



The full version of
this paper will
appear on bmj.com

Observational study of upper gastrointestinal haemorrhage in elderly patients given selective cyclo-oxygenase-2 inhibitors or conventional non-steroidal anti-inflammatory drugs

Muhammad Mamdani, Paula A Rochon, David N Juurlink, Alex Kopp, Geoffrey M Anderson, Gary Naglie, Peter C Austin, Andreas Laupacis

Editorial by Jones
See also p 619

Institute for Clinical
Evaluative Sciences,
2075 Bayview
Avenue-G215,
Toronto, Ontario,
Canada

Muhammad
Mamdani
scientist
Alex Kopp
analyst

Peter C Austin
scientist

Andreas Laupacis
chief executive officer

Kunin Lunenfeld
Applied Research
Unit, Baycrest
Centre for Geriatric
Care, Toronto

Paula A Rochon
*scientist and assistant
director*

Sunnybrook and
Women's College
Health Sciences
Centre, Toronto
David N Juurlink
*clinical
pharmacologist*

Department of
health policy,
management, and
evaluation, Faculty
of Medicine,
University of

University of
Toronto

Gary Naglie
*Mary Trimmer chair
in geriatric medicine
research*

Correspondence to:
M Mamdani
muhammad.
mamdani@ices.
on.ca

BMJ 2002;325:624-7

Abstract

Objective To compare rates of upper gastrointestinal haemorrhage among elderly patients given selective cyclo-oxygenase-2 (COX 2) inhibitors and non-selective non-steroidal anti-inflammatory drugs (NSAIDs).

Design Observational cohort study.

Setting Administrative data from Ontario, Canada, used from 17 April 2000 to 31 March 2001 to identify population based, NSAID-naive cohorts of patients.

Patients Subjects aged ≥ 66 years who started taking non-selective NSAIDs (n=5391), diclofenac plus misoprostol (n=5087), rofecoxib (n=14 583), or celecoxib (n=18 908) and a randomly selected control cohort not exposed to NSAIDs (n=100 000).

Main outcome measures Rate ratios of hospital admission for upper gastrointestinal haemorrhage in each drug cohort with adjustment for potential confounders.

Results Relative to controls, the multivariate model revealed an increased short term risk of upper gastrointestinal haemorrhage for users of non-selective NSAIDs (adjusted rate ratio 4.0 (95% confidence intervals 2.3 to 6.9)), diclofenac plus misoprostol (3.0 (1.7 to 5.6)), and rofecoxib (1.9 (1.3 to 2.8)) but not celecoxib (1.0 (0.7 to 1.6)). Relative to celecoxib, significantly higher risks of upper gastrointestinal haemorrhage were observed for non-selective NSAIDs (4.4 (2.3 to 8.5)), diclofenac plus misoprostol (3.2 (1.6 to 6.5)), and rofecoxib (1.9 (1.2 to 2.8)). Relative to rofecoxib, non-selective NSAID users were at significantly higher risk of upper gastrointestinal haemorrhage (1.9 (1.0 to 3.5)).

Conclusions This population based observational study found a lower short term risk of upper gastrointestinal haemorrhage for selective COX-2 inhibitors compared with non-selective NSAIDs.

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most commonly used drugs in the world¹ and are consumed by about 20-30% of elderly people in developed countries.²⁻³ Selective cyclo-oxygenase-2 (COX 2) inhibitors are a new group of NSAIDs that have rapidly gained acceptance in clinical practice.⁴

The adoption of selective COX 2 inhibitors has primarily been driven by the assertion that these drugs cause fewer gastrointestinal events than do conventional, non-selective NSAIDs.⁵

It is unclear to what degree COX 2 inhibitors increase gastrointestinal risk relative to not using NSAIDs, and the relative gastrointestinal safety of the

different COX 2 inhibitors is uncertain since they have not been directly compared in a single large study. Accordingly, we conducted a population based cohort study to compare the rate of upper gastrointestinal haemorrhage in over 40 000 NSAID-naive elderly users of rofecoxib, celecoxib, non-selective NSAIDs, and diclofenac plus misoprostol with that in 100 000 non-NSAID users.

Methods

Study design

We conducted a population based retrospective cohort study by linking administrative healthcare databases covering over 1.3 million patients aged 66 years or more in Ontario, Canada, from 17 April 2000 through to 31 March 2001.

Data sources

The administrative healthcare databases in Ontario allowed for cohort identification, comorbidity assessment, and endpoint ascertainment (see bmj.com for details).

Cohort definition

We compared users of rofecoxib, celecoxib, non-selective NSAIDs, or the combination of diclofenac plus misoprostol with a random sample of 100 000 controls dispensed none of these drugs. Despite the potential differences in morbidity between users of NSAIDs and non-users, we chose patients not using NSAIDs as the control group for two reasons: firstly, such a control group provides useful baseline risk estimates of upper gastrointestinal haemorrhage not related to NSAID use, and, secondly, most previous studies of the association between NSAID use and upper gastrointestinal haemorrhage have non-users of NSAIDs as controls. This allowed comparison of our incidence and relative risk estimates with other studies.

For the four drug cohorts, the first NSAID prescription during the study period after a patient's 66th birthday served as the index date. To create a cohort of NSAID-naive subjects within these four drug groups, we excluded individuals who were given an NSAID in the year preceding the index date. We also excluded subjects given NSAIDs from more than one of the study's four groups of drug on the same day.

To create the control cohort, all Ontario residents not included in any of the above cohorts were randomly assigned index dates from 17 April 2000 to 15 March 2001, as in the drug cohorts. Individuals aged 66 years and older who were alive on the assigned index date were screened for NSAID use. From those without a prescription for any NSAID in the year

Table 1 Characteristics of cohorts in study of elderly patients using different NSAIDs. Values are numbers (percentages) unless stated otherwise

	Study cohort				
	Community controls	Non-selective NSAIDs	Diclofenac + misoprostol	Rofecoxib	Celecoxib
No of patients (% women)	100 000 (55)	5391 (59)	5087 (62)	14 583 (72)	18 908 (70)
Mean (SD) age (years)	75.4 (7.3)	75.5 (7.0)	76.6 (7.1)	76.5 (6.9)	76.5 (6.8)
Residence in long term care facility	4 074 (4)	398 (7)	503 (10)	652 (4)	810 (4)
Low income status	21 073 (21)	1831 (34)	1725 (34)	4 445 (30)	5 673 (30)
Hospitalisation in past year	11 513 (12)	1023 (19)	925 (18)	2 900 (20)	3 651 (19)
Mean (SD) No of prescription drugs in past year	5.4 (5.4)	8.3 (6.4)	8.3 (6.4)	9.9 (6.5)	9.5 (6.4)
Use of gastroprotective agents within 180 days before entry to cohort	17 279 (17)	1329 (25)	1265 (25)	6 140 (42)	7 738 (41)
Use of narcotic analgesics within 180 days before entry to cohort	10 623 (11)	1419 (26)	1321 (26)	4 511 (31)	5 587 (30)
Hospitalisations or procedures in past 5 years:					
Malignancy	4 785 (5)	371 (7)	294 (6)	760 (5)	1 004 (5)
Prior upper gastrointestinal haemorrhage	1 440 (1)	64 (1)	66 (1)	369 (3)	476 (3)
Prior gastrointestinal or radiological procedure	17 839 (18)	1090 (20)	1043 (21)	4 731 (32)	5 855 (31)
Drug use in 120 days before index date to end of follow up:					
Aspirin	11 564 (12)	1014 (19)	945 (19)	2 629 (18)	3 311 (18)
Anticoagulants	6 716 (7)	244 (5)	266 (5)	1 515 (10)	1 929 (10)
Antihyperglycaemics	9 256 (9)	756 (14)	706 (14)	1 819 (12)	2 344 (12)
Antirheumatics	0	66 (1)	71 (1)	401 (3)	865 (5)
Glucocorticoids	3 789 (4)	458 (9)	384 (8)	1 928 (13)	2 471 (13)
Gastroprotective agents:	16 394 (16)	1699 (32)	1277 (25)	6 213 (43)	7 793 (41)
Proton pump inhibitors	6 139 (6)	432 (8)	405 (8)	3 156 (22)	3 868 (20)
Other*	11 615 (12)	1407 (26)	983 (19)	3 754 (26)	4 778 (25)

*Includes histamine-H₂ receptor antagonists, misoprostol, and sucralfate.

before the index date or during the observation period, we randomly selected 100 000 individuals to form the control cohort. This group was not matched for age or sex to any of the drug cohorts, but represented the general elderly population of Ontario not prescribed NSAIDs.

Duration of exposure

For each of the four drug cohorts, we defined the duration of exposure as the period of continuous, exclusive use of one of the study drug groups starting from the index date. In the non-selective NSAID group, subjects were allowed to switch between different non-selective NSAIDs during the observation period. The "days supply" recorded in the pharmacy claims database allowed us to estimate the intended duration of each prescription.

Follow up of subjects ended on their admission to hospital for upper gastrointestinal haemorrhage, exposure to an NSAID from another study group, discontinuation of the study drug, death, or the end of the observation period (31 March 2001).

For the control cohort, each individual was allowed at least 15 days of follow up from the index date, and the end of the observation period was randomly assigned unless a subject was admitted for upper gastrointestinal haemorrhage or died beforehand.

Statistical analysis

We conducted time-to-event analyses for upper gastrointestinal haemorrhage using Cox proportional hazard models with the control group as the reference. We adjusted the estimates for hospitalisations, diagnostic gastrointestinal procedures, drug use, age, sex, long term care, and low income status (for more details see bmj.com). We examined the number of distinct drugs dispensed in the year before the index date as an overall measure of comorbidity.⁶ We compared all pairwise

combinations of hazard ratios for the different drug groups.

Results

Cohort description

Of about 1.3 million potential subjects aged 65 years and older, 364 686 (28%) were given a prescription NSAID during the study period. From the total elderly population, we identified 5391 users of non-selective NSAIDs, 5087 users of diclofenac plus misoprostol, 14 583 users of rofecoxib, 18 908 users of celecoxib, and 100 000 controls (table 1) who met our inclusion criteria. Among the users of non-selective NSAIDs, most started with naproxen (32%), ibuprofen (23%), or diclofenac (20%). A greater proportion of rofecoxib and celecoxib users were women than in the other groups. The control group generally used less healthcare resources than the other study groups. More rofecoxib and celecoxib users had previously undergone upper gastrointestinal diagnostic procedures or received gastroprotective agents than the other groups (table 1). They were also more likely to receive anticoagulants, antirheumatics, and glucocorticoids. The characteristics of the rofecoxib and celecoxib groups, however, were virtually identical.

During over 55 000 person years of follow up, we observed 187 hospitalisations for upper gastrointestinal haemorrhage (table 2). Relative to the control group, the adjusted risk ratio was significantly higher for users of non-selective NSAIDs, diclofenac plus misoprostol, and rofecoxib, but not celecoxib (see figure). Analyses with age and sex matched controls, separate analyses for men and women, and analyses excluding subjects with a history of upper gastrointestinal haemorrhage all yielded similar findings.

Table 2 Upper gastrointestinal haemorrhage among elderly patients using different NSAIDs

	Study cohort				
	Community controls (n=100 000)	Non-selective NSAIDs (n=5391)	Diclofenac + misoprostol (n=5087)	Rofecoxib (n=14 583)	Celecoxib (n=18 908)
No of admissions for upper gastrointestinal haemorrhage	82	17	13	43	32
Mean (SD) days of follow up	138.7 (77.4)	91.7 (68.3)	97.8 (71.2)	146.9 (89.6)	170.3 (97.0)
Total follow up (person years)	37 981	1353	1361	5865	8818
No of upper gastrointestinal haemorrhages per 1000 person years	2.2	12.6	9.6	7.3	3.6
Model based risk ratios (95% CI):					
Unadjusted	1.0 (reference)	6.1 (3.6 to 10.2)	4.6 (2.5 to 8.2)	3.5 (2.4 to 5.0)	1.7 (1.1 to 2.6)
Adjusted	1.0 (reference)	4.0 (2.3 to 6.9)	3.0 (1.7 to 5.5)	1.9 (1.3 to 2.8)	1.0 (0.7 to 1.6)
Number needed to treat to harm (NNT(H))*	N/A	403	592	1389	N/A

*NNT(H) calculations are based on a follow up of 295 days from the Cox proportional hazard model estimates.

Relative to celecoxib users, a higher risk of hospitalisation for upper gastrointestinal haemorrhage was seen among users of non-selective NSAIDs (adjusted rate ratio 4.4; 2.3 to 8.5), diclofenac plus misoprostol (3.2; 1.6 to 6.5), and rofecoxib (1.9; 1.2 to 2.8). Relative to rofecoxib, a significantly higher risk of upper gastrointestinal haemorrhage was observed for non-selective NSAIDs (1.9; 1.0 to 3.5) but not diclofenac plus misoprostol (1.4; 0.7 to 2.7).

Discussion

Our findings suggest a lower risk of upper gastrointestinal haemorrhage associated with use of selective COX 2 inhibitors than with conventional, non-selective NSAIDs. While the risk of haemorrhage with rofecoxib was significantly lower than that with non-selective NSAIDs, it was significantly higher than that with celecoxib.

Study limitations

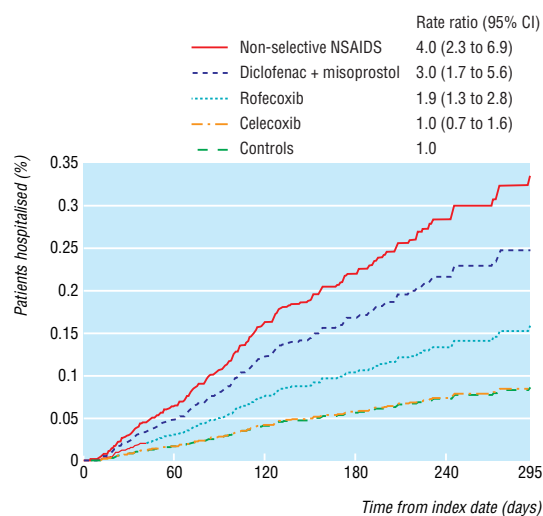
Although we attempted to control for many important confounders, we were unable to account for some potentially important factors such as smoking and alcohol consumption. However, despite a potentially heavier disease burden among the patients using rofecoxib and celecoxib (as a result of the limited use of

selective COX 2 inhibitors licensed in Ontario), they had lower risk ratios than the patients using non-selective NSAIDs. Our population based incidence estimates for upper gastrointestinal haemorrhage (table 2) among the controls and non-selective NSAID group are also consistent with those of other studies,^{7 8} as are our relative risks.^{7 9-11} In addition, when we analysed results among both users and non-users of gastroprotective agents, we still found lower adjusted relative risks for upper gastrointestinal haemorrhage for users of selective COX 2 inhibitors than among non-selective NSAID users (see bmj.com). Users of gastroprotective agents had a higher incidence of upper gastrointestinal haemorrhage than subjects in their respective groups not given gastroprotective agents. This implies that these agents were selectively prescribed to those at higher risk of upper gastrointestinal haemorrhage and were a marker for underlying gastrointestinal disease associated with a higher risk of upper gastrointestinal haemorrhage.

A second limitation is that we used administrative databases to identify and define exposure to study drugs and clinical outcomes. We have no direct measure of adherence or appropriateness of use. The NSAIDs, however, were examined as they are commonly used in this population.

We were unable to identify use of non-prescription NSAIDs. However, ibuprofen and aspirin are the only non-prescription non-selective NSAIDs available in Canada, and subjects in our study have a strong financial incentive to obtain these drugs by prescription, especially with regular use. The vast majority of NSAID use in our population is probably captured by our databases. The use of non-prescription aspirin is perhaps the biggest problem, but since the distribution of prescription aspirin use was similar in the study drug groups, the use of non-prescription aspirin is also likely to be equally distributed.

We identified outcomes using diagnostic codes that have been validated previously, but we were unable to capture other important information such as the severity of the gastrointestinal haemorrhage and more subtle outcomes such as non-bleeding ulcers. Also, it is possible that upper gastrointestinal haemorrhage is more readily diagnosed or reported among users of traditional NSAIDs than among users of specific COX 2 inhibitors. However, the diagnosis is not generally difficult to make, its coding has been validated, and the impact of this potential bias is likely minimal.



Adjusted Cox proportional hazard estimates for hospitalisation for upper gastrointestinal haemorrhage among elderly patients using prescribed NSAIDs

What is already known on this topic

Long term NSAID use is associated with the development of peptic and duodenal ulcers

Selective COX 2 inhibitors are claimed to cause fewer gastrointestinal problems than conventional, non-selective NSAIDs

It is unclear to what degree COX 2 inhibitors increase gastrointestinal risk relative to not using NSAIDs, and the relative gastrointestinal safety of the different COX 2 inhibitors is uncertain

What this study adds

The risk of upper gastrointestinal haemorrhage with the COX 2 inhibitors rofecoxib and celecoxib was significantly lower than with conventional NSAIDs, but the risk with rofecoxib was significantly higher than that with celecoxib

The risk of gastrointestinal haemorrhage with celecoxib was similar to that in controls not using NSAIDs

Relative gastrointestinal safety of rofecoxib and celecoxib

Our evaluation represents the first direct comparison of rofecoxib and celecoxib for a clinically meaningful gastrointestinal outcome using common comparator groups over the same period, with data reflecting clinical practice. The demographic characteristics of rofecoxib and celecoxib users were strikingly similar in our study, implying that selection of one COX 2 inhibitor over another is probably arbitrary in clinical practice. Therefore, the differences in unobserved covariates between the rofecoxib and celecoxib groups are probably minimal and would not explain the difference in upper gastrointestinal haemorrhage observed between the two drugs.

Conclusions

Our study found lower rates of upper gastrointestinal haemorrhage with selective COX 2 inhibitors than with non-selective NSAIDs. The significantly higher rate of upper gastrointestinal haemorrhage among users of rofecoxib than users of celecoxib was

unexpected. Although the absolute difference in rates of upper gastrointestinal haemorrhage was small, the difference, if true, is clinically important given the large numbers of patients prescribed selective COX 2 inhibitors. Large randomised controlled trials directly comparing the drugs are urgently needed to better examine these differences.

Contributors: see bmj.com

Funding: MM is supported by a New Investigator award from the New Emerging Teams (NET) of the Canadian Institutes of Health Research (CIHR). PAR is supported by a Career Scientist award from the CIHR. DNJ is supported by a fellowship award from the CIHR and from the Clinician-Scientist Program of the Department of Medicine 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 program grant (NET-54010). The NET program 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 conducted research in an unrelated content area at the request of an academic institution whose funding was supported by Pharmacia in the past two years, but none of the funding for this study was provided by any pharmaceutical company.

- Misoprostol for co-prescription with NSAIDs. *Drug Ther Bull* 1990;28:25-6.
- Barat I, Andreassen F, Damsgaard EMS. The consumption of drugs by 75-year-old individuals living in their own homes. *Eur J Clin Pharmacol* 2000;56:501-9.
- Sayer GP, Britt H, Horn F, Bhasale A, McGeechan K, Charles J, et al. *Measures of health and health care delivery in general practice in Australia*. Australian Institute of Health and Welfare. April 2000. (www.aihw.gov.au/publications/health/mhhcdgpa/index.html (accessed 27 May 2002))
- Hawkey CJ. COX-2 inhibitors. *Lancet* 1999;353:307-14.
- Feldman M, McMahon AT. Do cyclooxygenase-2 inhibitors provide benefits similar to those of traditional nonsteroidal anti-inflammatory drugs, with less gastrointestinal toxicity? *Ann Intern Med* 2000;132:134-43.
- Schneeweiss S, Seeger JD, Maclure M, Wang PS, Avorn J, Glynn RJ. Performance of comorbidity scores to control for confounding in epidemiologic studies using claims data. *Am J Epidemiol* 2001;154:854-64.
- Aalykke C, Lauritsen K. Epidemiology of NSAID-related gastroduodenal mucosal injury. *Best Pract Res Clin Gastroenterol* 2001;15:705-22.
- Hernandez-Diaz S, Rodriguez LAG. Incidence of serious upper gastrointestinal bleeding/perforation in the general population: review of epidemiologic studies. *J Clin Epidemiol* 2002;55:157-63.
- Hernandez-Diaz S, Rodriguez LA. Association between nonsteroidal anti-inflammatory drugs and upper gastrointestinal tract bleeding/perforation: an overview of epidemiologic studies published in the 1990s. *Arch Intern Med* 2000;160:2093-9.
- Griffin MR, Piper JM, Daugherty JR, Snowden M, Ray WA. Nonsteroidal anti-inflammatory drug use and increased risk for peptic ulcer disease in elderly persons. *Ann Intern Med* 1991;114:257-63.
- Gabriel SE, Jaakkimainen L, Bombardier C. Risk for serious gastrointestinal complications related to use of nonsteroidal anti-inflammatory drugs. A meta-analysis. *Ann Intern Med* 1991;115:787-96.

(Accepted 12 August 2002)

One hundred years ago Presents from patient

The case of *Radcliff v. Price*, which was heard by Mr. Justice Swinfen Eady last week, illustrates a principle of law with which every practitioner ought to be acquainted. The action was brought by the executors of an old lady who, during 1899 and 1900 had given her medical attendant a sum of £800, in three separate amounts of £500, £100, and £200. The executors claimed to recover these sums, setting up the legal presumption of influence and the absence of independent advice, but there was no suggestion of any misrepresentation to, or pressure put on, his patient by the defendant, or that the lady was, at the time of making the gifts, in any way incapable of managing her business transactions, or of weak intellect. The learned judge, in giving judgement for the executors, said: "It has been laid

down that the relation of patient and physician is a confidential relationship, and where it exists as it did in this case, the donor must have had competent and independent advice before a gift can be supported. There is no exception to this rule." In the result, he ordered the defendant to refund the whole amount, and to pay the costs of the action. There was no dispute with regard to the sums in question having been mere presents, as this was frankly admitted by the defendant. The case is of interest because it shows that the onus of proving the absence of undue influence is placed upon the medical man. As soon as this issue is satisfactorily proved, the Court will allow a gift to stand.

(*BMJ* 1902;1:794)