX-2 inhibitors, including anti-inflammatory medications such as rofecoxib (Vioxx), celecoxib (Celebrex) and others block production of this enzyme. Goodman's research, conducted on rabbits, shows that COX-2 inhibitors also impede the new bone growth that normally helps heal a fracture or stabilize a joint implant.

Belonging to a class of medications called nonsteroidal anti-inflammatory drugs, COX-2 inhibitors were developed in the late 1990s as an alternative to another group of medications called nonspecific NSAIDS, which inhibit the production of COX-2 along with the enzyme Cyclooxygenase-1, or COX-1.

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Nonspecific NSAIDS, including aspirin, ibuprofen, naproxen and others, often cause stomach irritation and a tendency to bruise easily. COX-2 inhibitors largely avoid these side effects.

Researchers confirmed years ago that nonspecific NSAIDS inhibited bone growth and healing, but the Stanford study is among the first to show that COX-2 inhibitors have the same effect.

In the tibia bone of eight New Zealand white rabbits, Goodman and his team implanted a titanium device called a harvest chamber, which resembles a small screw. The device has a removable, hollow inner core that allows researchers to periodically extract the tissue growing inside. The growth of new bone into the chamber simulates healing of a fracture or joint implant.

Researchers gave the rabbits the following oral treatments for four weeks each: plain water; water with naproxen; plain water again; and sugar-coated pellets of rofecoxib (a COX-2 inhibitor). After each treatment, researchers removed the harvest chamber's core and extracted the tissue growing inside. After preserving the tissue in liquid nitrogen, the researchers sectioned and processed it with special stains including monoclonal antibodies, allowing them to see how new bone had grown back.

Because a harvest chamber allows new tissue to be extracted multiple times as it grows back, the rabbits served as their own control groups (after consuming plain water) as well as the two experimental groups (after consuming naproxen and rofecoxib). The researchers found that while the tissue in the control group contained 24.8 percent and 29.9 percent new bone growth, the tissue harvested after the rabbits consumed naproxen and rofecoxib contained significantly less — 15.9 percent and 18.5 percent respectively.

The difference in new bone growth associated with the two drugs was statistically insignificant; practically speaking, the COX-2 inhibitor impeded new bone growth as much as the nonspecific NSAID.

While acknowledging the limitations of animal research, Goodman said this study "has great applicability to humans, because the healing process is virtually the same" for rabbit and human bones.

Goodman is having his own patients avoid COX-2 inhibitors for six weeks after a fracture or joint

implant, and he recommends other physicians do the same. "This research has very practical applications."

Goodman said his recommended six-week "time-out" period is an educated guess, because his study didn't address how long the bone-growth-suppressing effects of COX-2 inhibitors last. To answer that question, Goodman and his colleagues recently began another research study.