Physicians should be cautious when prescribing diclofenac

Authors of new research into the safety of one of the first and most commonly used non-steroidal anti-inflammatory drugs (NSAIDs) are calling on physicians to stop using it. In Canada, about 1.3 million prescriptions for diclofenac were dispensed in 2009.

The Feb. 12, 2013 study in *PLoS Medicine* (2013;10:e1001388) indicates that diclofenac use can increase the risk of heart attack or stroke in patients with pre-existing conditions such as diabetes, high cholesterol or other high risk factors for cardiovascular problems.

The study's coauthor says people with risk factors for cardiovascular disease are being prescribed diclofenac.

The relative risk of a serious cardiovascular event in patients taking diclofenac versus non-use of NSAIDs ranged from 1.4-1.6. This means those using diclofenac were approximately 1.5 times more likely to have cardiovascular complications than someone not using diclofenac. Naproxen's relative risk ranged from 0.92-1.2. Diclofenac has been on the market for nearly half a century.

Study coauthor, Dr. David Henry, says, "Diclofenac doesn't have any advantages, but has a substantial disadvantage."

"The world could do well without the drug," adds Henry, who is the chief executive officer for the Institute for Clinical Evaluative Sciences. He estimates that many people with risk factors for cardiovascular disease are being prescribed diclofenac, since he says prescriptions for this drug are used more by the over-65 population, among whom risk factors like heart disease, diabetes and high cholesterol are common.

The researchers are particularly concerned about the use of diclofenac in low- and middle-income countries where rates of cardiovascular disease are high and rising and diclofenac is often preferentially listed on the "essential medicines" list. Henry and coauthor, Dr. Patricia McGettigan, have petitioned the World Health Organization (WHO) to substitute naproxen for diclofenac on its essential medicines list, which provides governments with advice on which medicines should be subsidized. Henry says they have also petitioned WHO to recommend naproxen as the NSAID of choice, hoping that will lead to delisting diclofenac.

Along with ibuprofen and naproxen, diclofenac is a nonselective NASID. This class of drugs reduces the production of prostaglandins by blocking binding to cyclooxygenase enzymes 1 and 2 (COX-1 and COX-2) as an inhibitor. COX-2 inhibitors can pose cardiovascular risks.

Naproxen is less selective for COX-2 than diclofenac, which, Henry says could balance the cardiac risk chemically.

"We've waited for the regulatory agencies to act for many years on this drug," says Henry. "This message has been out there for quite a while."

He is referring to one of his earlier studies (*JAMA* 2006;296:1633-44), which aimed to determine the effect of selective and nonselective NSAIDs on cardiac risk. They found that rofecoxib and diclofenac posed similar cardiac risks for patients with and without cardiac risk factors. Rofecoxib was pulled from the market in 2004; diclofenac was not.

"The signals were there earlier," Henry says. "We're using a double standard here." He is calling on health organizations to take action against the drug.

Health Canada did not respond to inquiries about any plans to review the drug's safety or ban it from the market.

Dr. John Penning, the director of the Acute Pain Service at the Ottawa General Hospital, recommends doctors start with the safest drug, in this case naproxen, but says that patients should be given the option to try different drugs and find the medication that suits them best.

Some patients, he says, may be willing to take the risk. Penning explained that the absolute risk seems high when it's reported as a potential 35% increase, for example. But what this actually means for an individual is that one's chance of developing a condition might rise from 5% to 6.75%.

"If you're an 80-year-old person and they're going to tell you that this drug might increase your risk of having a heart attack from 0.5% to 1%, but it allows you to play with your grandkids — you're going to take that risk," Penning says.

Patients should be given the chance to make an informed decision, he says. Some were upset when that chance was taken away when rofecoxib was removed from the market nearly a decade ago.

"Finally they had come across a drug which helped them a lot, it allowed them to have a life, and the government decided 'no, you can't have it' — the patient was denied the right to make an informed decision," says Penning.

Penning agreed with studies stating that diclofenac should probably not be a first-line drug, but says it should still be an option for low-risk patients who have tried other options.

But Henry disagrees. He advises patients and doctors to take matters into their own hands, pending decisions from the WHO, and a review of the drug by the European Medicine Agency which began in October 2012.

"If regulatory agencies won't get rid of the drug, patients and doctors should just stop using it," he says. — Sarah Spitz, *CMAJ*

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