Cyclooxygenase-2 Selective Nonsteroidal Anti-Inflammatory Drugs and the Risk of Ischemic Stroke

A Nested Case-Control Study

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Background and Purpose

Several randomized trials and a large number of epidemiological studies have provided evidence of an increased risk of acute myocardial infarction associated with the use of cyclooxygenase (COX)-2 selective nonsteroidal anti-inflammatory drugs (NSAIDs). Few data are available concerning the risk of ischemic stroke associated with COX-2 inhibitors.

Methods

We performed a nested case-control study in a cohort of 469,674 patients registered within the UK General Practice Research Database (GPRD), who had at least 1 prescription of an NSAID between June 1, 2000 and October 31, 2004. A total of 3094 cases with ischemic stroke were identified and 11,859 controls were matched on age, sex, year of cohort entry and general practice. Odds ratios (ORs) of ischemic stroke associated with the use of COX-2 selective NSAIDs were calculated by conditional logistic regression.

Results

Current use of rofecoxib (OR = 1.71; 95% CI, 1.33 to 2.18), etoricoxib (OR = 2.38; 95% CI, 1.10 to 5.13), but not of celecoxib (OR = 1.07; 95% CI, 0.79 to 1.44) was associated with a significantly increased risk of ischemic stroke. For rofecoxib and etoricoxib, ORs tended to increase with higher daily dose and longer duration of use and were also elevated in patients without major stroke risk factors.

Conclusions

Our study suggests that COX-2 selective NSAIDs differ in their potential to cause ischemic cerebrovascular events. An increased risk of ischemic stroke may be influenced by additional pharmacological properties of individual COX-2 inhibitors. (Stroke. 2006;37:1725-1730.)

Key Words: epidemiology ■ cyclooxygenase 2 inhibitors ■ risk factors ■ stroke

The withdrawal of rofecoxib, based on an increased incidence of stroke and myocardial infarction in the placebo-controlled Adenomatous Polyp Prevention on Vioxx (APPROVe) trial, has led to a discussion on the cardiovascular safety of all cyclooxygenase (COX)-2 selective nonsteroidal anti-inflammatory drugs (NSAIDs). Similar results from placebo-controlled trials with celecoxib and valdecoxib suggested that the increased cardiovascular risk may be a class effect of all COX-2 inhibitors. The randomized COX-2 inhibitor trials usually analyzed a composite cardiovascular end point attributable to limitations in sample size. A large number of epidemiological studies investigated the risk of acute myocardial infarction associated with COX-2 inhibitors, but data on the risk of ischemic stroke associated with COX-2 selective NSAID use are limited. Two observational studies investigated the risk of cerebrovascular events associated with COX-2 inhibitors; however, they did not have information to adjust for cerebrovascular risk factors. We conducted a large nested case-control study using data from the UK General Practice Research Database (GPRD) to investigate the risk of ischemic stroke associated with COX-2 inhibitor use.

Patients and Methods

Data Source

Data were retrieved from the GPRD which was established in 1987 and contains the computerized medical records of >8.9 million patients enrolled by selected general practitioners. Data validity and quality is checked on an ongoing basis by GPRD staff. Information includes the patient’s characteristics (eg, age, sex, smoking, height and weight), prescriptions, diagnoses, referrals, and historical information. Validation studies have shown the high quality of recorded drug exposure and diagnoses also including stroke. This study was approved by the Scientific and Ethical Advisory Group of the GPRD.

Study Population

The cohort consisted of all patients with at least 1 prescription of an NSAID during June 1, 2000 and October 31, 2004. Cohort entry was...
the date of the first one of these prescriptions. Patients were required to be at least 40 years of age at cohort entry and to have been registered for at least 1 year with a practice with ensured data quality standards. We excluded all patients with a diagnosis of stroke (but not transient ischemic attack), cerebral aneurysm or tumor before cohort entry and all patients with a diagnosis of multiple sclerosis at any time. The accuracy of the index date would be questionable in patients with multiple sclerosis because symptoms may resemble those of stroke. Cohort exit was defined as the date of ischemic stroke, death, end of registration with the practice, first occurrence of an exclusion criterion or end of the study period (October 31, 2004), whichever came first. We identified all patients with a first database entry indicating a cerebrovascular accident or ischemic stroke (n=3997) and reviewed their computerized medical records blinded to NSAID-prescription data. Patients were excluded if they developed a stroke after an operation or major trauma and were included if they fulfilled at least 1 of the following criteria: hospitalization; confirmation of diagnosis in neuroimaging; documentation of residual damage; occurrence of new epilepsy; death from ischemic stroke; or therapy with antiplatelet drugs or coumarines after the diagnosis of stroke. The date of the stroke was defined as the index date.

For each case (n=3156), we randomly selected up to 4 controls among the risk set of cohort members. Controls were matched to cases on age (±2 years), sex, practice and year of cohort entry. The date resulting in the same time of follow-up as for the respective case was designated as the index date of the control.

**Exposure**

We identified all NSAIDs that had been prescribed in the year preceding the index date. We categorized NSAID use into the following exposure groups: rofecoxib, celecoxib, etoricoxib, diclofenac, ibuprofen, naproxen, and other NSAIDs. We determined the duration of each prescription by dividing the quantity of prescribed tablets by the number of tablets to be taken daily. We defined current exposure as a prescription of an NSAID that lasted into the 14-day period before the index date. Exposure was called recent if the supply ended between 15 and 183 days before the index date, and past if it ended between 184 days and 1 year, respectively. Nonuse was defined as no use of any NSAID during the year before the index date. Current users of >1 NSAID were not considered in the main analyses. Additionally, we performed sensitivity analyses using different time windows to define current use (0, 7, 30, 90 days).

Daily doses of COX-2 inhibitors were calculated by multiplying the tablet strength with the prescribed number of tablets per day and categorized into low and medium-high dose. The doses separating between these 2 categories were 25 mg for rofecoxib, 200 mg for celecoxib and 60 mg for etoricoxib. In current users of COX-2 inhibitors, we calculated the duration of continuous use by adding the duration of consecutive prescriptions. We categorized continuous use into <3, 3 to 12 and >12 months.

**TABLE 1. Characteristics of Cases and Matched Controls**

<table>
<thead>
<tr>
<th></th>
<th>Cases* (n=3094)</th>
<th>Controls* (n=11859)</th>
<th>Multivariate OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>1391 (45.0%)</td>
<td>5299 (44.7%)</td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>1703 (55.0%)</td>
<td>6560 (55.3%)</td>
<td></td>
</tr>
<tr>
<td>Age in years (mean±SD)†</td>
<td>73.2±10.8</td>
<td>73.2±11.0</td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>972 (31.4%)</td>
<td>4294 (36.2%)</td>
<td>1</td>
</tr>
<tr>
<td>Current</td>
<td>1171 (37.9%)</td>
<td>4375 (36.9%)</td>
<td>1.19 (1.07–1.32)</td>
</tr>
<tr>
<td>Past</td>
<td>635 (20.5%)</td>
<td>2160 (18.2%)</td>
<td>1.13 (0.99–1.29)</td>
</tr>
<tr>
<td>Unknown</td>
<td>316 (10.2%)</td>
<td>1030 (8.7%)</td>
<td>1.41 (1.19–1.67)</td>
</tr>
<tr>
<td>Body mass index</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;20</td>
<td>120 (3.9%)</td>
<td>432 (3.6%)</td>
<td>1.21 (0.96–1.52)</td>
</tr>
<tr>
<td>20–24</td>
<td>724 (23.4%)</td>
<td>3003 (25.3%)</td>
<td>1</td>
</tr>
<tr>
<td>25–29</td>
<td>1000 (32.3%)</td>
<td>3877 (32.7%)</td>
<td>1.02 (0.91–1.15)</td>
</tr>
<tr>
<td>≥30</td>
<td>551 (17.8%)</td>
<td>2123 (17.9%)</td>
<td>0.92 (0.81–1.06)</td>
</tr>
<tr>
<td>Unknown</td>
<td>699 (22.6%)</td>
<td>2424 (20.4%)</td>
<td>1.18 (1.03–1.36)</td>
</tr>
<tr>
<td>Comorbidity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treated with coumarines</td>
<td>59 (1.9%)</td>
<td>167 (1.4%)</td>
<td>1.19 (0.86–1.64)</td>
</tr>
<tr>
<td>Treated with ASS</td>
<td>173 (5.6%)</td>
<td>304 (2.6%)</td>
<td>1.87 (1.52–2.31)</td>
</tr>
<tr>
<td>No anticoagulation</td>
<td>140 (4.5%)</td>
<td>266 (2.2%)</td>
<td>2.05 (1.64–2.57)</td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not treated with drugs</td>
<td>212 (6.9%)</td>
<td>585 (4.9%)</td>
<td>1.32 (1.11–1.57)</td>
</tr>
<tr>
<td>Treated (insulin and/or OAD)</td>
<td>345 (11.2%)</td>
<td>742 (6.3%)</td>
<td>1.73 (1.49–2.00)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>723 (23.4%)</td>
<td>2053 (17.3%)</td>
<td>1.13 (1.00–1.27)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1500 (48.5%)</td>
<td>4583 (38.7%)</td>
<td>1.42 (1.30–1.55)</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>904 (29.2%)</td>
<td>2498 (21.1%)</td>
<td>1.23 (1.11–1.38)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>368 (11.9%)</td>
<td>1013 (8.5%)</td>
<td>1.06 (0.91–1.22)</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>649 (21.0%)</td>
<td>757 (6.4%)</td>
<td>3.69 (3.26–4.18)</td>
</tr>
<tr>
<td>Alcohol abuse</td>
<td>125 (4.0%)</td>
<td>310 (2.6%)</td>
<td>1.54 (1.22–1.95)</td>
</tr>
</tbody>
</table>

OAD indicates oral antidiabetic drug.

*Values are numbers (percentages) unless stated otherwise; †matching variables.
Statistical Analyses

The incidence rate ratio of ischemic stroke for use of each NSAID under study was estimated from odds ratios (ORs) calculated by conditional logistic regression using the SAS PHREG program (SAS 9.1 Institute Inc). We constructed individual models characterizing patients according to the daily dose or continuous duration of COX-2 inhibitor use. In one analysis we calculated ORs for new users of COX-2 inhibitors defined by no use of any COX-2 selective NSAID during the year preceding the start of COX-2 inhibitor treatment. To investigate whether the risk is modified by age, sex or the coexistence of important stroke risk factors (cerebrovascular disease, atrial fibrillation, hypertension), we conducted stratified analyses with respect to these factors and tested for interaction with these variables using the likelihood ratio test. This test compares for each variable the full model including interaction terms against the model without interaction terms. For all these analyses, the reference category consisted of patients without NSAID exposure within 1 year before the index date. P<0.05, 2-tailed, was considered significant and 95% CIs were calculated for all ORs.

All models simultaneously controlled for the use of other NSAIDs and the potential confounders atrial fibrillation (treated with coumarine, aspirin or untreated), diabetes (treated or untreated), hyperlipidemia (defined by a diagnosis of hyperlipidemia or use of lipid-lowering drugs), hypertension, coronary heart disease (defined by a diagnosis of coronary heart disease or myocardial infarction), heart failure, cerebrovascular disease (defined by a diagnosis of transient ischemic attack or cerebral arteriosclerotic disease), alcohol abuse (defined by a diagnosis of alcohol abuse, heavy drinking or alcohol-related diseases), body mass index (BMI), smoking (current, past, never, unknown), and other cerebrovascular risk factors presented in Table 1.

Results

There were 469,674 patients in the GPRD database fulfilling our cohort definition. Of those, 3,156 patients had experienced an ischemic stroke (55.0% men). We randomly selected 11,859 matched controls from the cohort risk set. All cases with at least 1 matched control (n=3094) were included in the analysis (Table 1). The remaining cases (n=62) were excluded because no control was found.

A total of 2,451 (79.2%) cases and 9,100 (76.7%) controls had been exposed to any NSAID during the year before their index date. Of those, 1,060 (34.3%) cases and 3,990 (33.7%) controls were current users of NSAIDs. Current use of rofecoxib and etoricoxib, but not of celecoxib was associated with a significantly increased risk of ischemic stroke (Table 2). The increased ORs for rofecoxib and etoricoxib remained significantly elevated when we limited the analysis to new users (data not shown). The use of time windows other than...
14 days to define current use resulted in similar risk estimates. From the nonselective NSAIDs, current use of diclofenac and the heterogeneous group of other NSAIDs including NSAID combinations were also associated with slightly elevated risk estimates. Recent use of rofecoxib, but not of etoricoxib or celecoxib was associated with an increased risk. Past COX-2 inhibitor use was not associated with an increased risk. ORs appeared to increase with higher daily dose and longer treatment duration for rofecoxib and etoricoxib, but not for celecoxib (Table 3). There was no significant interaction with gender (P=0.11) or age (P=0.43). We did not observe a significant modification of the risk for NSAIDs by the presence or absence of cerebrovascular disease, atrial fibrillation and hypertension (P=0.33; Table 4). Even in patients having none of these risk factors, ORs for rofecoxib and etoricoxib were elevated (Table 4). For etoricoxib, this was not statistically significant, most likely attributable to reduced power of the stratified analysis. A subgroup analysis of patients with complete information on smoking and body mass index (77.0% of study patients) showed similar results to our main analysis. The excess risks of ischemic stroke for current use of rofecoxib and etoricoxib were 0.21% and 0.41% per year, respectively, ie, 21 and 41 additional cases per 10 000 exposed persons per year.

Discussion
In this observational study, current use of rofecoxib and etoricoxib, but not of celecoxib was associated with an increased risk of ischemic stroke. ORs appeared to increase with higher daily dose and longer duration of rofecoxib and etoricoxib use. Even in patients without cerebrovascular disease, atrial fibrillation and hypertension, risk estimates for rofecoxib and etoricoxib were elevated.

Our study is in agreement with the results from the placebo-controlled APPROVe trial, which showed a 2-fold risk of ischemic stroke (0.9% versus 0.46%) for rofecoxib versus placebo. An increased risk of ischemic stroke was not observed for rofecoxib versus naproxen in the randomized Vioxx Gastrointestinal Outcome Research (VIGOR) trial (0.4% in both treatment groups). Our finding of no increased risk for celecoxib concurs with the results from the placebo-controlled Adenoma Prevention with Celecoxib (APC) trial, in which the percentage of nonfatal strokes was the same for celecoxib 400 mg/d and placebo (both 0.4%), because the maximum dose of celecoxib in our study was 400 mg per day. In the APC trial, slightly more patients (0.7%) developed a nonfatal stroke under 800 mg celecoxib per day than under placebo. However, in the randomized Celecoxib Long-term Arthritis Safety Study (CLASS) which compared daily doses of 800 mg celecoxib versus 150 mg diclofenac or 2400 mg ibuprofen, the percentage of cerebrovascular events was higher under diclofenac or ibuprofen than under the 800 mg dose of celecoxib.

For etoricoxib, the available data on the risk of ischemic stroke is inconsistent: an analysis of phase II and III trials submitted by the manufacturer to the FDA revealed rates of ischemic stroke of 0.40/100 patient-years for etoricoxib versus 0.07/100 patient-years for naproxen, whereas in the randomized Etoricoxib Diclofenac Gastrointestinal Evaluation (EDGE) trial, the rates of ischemic stroke were slightly higher under diclofenac 150 mg/day than under etoricoxib 90 mg /day (0.23/100 patient-years versus 0.15/100 patient-years, respectively). Our finding of an increased risk for etoricoxib has to be interpreted cautiously because it is based on small numbers of exposed patients.

There is hardly any data on the association between COX-2 inhibitors and risk of ischemic stroke from epidemiological studies available. Two studies using prescription event monitoring reported an increased risk associated with rofecoxib and celecoxib use as compared with meloxicam. In a direct comparison, rofecoxib appeared to be associated with a 43% higher risk than celecoxib, although this was not statistically significant. These studies were, however, limited by lack
of information on common risk factors for ischemic stroke and by a rather low number of physicians responding to the questionnaires.

Our study indicates that celecoxib might be safer with respect to ischemic stroke than rofecoxib or etoricoxib. COX-2 inhibition reduces vascular prostacyclin (prostaglandin E1) generation, which may lead to elevated blood pressure and accelerated atherogenesis.13 This suggests a class effect of COX-2 inhibitors influenced by the degree of COX-2 selectivity (celecoxib < rofecoxib < etoricoxib). However, we also observed an increased risk for diclofenac which is slightly less COX-2 selective than celecoxib. Additionally, there may be other mechanisms beyond COX-2 selectivity based on substance specific pharmacological properties. Celecoxib is associated with a significantly lower risk of hypertension and fluid retention as compared with nonselective NSAIDs and rofecoxib.14,15

In the randomized APPROVe and APC trials, the increased cardiovascular risks of rofecoxib and celecoxib became apparent only after 18 months1 and after 9 to 12 months2 of treatment, respectively. In our study, the risk also seemed to increase with longer treatment duration of rofecoxib and etoricoxib, but was already elevated for rofecoxib use of < 3 months. A randomized trial investigating the safety and efficacy of 3 days parecoxib followed by 11 days valdecoxib in a cardiovascular high-risk population revealed a nonsignificant higher number of patients experiencing cerebrovascular events as compared with placebo (2.9% versus 0.7%).16 This indicates that the risk of cerebrovascular events may also be increased after short-term COX-2 inhibitor use, but further data are needed in this respect.

One strength of our study is that all information was recorded prospectively so that recall bias can be ruled out. We validated all electronic patient records following the algorithm described in the Methods section. A GPRD study has shown that nearly 90% of computerized diagnoses of stroke were confirmed after reviewing the written records of 88 patients.8 Some limitations need also to be considered. We had no access to neuroimaging test results and therefore could not definitely confirm the diagnosis of the GP and the ischemic nature of the stroke, particularly in patients who were diagnosed as cerebrovascular accidents. One problem of all prescription-based database studies is the incomplete information on over-the-counter (OTC) drugs and certain confounders. Our study included 38.8% of cases and 22.1% of controls with low-dose aspirin use. Because of this small number of patients and incomplete information on patients buying aspirin OTC we could not investigate whether aspirin use would modify the risk of COX-2 inhibitor use. In the UK, ibuprofen is the only nonaspirin NSAID available OTC. Patients exposed to OTC ibuprofen may have been included in our reference group of nonusers. Because ibuprofen was not associated with an altered risk of ischemic stroke in our study, we would not expect that including these patients in our reference group will materially change the results. We included multiple cerebrovascular risk factors in the multivariate model to control for potential confounding; however, we did not have information on lifestyle factors (eg, physical activity), which may also influence the risk.

In summary, our study indicates that COX-2 selective NSAIDs may differ in their potential to cause harmful cerebrovascular effects. Several studies have shown that COX-2 inhibitors vary in their potential to raise blood pressure14 or to cause congestive heart failure.17 These differences may be of relevance for the observed risk differences in our study. Our results suggest that for the risk of ischemic stroke additional pharmacological properties beyond COX-2 inhibition are important.

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Disclosures
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References


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