Discontinuation of Nonsteroidal Anti-inflammatory Drug Therapy and Risk of Acute Myocardial Infarction

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Background: Systemic inflammation has been shown to be associated with an increased risk of acute myocardial infarction (AMI). However, the effect of the use of nonsteroidal anti-inflammatory drugs (NSAIDs) on the risk of AMI has not yet been well defined. We therefore studied the risk of AMI during NSAID exposure and after the cessation of NSAID therapy.

Methods: We conducted a large case-control analysis on the British General Practice Research Database. The study included 8688 cases with a first-time AMI between 1995 and 2001 and 33923 controls, matched to cases on age, sex, calendar time, and general practice attended.

Results: After adjusting for hypertension, hyperlipidemia, diabetes mellitus, ischemic heart disease, rheumatoid arthritis, systemic lupus erythematosus, acute chest infection, body mass index, smoking, and aspirin use, the risk of AMI was 1.52 (95% confidence interval [CI], 1.33-1.74) for subjects who stopped taking NSAIDs 1 to 29 days prior to the index date, compared with nonusers. The risk was highest in subjects with rheumatoid arthritis or systemic lupus erythematosus (adjusted OR, 3.68 [95% CI, 2.36-5.74]) and for subjects who discontinued therapy with NSAIDs after previous long-term use (adjusted OR, 2.60 [95% CI, 1.84-3.68]). Current and past NSAID use (discontinued therapy ≥60 days prior to the index date) were not associated with an increased risk of AMI (adjusted OR, 1.07 [95% CI, 0.96-1.19] and 1.05 [95% CI, 0.99-1.12], respectively).

Conclusion: Our findings suggest that the risk of AMI is increased during several weeks after the cessation of NSAID therapy.

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Here is increasing evidence that intravascular inflammation plays a key role in the development of atherosclerosis and acute coronary events. Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used for the treatment of pain and inflammation. They exert their effect by reversible, competitive inhibition of cyclooxygenase (COX), an important enzyme in the regulation of molecular pathways of pain and inflammation. In addition to COX inhibition, NSAIDs also decrease thromboxane A2 production, potentially leading to an inhibition of platelet aggregation. In theory, these 2 pharmacological mechanisms could reduce the risk of acute myocardial infarction (AMI) during exposure to nonaspirin NSAIDs.

In fact, several recent observational studies explored the risk of AMI in subjects taking nonaspirin NSAIDs. The relative risk estimates for current NSAID use in these studies were consistently reported to be around 1.0, and most authors concluded that current exposure to nonaspirin NSAIDs does not substantially lower the risk of AMI. However, a possible limitation of these studies is that it is difficult to distinguish between the effect of the underlying inflammation—a main reason for using NSAIDs—and the potential NSAID effect on the AMI risk, since the 2 are highly correlated. Relative risks around 1.0 for current NSAID use may also be the result of an NSAID effect; in other words, current NSAID exposure may lower an inflammation-induced increased risk of AMI risk toward 1.0, but not below.

In a recent study, we explored the effect of current NSAID use on the risk of AMI in 3319 cases with a first-time AMI between 1992 and 1997 and 13139 controls using the United Kingdom (UK)-based General Practice Research Database (GPRD). Study subjects were free of diagnosed cardiovascular or metabolic risk factors. We reported a relative risk close to 1.0 for current NSAID use, but observed a more than 2-fold increased risk.
of AMI for long-term users of NSAIDs who discontinued NSAID therapy before the AMI.

The aim of the present study was to further assess the association between timing of discontinuation of NSAID exposure and the risk of first-time AMI. For this purpose, we conducted another large case-control analysis on the GPRD, including incident AMI cases from 1995 to 2001 with or without clinical risk factors for AMI.

METHODS

STUDY POPULATION AND DATA SOURCE

The GPRD is a large and well-validated database, which has been previously described in detail. Briefly, more than 3 million residents in the UK have been registered with selected general practitioners (GPs) who agreed to provide data for research purposes to the GPRD. The database has been the source of numerous epidemiological studies, and the accuracy and completeness of the data have been well documented and validated.

The GPRD contains information about patients including demographics and characteristics (eg, height, weight, and smoking status), symptoms, clinical diagnoses, referrals to consultants, hospitalizations, and drug prescriptions. Drug prescriptions are recorded in detail using a drug dictionary based on the UK Prescription Pricing Authority. These codes define the active compound, the route of administration, and in most instances the intake regimen prescribed for each prescription the active compound, the route of administration, and the index date for each case and control. A subject was defined as “current user” if the supply of the last prescription for an NSAID lasted up to the index date or beyond. Subjects whose therapy ended before the index date were categorized according to the time lag between the end of therapy and the index date (1-29, 30-59, ≥60 days). Subjects were further classified according to the number of prescriptions for NSAIDs (ie, 1-19, 20-39, ≥40 prescriptions for acemetacin, diclofenac, diflunisal, etodolac, fenbufen, fenoprofen, flurbiprofen, ibuprofen, indomethacin, ketoprofen, mefenamic acid, nabumetone, naproxen, piroxicam, sulindac, tenoxicam, or tiaprofenic acid).

STATISTICAL ANALYSIS

We conducted a matched analysis (conditional logistic regression model) using the software program SAS, version 8.1 (SAS Institute Inc, Cary, NC). Relative risk estimates (odds ratios [ORs]) are presented with 95% confidence intervals (CIs).

For each case and control, the independent effects of various potential confounders on the AMI risk were assessed, such as body mass index (BMI, calculated as weight in kilograms divided by the square of height in meters) (<25, 25-29.9, ≥30, or unknown), smoking status (never, exsmoker, current, or unknown), aspirin use, hypertension, hyperlipidemia, diabetes mellitus, ischemic heart disease, other cardiac diseases (arrhythmias or congestive heart failure), arterial vascular diseases (claudication, stroke, transient ischemic attack, or arterial thromboembolic events), kidney diseases, acute chest infection, and diseases with systemic inflammation (rheumatoid arthritis or systemic lupus erythematosus [SLE]).

RESULTS

The analysis encompassed 8688 cases with a first-time AMI and 33923 matched controls. Table 1 displays the age and sex distribution of cases and controls as well as their smoking status, BMI, and presence of cardiovascular or metabolic diseases related to an altered AMI risk. Patients were predominantly male (62.9%), and 50.0% were at 70 years or older at the date of the AMI.

INCREASED RISK OF FIRST-TIME AMI AFTER DISCONTINUATION OF NSAID THERAPY

Compared with nonusers of NSAIDs, the OR of developing a first-time AMI during current NSAID exposure was 1.07 (95% CI, 0.96-1.19), adjusted for BMI, smoking, hypertension, hyperlipidemia, diabetes mellitus, ischemic heart disease, arrhythmias or congestive heart failure, vascular diseases, kidney diseases, acute chest infection, and aspirin use. The adjusted ORs for subjects who stopped taking NSAIDs 1 to 29, 30 to 59, or 60 days or more prior to the index date were 1.52 (95%
CI, 1.33-1.74), 1.44 (95% CI, 1.21-1.70), and 1.05 (95% CI, 0.99-1.12), respectively (Table 2).

Additional stratification by duration of NSAID use showed that the risk of AMI after discontinuing NSAID therapy 1 to 29 days before the index date was highest for long-term NSAID users (≥40 NSAID prescriptions; adjusted OR, 2.60 [95% CI, 1.84-3.68]) and lower for users of 1 to 19 prescriptions (adjusted OR, 1.07 [95% CI, 1.01-1.48]) (Table 2).

To test for effect modification, we further stratified the analysis by sex, age (age <70 vs ≥70 years at the index date), and a history of diagnosed hypertension, hyperlipidemia, diabetes mellitus, or ischemic heart disease. There was no suggestion of effect modification by age, sex, or underlying diseases except for ischemic heart disease; the adjusted OR for subjects who stopped using NSAIDs 1 to 29 days prior to the index date was 1.46 (95% CI, 1.23-1.73) for subjects without and 2.85 (95% CI, 1.79-4.54) for subjects with ischemic heart disease.

We also stratified cases and controls who stopped using NSAIDs 1 to 29 days prior to the index date by individual NSAID. The ORs for the most frequently used NSAIDs (diclofenac, ibuprofen, indomethacin, ketoprofen, naproxen, and piroxicam) were all similar (data not shown). Compared with nonuse, current aspirin use yielded an adjusted OR of 0.83 (95% CI, 0.76-0.91).

In recent years, the role of vascular inflammation in the development of atherosclerosis and subsequent cardio-
vascular concentration of C-reactive protein, a marker for systemic inflammation, has been shown to predict the risk of future AMI and stroke in men and women. With the exception of newer, selective COX-2 inhibitors, most currently used NSAIDs inhibit nonselectively both COX-1 and COX-2, thereby decreasing systemic inflammation. Also, NSAIDs decrease thromboxane A₂ production, whereby the clinical relevance of the partial inhibition of platelet aggregation by nonaspirin NSAIDs is not fully understood.

The results of this large case-control analysis suggest that the risk of developing a first-time AMI is increased for a period of several weeks after discontinuation of NSAID use, particularly in subjects who used NSAIDs on a long-term basis. The risk of AMI was not increased for subjects who currently used NSAIDs at the index date nor for past users who stopped using NSAIDs more than 2 months before.

The causes for the observed association between recent cessation of NSAID therapy and increased risk of AMI remain to be defined. It may be the result of an inflammatory rebound effect in the vascular tissue and/or the consequence of activated platelet aggregation after termination of the pharmacological inhibition of COX and thromboxane A₂. It has been shown that patients with acute coronary syndromes exhibit signs of systemic and widespread coronary inflammation. Furthermore, a recent study reported a lower 1-year mortality for patients who regularly used NSAIDs after an AMI compared with patients with AMI not taking NSAIDs. Thus, it is conceivable that NSAIDs suppress inflammation in coronary arteries and that cessation of NSAID use may allow a flaring up of the inflammation in the vessel wall, thereby resulting in plaque instability and subsequent AMI.

The increased risk of AMI shortly after discontinuing NSAID therapy was found to be independent of sex, age, or underlying diseases, with the exception of a history of ischemic heart disease. We observed that the risk was highest in subjects who stopped using NSAIDs after an AMI compared with patients with AMI not taking NSAIDs. Thus, it is conceivable that NSAIDs suppress inflammation in coronary arteries and that cessation of NSAID use may allow a flaring up of the inflammation in the vessel wall, thereby resulting in plaque instability and subsequent AMI.

A spurious association may have resulted from a bias that could be called "inverse confounding by indication." In other words, cessation of NSAID use may be the consequence of clinical symptoms related to the future AMI. To address this potential problem, we reviewed a random sample of records of case patients who stopped using NSAIDs at various points in time. Even though in many case records no obvious reason for the cessation of NSAID therapy was available, there was no evidence that clinical symptoms directly or indirectly related to AMI were more frequent in recent than in past NSAID users. In addition, we quantified all practice visits in the 2 months immediately preceding the index date for cases and controls to explore whether cases were less likely than controls to see the GP shortly prior to the index date (and thus be less likely to get a prescription for NSAIDs). However, the opposite was true; compared with controls, cases had substantially more practice visits recorded prior to the index date, but adjusting the analysis for the number of GP visits did not materially alter the results. It is a limitation of this observational study that we were not in a position to clearly distinguish between various indications for NSAIDs in the study population, since indications may have overlapped or may have changed over time. This as well as the lack of recorded laboratory parameters, particularly C-reactive protein, did not allow us to classify patients according to timing or extent of systemic inflammation.

The classification of exposed subjects according to the date of the end of therapy is less perfect in clinical practice than in our model, since subjects may not take drugs exactly as prescribed by the GP. However, we categorized all users by the same algorithm and regardless of case-control status, and therefore exposure misclassification was likely to be random. On the other hand, it is a particular strength of the present study that the detailed recording of drug exposure in the GPRD allowed us to estimate the date of the end of the NSAID therapy. During the period in which we sampled cases and controls for this study, there was too little exposure to selective COX-2 inhibitors for a meaningful analysis. Thus, this analysis does not contribute to the discussion whether COX-2 inhibitors alter the risk of AMI.

We found an increased risk of AMI in patients with rheumatoid arthritis or SLE, which are both diseases with increased systemic (including vascular) inflammation. Indeed, rheumatoid arthritis has been associated with coronary artery disease as well as intimal and medial thickening of carotid arteries and SLE has also been related to an increased risk of atherosclerosis and coronary heart disease. Furthermore, associations between chronic chest infections and AMI have been described, and the previously reported increased risk of AMI for subjects with acute chest infections has again been observed in this study.

In summary, this large case-control analysis suggests that there is a vulnerable period of several weeks with an increased risk of first-time AMI after discontinuation of prolonged NSAID use. The risk of AMI was not elevated for current NSAID users, suggesting that NSAIDs may counterbalance an increased risk caused by inflammation. This interpretation is contrary to previous studies reporting no effect of current NSAID exposure on the risk of AMI. Our results suggest that abrupt discontinuation of NSAID therapy may have to be avoided and that physicians should carefully review the disease status and the current medication profile before terminating a therapy with NSAIDs. This may be particularly valid for patients with chronic inflammatory diseases and/or for subjects who used NSAIDs for a long time. The present findings need to be confirmed by additional studies, given their potential clinical implications.
REFERENCES