Pharmacoepidemiology

Factors Associated with Celecoxib and Rofecoxib Utilization

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BACKGROUND: The cyclooxygenase-2 (COX-2) selective nonsteroidal antiinflammatory drugs (NSAIDs) celecoxib and rofecoxib (before its removal) are marketed as having fewer gastrointestinal (GI)-related complications than nonselective NSAIDs. However, adverse reaction data suggest that the use of COX-2 selective NSAIDs is associated with clinically significant GI events.

OBJECTIVE: To assess whether patients receiving celecoxib and rofecoxib have a greater underlying disease burden than patients prescribed nonselective NSAIDs.

METHODS: The study population consisted of members of 11 health plans, aged >34 years, with a pharmacy claim for celecoxib or rofecoxib or a nonselective NSAID dispensed between February 1, 1999, and July 31, 2001, who had been continuously enrolled for >364 days before the dispensing date. Celecoxib and rofecoxib patients were randomly selected without replacement from a pool of eligible users in each of the 30 months. Nonselective NSAID users were randomly chosen without replacement within each month on a 2:1 ratio to cases; they could be chosen in more than one month. Univariate analyses comparing 9000 cases and 18 000 controls were performed, followed by a multiple logistic regression analysis conditioned on time.

RESULTS: Increasing age, treatment by a rheumatologist or an orthopedic specialist, treatment with a high number of different medications in the past year, treatment with oral corticosteroids in the past year, and having had a previous GI bleed increased the likelihood of receiving celecoxib or rofecoxib, whereas treatment with a high number of nonselective NSAID prescriptions in the past year decreased it. Treatment with a high number of different medications was a predictor of increased prevalence of underlying diabetes mellitus and cardiovascular disease.

CONCLUSIONS: Patients having a greater underlying disease burden were more likely to receive COX-2 selective NSAIDs than nonselective ones. Paradoxically, patients at higher risk for cardiovascular disease were channeled toward treatment with COX-2 selective NSAIDs, many of which may confer an increased risk of acute myocardial infarction and other adverse cardiovascular outcomes.

KEY WORDS: celecoxib, cyclooxygenase-2 inhibitors, determinants of prescribing, disease burden, nonsteroidal antiinflammatory drugs, rofecoxib.

Ann Pharmacother 2005;39:597-602.

Published Online, 8 Mar 2005, *www.theannals.com*, DOI 10.1345/aph.1E298

The cyclooxygenase-2 (COX-2) selective nonsteroidal antiinflammatory drugs (NSAIDs) celecoxib and rofecoxib were approved in December 1998 and May 1999, respectively, for the treatment of osteoarthritis, rheumatoid arthritis (celecoxib only), and acute pain management, including menstrual pain. This new subclass of drugs is marketed as having fewer gastrointestinal (GI)-related complications compared with nonselective NSAIDs.[1,2] This claim is supported by the American College of Rheumatology's recommendation that COX-2 selective NSAIDs should be first-line treatment for patients with osteoarthritis who are at increased risk of gastric ulcers.[3] These drugs became one of the most rapidly adopted new product groups in recent years.

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The study was supported by Cooperative Agreement FD-U-0001643-03 and FD-U-0002067-01-03 from the Food and Drug Administration. The original manuscript was submitted before Dr. Rawson joined GlaxoSmithKline and prior to the withdrawal of rofecoxib from the market. Thus, there are no conflicts of interest.

The views expressed in this study are those of the authors and do not necessarily represent those of the US Food and Drug Administration or imply its endorsement.

However, data from the Adverse Event Reporting System (AERS) of the Food and Drug Administration (FDA) suggest that the use of COX-2 selective NSAIDs is associated with clinically significant GI events, including fatalities. Unfortunately, it is not known whether these events are related to the use of the drugs or whether the drugs are selectively prescribed to patients who have a greater risk of GI complications (channeling bias).[4] A similar phenomenon occurred in the 1980s when a slow-release version of indomethacin, especially formulated to reduce the risk of GI adverse effects, was shown to have been differentially prescribed to individuals prone to such events, who continued to suffer from them both during and after treatment.[5]

In addition, an increased risk of acute myocardial infarction (AMI) was found in rofecoxib patients in both a controlled trial[2] and observational studies.[6,7] Following the identification of a twofold increased risk of AMI in patients taking rofecoxib in a colon polyp prevention randomized controlled trial,[8] the drug was withdrawn from the market worldwide by its manufacturer at the end of September 2004.[9]

The objective of the present study was to examine variables available in a large administrative healthcare database to assess whether patients for whom celecoxib or rofecoxib was prescribed have a greater underlying disease burden than those for whom nonselective NSAIDs were prescribed. We examined whether risk factors for GI complications and other major comorbidities were more common among celecoxib and rofecoxib users than users of nonselective NSAIDs.

Methods

The study population consisted of members of 11 geographically diverse health plans with pharmacy benefits.[10] Each plan is an independent practice association model in which physicians and facilities are typically reimbursed on a discounted fee-for-service basis. The study utilized a longitudinal administrative claims research database maintained for the members of the health plans. The database is organized into separate enrollment, facility, provider, and pharmacy claims files, which can be linked using encrypted member and provider identifiers. The data are generally complete because providers must file claims to receive payment for services.

The study population consisted of commercial and Medicare members with a pharmacy claim for celecoxib or rofecoxib or a nonselective NSAID (diclofenac, diflunisal, etodolac, fenoprofen, flurbiprofen, ibuprofen, indomethacin, ketoprofen, meclofenamate, mefenamic acid, meloxicam, nabumetone, naproxen, oxaprozin, piroxicam, salsalate, sulindac, tolmetin, or trisalicylate) with a prescription dispensing date between February 1, 1999, and July 31, 2001. Since the number of prescriptions for oral suspension and rectal suppository forms of these NSAIDs was few, these products were excluded from the list of NSAIDs. Study members were required to have at least 365 days of continuous enrollment with the relevant health plan prior to the dispensing date so that comorbidity information from the prior 12 months could be included in the analysis. In addition, since the principal indication for celecoxib and rofecoxib is the treatment of osteoarthritis and rheumatoid arthritis, study inclusion was limited to members aged ≥35 years because they are at greater risk of developing these 2 disorders.

The design for this study was a modified nested case–control with incidence density matching on time.[11] With this approach, the cases were incident (ie, newly prescribed) celecoxib or rofecoxib users. Once a patient was identified as a case, he or she was ineligible for further selection. This approach was used because of the dynamic change in COX-2 selective NSAID use that occurred over the study period, which corresponded to the time near initial market introduction and penetration. To adjust for the potential confounding effect of these changes, it was essential that calendar time be taken into account as a potential confounding variable for COX-2 selective NSAID use. Therefore, patients were selected from across the entire 30-month study period by randomly choosing 1500 cases without replacement from the pool of eligible celecoxib and rofecoxib users per month for each of the 30 months we studied. To be eligible for selection, a member must have received the first prescription for celecoxib or rofecoxib during the respective month. Once chosen, a case could not be selected in any subsequent month.

A comparison group of controls, comprising members with pharmacy claims for nonselective NSAIDs with service dates in each month of the same study period, was selected. Members were randomly chosen without replacement within each of the 30 months on a 2:1 ratio to cases (3000/mo) from the eligible pool of controls for that month. To be eligible for the control pool within a month, the member must have received a nonselective NSAID prescription during the month and could only be selected once from the pool within any given month. In each subsequent month, a previously selected control was eligible for re-selection as a control provided that he or she filled a nonselective NSAID prescription during that particular month. A member who became a case (new COX-2 selective NSAID user) was no longer selected as a control.

This procedure identified 45 000 cases and 90 000 controls. Diagnosis and procedure codes for these individuals were derived from hospital and physician claims data, and prescription information was identified from pharmacy claims data from the year prior to their selection. Logistic regression conditioned on time-matched case–control sets was used in the analysis, with coefficients calculated using the SAS procedure PHREG (Cary, NC).[12] After the cases and controls were selected, it was learned that this SAS procedure has a known error with large datasets.[13] By trial and error, we ascertained that the largest number of cases and controls that could be successfully utilized by the software was approximately 27 000. Consequently, 300 cases and 600 controls were randomly selected from each of the 30 months to give a total sample of 9000 cases and 18 000 controls for analysis.

Initially, demographic and clinical variables were compared in a univariate manner between the cases and controls. These included the patient's age and gender and the indication for treatment as far as could be ascertained from physician and hospital claims data and the physician specialty associated with the claim, together with the total number of nonselective NSAIDs and the total number of medications received in the past year derived from pharmacy claims. In addition, the administrative data were used to identify service claims with diagnoses of GI bleeding, diabetes, cardiovascular disease, renal disease, liver disease, cancer, and chronic obstructive pulmonary disease (COPD). These diseases and conditions were selected on the basis of case reports submitted to the FDA's adverse drug reaction database. A patient was considered to have a specific disease if there was a claim for a physician visit or a hospitalization with an appropriate diagnosis code or a pharmacy claim for the dispensing of an appropriate medication.

Selected variables were cross-tabulated to examine whether associations existed between them before including them in the multivariable analysis. A backward stepwise multiple conditional logistic regression analysis was then performed using the SAS PHREG procedure with the dependent variable defining whether the patient was a case or a control.[12,14] An α (type 1) error level of 0.05 was used as the inclusion criterion, that is, a variable was included in the model if its coefficient was significantly ($p < 0.05$) different from zero. Since the comorbidities were numerous, a disease score variable was created to minimize the possibility of over-parameterization. This score was based on diagnosis codes for renal disease, liver disease, cancer, and COPD, with coding as 1 for each of these disorders that the patient had, and summing across the 4 disease categories.

An institutional review board reviewed the study protocol and determined that it was exempt from the need for ethical approval because the study only involved administrative claims data that are recorded and analyzed in a way that is not linked with the subject.

Results

The study variables were examined in univariate analyses (Table 1). Of note, new celecoxib and rofecoxib users were more likely to be older, female, taking multiple other medi-

cations, and to have diabetes, cardiovascular disease, or a history of GI bleeding. Indication for treatment and physician specialty were strongly associated with each other (Table 2). Given this colinearity and the potential inaccuracy of claims-based indication-related diagnoses, we decided to include specialty rather than indication in subsequent analyses. Additional analyses showed that the total number of different medications used in the past year was strongly associated with the disease score and with increasing severity of diabetes and cardiovascular disease (Table 3). It therefore was not possible to accurately measure their independent effects from a single model.

Table 1. Univariate Analyses[a] of Characteristics of Patients Exposed to Celecoxib or Rofecoxib versus Nonselective NSAIDs

Characteristic	Celecoxib/ Rofecoxib (n = 9000)	Nonselective NSAID (n = 18 000)	p Value
Age, y (mean ± SD)	56.7 ± 12.8	53.3 ± 11.7	<0.0001
Gender, n (%)			<0.0001
male	3521 (39.1)	7821 (43.4)	
female	5479 (60.9)	10 179 (56.6)	
Indication, n (%)			<0.0001
osteoarthritis	3125 (34.7)	4010 (22.3)	
rheumatoid arthritis	933 (10.4)	1679 (9.3)	
other	4942 (54.9)	12 311 (68.4)	
Prescriber specialty, n (%)			<0.0001
family practitioner/generalist	5216 (58.0)	11 356 (63.1)	
rheumatologist	434 (4.8)	612 (3.4)	
orthopedic/surgical specialist	1467 (16.3)	1657 (9.2)	
other specialist	1883 (20.9)	4375 (24.3)	
Total medications in past year, n (%)			<0.0001
0–5	2620 (29.1)	8551 (47.5)	
6–10	3217 (35.7)	5727 (31.8)	
≥11	3163 (35.1)	3722 (20.7)	
Total NSAIDs in past year, n (%)			<0.0001
0	4513 (50.1)	5388 (29.9)	
1–5	3420 (38.0)	7592 (42.2)	
6–10	792 (8.8)	3364 (18.7)	
≥11	275 (3.1)	1656 (9.2)	
Oral corticosteroid use in past year, n (%)			<0.0001
no	8575 (95.3)	17 431 (96.8)	
yes	425 (4.7)	569 (3.2)	
Diabetes, n (%)			<0.0001
no	7867 (87.4)	15 971 (88.7)	
physician or pharmacy claim only	925 (10.3)	1802 (10.0)	
hospitalization claim	208 (2.3)	227 (1.3)	
Cardiovascular disease, n (%)			<0.0001
no	5180 (57.6)	11 385 (63.2)	
physician or pharmacy claim only	3471 (38.6)	6239 (34.7)	
hospitalization claim	349 (3.9)	376 (2.1)	
Renal disease, n (%)			0.01
no	8949 (99.4)	17 937 (99.6)	
yes	51 (0.6)	63 (0.4)	
Liver disease, n (%)			0.67
no	8970 (99.7)	17 934 (99.6)	
yes	30 (0.3)	66 (0.4)	
Cancer, n (%)			<0.0001
no	8823 (98.0)	17 751 (98.6)	
yes	177 (2.0)	249 (1.4)	
COPD, n (%)			<0.0001
no	8234 (91.5)	16 803 (93.4)	
yes	766 (8.5)	1197 (6.6)	
GI bleeding			<0.0001
no	6285 (69.8)	14 389 (79.9)	
physician or pharmacy claim	2657 (29.5)	3576 (19.9)	
hospitalization claim	58 (0.6)	35 (0.2)	
Combined disease score[b] (mean ± SD)	0.23 ± 0.47	0.19 ± 0.42	<0.0001

COPD = chronic obstructive pulmonary disease; GI = gastrointestinal; NSAIDs = nonsteroidal antiinflammatory drugs.
[a] *t*-Test for continuous variable, χ^2 for categorical variables.
[b] Additive score of renal disease, liver disease, cancer, and COPD.

The final logistic regression model included age, gender, prescriber specialty, total medications used in the past year, total nonselective NSAID prescriptions in the past year, oral corticosteroid use in the past year, and GI bleeding history. All of the variables, except gender, were statistically significant (Table 4). Increasing age, being treated by a rheumatologist or an orthopedic specialist, having received a high number of medications in the past year, and having had a previous GI bleed strongly increased the likelihood of receiving celecoxib or rofecoxib, whereas having been prescribed a high number of nonselective NSAIDs in the past year reduced it.

Discussion

COX-2 selective NSAIDs have been promoted as an advance in GI safety over nonselective NSAIDs, whose GI toxicity is substantial.[15] However, the cost of the COX-2 selective NSAIDs is considerably more than that of nonselective NSAIDs, which, together with their rapidly increasing use, has raised concerns about whether they are being used in a cost-effective manner.[16] This has led to suggestions that COX-2 selective NSAIDs should be restricted to patients at highest risk and, thus, most likely to benefit from improved GI safety.

Our data indicate that factors such as increasing age, being treated by a rheumatologist or an orthopedic specialist, having received a high number of medications in the past year (including oral corticosteroids), and having had a previous GI bleed (especially if it required hospitalization) strongly influenced the likelihood of receiving a COX-2 selective NSAID. Of note, use of a high number of medications in the past year was a predictor of higher risk of underlying diabetes mellitus and cardiovascular disease.

The implications of this last observation are potentially complex and important. During preparation of this manuscript, rofecoxib was withdrawn from the market worldwide by its manufacturer[9] following the discovery that risk of AMI was increased twofold among patients

using standard doses (25 mg/day) in a randomized controlled trial on colon polyp prevention.[8] An earlier controlled trial[2] and several observational studies[6,7] found an increased risk of AMI with high-dose (>25 mg/day) use of rofecoxib. Subsequently, concern over cardiovascular risk has been raised with other COX-2 selective NSAIDs.

Valdecoxib was recently found to increase the risk of AMI and other adverse cardiovascular outcomes when used to treat pain following coronary artery bypass graft surgery.[17,18] Lumiracoxib was also discovered to increase the risk of cardiovascular events in a controlled clinical trial compared with naproxen therapy.[19] This effect was especially large in the subset of patients not taking low-dose aspirin. By contrast, celecoxib was not found to increase cardiovascular risk[1,6,7] until it was announced, in December 2004, that a large colorectal cancer prevention clinical trial conducted by the National Cancer Institute had been stopped because an interim analysis showed a 2.5-fold increased risk of major cardiovascular events in patients taking celecoxib compared with those on placebo.[20-22] The paradox emerges that patients with higher cardiovascular risk are being channeled toward the preferential use of COX-2 selective inhibitors, many of which may confer increased cardiovascular risk themselves.

The issue of low-dose aspirin use or non-use has added another level of complexity to the problem. Some studies have found the highest risk of AMI to be among patients not taking low-dose aspirin.[2,19] The argument then follows that aspirin use or non-use is responsible for the cardiovascular effects noted with a number of the COX-2 selective NSAIDs. The evidence suggests that aspirin use is probably not an explanation for the differences in risk observed between some COX-2 selective NSAIDs and their nonselective NSAID comparators. A number of different studies have found that aspirin use does not vary by type of NSAID used and hence cannot be responsible for the observed risk with some COX-2 selective NSAIDs.[7,23-25] Two major questions flow from this. The first relates to whether individual drugs or perhaps all COX-2 selective NSAIDs have cardiovascular toxicity and whether this risk is greater in particular subgroups of patients, such as those with underlying cardiovascular disease, either known or, as is often the case, latent. The second relates to the use of low-dose aspirin by patients treated with COX-2 selective NSAIDs and whether such use can effectively counter any increased cardiovascular risk without increasing GI toxicity.

We also found that treatment with a high number of nonselective NSAID prescriptions in the past year reduced

Table 2. Association Between Physician Specialty and Indication for Treatment[a]

	Osteoarthritis		Rheumatoid Arthritis		Other Diagnosis	
Physician Specialty	**n**	**%**	**n**	**%**	**n**	**%**
Family practitioner/generalist	4550	63.8	1597	61.1	10 425	60.4
Rheumatologist	312	4.4	472	18.1	262	1.5
Orthopedist/surgical specialist	1215	17.0	169	6.5	1740	10.1
Other specialist	1058	14.8	374	14.3	4826	28.0
TOTAL	7135	100.0	2612	100.0	17 253	100.0

[a] χ^2 6 df: 2369.2; $p < 0.0001$.

Table 3. Association Between Total Number of Medications in Past Year and Other Variables

	Medications in Past Year						
	0–5		6–10		≥11		
Parameter	**n**	**%**	**n**	**%**	**n**	**%**	
Diabetes services							
none	10 679	95.6	7875	88.0	5284	76.7	
physician or pharmacy only	476	4.3	982	11.0	1269	18.4	
hospitalization	16	0.1	87	1.0	332	4.8	
TOTAL	11 171	100.0	8944	100.0	6885	100.0	χ^2 4 df: 1641.2; $p < 0.0001$
Cardiovascular services							
none	8905	79.7	5008	56.0	2652	38.5	
physician or pharmacy only	2212	19.8	3750	41.9	3748	54.4	
hospitalization	54	0.5	186	2.1	485	7.0	
TOTAL	11 171	100.0	8944	100.0	6885	100.0	χ^2 4 df: 3495.3; $p < 0.0001$
Disease score							
0	9961	89.2	7248	81.0	4733	68.7	
1	1174	10.5	1609	18.0	1892	27.5	
≥2	36	0.3	87	1.0	260	3.8	
TOTAL	11 171	100.0	8944	100.0	6885	100.0	χ^2 4 df: 1307.8; $p < 0.0001$

the likelihood of celecoxib and rofecoxib use. This latter finding could be due to physicians deciding to continue nonselective NSAID treatment if patients had tolerated them well and were responding well to treatment. Female gender was not found to influence the chance of receiving celecoxib or rofecoxib. Apart from this, our results are consistent with those of Solomon et al.,[26] who examined the determinants of COX-2 selective NSAID prescribing using data from a pharmacy benefits program for low- to moderate-income Medicare beneficiaries, and of Rahme et al.,[27] who performed a similar analysis using administrative data from the Canadian province of Quebec. Both of these studies focused on patients aged ≥65 years, while our study included patients as young as 35 years.

Similar to other studies based on administrative claims data, our research has its limitations. The claims data include only prescription medications for which a claim was made. Over-the-counter NSAIDs are not included, although we believe that such drugs are less likely to be recommended for significant arthritic conditions. The diagnoses that we used to identify patients with specific diseases are not validated in the process of reimbursing the physician or facility. Previous studies using this data resource have, nevertheless, shown good validity for more serious disorders requiring a health service visit.[10] However, based on experience elsewhere,[28] nonspecific conditions, such as dyspepsia or GI discomfort, that may influence the prescribing of COX-2 selective NSAIDs are likely to be less well recorded.

Conclusions

This analysis presents evidence that patients who receive celecoxib or rofecoxib are more likely to have been treated by a rheumatologist or an orthopedic specialist and to have a significant underlying burden of disease. Concerns about cardiovascular toxicity with COX-2 selective NSAIDs and evidence that patients at higher risk of cardiovascular disease are being channeled toward their use points to an emerging paradox that patient harm may be compounded in a large segment of the population.

Table 4. Multivariable Analysis[12] of Selected Characteristics of Patients Exposed to Celecoxib or Rofecoxib versus Nonselective NSAIDs

Characteristic	OR	95% CI
Age	1.03	1.03 to 1.03
Prescriber specialty		
rheumatologist	2.06	1.90 to 2.24
orthopedic/surgical	2.33	2.02 to 2.69
other specialist	0.88	0.82 to 0.94
Total medications in past year		
6–10	1.97	1.84 to 2.10
≥11	3.11	2.88 to 3.35
Total NSAIDs in past year		
1–5	0.44	0.41 to 0.47
6–10	0.17	0.16 to 0.19
≥11	0.11	0.10 to 0.13
Oral corticosteroid use in past year		
yes	1.24	1.08 to 1.43
GI bleeding		
physician/pharmacy claim	1.35	1.26 to 1.44
hospitalization claim	2.51	1.60 to 3.94

GI = gastrointestinal; NSAIDs = nonsteroidal antiinflammatory drugs.

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We thank Howard Liang MS and Bharati Manda MS for technical support.

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EXTRACTO

TRASFONDO: Celecoxib y rofecoxib, 2 fármacos antiinflamatorios no esteroideos (NSAIDs, por sus siglas en inglés) selectivos de la ciclooxigenasa-2 (COX-2), se anuncian como teniendo menos complicaciones relacionadas al sistema gastrointestinal que los NSAIDs no selectivos. Sin embargo, información sobre reacciones adversas sugiere que el uso de NSAIDs selectivos de COX-2 está asociado con eventos gastrointestinales clínicamente significativos.

OBJETIVO: Evaluar si pacientes en celecoxib y rofecoxib tienen una carga mayor de enfermedad subyacente que pacientes a quienes se les han prescrito NSAIDs no selectivos.

MÉTODOS: La población del estudio consistió de miembros de 11 planes de salud, mayores de 34 años de edad, con una reclamación de farmacia para celecoxib o rofecoxib o un NSAID no selectivo despachado entre el 1 de febrero de 1999 y el 31 de julio de 2001, que habían estado inscritos continuamente por más de 364 días antes de la fecha de despacho. Los pacientes en celecoxib y rofecoxib fueron seleccionados al azar sin reemplazo de un fondo común de usuarios elegibles en cada uno de los 30 meses. Los usuarios de NSAIDs no selectivos fueron seleccionados al azar sin reemplazo dentro de cada mes, en una proporción a casos de 2:1; ellos podían ser seleccionados en más de un mes. Se realizaron análisis de univariante comparando 9000 casos y 18 000 controles seguidos por un análisis de regresión logística múltiple condicionado en tiempo.

RESULTADOS: El aumento en edad, el tratamiento por un reumatólogo o un especialista ortopédico, el tratamiento con un gran número de medicamentos diferentes durante el último año, el tratamiento con corticosteroides orales en el último año, y el haber tenido una hemorragia gastrointestinal previa aumentaron la probabilidad de recibir celecoxib o rofecoxib, mientras que el tratamiento con un gran número de prescripciones por NSAIDs no selectivo en el último año la disminuyó. El tratamiento con un gran número de medicamentos diferentes fue un vaticinio de un aumento en la prevalencia de diabetes mellitus y enfermedad cardiovascular subyacentes.

CONCLUSIONES: Los pacientes con una carga mayor de enfermedad subyacente tuvieron más probabilidades de recibir NSAIDs selectivos de COX-2 que NSAIDs no selectivos. Paradojicamente, los pacientes a mayor riesgo de enfermedad cardiovascular fueron canalizados hacia el tratamiento con NSAIDs selectivos de COX-2, muchos de los cuales pueden conferir un mayor riesgo de infarto agudo del miocardio y otros resultados cardiovasculares adversos.

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RÉSUMÉ

OBJECTIF: Le célécoxib et le rofécoxib sont 2 anti-inflammatoires non stéroïdiens (AINS) sélectifs de la cyclo-oxygénase-2 (COX-2) qui semblent induire moins d'effets au niveau gastro-intestinal que les AINS traditionnels non sélectifs. L'utilisation de ces agents ne semble pas toutefois dépourvue d'événements gastro-intestinaux cliniquement significatifs. Le but de cette étude est d'évaluer si la population utilisant le célécoxib et le rofécoxib a un profil plus important de maladies sous-jacentes par rapport aux patients se faisant prescrire des AINS traditionnels.

MÉTHODOLOGIE: La population à l'étude était composée de membres âgés de plus de 34 ans faisant partie d'un des 11 plans de soins de santé identifiés par les investigateurs. Pour être admis dans cette étude pharmacoépidémiologique, les patients devaient avoir fait au moins une demande de réclamation pour le célécoxib, le rofécoxib, ou un AINS traditionnel non sélectif entre le 1er février 1999 et le 31 juillet 2001 et devaient avoir été participant au régime de soins pour au moins 365 jours ou plus avant la date de délivrance du médicament. Les patients ayant reçu le célécoxib ou le rofécoxib étaient sélectionnés au hasard, sur une base mensuelle, d'un groupe d'utilisateurs et suivis pendant les 30 mois de l'étude sans toutefois pouvoir être remplacés. Les utilisateurs d'AINS non sélectifs étaient quant à eux choisis dans une proportion de 2 pour 1 par rapport au groupe des COX-2. Des analyses univariées comparant les 9000 cas témoins et les 18 000 cas contrôles ont été effectuées suivies par une analyse de régressions multiples avec la variable temps comme facteur conditionnel.

RESULTATS: L'âge avancé, un suivi médical par un rhumatologue ou un orthopédiste, un traitement oral de corticostéroïdes ou l'utilisation d'une polypharmacie dans les 12 mois précédant l'étude ainsi qu'une histoire médicale de saignements gastro-intestinaux ont constitué les facteurs favorisant l'utilisation de célécoxib ou de rofécoxib. L'élément de polypharmacie était d'ailleurs un élément prédictif d'une prévalence élevée pour le diabète et les maladies cardiovasculaires.

CONCLUSIONS: Les patients ayant un plus grand nombre de maladies sous-jacentes risquent de recevoir une prescription pour un COX-2 plutôt que pour un AINS non sélectif. Les patients ayant un plus haut risque de maladie cardiovasculaire peuvent ainsi recevoir plus souvent un AINS COX-2 dont certains ont été associés avec un risque plus élevé d'infarctus du myocarde et d'événements cardiovasculaires.

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