The Association between Exposure to COX-2 Inhibitors and Schizophrenia Deterioration. A Nested Case-Control Study

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Key words
- schizophrenia
- COX-2 inhibitors
- pharmacoepidemiology

Abstract

Background: COX-2 inhibitors (COX-2i) have been reported to have beneficial effects on schizophrenia. This observational study assesses the association between exposure to COX-2i or/and NSAIDs and schizophrenia deterioration.

Methods: We conducted a case-control study within a cohort (n=3,485) of antipsychotic users with a schizophrenia diagnosis (ICD-9=295.x) in IMS-Lifelink, a US claims database. Case events indicating exacerbation of schizophrenia were: switching antipsychotic medication, starting combination therapy, using parenteral antipsychotics or an increasing dose. For each case one control was selected. Exposure to COX-2i/NSAIDs (current/recent/none) and cumulative exposure in Defined Daily Doses 90 days before the index/event date were assessed. Age, sex and co-medication were evaluated as confounders. Logistic regression analysis was used to assess the association.

Results: 1,443 case events occurred. For current use, no benefit on schizophrenia case events from exposure to COX-2i was found (adjusted OR 1.16; 95% CI 0.83–1.62). Instead, recent COX2i use with a duration of 0 to 93 days was associated with an increased risk for schizophrenia deterioration (adjusted OR 2.56; 95% CI 1.35–4.87). This association was strongest in rofecoxib. No relation was found for NSAIDs.

Conclusion: The use of COX-2i was not associated with a decreased risk for schizophrenia deterioration in this population.

Introduction

Cyclooxygenase-2 (COX-2) inhibitors were initially marketed for the treatment of pain in osteoarthritis and, in the USA, for acute pain. Research into the effects of this drug class has extended beyond these indications. In recent years several new functions of the different isoforms of the cyclooxygenase enzyme in (patho-)physiological processes have been discovered. One of these discoveries is the existence of constitutively expressed cyclooxygenase-2 in the central nervous system. This finding has sparked interest in the potential therapeutic benefits of the selective inhibition of cyclooxygenase-2 in psychiatric illnesses [4,9]. Furthermore, these findings may also lead to a better understanding of the pharmacological basis of psychiatric adverse events that have been reported for non-steroidal anti-inflammatory drugs (NSAIDs) [11].

Recent studies have suggested that COX-2 inhibitors could have a beneficial effect on disease status in patients with schizophrenia when added to regular pharmacological treatment with an antipsychotic [7]. In a small randomized controlled clinical trial (n=50) in patients with an acute exacerbation of schizophrenia, the addition of celecoxib to risperidone improved positive and negative syndrome scale (PANSS) scores in schizophrenia patients [6]. A more recent trial (n=60) showed a significant superiority of a risperidone and celecoxib combination over risperidone alone in total PANSS scores, treatment of positive symptoms, and general psychopathology symptoms [1]. However, these results were not confirmed in another trial among continuously ill outpatients (n=38) [12].

The objective of this study was to assess the association between exposure to COX-2 inhibitors, NSAIDs, or both and the deterioration of schizophrenia in a daily practice setting.

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Methods

Setting

We conducted a case-control study nested within a cohort of pharmacologically treated patients with schizophrenia, using data from the IMS-Lifelink database. IMS-Lifelink is a US claims database and contains information on the health care utilisation of 1.8 million current and former employees and their dependents. The enrollees are situated mostly in the Midwest and on the East Coast of the United States. The database includes data on claims for prescriptions, hospitalisations, diagnostic/therapeutic procedures, and physician visits. The database covers a period from 1992 to 31 December 2002.

Cohort selection

A study cohort was selected from the Lifelink database. A patient was included in the cohort if a diagnosis of schizophrenia (ICD-9 code 295.X) was recorded anywhere in the diagnosis history after 1992 and if at least three prescriptions were claimed for an oral antipsychotic drug (IMS USC codes 64190 – phenothiazine derivatives – and 64110 – other antipsychotics) after 1 January 2000. The study period ended on the 31st of December 2002.

The date of the first prescription for an antipsychotic drug after 1 January 2000 marked the start of follow-up; this coincides with the introduction of COX-2 inhibitors. Follow-up ended with either the end of the study period, the date on which a patient left the insurance scheme, or when no prescription for an antipsychotic drug was filled for 180 days, whichever came first. In the latter case, the date of the last prescription was recorded as the end of follow-up.

Patients were not eligible for inclusion in the cohort when information about their coverage by the insurance scheme was lacking from 1 January 1999 onwards, or if patients were not fully covered during the study period. Furthermore, to detect changes in the prescribed daily dose, one of our case events described below, theoretical daily doses were calculated from the prescription records using the number of units dispensed and the number of days for which the drug was supplied according to the pharmacy. Based on this, we also excluded patients with unrealistically high or low calculated daily doses, defined as less than 25% of the smallest tablet size or more than two times the maximum daily dose according to the Food and Drug Administration label or Thomson's Micromedex®.

Case definition

A patient was defined as a case if a medication event occurred during follow-up which we considered to be a marker for the deterioration of schizophrenia. We evaluated the following events:

- Prescription for a parenteral antipsychotic drug;
- Switching to another antipsychotic: a prescription is dispensed for an antipsychotic with an active substance different from the prior prescription during the follow-up period. The prior substance does not return in the medication history in the next 180 days;
- Start of combined use: a prescription for a second antipsychotic substance appears, the substance of the prior antipsychotic prescription returns within the next 180 days after the addition of the second substance;
- Dose increase: an increase in the calculated daily dose of >30% compared to the previous prescription.

Only the first case event that occurred was taken into account for this analysis, patients were not followed up after the date of this case event. The date of the prescription for the case event was the index date. Furthermore, patients had to be at least 18 years old when the case event occurred. Patients had to use a single antipsychotic (monotherapy) at the start of follow-up. Finally, the medication event should be preceded by a continuous follow-up period of at least 90 days. If the patient did not meet these criteria, the patient was excluded.

Selection of controls

One control was randomly selected for each case using risk-set sampling from all patients in the cohort who had not experienced a case event on the index date. The date on which the case event occurred was the index date for the control. Patients had to be at least 18 years old on the index date to be eligible for selection as a control.

Exposure definition

Exposure to COX-2 inhibitors and (other) NSAIDs before the index date was assessed in two ways. Firstly, we assessed exposure as either 'current', 'recent' or 'none'. A patient was considered a 'current' user when the index date was between the start date of a prescription for an NSAID or a COX-2 inhibitor and the theoretical end date of the prescription, based on the number of days for which the NSAID or COX-2 inhibitor was dispensed according to the pharmacy. 'Recent' users received a last prescription for an NSAID or a COX-2 inhibitor that ended between 1 and 90 days before the index date. All other subjects were classified as 'non-exposed'. For 'current' and 'recent' users the relationship between the duration of NSAID or COX-2 inhibitor use and the outcome event was assessed by taking the duration of NSAID or COX-2 inhibitor exposure into account. The duration of exposure was the number of days between the theoretical end date of the last NSAID or COX-2 inhibitor prescription before the index date and the earliest prior prescription for a NSAID or COX-2 inhibitor without intervening gaps of more than 90 days between the theoretical end date of a COX-2 inhibitor prescription and the following prescription. The NSAID or COX-2 inhibitor groups were divided in three duration levels based on tertiles of the COX-2 inhibitor group.

Secondly, we calculated cumulative exposure in the 90 days before the index date as defined daily dose (DDDs), a dosage measure defined by the World Health Organisation. When a DDD was not available, an average daily dose in adults was retrieved from Thomson's Micromedex®. Cases and controls were divided in three exposure levels with regard to DDDs, based on tertiles.

Statistical analysis

A logistic regression model was used to estimate the association between the occurrence of a marker for a change in disease status and the use of COX-2 inhibitors or other NSAIDs. Results were expressed as odds ratios (ORs) with 95% confidence intervals (CI). We adjusted for potential confounding by including in the model: age, sex and use of other medications in the past 365 days (antiepileptics, antidepressants, Parkinson's medication or corticosteroids). All analyses were performed with SPSS, version 13 (SPSS Inc, Chicago Ill.).

Table 1 Characteristics of cases and controls

	Cases n = 1443 (%)	Controls n = 1443 (%)
Mean age at index/event date [SD]	55.3 [14.1]	57.1 [13.3]
Male sex	623 (47.9)	678 (47.2)
Co-morbidities, ≥ 1 diagnosis after 1 January 1992		
Dementias – ICD 290	128 (8.9)	83 (5.8)
Alcohol-induced mental disorders – ICD 291	43 (3.0)	27 (1.9)
Drug-induced mental disorders – ICD 292	47 (3.3)	24 (1.7)
Transient mental disorders due to other conditions – ICD 293	164 (11.4)	132 (9.1)
Persistent mental disorders due to other conditions – ICD 294	133 (9.2)	99 (6.9)
Episodic mood disorders – ICD 296	1101 (76.3)	958 (66.4)
Delusional disorders – ICD 297	180 (12.4)	126 (8.7)
Other nonorganic psychoses – ICD 298	556 (38.5)	433 (30.0)
Pervasive developmental disorders – ICD 299	8 (5.5)	5 (3.5)
Drug use (in 365 days before event/index date)		
Oncolytics	22 (1.52)	26 (1.8)
Corticosteroids	153 (10.6)	129 (8.9)
Lipid-lowering drugs	289 (20.0)	323 (22.4)
Cardiac drugs (e.g., digoxin)	173 (12.0)	153 (10.6)
RAAS inhibitors	315 (21.8)	304 (21.1)
Acid-lowering drugs	427 (29.6)	348 (24.1)
Antiepileptics	578 (40.1)	413 (28.6)
Antidiabetic drugs	265 (18.4)	232 (16.1)
Drugs used for the treatment of Parkinson's disease	385 (26.7)	328 (22.7)
Drugs used for the treatment of mania	170 (11.8)	161 (11.1)
Antidepressants	881 (61.1)	700 (48.5)

Results

The Lifelink database contained 10,066 patients with at least one schizophrenia diagnosis after 1 January 1992. Our final cohort of antipsychotic users comprised 3,385 patients. After the start of follow-up an event occurred in 1,443 patients. Based on the calender date 1,443 controls were sampled from the cohort. A description of cases and controls is given in **Table 1**. The high prevalence of antiepileptics in the cases and controls is caused by valproic acid, carbamazepine and clonazepam, which are frequently used for psychiatric indications in this population. The median follow-up before an event occurred in the cases was 302 days (average: 374 days). **Table 2** shows that the most common event was a dose increase (49.4%), the use of parenteral antipsychotics was least common (2.3%).

When we assessed the relationship between COX-2 inhibitor/NSAID use before the event/index date and the outcome event, current use was not associated with a decrease in schizophrenia case events (adjusted OR 1.16; 95% CI 0.83–1.62). **Table 3** shows the results of the analysis in more detail for the different exposure durations and levels. Recent COX-2 inhibitor users with a duration of use of 0 to 93 days, had an increased risk for the deterioration of their disease (adjusted OR: 2.56; 95% CI 1.35–4.87). No relation was found for NSAIDs.

Table 2 Number of patients with the various types of medication (case) events in the cohort (n = 3,385)

	* patients with the event (%)
Use of a parenteral antipsychotic	33 (2.3%)
Switch to a different antipsychotic	372 (25.8%)
Start combination therapy	325 (22.5%)
Dose increase > 30%	713 (49.4%)

When the data were analysed for the different levels of recent exposure in defined daily doses (DDDs), we found an association between the use of COX-2 inhibitors and an increased risk for unfavourable medication events for the 0–45 DDD group (adjusted OR: 1.78; 95% CI 1.15–2.80). Other NSAIDs did not show a significant association in the crude or adjusted analysis at any exposure level.

When stratifying the results for recent use according to the type of COX-2 inhibitor, we found that rofecoxib, the most selective COX-2 inhibitor of the compounds in this study, showed a stronger association between recent use and deterioration of schizophrenia (adjusted OR 2.88; 95% CI 1.29–6.43) than celecoxib (adjusted OR 1.29; 95% CI 0.82–2.03).

Discussion

Our results do not provide evidence for the hypothesis that the use of COX-2 inhibitors is associated with a favourable effect on schizophrenia. Instead, we found a significant association between the discontinuation of COX-2 inhibitors in the 90 days before the event date and deterioration of the disease state.

The mechanism behind the supposed beneficial effect of COX-2 inhibitors in schizophrenia is still unresolved. In general, two theories can be identified [13]. The first theory focuses on the role of cyclooxygenase-2 in immunological processes: COX-2 inhibitors may reduce the levels of cytokines up-regulated in the brain by cyclooxygenase-2 – such as IL-2, IL-6, IL-10 and TNF-alpha – and thereby reduce inflammatory processes that have been associated with schizophrenia. However, clinical studies have not been able to substantiate this mechanism [2,9]. A second theory states that COX-2 inhibitors modify the glutamergic signalling pathway, reducing the over-activation of NMDA receptors, which have been implicated in the pathogenesis of schizophrenia.

These two theories cannot explain our finding that recent use of COX-2 inhibitors was associated with a deterioration of schizophrenia. A hypothesis from the cardiovascular field may account for the findings in this study. It has been hypothesised that the adverse effects seen in the COX-2 inhibitor class, and which precipitated the market withdrawal of rofecoxib, may be caused by a 'compensatory host response' [3]. Under this hypothesis, the withdrawal of cyclooxygenase-2 inhibition after discontinuation of a COX-2 inhibitor leads to a sudden increase in the activity of cyclooxygenase-2-mediated processes. When applied to schizophrenia, the withdrawal of a COX-2 inhibitor would thus increase cyclooxygenase-2 activity, influencing the inflammatory and neurotransmission pathways related to schizophrenia. To further investigate this, we also studied the association between the duration of prior COX-2 inhibitor use and the dete-

Table 3 The association between the risk for deterioration of schizophrenia and type or cumulative level of COX-2 inhibitor/NSAID exposure: nested case-control analysis

	Cases n = 1443	Controls n = 1443	Crude OR (95 % CI)	Adjusted OR* (95 % CI)
Current/recent exposure				
None	1147	1203	Reference	Reference
COX-2 inhibitor recent				
0–93 days total	39	13	3.15 (1.67–5.93)	2.56 (1.35–4.87)
94–324 days total	17	22	0:81 (0.43–1.54)	0.74 (0.39–1.42)
>324 days total	20	9	2.33 (1.06–5.14)	2.22 (0.99–4.98)
COX-2 inhibitor current				
0–93 days total	26	13	2.10 (1.07–4.10)	1.83 (0.92–3.64)
94–324 days total	26	28	0.97 (0.57–1.67)	0.98 (0.57–1.70)
324 days total	34	33	1.08 (0.67–1.76)	1.03 (0.63–1.70)
NSAID recent				
0–93 days total	43	38	1.19 (0.76–1.85)	1.00 (0.64–1.57)
94–324 days total	9	6	1.57 (0.56–4.43)	1.38 (0.48–3.93)
324 days total	15	10	1.57 (0.70-3.52)	1.51 (0.67-3.43)
NSAID current				
0–93 days total	15	15	1.05 (0.51–2.16)	0.91 (0.44–1.90)
94–324 days total	5	10	0.52 (0.18–1.54)	0.47 (0.16–1.41)
324 days total	24	30	0.84 (0.49–1.44)	0.84 (0.48–1.46)
Combined NSAID/COX-2	23	13	1.86 (0.94–3.68)	1.69 (0.84–3.40)
Cumulative exposure in DDDs, 90 days before index date				
None	1149	1203	Reference	Reference
COX-2 inhibitor only				
1–45 DDDs	44	30	1.97 (1.29–3.09)	1.78 (1.15–2.80)
46–90 DDDs	31	42	1.28 (0.86–1.91)	1.24 (0.82–1.87)
>90 DDDs	35	37	1.15 (0.75–1.77)	1. 02 (0.65–1.58)
NSAID only				
1–30 DDDs	61	32	1.54 (0.96–2.46)	1.40 (0.87–2.26)
31–75 DDDs	55	45	0.77 (0.48–1.24)	0.68 (0.42–1.10)
>75 DDDs	45	41	0.99 (0.62–1.58)	0.91 (0.56–1.47)
Combined NSAID/COX-2 inhibitor	23	13	1.85 (0.93–3.67)	1.68 (0.84–3.38)

*Adjusted odds ratios (ORs) are based on multivariate logistic regression models including age, sex and use of antipepileptics, antidepressants, drugs used for the treatment of Parkinson's disease or corticosteroids in the year before the index date

rioration of schizophrenia disease status. However, since we found no statistically significant relation in this analysis, we cannot substantiate the 'compensatory host response' theory. Thus, the most likely explanation is a false positive finding related to multiple hypothesis testing.

A fourth hypothesis could be that COX-2 inhibitors do have a protective effect and that withdrawal of this 'protection' leads to a sudden deterioration in health status. However, our data do not allow us to explore this hypothesis in detail.

Within the class of COX-2 inhibitors, there is strong variation in the COX-1/COX-2 ratio for cyclooxygenase-isoform activity, with rofecoxib being a more selective inhibitor of cyclooxygenase-2 than celecoxib. Furthermore, rofecoxib also has a higher brain penetrance. However, the analysis for rofecoxib and celecoxib showed a similar pattern to the overall results.

When interpreting the results of this study, there are some limitations that have to be taken into account. Firstly, we used changes in antipsychotic medication as the outcome measure. In clinical trials, the beneficial effects of celecoxib were seen when the PANSS scale was used as the main outcome measure. A non-scale outcome, such as the medication events evaluated here, may be unsuitable for detecting clinically small effects. However, we believe that the selected outcome events constitute a meaningful measure of schizophrenia deterioration in an observational setting and can provide information about the effects of drug use or other interventions. For individual outcomes, we find support for our assumption in earlier studies. For example, our hypothesis that switching is an indicator for disease deterioration can be substantiated by an earlier study which showed that switching is often caused by a lack of therapeutic effect or adverse effects [5]. In our study, case events were preceded by a continuous follow-up period of at least 90 days, making switching because of adverse events which occur soon after the start of therapy less likely. Therefore, lack of effect seems to be the most plausible reason for a medication switch. We have assumed that lack of therapeutic effect is also the most important reason for the other medication events.

In future observational studies it may be worthwhile to look at other outcome measures besides medication use such as hospitalisations, which were not included in this study because of unreliable coding in the database.

Furthermore, the information available about patient characteristics was limited. Validation of diagnoses is a challenging aspect of observational database studies. We tried to minimise misclassification by requiring patients to have at least three prescriptions for an antipsychotic in addition to having a diagnosis of schizophrenia based on first three digits of the ICD-9 code. Also, it was not possible to reliably determine the time since the first schizophrenia diagnosis or disease severity, which may be a relevant factor for the effects of COX-2 inhibitors in this disease. In one of the clinical trials, recently diagnosed patients showed more improvement when celecoxib was added to an antipsy-

chotic treatment than patients for whom the diagnosis was made a longer time ago [9]. The peak incidence of schizophrenia is between 20–30 years of age, the median age of our population was 55.3 years for the cases and 57.1 for the controls. Similarly, the patients studied in a claims database may be in the later stages of their disease, have late-onset schizophrenia, or have a relatively stable disease. The median follow-up to first medication event of 302 days may indicate stable disease. This may not be the population in which COX-2 inhibitors have a beneficial effect on schizophrenia disease status. Further observational research might be done on datasets that allow more detailed categorization of schizophrenia.

A third limitation is the nature of the data source used. Since IMS-Lifelink is a claims database, we may not have captured all drug use by patients. This may especially be the case for over the counter non-selective NSAIDs. However, if this exposure misclassification has occurred, we believe that it is non-differential with regards to the cases and controls and therefore will not have influence the outcome of this study in a major way.

The non-selective NSAIDs are known to vary in their COX-2i selectivity; future studies could also further categorize non-selective NSAIDs.

Furthermore, Lifelink is an employee claims database containing information about employees and their dependants. This makes it likely that patients in this database have a higher socioeconomic status than the average patient with schizophrenia. However, we have no evidence to suggest that socioeconomic status is associated with the effectiveness of COX-2i and NSAIDs in preventing the deterioration of schizophrenia.

In conclusion, the use of COX-2 inhibitors was not associated with a decreased risk for the deterioration of schizophrenia in this observational study. However, the observational design may limit the generalisation of this finding. Future studies could look into this effect in more detail, as well as the effects of COX-2 inhibitors in certain patient subgroups, such as those who were recently diagnosed.

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