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PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

Was the thrombotic risk of rofecoxib predictible from the French Pharmacovigilance Database before 30 September 2004?

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Abstract
Objectives Rofecoxib was withdrawn from the market on 30 September 2004 following the results of a randomized controlled trial. Following this sudden decision, several controversies occurred in the literature to determine whether this adverse drug reaction (ADR) could have been detected earlier. The aim of this study was to investigate whether this kind of signal could have been seen using the French Pharmacovigilance Database before this date of rofecoxib withdrawal.
Methods Using cases registered in the French Pharmacovigilance Database from May 2000 to December 2006, we applied the case–noncase method to "serious" thrombotic ADRs reported with oral formulations of rofecoxib or celecoxib in patients older than 15 years. Cases were all notifications of thrombotic ADRs [World Health Organization Adverse Reaction Terminology (WHO-ART) codes 1300] occurred under coxib (rofecoxib, celecoxib) and noncases all other reports registered in the database (whatever the drug). We calculated a cumulative odds ratio (OR) from 20 May 2000 to 31 December 2006, with a special interest for the period before the 30 September 2004.
Results Among the 50,087 "serious" ADRs registered in the database during this period, 1,127 were thrombotic ones. Rofecoxib exposure was significantly associated with high values of odds ratio (OR) [4.2 (95% CI 1.97–8.61)] for thrombotic ADRs as early as the end of 2001. The values of ADR reporting ORs remained high (3.0–3.5) until 2006. For celecoxib, a significant trend occurred only from September 2004.
Conclusion Despite the compulsory limits of the case/noncase methodology, this study found an association between rofecoxib exposure and the occurrence of "serious" thrombotic ADRs as early as the end of the first year of rofecoxib marketing in France. The association between celecoxib and the occurrence of such ADRs appears less clear. Our work also shows the potential use of careful analysis of pharmacovigilance databases (investigating, for example, cumulative values of risk) in the early identification of new ADRs.

Keywords Rofecoxib · Celecoxib · Thrombotic adverse drug reaction · Pharmacovigilance

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Introduction

Drugs inhibiting the cyclooxygenase-2 (COX 2) enzyme, named coxibs, were introduced in the early 2000s to reduce the number of digestive adverse drug reactions (ADRs) of classic nonsteroidal anti-inflammatory drugs (NSAIDs) [1–

3]. Among their ADRs, one of the most serious was the occurrence of thrombotic events, leading after consideration of the results coming from the Adenomatous Polyp Prevention on VIOXX (APPROVe) trial [4] to the withdrawal of rofecoxib from the market by the firm the 30 September 2004. Following this sudden decision from the pharmaceutical company, several controversies occurred in the literature to determine this ADR could have been detected earlier [5–9].

In fact, before the APPROVe trial, several signals were already coming from clinical trials [The VIOXX Gastrointestinal Outcomes Research (VIGOR) trial [2]), cohort or case-control studies (for reviews and references see [5, 10, 11]). However, few data came from pharmacovigilance networks, i.e., databases including spontaneous declarations of ADRs from physicians. The pharmacovigilance databases were developed in order to follow the safety of drugs after their administrative approval and allow rapid detection of new and/or unexpected ADRs [12]. Thus, it was the aim of our study to evaluate the putative association between coxibs and reports of thrombotic ADRs, with a special interest for the period from May 2000 (date of first marketing in France of the first coxib, rofecoxib) to 30 September 2004, using the case/noncase method in the French Pharmacovigilance Database.

Methods

Case/noncase method

The case/noncase approach measures disproportionality of combination between a drug and a particular ADR in a pharmacovigilance database [13–17]. In the case/noncase method, cases are reports corresponding to the ADR of interest and noncases other reports. The method allows comparison of drug exposure among cases and noncases and calculation of an ADR reporting odds ratio (OR) with its 95% confidence interval (95% CI).

Source

The reporting of ADRs has been compulsory in France since 1984. According to law, physicians must report "serious" as well as "unexpected" ADRs to their regional pharmacovigilance center (31 in France). All suspected ADRs are registered in the French Pharmacovigilance Database [12]. For each report, information about patient (age, gender, medical history) and drug exposure (suspected and other used drugs) are recorded. A brief summary of the clinical history with the main results is added at the end of each case report. ADRs are coded according to the ADR terminology of the World Health Organization Adverse Reaction Terminology (WHO-ART) [18]. According to WHO definition [12, 18], all reports resulting in death, leading to hospitalization or prolongation of hospitalization, persistent or significant disability, incapacity, or being life threatening are considered as "serious". We used ADRs (recorded in the database until the end of 2006) that occurred in patients older than 15 years (coxibs are contraindicated in children) between 25 May 2000 (date of marketing of the first coxib, rofecoxib, in France) and 31 December 2006, with a special interest for the period 20 May 2000 to 30 September 2004.

Selection of cases and noncases

All reports of "serious" thrombotic ADRs, recorded in the French Pharmacovigilance Database until the end of 2006, were included. We listed all reports including a WHO-ART code related to arterial thrombosis in the coronary system as well as in the peripheral vascular system (including cerebral thrombosis or peripheral arterial thrombosis) for the classes 1020, 1040, and 1810. We excluded all reports for which age, gender, or date of occurrence were lacking. Cases were reports that occurred under coxib exposure and noncases all other reports of thrombotic ADRs observed with other drugs and recorded in the database during the same period.

Exposure definition

Exposure in cases and noncases was defined by the presence in the report of a least one drug (coxib for cases, other drugs for noncases) for which chronology of administration was assessed "compatible" with ADR occurrence according to the French method of ADR imputation [19]. During the study period, only two coxibs (rofecoxib and celecoxib) with oral formulation were marketed in France. We did not include drug doses, as it is difficult to exhaustively record doses in this database.

Statistical analysis

We performed a logistic regression analysis with adjustment for age and gender to evaluate association between thrombotic ADRs and coxib exposure. Finally, we estimated cumulative OR and 95% CI for the two marketed coxibs from 25 May 2000 (date of marketing of the first coxib, rofecoxib, in France) and 31 December 2006, with a special interest for the period 20 May 2000–30 September 2004. All calculations were made with SAS® 9.3 statistical software.

Results

A total of 50,087 "serious" ADRs in patients older than 15 years occurred and were recorded in the French Pharma-

Table 1 Number of "serious" thrombotic adverse drug reactions (ADRs) according to World Health Organization Adverse Reaction Terminology (WHO-ART) codes: 1020, 1040, 1810 occurred under exposure to oral formulations of coxib (rofecoxib, celecoxib) and other drugs between 25 May 2000 (date of marketing of the first coxib, rofecoxib, in France) and 31 December 2006 in patients older than 15 years and recorded in the French Pharmacovigilance Database until the end of 2006

Thrombotic ADRs	2000	2001	2002	2003	2004	2005	2006	Total
With coxibs	1	13	9	11	17	13	1	65
With other drugs	93	189	157	160	198	192	138	1,127
Total	94	202	166	171	215	205	139	1,192

covigilance Database between 25 May 2000 and 31 December 2006, 995 in patients exposed to coxibs (650 to celecoxib, 356 to rofecoxib with 11 to both coxibs). During the study period, 1,127 "serious" thrombotic ADRs were reported in the database, 65 in patients exposed to coxibs (41 to celecoxib, 27 to rofecoxib with three to both coxibs) (Table 1).

Table 2 shows the cumulative values of the association between reported thrombotic ADRs and exposure to at least one coxib in the French Pharmacovigilance Database between 25 May 2000 and 31 December 2006. Rofecoxib exposure was significantly associated with thrombotic ADRs as early as the end of 2001. The values of the estimated cumulative OR remained high (≥ 3) during the entire study period, i.e., until the end of 2006.

For celecoxib, the cumulative estimated OR was not significant until the end of 2003. A significant cumulative estimated OR was only observed from September 2004 (1.7) with higher values (3.0) in 2005 and 2006. Finally, a significant association was found for both coxibs (taken as a whole) as early as the end of 2002.

Discussion

The aim of this study was to investigate a putative association between rofecoxib use and occurrence of "serious" thrombotic ADRs as reported in the French Pharmacovigilance Database to determine whether a special analysis of this database could

Table 2 Association between thrombotic [World Health Organization Adverse Reaction Terminology (WHO-ART) codes: 1020, 1040, 1810] adverse drug reactions (ADRs) and exposure to at least one coxib in the French Pharmacovigilance Database, Cumulative values (according to date of occurrence) for both coxibs (and each coxib alone) between 25 May 2000 (date of marketing of the first coxib, rofecoxib, in France) and 31 December 2006 in patients older than 15 years for thrombotic ADRs recorded in the French Pharmacovigilance Database until the end of 2006

Period		Odds ratio	95% confidence interval	*P* value
May 2000		–	–	–
2000–2001	Both coxibs	1.7	0.96–2.9	0.07
	Rofecoxib	4.2	1.97–8.61	0.0002
	Celecoxib	0.9	0.4–2.0	0.8
2000–2002	Both coxibs	1.8	1.2–2.8	0.007
	Rofecoxib	3.4	2.0–6.0	<0.0001
	Celecoxib	1.0	0.5–1.9	1.0
2000–2003	Both coxibs	2.1	1.5–3.0	<0.0001
	Rofecoxib	3.1	1.9–5.1	<0.0001
	Celecoxib	1.6	0.96–2.6	0.07
2000–Sept 2004	Both coxibs	2.2	1.6–3.0	<0.0001
	Rofecoxib	3.0	1.9–4.7	<0.0001
	Celecoxib	1.7	1.1–2.6	0.03
2000–2004	Both coxibs	2.6	1.9–3.5	<0.0001
	Rofecoxib	3.3	2.2–5.0	<0.0001
	Celecoxib	2.3	1.5–3.3	<0.0001
2000–2005	Both coxibs	3.2	2.4–4.1	<0.0001
	Rofecoxib	3.5	2.4–5.3	<0.0001
	Celecoxib	3.0	2.1–4.1	<0.0001
2000–2006	Both coxibs	3.2	2.4–4.1	<0.0001
	Rofecoxib	3.6	2.4–5.4	<0.0001
	Celecoxib	3.0	2.2–4.1	<0.0001

be useful to evidence "serious" unexpected ADRs not easily detectable. We found a positive association between rofecoxib use and occurrence of such ADRs as early as the end of the first year of its marketing in France (2001). The association between celecoxib and the occurrence of such ADRs appears less evident.

However, our results suffer from several compulsory methodological drawbacks, the main one being underreporting. In fact, underreporting of ADRs in pharmacovigilance is well documented. This is due to several factors, such as the "seriousness" or knowledge about the ADR (expected or unexpected), as well as the novelty of the drug [20]. Thus, in case of coxibs, we could expect a relative overreporting due to the novelty of this pharmacological class. However, we should recall that thrombotic ADRs with coxibs were largely unknown during the first years of coxib marketing. Thus, a publication bias should not interfere with the results of this study. Another limitation of the study is, as in each case control-study in general and in each case/noncase study in particular, the choice of the control group. In the context of this study, we did not account for some potentially important confounders (underlying disease, other drugs…). Thus, it is important to emphasize that our study was performed (and should be only interpreted) in a context of signal detection (and not in order to obtain a precise quantification of risk). Finally, despite its inherent limits, use of the case/noncase methodology was found to be one of the useful methods of generating safety signals in pharmacovigilance [16, 17, 21–23].

Another important potential bias for this study should be mentioned: the notoriety bias. In fact, one could suggest that some French physicians or pharmacists could have been aware of this potential thrombotic ADR as early as 2001, leading to an overreporting to the French network of pharmacovigilance centers. In fact, as noted by Topol in October 2004 [24], the US Food and Drug Administration (FDA) discussed during its 8 February 2001 meeting the potential cardiovascular risks associated with rofecoxib. Topol's group published a review of randomized clinical trials emphasizing the potential risk in August 2001 [25]. Unfortunately, these data were not relayed to French medical journals. The meta-analysis from Jüni's group [26] indicating that the cardiovascular risk of rofecoxib was known several years before its withdrawal was only published in December 2004 and thus cannot interfere with the reports to the French Pharmacovigilance Database during the year 2001. The French drug agency Agence Française de Sécurité Sanitaire des Produits de Santé (AFSSaPS) published several papers and alerts regarding the cardiovascular risk of coxibs on its Web site (www.afssaps.sante.fr). The first (24 August 2001) was related to Mukherjee et al.'s paper [25] and noted that the work "was not designed to investigate this risk." The next alert coming from AFSSaPS was sent on 28 June 2002. It mainly focused on the gastrointestinal ADRs and included only one sentence regarding cardiovascular risk of coxibs: "the arterial thrombotic risk is currently under investigation." The following AFSSaPS release (22 July 2002) was only related to digestive ADRs. French physicians did not received additional news from AFSSaPS regarding coxibs until 1 July 2004. One should also note that French physicians could have received some informations from *La Revue Prescrire*, an independent journal of drug information. The text regarding "the cardiovascular ADRs of coxibs" was only published in September 2002 [27] and thus could not have interfered with 2001 results. The same comments could be made for data coming from the first clinical trials (VIGOR) [2, 3]. French physicians are known to generally not read the main international medical publications. They primarily become aware of data regarding new drugs from pharmaceutical representatives (who, of course, do not develop during their visits data about ADRs). Thus, it is possible to exclude this confounding bias linked to a potential knowledge of these thrombotic ADRs by French physicians or pharmacists (who are those who must report ADRs to the French pharmacovigilance network).

Taking into account these compulsory limitations, our study allows some interesting comments. The main result of our study was that a significant signal was available in the French Pharmacovigilance Database as early as the first year of marketing, i.e., at the end of 2001. The cumulative OR remained high during the entire study, with values around 3.0 and 3.4 between 2002 and September 2004. Similar significant values (3.2–3.6) were observed between 2004 and 2006.

Besides the results of clinical trials, meta-analyses or pharmacoepidemiological studies [5, 22], it is interesting to compare our result to other analyses performed in spontaneous reporting schemes of ADRs. In the study published by Zhao et al. [28] in 2001 on the WHO Uppsala Monitoring Centre (UMC) database, the values for myocardial infarction and cerebro/cardiovascular events were significantly higher for rofecoxib compared with background expectations (without any difference with celecoxib). Values for thrombotic events were not significantly different compared with the background expectations. In the UK, the number of spontaneous reports via the Yellow Card Scheme did not differ significantly from background expectations [5]. Using Prescription-Event Monitoring (PEM) data from July to November 1999, Layton et al. found a higher adjusted cerebrovascular thromboembolic event group rate under rofecoxib [relative risk (RR) 1.68 (95% CI 1.15–2.46)] in comparison with meloxicam, with no difference for cardiovascular thromboembolic events [29]. Similar results [RR 1.66 (95% CI 1.10–2.51)] were obtained by the same group using the same method and the same comparator

with celecoxib (during the period May to December 2000) [30]. However, these authors found no difference between rofecoxib and celecoxib for this kind of ADR [31]. In Canada, no definite conclusion was made in 2002 from the 70 reports of suspected cerebro/cardiovascular reactions with celecoxib and the 68 similar ones with rofecoxib due to several putative confounding factors (preexisting medical conditions, prevalence of cardiovascular diseases…) involved in the pathophysiology of thrombotic events [32]. The differences between our results and the other analyses could be explained, at least partly, by the relatively high level of spontaneous reporting of ADRs in France in comparison with other countries [12]. Another factor putatively explaining these differences could be the use in our study of cumulative OR values. This method allows the confirmation (or not), year after year, of a putative signal previously observed, which could be explained by chance or other hazard factors.

The exact mechanism of the prothrombic properties of rofecoxib remains to be elucidated but cuold involve an increase in thromboxane A2 synthesis, especially in patients at high risk of cardiovascular adverse events [5]. Recently, Warmer and Mitchell [33] suggested that the COX-2 selectivity alone could not explain the cardiovascular risk. They discussed the importance of decrease in urinary thromboxane A2 metabolites, platelet inhibition, and increase in bleeding time induced by NSAIDs, all functions known to be mediated by COX-1 enzyme.

Another interesting point concerns celecoxib. In fact, the existence of a thrombotic risk with celecoxib has been largely discussed. Some authors have found a significant association, whereas others did not confirm these data (for reviews and references see [5, 10, 11, 26]). Our study does not allow a definite conclusion, as a significant association was only found in September 2004, with cumulative OR values higher than 2 in 2004 and later. Thus, for explaining these elevated values, one could suggest a notoriety bias following rofecoxib withdrawal. Of course, such a bias cannot explain the results found with rofecoxib for September 2004, as it is important to recall that we worked from the date of occurrence of ADR (and not its date of registration in the database).

In conclusion, despite the compulsory limits of the case/noncase methodology, this study reveals an association between rofecoxib exposure and the occurrence of "serious" thrombotic ADRs as early as the end of the first year of rofecoxib marketing in France. Our work also shows the potential use of spontaneous reports and careful analysis of pharmacovigilance databases (investigating, for example, cumulative values of risk) in the early identification of new ADRs.

Conflict of interest statement None.

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