Rofecoxib may cause heart attacks in first weeks of use

Janice Hopkins Tanne *New York*

A small but significant number of elderly people who began taking rofecoxib (Vioxx) had heart attacks in the first two weeks, a study has found. Previously the risk was thought to occur only after 18 months of treatment.

The study was posted online ahead of publication on 2 May by the *CMAJ*, the journal of the Canadian Medical Association (www.cmaj.ca, doi: 10.1503/cmaj.051679).

"A small proportion of patients using rofecoxib for the first time had their first MI [myocardial infarction] shortly after starting the drug," the paper says. The risk was highest in the first six to 13 days (median nine days) after they started treatment with the drug. The risk did not

increase with length of treatment and returned to the baseline risk within eight to 30 days after treatment was stopped.

The risk of a heart attack was more acute than previously recognised, the authors write. "About one-quarter of current users of rofecoxib who had an MI experienced this event within a few weeks of receiving their first prescription."

The researchers, from McGill University in Montreal and Queen's University in Kingston, Ontario, used information about people aged 66 years or older who had not previously had a heart attack and who were taking rofecoxib or celecoxib (Celebrex) for the first time.

The data were collected in Quebec province's computerised health database from January 1999 to June 2002. A time matched, nested case-control approach was used to analyse information on drug use and heart attacks, and the study compared current users and non-users of the two drugs in the year preceding the date of the heart attack.

Rofecoxib was taken off the market in September 2004. Celecoxib is still on the market but carries a black box warning from the US Food and Drug Administration. A risk of heart attack from use of celecoxib cannot be excluded, the researchers say. Other drugs in the class of cyclo-oxygenase-2 (COX 2) inhibitors also showed signs of early cardiovascular toxicity, they say.

The researchers looked at almost 114 000 people who had received a prescription for a non-steroidal anti-inflammatory drug. Their mean age was 75.2. The researchers found 239 rofecoxib users and 287 celecoxib users who had a first heart attack while taking the prescribed drug.

The risk of a first heart attack was higher among people who were prescribed rofecoxib for the first time than among matched controls who did not use prescribed non-steroidal anti-inflammatory drugs in the year preceding their heart attack (rate ratio 1.67 (95% confidence interval 1.21 to 2.30)), the investigators report.

First time users of celecoxib also had a slightly higher risk of heart attack, but the difference was not significant (rate ratio 1.29 (0.90 to 1.83)).

The investigators say that their study may not have been large enough to analyse the risk for users who continue to use COX 2 inhibitors beyond the first prescription. Also, only patients admitted to hospital were included in the database, meaning that cases involving silent heart attacks and sudden death may have been excluded. The investigators did not have information on smoking, obesity, physical activity, family history, socioeconomic status, or use of non-steroidal anti-inflammatory agents bought over the counter.

A spokesman for Merck, the makers of rofecoxib, said it was important to remember the Canadian study was an observational one. The company continues to believe that randomized clinical trials provide stronger evidence than observational studies about the efficacy and safety of medicines.

Lamer quits as chairman of CMAJ governance panel

David Spurgeon *Quebec*

Unspecified and unforeseen health problems have forced Mr Justice Antonio Lamer, formerly of the Canadian Supreme Court, to resign as chairman of the *CMAJ*'s governance review panel. The Canadian Medical Association's journal had set up the panel after two top editors were sacked, in what many saw as a dispute over editorial independence (*BMJ* 2006;332:503).

"This is not a decision I took lightly, but it was the only one available to me. Fortunately, if anyone understands the importance of putting health first, it's the doctors of Canada. I would like to wish the members of the panel well in their work, and I trust my announcement will not delay their efforts for too long," Mr Lamer said in the statement.

The CMA had established the panel to give it advice and guidance on how to best deal with what the association called "the complex relationship between editorial independence

and accountability at the *CMAJ*."

Mr Lamer's announcement followed closely the failed attempts to recruit new members to the panel. Among those who were first invited to join the panel and who then had his invitation rescinded was Philip Devereaux, a clinical investigator at McMaster University and former member of the *CMAJ*'s editorial board. He had resigned from the board in March with most of the other board members, in protest against the firings of John Hoey, the editor in chief, and Anne Marie Todkill, a senior deputy editor.

Dr Devereaux said that he was invited to join by John Dossetor, an emeritus professor of medicine and bioethics at the University of Alberta and co-chairman of the panel. When he called later to discuss the invitation, however, he was told by Dr Dossetor that it was being rescinded because the association was unhappy with the choice.

Mr Justice Lamer's resignation follows several failed attempts to recruit new members to his panel

Gordon Guyatt, of McMaster University, who earlier withdrew a successful series of articles that had been published in the *CMAJ*, was also invited to join the panel. He wrote to Mr Lamer and Dr Dossetor to decline because he had lost confidence in the participants and the process.

"What happened in the invite/disinvite/reinvite decisions remains troubling," Dr

Guyatt wrote in a letter to Mr Lamer and Dr Dossetor. "Whatever the extent of the CMA's influence, it feels to me that the sequence of events reflects basic problems in the panel's process and mandate."

Dr Anita Palepu was one of three former editors of the *CMAJ* to write a letter of concern about the panel to Mr Lamer and Dr Dossetor. She was invited to join the panel but declined.

Dr Ruth Collins-Nakai, the CMA's president, said that it was not up to the association to decide the membership of the panel: the panel had asked for some names, which the CMA had provided. "The only stipulation from our point of view was that they would not have previously passed judgment in terms of the process publicly."

Meanwhile, some former editorial board members of the *CMAJ* are planning to start a new medical journal that would be international in scope. Dr Jerome Kassirer, a former editor of the *New England Journal of Medicine*, has expressed his firm support for their action (<http://cnews.canoe.ca/CNEWS/MediaNews/2006/04/27/pf-1553883.html>).