Gastrointestinal bleeding after the introduction of COX 2 inhibitors: ecological study

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Recent evidence suggests a lower risk of upper gastrointestinal haemorrhage for selective cyclo-oxygenase-2 (COX 2) inhibitors compared with non-selective non-steroidal anti-inflammatory drugs (NSAIDs) at the patient level,[1–3] although COX 2 inhibitors are likely not devoid of gastrointestinal toxicity. At the population level, however, the widespread proliferation of COX 2 inhibitors might lead to an increase in the overall numbers of people exposed to anti-inflammatory drugs with uncertain implications on rates of population-wide gastrointestinal events. We did an ecological study to examine temporal changes in the use of NSAIDs and upper gastrointestinal haemorrhage hospitalisation rates among a population of older individuals after the introduction of COX 2 inhibitors.

Participants, methods, and results

We did a population based cross sectional time series analysis using administrative healthcare databases covering more than 1.3 million residents of Ontario, Canada, aged at least 66 years.[4] This population has universal access to hospital care, doctors' services, and prescription drugs on a formulary. The study's timeframe was divided into 15 intervals of six months from 1 September 1994 to 28 February 2002. Rofecoxib and celecoxib were introduced on the provincial drug formulary in April 2000 and meloxicam was introduced in March 2001. The prevalence of use of NSAIDs in each interval was determined by dividing the unique number of individuals dispensed any NSAID (either non-selective NSAIDs or COX 2 inhibitors) by the total number of individuals alive at the beginning of the interval. Similarly, we examined hospitalisation rates for upper gastrointestinal haemorrhage. As secondary endpoints, we examined hospitalisations for myocardial infarction and heart failure. We standardised all rates for age and sex. As supplementary analyses, we also examined changes in the use of gastroprotective agents, oral corticosteroids, prescription aspirin, and warfarin, since these factors may be strongly related to upper gastrointestinal haemorrhage. We used time series analysis involving autoregressive integrated moving average models to evaluate changes over time with the package SAS 8.2 (SAS, Cary, NC).[5]

The prevalence of use of NSAIDs among Ontario's population of older people increased from 14.0% just before the introduction of COX 2 inhibitors to 19.8% by the end of the observation period (figure; $P<0.01$), representing an absolute increase of more than 90 000 additional individuals annually using NSAIDs, entirely attributable to the use of COX 2 inhibitors rather than switching from non-selective NSAIDs to COX 2 inhibitors. The rate of hospitalisation for upper gastrointestinal haemorrhage was decreasing before the introduction of COX 2 inhibitors, but increased from about 15.4 to 17.0 per 10 000 older persons after their introduction (figure; $P<0.01$), representing an absolute increase of more than 650 upper gastrointestinal haemorrhage hospitalisations annually. Other than a small but statistically significant increase in the prevalence of gastroprotective agent use, we saw no significant differences in the use of drugs that might affect upper gastrointestinal risk over expected projections. Also, we saw no significant differences in hospitalisation rates for myocardial infarction or heart failure greater than expected projections.

Comment

In this population based study a 41% rise in NSAID use, entirely due to increased use of COX 2 inhibitors, was accompanied by a 10% increase in hospitalisation rates for upper gastrointestinal haemorrhage. Although we cannot prove causation, we believe that the striking temporal correlation, biological plausibility, and lack of any other trends that would explain the association strongly suggest that the two events are directly related. Coding practices for hospital admissions for upper gastrointestinal haemorrhage period did not change significantly during our study. However, we could not evaluate whether the potential improvement in population level pain relief offsets the increase in hospitalisations for upper gastrointestinal haemorrhage.

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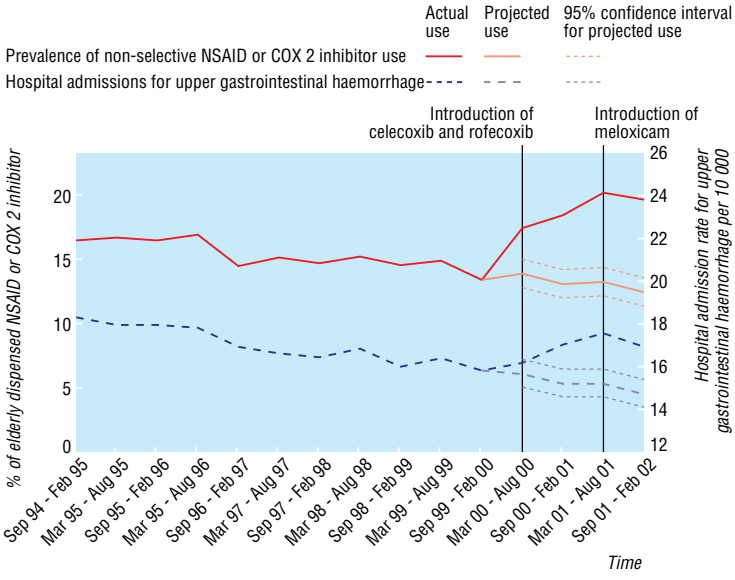
This article was posted on bmj.com on 11 May 2004: http://bmj.com/cgi/doi/10.1136/bmj.38068.716262.F7

BMJ 2004;328:1415–6



Age and sex standardised prevalence of the use of NSAIDs and hospitalisation rates for upper gastrointestinal haemorrhage over time among elderly people in Ontario

The findings of this study suggest that even if a new drug is associated with lower side effects than previous drugs in its class at the patient level, a marked increase in its use can be associated with an apparently paradoxical adverse impact on the population.

Contributors: MM, DNJ, GN, PCA, and AL designed the study; MM, DNJ, PCA, and AK did the study. GN, PCA, and AL advised and supervised. PCA gave statistical advice. MM is guarantor.

Funding: MM is supported by a New Investigator award from the New Emerging Teams of the Canadian Institutes of Health Research (CIHR). DNJ is supported by a New Investigator award from the CIHR and by the University of Toronto Drug Safety Research Group. GN is supported by the Mary Trimmer Chair in Geriatric Medicine Research at the University of Toronto. AL is a senior scientist of the CIHR. This study was supported by a CIHR operating grant (MOP-49527) and a CIHR Chronic Disease New Emerging Team programme grant (NET-54010). The NET programme receives joint sponsorship from the Canadian Diabetes Association, the Kidney Foundation of Canada, the Heart and Stroke Foundation of Canada, and the CIHR Institutes of Nutrition, Metabolism and Diabetes and Circulatory and Respiratory Health.

Competing interests: MM has done research in an unrelated content area upon the request of an academic institution whose funding was supported by Pharmacia in the past three years, but none of the funding for this study was provided by any pharmaceutical company.

Ethical approval: Sunnybrook and Women's College Health Sciences Centre Ethics Review Board.

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(Accepted 22 January 2004)

doi 10.1136/bmj.38068.716262.F7

DRUG POINTS

Nose bleeds associated with use of risperidone

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BMJ 2004;328:1416

The New Zealand Intensive Medicines Monitoring Programme has received two reports of nose bleeds associated with risperidone. A 57 year old woman began having profuse nose bleeds associated with headaches immediately after starting to take risperidone 1 mg daily. She had no history of hypertension and was taking no other medicines. Risperidone was discontinued four days later and the nose bleeds stopped. A 42 year old man with no history of nose bleeds began having spontaneous nose bleeds while taking risperidone; coagulation tests were reported as normal.

The World Health Organization's international drug monitoring database contained an additional 54 reports of nose bleeds associated with risperidone, of which 37 had sufficient information for causality assessment. In 22 cases, nose bleeds began within three weeks of starting risperidone. In 10 of 12 patients for whom dechallenge data were available the reaction abated on stopping risperidone. Three of the 10 patients underwent rechallenge: two did not have nose bleeds again, but the third, a 15 year old boy, had a recurrence after the rechallenge.

Several pharmacological mechanisms might explain this adverse reaction. Thrombocytopenia is a recognised adverse effect of atypical antipsychotic medicines and has been reported with risperidone.[1] Although one of the New Zealand patients was reported to have a normal blood count, in nine of the 37 WHO cases thrombocytopenia was reported.

Risperidone is also a potent 5-HT_2A receptor antagonist. Sarpogrelate, another 5-HT_2A antagonist, increases blood flow in the coronary microcirculation by reducing platelet aggregation and vasoconstictor release from platelets.[2] Risperidone could plausibly have a similar effect in other parts of the microcirculation.

The New Zealand and UK product information for risperidone does not mention nose bleeds. The US *Physicians Desk Reference* states that in premarketing studies nose bleeds occurred in 1 in 100 to 1 in 1000 patients.[3] Literature searches did not identify any reports of nose bleeds associated with risperidone, and so we believe these are the first published cases of this adverse drug reaction.

Contributors: MH-W assessed the original New Zealand case reports, performed the literature searches, identified the signal, and wrote the manuscript. DWJC accessed and evaluated the cases from the World Health Organization's database, proposed a possible mechanism, and reviewed the manuscript.

Funding: The Intensive Medicines Monitoring Programme receives most of its funding from New Zealand's Ministry of Health.

Competing interests: None declared.

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Endpiece

The end of the party

The closing years of life are like the end of a masquerade party, when the masks are dropped.

Arthur Schopenhauer (1788-1860), German philosopher

Fred Charatan,
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