Diclofenac and acute myocardial infarction in patients with no major risk factors

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What is already known about this subject

- We recently published the results of a study on the risk of acute myocardial infarction (AMI) in users of five nonsteroidal anti-inflammatory drugs during the years 2001 to 2005.
- The results demonstrated, as has been reported in randomized trials, that rofecoxib and celecoxib increase the risk of AMI when taken for at least 10 months.
- As expected, ibuprofen and naproxen did not materially increase the risk.
- However, long-term users of diclofenac were at an increased risk of AMI similar to that of users of rofecoxib and celecoxib.

What this study adds

- Extensive use of diclofenac, similarly to rofecoxib and celecoxib, substantially increases the risk of AMI.
- There is little suggestion of such an effect in users of ibuprofen and naproxen.

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Aims

To explore further a recent finding that long-term users of diclofenac are at increased risk of acute myocardial infarction (AMI) similar to users of rofecoxib and celecoxib.

Methods

Using the General Practice Research Database, we conducted three separate nested case-control studies of three nonsteroidal anti-inflammatory drugs (NSAIDs) where use started after 1 January 1993 – diclofenac, ibuprofen and naproxen. Cases of AMI were identified between 1 January 1993 and 31 December 2000. Relative risk (RR) estimates for AMI in patients with no major clinical risk factors were determined for each NSAID according to number of prescriptions received compared with one prescription. Results were adjusted for variables possibly related to risk of AMI.

Results

There was no material elevation of AMI risk according to the number of prescriptions for ibuprofen [RRs and 95% confidence intervals (CIs) 1.0 (0.6, 1.6) and 1.7 (0.9, 3.1) for use of 10–19 and 20+ prescriptions, respectively, compared with one prescription] or naproxen [RRs 1.0 (0.5, 2.2) and 2.0 (0.9, 4.5) for use of 10–19 and 20+ prescriptions, respectively]. However, a substantial increased risk similar to that obtained in our prior study was found in patients who received ≥ 10 prescriptions for diclofenac [RRs 1.9 (1.3, 2.7) and 2.0 (1.3, 3.0) for use of 10–19 and 20+ prescriptions, respectively].

Conclusions

Extensive use of diclofenac substantially increases the risk of AMI. There is little suggestion of such an effect in users of ibuprofen and naproxen.

Introduction

We recently published a study of certain traditional nonsteroidal anti-inflammatory drugs (NSAIDs) and cyclooxygenase (COX)-2 inhibitors in relation to acute myocardial infarction (AMI) [1]. This study was restricted to cases of AMI that occurred in 2001 or later in order to allow sufficient time to pass after marketing of rofecoxib and celecoxib, which were not marketed until 1999 and 2000, respectively, in the UK, and we restricted the study to people who began use of their NSAID for the first time after 1999 when rofecoxib was marketed. An unexpected finding of this study was that prolonged use of the NSAID diclofenac increased the risk of AMI.

Since diclofenac, ibuprofen and naproxen had been on the market in the UK for many years prior to 1999, we conducted a new study to evaluate the effect of these NSAIDs on AMI in the years prior to 2001 where we had much additional data on all three drugs and where we could again evaluate the unexpected finding with prolonged use of diclofenac in a separate and larger study population. Many other studies conducted to explore the relation of NSAIDs and AMI have included diclofenac use, but they have not looked specifically at duration of use. These studies are summarized in a recently published meta-analysis [2]. Some of these studies did find a modest increase in the risk of AMI [3, 4] in current diclofenac users of any duration, but some did not [2].

In the present study of three NSAIDs and the risk of AMI, we employed a study design used in our recently published study [1]. It was designed to assess the relation of long-term use (>10 months) of diclofenac, ibuprofen and naproxen rather than considering current use *per se*. In addition, as before, we assessed the risk of AMI in patients who had no prior recorded clinically important risk factors for AMI. The study was based on data from the General Practice Research Database (GPRD), a database whose completeness and validity have been repeatedly demonstrated [5]. The study protocol was approved by the Scientific and Ethical Advisory Committee (SEAG) of the GPRD.

Methods

Base population

We used data from the GPRD, a large UK-based database which encompasses over three million people who are enrolled with selected general practitioners (GPs), to conduct this study. The information recorded on drug exposure and the comprehensive nature of recorded diagnoses in the GPRD have been validated and proved to be of high quality [5]. Briefly, the GPRD encompasses

more than 3 million people in the UK who are enrolled with some 300 selected general practices whose GPs use office computers and have agreed to provide data for research purposes. GPs have been trained to record medical information, including demographic data, medical diagnoses, details of hospital stays and deaths in a standard, anonymous form. The physicians generate prescriptions directly with the computer, and this information is automatically transcribed into the computer record.

We identified all people in the GPRD aged 30–79 years who had a first recorded use of diclofenac, ibuprofen or naproxen after 1 January 1993. We conducted three separate nested case–control studies, one focusing on each of the three study NSAIDs. The study period ended on 31 December 2000.

Cases

For each of the three NSAIDs separately, we identified all people in the base population with a first time code for AMI between 1 January 1993 and December 2000, who were aged 30–79 and who had at least one prescription for the NSAID of interest before their index date (the date of the first recorded diagnosis of AMI) and who had at least 2 years of history recorded in the GPRD before their index date. In order to measure more directly the potential effect of the NSAIDs of interest on the risk of AMI, we excluded cases with any of the following diagnoses more than 1 month prior to the diagnosis of AMI: ischaemic heart disease (angina, previous myocardial infarction, cardiac catheterization, coronary artery angioplasty or coronary artery bypass surgery), diabetes, treated hypertension, and cancer (other than nonmelanoma skin cancer). The computerized record of a 50% sample of cases was reviewed by hand to ensure that cases fulfilled the eligibility criteria. Patients may have been included in more than one study if they had a first recorded prescription for more than one study drug after 1 January 1993.

Control selection

Each case was matched to up to four controls by year of birth (within 2 years), sex, calendar time (index date) and general practice. The 'index date' for each control was the date of AMI in their matched case. The same exclusion and inclusion criteria applied to cases were applied to the controls, including the criteria that first study drug use occur before the index date, presence of at least 2 years of recorded history in the GPRD before the index date, and exclusion for the same diseases listed above for the cases.

Exposure

Exposure for all study subjects was determined from the computer record for the time prior to the index date. Subjects were considered exposed if they had received two or more prescriptions for the study NSAID of interest prior to the index date but after 1 January 1993. Those with receipt of only one prescription of the study NSAID before their index date comprised the reference group.

Analysis

We examined the effect of each NSAID of interest in a separate study (one in each of the three study populations of people who had at least one prescription for the NSAID of interest). We used conditional logistic regression to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for various levels of exposure (2–4, 5–9, 10–19 and ≥ 20 prescriptions) of the primary NSAID of interest in each study compared with a single prescription as the reference level of exposure. We controlled each of the analyses for smoking (never, current, past, unknown), body mass index ($<24 \text{ kg m}^{-2}$, $24\text{--}28 \text{ kg m}^{-2}$, $>28 \text{ kg m}^{-2}$, unknown), history of rheumatoid arthritis (RA), history of hyperlipidaemia and use of the other study NSAIDs and aspirin before the index date. Exposure to the other study NSAIDs (i.e. those other than the NSAID of primary interest in each study) and aspirin was defined as ≥ 10 recorded prescriptions at any time before the index date for each drug separately (with <10 prescriptions, including none, as the reference level).

Cumulative dose was calculated as the sum, over all prescriptions, of the product of the number of pills in a prescription and the strength of the pills in that prescription. The correlation between number of prescriptions and duration of use and the correlation between number of prescriptions and cumulative dose were estimated using a nonparametric measure (Spearman's correlation coefficient).

Statistical calculations were carried out using SAS Release 9.1 (SAS Institute Inc., Cary, NC, USA).

Results

Base population

We identified all patients from the study base population of diclofenac, ibuprofen and naproxen users, who had a first time AMI, and compared their NSAID exposure with that of the controls who did not have an AMI. Characteristics of the cases and controls are given in Table 1. The mean duration of recorded history prior to the index date for cases and controls combined was 7.5 years in the diclofenac study, 7.3 years in the

Table 1

Characteristics of cases and controls

Characteristic	Cases		Controls	
	<i>n</i>	%	<i>n</i>	%
<i>Diclofenac study (806 cases, 3216 controls)</i>				
Age (years)				
≤ 59	308	38	1227	38
60–69	267	33	1097	34
≥ 70	231	29	892	28
Sex				
Female	246	30.5	981	30.5
Male	560	69.5	2235	69.5
Current smoker	289	36	694	21.5
Rheumatoid arthritis	28	3.5	67	2
Hyperlipidaemia	25	3	56	2
<i>Ibuprofen study (928 cases, 3703 controls)</i>				
Age (years)				
≤ 59	343	37	1396	38
60–69	326	35	1296	35
≥ 70	259	28	1011	27
Sex				
Female	300	32	1196	32
Male	628	68	2507	68
Current smoker	326	35	827	22
Rheumatoid arthritis	25	3	39	1
Hyperlipidaemia	27	3	65	2
<i>Naproxen study (312 cases, 1228 controls)</i>				
Age (years)				
≤ 59	122	39	488	40
60–69	110	35	451	37
≥ 70	80	26	289	23
Sex				
Female	94	30	368	30
Male	368	70	860	70
Current smoker	125	40	300	24
Rheumatoid arthritis	11	3.5	27	2
Hyperlipidaemia	13	4	24	2

ibuprofen study and 7.6 years in the naproxen study, and durations of recorded history were similar for cases and controls within each study. The age distribution of cases and controls was similar for the three study NSAIDs. About 38% of cases and controls in all three studies were aged ≤ 59 years, just over one-third were 60–69, and around 27% were ≥ 70 years. Finally, around 70% of all study subjects were male.

Diclofenac

Among subjects who received one or more prescriptions for diclofenac, 806 cases of AMI and 3216 matched controls were identified who also received diclofenac for the first time after 1 January 1993 and before their index

date. The adjusted relative risk (RR) estimate for cases and controls among all diclofenac users combined who were prescribed at least two prescriptions (range 2–109) compared with those who were prescribed only one prescription was 1.3 (95% CI 1.1, 1.5). The adjusted RR estimates, according to the number of prescriptions received, are given in Table 2. The adjusted RR estimates for those prescribed 2–4 and 5–9 prescriptions compared with one prescription were 1.2 (95% CI 1.0, 1.4) and 1.4 (95% CI 1.1, 1.9), respectively. For people who were prescribed 10–19 prescriptions, the RR estimate was 1.9 (95% CI 1.3, 2.7) and for those prescribed ≥ 20 prescriptions it was 2.0 (95% CI 1.3, 3.0). When current use was analysed, it was found that current use compared with noncurrent use did not materially change the effect measures at any level of use (according to number of prescriptions filled). Any current use of diclofenac compared with noncurrent use (unadjusted for the number of prescriptions) yielded an OR of 1.3 (95% CI 1.0, 1.6), but this was predominantly explained by long-term users who also tended to be current users. When current (vs. noncurrent) use and numbers of prescriptions were both included in the analysis, the OR for current use decreased to 1.1 (95% CI 0.8, 1.3). That is, the effect of current use is confounded by the number of prescriptions, and current use of diclofenac did not appear to be independently associated with an increased risk of myocardial infarction.

Ibuprofen

Among ibuprofen users who received one or more prescriptions, we identified 928 cases of AMI and 3705

controls who received ibuprofen for the first time after 1 January 1993 and before their index date. The RR estimate comparing cases and controls for all ibuprofen users who were prescribed at least two prescriptions (range 2–85) compared with those who were prescribed only one prescription was 1.1 (95% CI 1.0, 1.3). The adjusted RR estimates according to number of prescriptions received are shown in Table 3. The adjusted RR estimates for use of 2–4, 5–9 and 10–19 prescriptions compared with users of only one prescription were close to 1.0. The adjusted RR estimate in users of ≥ 20 prescriptions was 1.7 (95% CI 0.9, 3.1). There was no increase in risk of current use of ibuprofen compared with noncurrent use, nor did the effect measures change at any level of number of prescriptions used when current use was included in the model as a covariate.

Naproxen

Among subjects who received one or more prescriptions for naproxen, 312 cases and 1228 controls were identified who received naproxen for the first time after 1 January 1993 and before their index date. The RR estimate for AMI comparing cases and controls for all naproxen users who were given at least two prescriptions (range 2–57) compared with those who were given only one prescription was 1.1 (95% CI 0.8, 1.4). The adjusted RR estimates by number of prescriptions are given in Table 4. The adjusted RR estimates for use of 2–4, 5–9 and 10–19 prescriptions compared with users of only one prescription were all 1.0. The adjusted RR

Table 2

Distribution of cases and controls and risk estimates of acute myocardial infarction by number of prescriptions of diclofenac

No. of prescriptions	No. of cases	No. of controls	RR estimate*	95% CI
1	411	1866	1.0	Ref.
2–4	226	894	1.2	1.0, 1.4
5–9	81	251	1.4	1.1, 1.9
10–19	52	124	1.9	1.3, 2.7
20+	36	81	2.0	1.3, 3.0
Total	806	3216		

*Adjusted for body mass index, smoking, rheumatoid arthritis, hyperlipidaemia and use of other nonsteroidal anti-inflammatory drugs (≥ 10 prescriptions vs. < 10 , separately for ibuprofen, naproxen, and aspirin).

Table 3

Distribution of cases and controls and risk estimates of acute myocardial infarction by number of prescriptions of ibuprofen

No. of prescriptions	No. of cases	No. of controls	RR estimate*	95% CI
1	577	2425	1.0	Ref.
2–4	260	977	1.1	0.9, 1.3
5–9	51	175	1.2	0.9, 1.7
10–19	24	88	1.0	0.6, 1.6
20+	16	38	1.7	0.9, 3.1
Total	928	3703		

*Adjusted for body mass index, smoking, rheumatoid arthritis, hyperlipidaemia and use of other nonsteroidal anti-inflammatory drugs (≥ 10 prescriptions vs. < 10 , separately for naproxen, diclofenac, and aspirin).

Table 4

Distribution of cases and controls and risk estimates of acute myocardial infarction by number of prescriptions of naproxen

No. of prescriptions	No. of cases	No. of controls	RR estimate*	95% CI
1	185	779	1.0	Ref
2–4	90	335	1.0	0.8, 1.4
5–9	18	63	1.0	0.6, 1.8
10–19	9	32	1.0	0.5, 2.2
20+	10	19	2.0	0.9, 4.5
Total	312	1228		

*Adjusted for body mass index, smoking, rheumatoid arthritis, hyperlipidaemia, and use of other nonsteroidal anti-inflammatory drugs (≥ 10 prescriptions vs. < 10 , separately for ibuprofen, diclofenac, and aspirin).

estimate in users of ≥ 20 prescriptions was 2.0 (95% CI 0.9, 4.5). There was no increase in risk of current use compared with noncurrent use among users of naproxen, nor did the effect measures change at any level of number of prescriptions used when current use was included in the model as a covariate.

In all three studies, the proportion of current smokers was substantially higher among cases than among controls (see Table 1). Proportionally more cases than controls also had a history of RA and hyperlipidaemia.

Discussion

The current study, which was substantially larger than the first one [1], has again provided persuasive evidence that prolonged use of diclofenac increases the risk of AMI in patients with no prior strong risk factors by around twofold. The RR estimates rose progressively with increasing duration of use and reached around 2.0 at levels of use of ≥ 10 prescriptions, similar to the findings of our earlier study. There was no statistically significantly increased risk for AMI at any level of ibuprofen or naproxen use. The RR estimates for ibuprofen were close to 1.0 for all levels of number of prescriptions except for ≥ 20 prescriptions, where the RR estimate was 1.7 (95% CI 0.9, 3.1). Since our previously published study on NSAIDs and AMI yielded an RR estimate of 1.0 for those who received ≥ 20 prescriptions for ibuprofen, we conclude that the preponderance of evidence from our two studies indicates that ibuprofen does

not increase the risk for AMI. However we cannot rule out the possibility of an increased risk, particularly at the highest dose. Naproxen had a pattern of effect similar to that of ibuprofen, and as the randomized VIGOR trial reported that naproxen has a far lower risk for AMI compared with rofecoxib, we conclude that, taken together, these data provide little evidence that naproxen use materially increases the risk of AMI. However, the possibility of an increased risk cannot be excluded, especially with ≥ 20 prescriptions. Moreover, because there are limited data on long-term use of both ibuprofen and naproxen in this study, we have less information on the effects of heavy use of these two NSAIDs than we do for diclofenac.

We controlled for aspirin use in each adjusted model that assessed the risk of a study NSAID on the risk for AMI. Although we are able to capture only aspirin use prescribed by a GP, we did assess the effect of ≥ 10 prescriptions for aspirin compared with < 10 prescriptions for aspirin and in no instance was there a material difference in the main effect measures for any of the three study drugs. Nor was there any substantial independent effect of aspirin use on the risk of AMI among users of the three study NSAIDs.

Cumulative dose and total duration of use were highly correlated with the number of prescriptions in each of the three studies. For diclofenac there was a significant effect of increasing cumulative dose when the total amount prescribed to each subject was treated as a continuous variable. We found a 5% increase in risk of AMI for each 10 000-mg unit increase in cumulative dose of diclofenac (range of cumulative dose per subject = 50–335 300 mg). By contrast, the effects of cumulative dose were minimal in the analyses of ibuprofen and naproxen.

It is of note that diclofenac has the highest COX-2 selectivity among the traditional NSAIDs [6]. Therefore, it is not surprising that the effect of diclofenac in this analysis was similar to the effects found for rofecoxib and celecoxib in our previous study [1].

All patients included in these three studies had filled at least one prescription for the NSAID evaluated in the study. This method was used to obtain some degree of comparability between all subjects and to reduce bias and confounding. Matching on age, gender, calendar time and general practice was used to further control for important potential confounding factors. Subjects with only one prescription for the study NSAID were classified as non-exposed. This reference group was based on randomized studies [7–9] which provided evidence that the receipt of only one prescription does not increase the risk of AMI.

A major difference between our observational studies and those previously published is that, predicated on the results of the clinical trials, we elected to evaluate duration of use for each NSAID as the primary exposure variable rather than currency of use which was used in other studies. In reviewing our results, we noted that only 30% of cases were currently exposed at the index date. Therefore, had we used current use as the primary exposure definition we would have lost 70% of the information available in these data.

The public health implication of this finding is substantial. We estimate, based on the GPRD, that more than 15 million people in the UK have been prescribed diclofenac in the past 20 years. Approximately 11% of these are estimated to have received ≥ 10 prescriptions. In addition, we estimate, based on US claims data, that over 5 million people in the USA have taken diclofenac in the past 5 years.

Of further public health importance, on 23 August 2006 Reuters reported that Merck had received an 'approvable letter' from the Food and Drug Administration for their new COX-2 selective NSAID Arcoxia (<http://money.cnn.com/2006/08/23/news/companies/merck.reut/index.htm>). Randomized trials comparing the new Merck NSAID with diclofenac found no difference in risk of myocardial infarction between the two drugs. Since the risk of AMI in diclofenac users appears to be elevated, this implies that the risk in the new Merck drug may also be elevated.

In summary, it is the amount of NSAID use that appears to be the critical determinant of the relation of diclofenac to AMI, not the timing of exposure. In the current study, an increased risk appears to be present in diclofenac users, but not in users of ibuprofen or naproxen.

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