Risk of hospitalization for angio-oedema among users of newer COX-2 selective inhibitors and other nonsteroidal anti-inflammatory drugs

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What is already known about this subject

- There is some evidence that the risk of cutaneous reactions is lower in patients taking newer cyclooxygenase (COX)-2 selective inhibitors than in users of other nonsteroidal anti-inflammatory drugs (NSAIDs).
- However, the data are inconclusive and formal epidemiological evidence is lacking.

What this study adds

- This population-based case-control study found no elevated risk for angio-oedema amongst users of newer COX-2 selective inhibitors, whilst users of other NSAIDs were shown to have an increased risk.
- Our data support the hypothesis that newer COX-2 selective inhibitors are safe in relation to angio-oedema.
- However, given other current health concerns related to these drugs, their use should continue to be carefully monitored.

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Aim

To examine the risk of angio-oedema among users of the newer cyclooxygenase (COX)-2 selective inhibitors celecoxib and rofecoxib and other non-aspirin nonsteroidal anti-inflammatory drugs (NSAIDs) in a population-based case-control study.

Methods

Cases of angio-oedema were identified from hospital discharge registries from three Danish counties between 1 January 2000 and 31 December 2003 ($n = 377$) and 10 matched population controls per case were selected from the Civil Registration System ($n = 3747$). Data on newer COX-2 selective inhibitor and other NSAID use (current and former) were obtained from prescription databases. Data on potential confounding factors were also collected. Conditional logistic regression was used to compute relative risks for angio-oedema according to drug exposure.

Results

The crude relative risks for the newer COX-2 selective inhibitors were higher than those for other NSAIDs. After adjustment for confounding, the relative risk for current use of newer COX-2 selective inhibitors was 0.96 [95% confidence interval (CI) 0.46, 2.03], whereas the risk for other NSAIDs was 1.77 (95% CI 1.23, 2.58).

Conclusion

Our data support the hypothesis that newer COX-2 selective inhibitors are safe in relation to angio-oedema. However, given other current health concerns related to these drugs, their use should continue to be carefully monitored.

Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most commonly used drugs worldwide, with a well-known risk of gastrointestinal toxicity [1]. They are also considered to be a leading cause of cutaneous adverse drug reactions such as angio-oedema [2], which, if it involves the upper respiratory tract, can lead to life-threatening obstruction of the laryngeal airway [3].

Newer cyclooxygenase (COX)-2 selective inhibitors were specifically developed as NSAIDs with improved gastrointestinal tolerability, causing less ulceration and bleeding than the older NSAIDs [4]. There is some evidence that the risk of cutaneous reactions is lower in patients taking newer COX-2 selective inhibitors. This comes mainly from the results of controlled drug challenge studies [5–8], in which patients with a history of previous reaction to NSAIDs were given one or more doses of a COX-2 selective inhibitor and monitored for adverse effects. However, the results were not consistent and several case reports have reported angio-oedema to be induced by newer COX-2 selective inhibitors [9–11].

Since COX-2 selective inhibitors are among the most widely used drugs worldwide and their cardiovascular safety has been challenged, any increased risk has major public health implications. To our knowledge, no population-based studies of the association between newer COX-2 selective inhibitors and hospitalization for angio-oedema have been conducted to date. Therefore, we examined the risk of angio-oedema among users of newer COX-2 selective inhibitors and other non-aspirin NSAIDs in a Danish population-based case-control study.

Methods

This case-control study was conducted within three Danish counties; North Jutland, Viborg and Aarhus (population approximately 1.4 million). The Danish National Health Service provides tax-supported health-care for all inhabitants, including costs of prescribed drugs. Unambiguous linkage was performed between existing medical administrative registries using the civil registry number, a unique number assigned to each Danish citizen at birth.

Identification of angio-oedema cases and population controls

To identify cases of angio-oedema, we used the population-based hospital discharge registries from the three counties, which retain data on all discharges, including inpatients, outpatients and emergency department visits, from nonpsychiatric hospitals since 1972 (Viborg County) or 1977 (North Jutland and Aarhus counties).

We identified patients with a first discharge diagnosis of angio-oedema [*International Classification of Diseases*, 10th revision (ICD-10) [12] code T.78.3] between 1 January 2000 and 31 December 2003, who had been living within the counties for less than 1 year. In total, 377 cases were available for analyses (Table 1). Using the Civil Registration System, which retains data on vital status, address and emigration, we aimed to select 10 controls from the general population for each case matched by age (same year of birth) and sex ($n = 3747$) using the risk set sampling technique [13] [i.e. the controls had to be alive and at risk of a first hospitalization

Table 1

Descriptive characteristics of angio-oedema cases and controls

Characteristic	Cases ($n = 377$)	Controls ($n = 3747$)
Age (years), n (%)		
0–15	29 (7.7)	287 (7.7)
16–60	209 (55.4)	2064 (55.1)
≥60	139 (36.9)	1396 (37.3)
Sex, n (%)		
Male	171 (45.4)	1710 (45.6)
Female	206 (54.6)	2037 (54.4)
Prescriptions for*, n (%)		
Celecoxib	7 (1.9)	24 (0.6)
Rofecoxib	7 (1.9)	36 (1.0)
Any COX-2 inhibitor	13 (3.4)	58 (1.5)
Etodolac	3 (0.8)	17 (0.5)
Ibuprofen	25 (6.6)	116 (3.1)
Diclofenac	13 (3.4)	79 (2.1)
Naproxen	5 (1.3)	16 (0.4)
Ketoprofen	1 (0.3)	7 (0.2)
Indomethacin	1 (0.3)	2 (0.1)
Other non-aspirin NSAIDs	6 (1.6)	26 (0.7)
Any non-aspirin NSAID	49 (13.0)	254 (6.8)
ACE inhibitors	94 (24.9)	150 (4.0)
Angiotensin II receptor antagonists	6 (1.6)	109 (2.9)
Other antihypertensives	114 (30.2)	590 (15.7)
Anti-thrombotics	37 (9.8)	185 (4.9)
Aspirin	23 (6.1)	118 (3.1)
Paracetamol	45 (11.9)	149 (4.0)
Penicillins	71 (18.8)	254 (6.8)
Other antibiotics	25 (6.6)	126 (3.4)
Hospital admissions for asthma*, n (%)	31 (8.2)	82 (2.2)

*Recorded in the 90 days before hospitalization with angio-oedema. NSAID, Nonsteroidal anti-inflammatory drug.

for angio-oedema according to their discharge history at the time the corresponding case was diagnosed (index date)].

Use of newer COX-2 selective inhibitors and other non-aspirin NSAIDs

Data on prescriptions for non-aspirin NSAIDs were obtained from population-based prescription databases maintained in the counties, which retain information on refundable drugs, including type of drug and date of dispensing of the drug. Data were available from 1991 (North Jutland County), 1996 (Aarhus County) and 1998 (Viborg County), respectively. Thus, complete coverage was ensured for the entire period of this study. Use of the newer COX-2 selective inhibitors rofecoxib and celecoxib (the only two on sale in Denmark during the study period) and other non-aspirin NSAIDs, including etodolac, ibuprofen, diclofenac, naproxen, ketoprofen and indomethacin was assessed. All types of non-aspirin NSAIDs, except low-dose ibuprofen (200 mg per tablet), were available in Denmark only by prescription. We classified individuals according to their most recent use: current users (filled a prescription 0–90 days before the index date), former users (filled a prescription more than 90 days before the index date) or non-users (no recorded prescriptions for any non-aspirin NSAID before the index date). The minimum length of available prescription history on cases and controls was 1 year.

Confounding factors

Using the prescriptions database, we extracted data on the following potential confounding factors: prescriptions for aspirin, paracetamol, angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor antagonists, other antihypertensives (β -blockers, calcium antagonists, diuretics), antithrombotics (low-dose aspirin, dipyridamol, clopidogrel, warfarin, phenprocoumon), penicillin and other antibiotics, filled in up to 90 days before the index date. Data on asthma admissions up to 90 days before the index date were obtained from the hospital discharge registries.

Statistical analysis

We created contingency tables for the main study variables and case and control status. We used conditional logistic regression to compute crude and adjusted odds ratios (OR) with 95% confidence intervals (CIs) for angio-oedema according to drug exposure. Since we used risk set sampling of controls, these ORs are unbiased estimates of the corresponding rate ratios [14]. Non-users were used as the reference group in all analyses. To adjust for confounding, we used the change-in-

estimate method [15], in which variables (evaluated one at a time) were selected if their inclusion led to a $\geq 10\%$ change in the risk estimates of interest. All analyses were conducted using STATA version 9.0 (StataCorp, College Station, TX, USA).

Results

The characteristics of the cases and controls and their prescriptions for non-aspirin NSAIDs during the 90 days before the index date are given in Table 1. Overall, 3.4% of cases and 1.5% of controls filled in a prescription for a newer COX-2 selective inhibitor in the 90 days before the index date, while 13.0% of cases and 6.8% of controls filled in a prescription for other non-aspirin NSAIDs. The most commonly prescribed NSAIDs were ibuprofen (6.6% of cases and 3.1% of controls) and diclofenac (3.4% of cases and 2.1% of controls). Table 1 also shows prescriptions for the other drugs considered to be potential confounding factors. These drugs were widely prescribed and there were large differences between the cases and controls, particularly for ACE inhibitors, which were used by 24.9% of cases and 4.0% of controls in the 90 days before the index date.

Table 2 shows the crude and adjusted ORs for angio-oedema according to prescription for newer COX-2 selective inhibitors or other NSAIDs. The crude ORs for the newer COX-2 selective inhibitors were higher than those for other NSAIDs, i.e. the OR for current use of all newer COX-2 selective inhibitors was 2.32 (95% CI 1.25, 4.32) compared with 2.10 (95% CI 1.51, 2.93) for other NSAIDs. After adjustment, the estimate for the newer COX-2 selective inhibitors decreased to 0.96 (95% CI 0.46, 2.03), whereas the estimate for other NSAIDs decreased to 1.77 (95% CI 1.23, 2.58). The adjusted ORs for current use of celecoxib and rofecoxib, when analysed separately, were 1.03 (95% CI 0.37, 2.91) and 1.01 (95% CI 0.37, 2.75), respectively. Use of ACE inhibitors was the strongest confounder of the relationship between newer COX-2 selective inhibitors and angio-oedema.

The adjusted OR for former use of other NSAIDs was 1.44 (95% CI 1.13, 1.82). For former use of newer COX-2 selective inhibitors, the crude ORs were lower than those for current use. However, this trend reversed after adjustment and was most apparent for celecoxib, with an OR for former users of 2.22 (95% CI 0.99, 5.02).

The other NSAIDs were split into seven categories (six specific drugs and an 'other' category) as listed in Table 1. Separate analysis of these seven drug categories showed an increased OR for angio-oedema with current use for all except ketoprofen (data not shown).

Table 2

Crude and adjusted ORs for angio-oedema according to prescription

Category of use	Cases	Controls	Crude OR (95% CI)*	Adjusted OR (95% CI)†
Celecoxib				
Current	7	24	2.98 (1.27, 7.01)	1.03 (0.37, 2.91)
Former	11	40	2.87 (1.44, 5.71)	2.22 (0.99, 5.02)
Rofecoxib				
Current	7	36	2.00 (0.87, 4.60)	1.01 (0.37, 2.75)
Former	11	70	1.62 (0.83, 3.15)	1.27 (0.59, 2.76)
Any COX-2 inhibitor				
Current	13	58	2.32 (1.25, 4.32)	0.96 (0.46, 2.03)
Former	15	98	1.60 (0.90, 2.84)	1.24 (0.65, 2.36)
Non-aspirin NSAID				
Current	49	254	2.10 (1.51, 2.93)	1.77 (1.23, 2.58)
Former	188	1515	1.52 (1.21, 1.90)	1.44 (1.13, 1.82)

*Never users constitute the reference group. †Adjusted for prescriptions for ACE inhibitors, other antihypertensives, paracetamol, penicillins and other antibiotics. NSAID, Nonsteroidal anti-inflammatory drug.

Discussion

We found no increased risk of angio-oedema amongst current users of the newer COX-2 selective inhibitors, celecoxib and rofecoxib, after adjustment for confounding. In contrast, current users of other NSAIDs were shown to have an increased risk. Our data suggest that, compared with other NSAIDs, newer COX-2 selective inhibitors may be relatively safe in relation to angio-oedema. This is thought to be due to the fact that COX-2 selective inhibitors do not inhibit the enzyme COX-1, which may be involved in the pathogenesis of urticaria and angio-oedema related to NSAIDs [16].

Our findings are in accordance with previous adverse event monitoring studies. In a USA-based review of adverse drug events reported to one hospital between January 1999 and June 2002, only three patients were reported to experience allergic reactions related to COX-2 selective inhibitors, one of which was classified as angio-oedema [17]. In the UK, studies into the safety of celecoxib and rofecoxib as used in general practice have been undertaken [18, 19]. Users were identified from National Health Service prescriptions issued by general practitioners (GPs) between May and December 2000 (celecoxib) and February and November 2000 (rofecoxib) and event reports were obtained by sending questionnaires to the prescribing GP at least 6 months after the date of the first prescription. For celecoxib, only three reports of angio-oedema were found, two of which were assessed as 'possibly' related (out of 17 458

returned questionnaires) and for rofecoxib only one case was reported and assessed as 'possibly' related (out of 15 268 returned questionnaires).

It has been suggested that newer COX-2 selective inhibitors can be safely used in most patients with a history of adverse cutaneous reactions to other NSAIDs. However, the results of previous controlled drug challenge studies are not entirely consistent, with reports of up to 33% (10 out of 30 patients) reacting to the COX-2 selective inhibitor celecoxib [20] and 29% (eight out of 23 patients) reacting to rofecoxib [21], whereas other studies report that no reactions to these drugs were observed [5–8]. These studies used varying doses of NSAIDs and the majority were carried out on only one occasion, with a single dose administered. Referring to several case reports, Marshall states that patients were more likely to develop intolerance after at least a week of therapy rather than after one dose [11]. However, Nettis *et al.* followed up patients with a history of adverse reactions to NSAIDs who had undergone oral challenge with rofecoxib (without reaction) and had continued to use the drug. Between 1 and 3 years later, only seven (5%) of the 131 patients reported experiencing cutaneous reactions to rofecoxib [22].

The increased risk of angio-oedema associated with the use of other NSAIDs found in our study is consistent with previous reports from adverse event monitoring studies [23, 24] and controlled drug challenges [14]. We found no consistently increased risks when examining

specific conventional NSAIDs; however, it should be noted that these analyses were based on relatively small numbers of exposed cases and controls. The drugs classified as other NSAIDs in this study inhibit both the COX-1 and COX-2 isoenzymes, although there are different methods of inhibition [25], which may lead to differing risk estimates for angio-oedema and other reactions.

The cellular and biochemical events that occur during adverse reactions to NSAIDs remain uncertain [26]. COX inhibition, leading to the diversion of arachidonic acid metabolism from the production of prostaglandins to cysteinyl leukotrienes, has been proposed as the major mechanism producing NSAID-related respiratory reactions and may also be involved in cutaneous reactions to NSAIDs [26, 27]. There is evidence that newer COX-2 selective inhibitors do not trigger cysteinyl leukotriene biosynthesis in aspirin-sensitive asthmatics [28] and this may explain their safety in relation to asthma and also angio-oedema. However, there is also increasing evidence of an association between use of COX-2 inhibitors containing sulphonamide residue (celecoxib and valdecoxib) and more severe skin reactions, such as Stevens–Johnson syndrome and toxic epidermal necrolysis, and so the use of these drugs needs to be carefully monitored [29].

Former use of other NSAIDs was less strongly associated with risk of angio-oedema than current use, indicating that the association is probably not causal. Although no prescriptions had been issued for at least 90 days among former users, occasional use of drugs left over from an old prescription cannot be ruled out. Former use of newer COX-2 selective inhibitors, however, was more strongly associated with risk of angio-oedema than current use, suggesting that this was confounded to a lesser extent by the use of ACE inhibitors and other drugs. This may reflect a well-known channelling bias, e.g. patients prescribed COX-2 selective inhibitors may have an adverse cardiovascular risk profile compared with patients being prescribed other NSAIDs [30, 31], resulting in an increased use of ACE inhibitors among users of COX-2 selective inhibitors.

The main strengths of this study are its population-based design covering a time period of >3 years and the complete histories of prescriptions. However, it has several limitations. First, it included only hospitalized patients. However, since valid measures of effect size depend only on the odds of the exposed to non-exposed among cases and controls and not the completeness of case ascertainment, incomplete case ascertainment may be critical in a follow-up study, but less problematic in a case–control design. As long the case identification is

unrelated to the exposure of interest, a hospital registry is a valid source of case identification in a case–control study [32]. Our null result for newer COX-2 selective inhibitors strongly indicates that the case ascertainment is unrelated to the exposure. Second, we had no data on over-the-counter sale of NSAIDs (low-dose ibuprofen and aspirin). Although low-dose ibuprofen was available without prescription, pensioners and regular users of this drug are typically all registered in the databases because the cost is partly refunded when ibuprofen is prescribed by a physician. In our analyses, ibuprofen use was found to be associated with increased risk of angio-oedema. A third limitation is that some patients appear in more than one drug category, e.g. in both the newer COX-2 selective inhibitor and former other NSAID groups. Analyses were undertaken to explore the effect of this on the results by excluding users appearing in more than one category (146 in total). However, no effect on the risk estimates was found. A fourth limitation concerns the small numbers when splitting COX-2 selective inhibitor and other NSAID use into specific drug categories. Finally, our study provided information only on the safety of rofecoxib and celecoxib and not on other newer COX-2 selective inhibitors including valdecoxib and etoricoxib.

In conclusion, this study found no increased risk for angio-oedema amongst users of the newer COX-2 selective inhibitors, celecoxib and rofecoxib, whereas users of other NSAIDs were shown to have an increased risk. Our data support the hypothesis that newer COX-2 selective inhibitors are safe in relation to angio-oedema. However, given other current health concerns related to these drugs (rofecoxib is no longer on the market due to its association with cardiovascular events), their use should continue to be carefully monitored.

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