Study finds Vioxx took deadly toll

By CAROLYN ABRAHAM
MEDICAL REPORTER
Tuesday, January 25, 2005 - Page A1

Vioxx, the blockbuster arthritis and pain medication pulled off the market last September, could have killed more than 40,000 people in the United States, according to an FDA scientist who has said his employer silenced his earlier warnings about the drug's safety.

David Graham, associate director of science for the U.S. Food and Drug Administration's Office of Drug Safety and lead author of a study published on-line by The Lancet yesterday, found that Vioxx raised a person's risk of coronary heart disease by 34 per cent, compared with other anti-inflammatory drugs, including Celebrex, its onetime rival in the class of drugs known as cox-2 inhibitors.

(Celebrex has also been linked to heart attacks at high doses).

Dr. Graham and colleagues estimate that during the five years Vioxx was sold in the United States, it caused between 88,000 and 140,000 excess cases of serious heart disease. Based on national statistics of heart disease and deaths, the researchers estimate that close to half of those cases, or 44 per cent, would have resulted in fatalities. This means anywhere from 39,000 to 61,000 deaths in the United States could be linked to Vioxx.

"It's a huge number," said Dr. Graham, now widely known as a whistle-blower scientist.

"In the future, when trials show that a new treatment confers a greater risk of a serious adverse effect than a standard treatment, we must be much more careful about allowing its unrestrained use."

Dr. Graham said in an interview yesterday that it was fair to extrapolate the U.S. numbers to Canada. According to IMS Health, a private company that tracks prescription-drug sales, pharmacies in Canada dispensed more than 15 million prescriptions for Vioxx after it hit the market in 1999.

"The population of Canada is about an eighth, or ninth, in terms of the size. And the level of use, or exposure to, Vioxx in Canada was the same, if not greater, than in the U.S.," Dr. Graham said.

Such an extrapolation would suggest Vioxx could be associated with as many as 4,000 to 7,000 deaths in Canada.

But Muhammad Mamdani, a senior scientist with the Institute for Clinical Evaluative Sciences in Toronto who has studied Vioxx and other cox-2 inhibitor drugs in its class, cautioned that those numbers "seem a bit more like back-of-the envelope calculations."

"Do I believe those numbers? Not really," he said. "They could be higher or they could be lower. It's dangerous to extrapolate a number from the data."

Certain factors might skew the information, Dr. Mamdani said. For example, he noted most of the heart problems uncovered were linked to patients taking Vioxx at doses higher than 25 milligrams a day.

As well, he said, people taking Vioxx in the study may have been at higher risk of coronary disease: "People who use traditional NSAIDS [non-steroidal anti-inflammatory drugs such as ibuprofen] are typically healthier."

He said if Vioxx had such a dramatic effect on heart attack rates, researchers here would have detected a spike. Instead, he said, none was apparent.

Still, Dr. Mamdani added: "I think David Graham's work should be commended. It shows in a reasonably convincing manner that there's a problem there."

No one from Health Canada would comment on Dr. Graham's study. But spokeswoman Jirina Vlk said Health Canada officials are combing through "volumes" of safety information to assess the cardiovascular and other problems Vioxx caused here before Merck & Co. pulled its drug off markets worldwide on Sept. 30.

That move followed evidence that Vioxx doubled the risk of heart attacks and strokes in a clinical trial studying whether the drug could prevent colon cancer. Other studies have suggested that the drug, which blocks an enzyme linked to pain and swelling, contributes to blood clotting and hypertension. But the cancer study was not the first to point to the heart risks of taking Vioxx.

Dr. Graham decided to lead a Vioxx study after a large trial intended to highlight the gastrointestinal safety of the drug instead suggested it carried five times the risk of heart problems compared with naproxen, an older anti-inflammatory and pain-killing medication.

At the time, Merck officials suggested naproxen actually protected the heart, which made it appear as though Vioxx was having a damaging effect. Dr. Graham decided to investigate further.

He and colleagues analyzed data from 1.4 million people between the ages of 18 and 84 in California who were treated between January of 1999 and December of 2001 with one of the new cox-2 drugs and those taking the older NSAIDS.

Not only did they find that naproxen did not protect against serious heart disease, they uncovered the risk that Vioxx posed.

But Dr. Graham said that his supervisors at the FDA discouraged him from presenting his findings to a drug-safety meeting last summer. As well, he said, "They tried to block it from being published."

"I was threatened with severe consequences if I went forward. I took that to mean I would be fired," said Dr. Graham, who testified at a U.S. Senate committee hearing last fall that he felt the FDA fumbled its duties on the Vioxx file.

FDA officials deny Dr. Graham's allegations and say they feel Dr. Graham's study required further review before it could be submitted.