

# Hepatic Disorders in Patients Treated with COX-2 Selective Inhibitors or Nonselective NSAIDs: A Case/Noncase Analysis of Spontaneous Reports

David Sanchez-Matienzo, MD, MPH; Alejandro Arana, MD, MPH, FISPE;  
Jordi Castellsague, MD, MPH; and Susana Perez-Gutthann, MD, MPH, PhD, FISPE

*Global Epidemiology, Safety and Risk Management, Pfizer Worldwide Development, Barcelona, Spain*

## ABSTRACT

**Background:** Hepatic adverse events associated with the use of nonaspirin drugs and NSAIDs are uncommon, but the widespread use of these drugs may impact public health.

**Objective:** We conducted a case/noncase analysis of spontaneous reports to compare the hepatic safety profile of cyclooxygenase (COX)-2 selective inhibitors with that of nonselective NSAIDs.

**Methods:** This case/noncase analysis was conducted using the US Food and Drug Administration Freedom of Information (FDA/FOI) database (through quarter 1, 2003) and the World Health Organization Uppsala Monitoring Centre (WHO/UMC) database (through quarter 3, 2003). Council for International Organizations of Medical Sciences and WHO Adverse Reaction Terminology preferred terms were used to classify hepatic disorders with broad and specific case definitions. After reports involving established hepatotoxic drugs (bromfenac, nimesulide, sulindac) were excluded, the proportion of reports (PRs) of each case definition was calculated for each NSAID. Crude and adjusted reporting odds ratios (RORs) were used to compare the overall proportions of hepatic disorders and hepatic failure of celecoxib and rofecoxib versus nonselective NSAIDs.

**Results:** A total of 158,539 and 185,253 reports of NSAIDs were identified in the FDA/FOI and WHO/UMC databases and 25% and 16%, respectively, involved other hepatotoxic drugs. The PRs of hepatic disorders for all COX-2 selective inhibitors and nonselective NSAIDs were 3.0% in the FDA/FOI database and 2.7% in the WHO/UMC database. In the FDA/FOI and WHO/UMC databases, respectively, nimesulide (16.7% and 14.4%), bromfenac (12.0% and 20.7%), diclofenac (8.1% and 4.7%), and sulindac (6.1% and 9.9%) were reported to be associated with higher proportions of overall hepatic disorders com-

pared with those of other NSAIDs. Crude and adjusted RORs for the prevalences of overall hepatic disorders and hepatic failure with celecoxib and rofecoxib versus the other NSAIDs were <1 (indicating that the proportion was not higher than that of the comparator) in both databases. The interpretation of the results was unchanged when bromfenac, nimesulide, and sulindac were excluded from the analysis.

**Conclusions:** In this case/noncase analysis, bromfenac, nimesulide, sulindac, and diclofenac had higher proportions of reports of hepatic disorders compared with those of other NSAIDs in the FDA/FOI and WHO/UMC databases. The analysis did not raise a safety concern for celecoxib or rofecoxib versus NSAIDs for overall hepatic disorders and hepatic failure. (*Clin Ther.* 2006;28:1123–1132) Copyright © 2006 Excerpta Medica, Inc.

**Key words:** NSAIDs, hepatotoxicity, case/noncase study.

## INTRODUCTION

Hepatic adverse events associated with the use of nonaspirin drugs and NSAIDs are uncommon, but the widespread use of these drugs may impact public health. Epidemiologic studies have reported the incidence of acute liver injury to be 1 to 9 cases per 100,000 users of NSAIDs.<sup>1–3</sup> However, this risk may increase with the concurrent use of other hepatotoxic medications. Different types of hepatic disorders have been reported with the use of practically all NSAIDs.<sup>4–10</sup> Although most cases are mild and asymptomatic, with

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liver test results returning to normal on cessation of treatment, hepatic injury is one of the leading causes of withdrawal of drugs from the market. Bromfenac was removed from the US market in 1998, after 1 year on the market, when several cases of liver failure were associated with use of the drug.<sup>4,5</sup> During recent years, nimesulide was withdrawn in various countries (eg, Finland, Israel, Portugal, Spain) after spontaneous reporting suggested an increased risk for liver injury.<sup>6-9</sup> In addition, sulindac has been associated with serious liver injury in several series of cases,<sup>10</sup> and epidemiologic studies have found it to be associated with a higher risk for acute liver injury compared with other NSAIDs.<sup>1,11,12</sup>

A review of 14 controlled studies of patients with arthritis showed that the overall incidence of hepatic adverse events in patients receiving celecoxib was similar to that for placebo but lower than that for NSAIDs.<sup>13</sup> However, both celecoxib and rofecoxib have been associated with liver disorders through spontaneous reporting during the postmarketing period.<sup>14-17</sup>

Case/noncase analysis of spontaneous reports from international public data sources can be used as an early postmarketing activity to monitor the tolerability of drugs in the general population.<sup>18-21</sup> We used this method to compare the hepatic tolerability of cyclooxygenase (COX)-2 selective inhibitors with that of nonselective NSAIDs.

## MATERIALS AND METHODS

We conducted a case/noncase disproportionality study of spontaneous reports<sup>20-22</sup> of hepatic disorders in patients treated with COX-2 selective inhibitors and nonselective NSAIDs in 2 public data sources of spontaneous reports of adverse drug reactions (ADRs).

In this case/noncase analysis, *case* was defined as a reported event of the outcome of interest, and all the other reports were considered *noncases* (controls). The distribution of the exposure of the drugs of interest is compared among cases and noncases using measures of disproportionality.<sup>20</sup>

### Data Sources

#### *US Food and Drug Administration Freedom of Information Database*

The Adverse Events Reporting System (AERS), previously the Spontaneous Reporting System (SRS),<sup>23</sup> is a computerized information database designed to support the US Food and Drug Administration's (FDA's)

postmarketing safety surveillance program for all approved drug and therapeutic biologic products.<sup>24</sup> Since 1968, the FDA has required that drug manufacturers report ADRs during clinical development. Also, health care professionals and consumers send the FDA reports voluntarily through the MedWatch program.<sup>25</sup> The structure of the database is in compliance with International Conference on Harmonisation Guidance for Industry on case safety reports.<sup>26</sup> All reported adverse-event terms were coded using the *Medical Dictionary for Regulatory Activities* (MedDRA).<sup>27</sup>

The FDA Freedom of Information (FDA/FOI) data source<sup>28</sup> contains public information on selected fields from SRS/AERS. New reports are added quarterly. This study is based on the FOI data updated to the end of quarter 1 of 2003. The SRS/AERS combined data source was analyzed with software interface QSCAN version 2.1 (QED Solutions Inc., McLean, Virginia).

#### *World Health Organization/Uppsala Monitoring Centre Database*

Since 1968, the Uppsala Monitoring Centre (UMC), Sweden, has collected reports of ADRs from the 78 countries of the World Health Organization (WHO) Collaborating Program for International Drug Monitoring. The database contains >3.5 million spontaneous reports.<sup>29</sup> New reports are added quarterly.

All ADRs listed in the WHO/UMC safety data source are based on WHO Adverse Reaction Terminology (WHO-ART) preferred terms. The WHO-ART dictionary was developed and is maintained by the WHO/UMC.<sup>30</sup> This study is based on the WHO data up to the end of quarter 3 of 2003. This information does not represent the opinion of WHO. The WHO/UMC data source was analyzed using QSCAN 2.1.

### Case Definition

The FDA/FOI data were analyzed using several case definitions from the draft proposal of the Council for International Organizations of Medical Sciences (CIOMS) on standardized search queries based on MedDRA.<sup>31</sup> We selected preferred terms to build both broad and specific case definitions (**Appendix**). Specific case definitions considered were *abnormal hepatic function*, *hepatic failure*, *hepatitis*, *hepatocellular damage*, and *jaundice*. A broad definition of *overall hepatic disorders* included any of the specific conditions. A similar approach was used to build case defi-

nitions in the WHO/UMC data source. Cases might be reported more than once for any agent.

### Drugs of Exposure

We selected the following: COX-2 selective inhibitors (celecoxib and rofecoxib), preferential COX-2 inhibitors (nimesulide), indole acetic acid derivatives (indomethacin and sulindac), phenylacetic acid derivatives (diclofenac and bromfenac), propionic acid derivatives (naproxen and ibuprofen), oxicams (piroxicam and meloxicam), and acetic acid derivatives (etodolac and ketorolac). We also built an independent category, *multiple NSAIDs*, for reports in which >1 COX-2 selective inhibitor and/or nonselective NSAID was concomitantly reported.

A list of established hepatotoxic drugs was developed.<sup>32</sup> The medications included were allopurinol, amiodarone, amoxicillin, ampicillin, busulfan, captopril, carbamazepine, cephalexin, chlorpromazine, cimetidine, cloxacillin, cyclophosphamide, dextropropoxyphene, erythromycin, estrogens, famotidine, felbamate, floxacillin, halothane, isoniazid, levodopa, methyl-dopa, methotrexate, minocycline, nitrofurantoin, omeprazole, oxytetracycline, paracetamol/acetaminophen, penicillamine, phenobarbitone, phenytoin, propoxyphene, ranitidine, sulfasalazine, sulfonamides, tolbutamide, trimethoprim/sulfamethoxazole, troglitazone, and valproic acid.

### Measures of Disproportional Reporting

For each drug of interest, we calculated the proportion of reports (PRs) by dividing the number of reports for a case definition by the total number of reports for the drug. Reports that included concomitance of any established hepatotoxic drug were excluded from this analysis.

In addition, we estimated crude and adjusted reporting odds ratios (RORs) of hepatic disorders and hepatic failure, comparing celecoxib and rofecoxib with nonselective NSAIDs. For any outcome of interest, an ROR <1 meant that the proportion was not higher than that of the comparator.<sup>33</sup> RORs adjusted for age, sex, and use of hepatotoxic drugs were estimated using multiple logistic regression (adjustment 1). We conducted a sensitivity analysis, excluding all reports associated with the hepatotoxic NSAIDs bromfenac, nimesulide, and sulindac (adjustment 2). All analyses were conducted using SAS version 8.0 (SAS Institute Inc., Cary, North Carolina) and STATA version 7.0 (StataCorp LP, College Station, Texas).

### RESULTS

A total of 158,539 spontaneous reports of NSAIDs were identified in the FDA/FOI data source. Of these, 64% were from women. We excluded reports including concomitant use of other hepatotoxic drugs—39,718 (25%) of the total reports. The PRs of nimesulide and celecoxib used concomitantly with other hepatotoxic drugs were higher compared with other NSAIDs (46.8% and 35.0%, respectively, vs  $\leq 31.0\%$ ), and the PRs of rofecoxib and celecoxib use by patients aged  $\geq 65$  years was higher compared with other NSAIDs (38.4% and 35.3%, respectively, vs  $\leq 34.0\%$ ) (Table I).

The WHO/UMC data source included a total of 185,253 reports of NSAIDs. Approximately 64% were for women, and we excluded 28,806 (16%) reports that mentioned concomitant use of other hepatotoxic drugs. The PRs of concomitance with other hepatotoxic drugs were higher with ketorolac and ibuprofen compared with all other drugs.

After reports involving the concomitant use of other hepatotoxic drugs were excluded, the PRs of NSAIDs associated with hepatic disorders were 3.0% (3594/118,821) in the FDA/FOI data source and 2.7% (4297/156,447) in the WHO/UMC data source.

The PRs for the hepatic disorders in the FDA/FOI data source are shown in Table II. The PRs of overall hepatic disorders were higher with nimesulide (16.7%), bromfenac (12.0%), diclofenac (8.1%), and sulindac (6.1%) compared with those of other NSAIDs. The same was true for each specific hepatic disorder. The PRs in the WHO/UMC data source were similar to those of the FDA/FOI data source (Table III). The PRs of overall hepatic disorders were higher with bromfenac (20.7%), nimesulide (14.4%), and sulindac (9.9%) compared with those of other NSAIDs. The PR of overall hepatic disorders for diclofenac was 4.7%. The PRs of overall hepatic disorders were similar or higher with naproxen and ketorolac in the FDA/FOI data source and ketorolac and meloxicam in the WHO/UMC data source compared with those of other NSAIDs. PRs of hepatic failure were lower with naproxen, ibuprofen, and COX-2 selective inhibitors in the FDA/FOI data source and meloxicam, indomethacin, and naproxen in the WHO/UMC data source compared with those of other NSAIDs (Figures 1 and 2).

Crude analysis of RORs comparing the PRs of NSAIDs with and without the concomitant use of other hepatotoxic drugs showed values of 1.25 (95% CI, 1.17–1.34) in the FDA/FOI data source, and 1.18

Table I. Frequencies of potential confounders in the US Food and Drug Administration Freedom of Information (FDA/FOI) and World Health Organization Uppsala Monitoring Centre (WHO/UMC) data sources.<sup>28,29</sup> Values are %.

Drug	Concomitant Use of Hepatotoxic Drugs		Age ≥65 Years	
	FDA/FOI	WHO/UMC	FDA/FOI	WHO/UMC
Nimesulide	46.8	13.2	27.8	20.3
Celecoxib	35.0	17.4	35.3	34.2
Sulindac	31.0	16.7	33.4	33.2
Meloxicam	30.1	5.9	38.0	13.5
Diclofenac	29.4	11.0	34.0	17.6
Etodolac	28.0	13.5	29.8	21.7
Indomethacin	27.9	17.1	25.0	18.0
Ibuprofen	25.0	18.1	17.6	13.8
Rofecoxib	20.9	5.8	38.4	32.4
Piroxicam	19.4	7.5	29.4	17.9
Naproxen	18.7	15.3	21.6	16.7
Ketorolac	17.6	69.6	22.0	19.1
Bromfenac	15.5	8.7	8.7	9.1
Multiple NSAIDs*	48.1	15.0	34.8	22.5

\*Includes reports involving >1 cyclooxygenase-2 selective inhibitor and/or nonselective NSAID.

Table II. Proportions of reports (PRs) of hepatic case definitions among cyclooxygenase (COX)-2 selective inhibitors and NSAIDs in the US Food and Drug Administration Freedom of Information data source, updated to the end of quarter 1 of 2003.\*<sup>28</sup> Values are %.

Drug	Overall Hepatic Disorders	Abnormal Hepatic Function	Jaundice	Hepatocellular Damage	Noninfectious Hepatitis	Hepatic Failure	Total No. of Reports
Nimesulide	16.7	4.4	5.6	4.4	4.4	4.4	90
Bromfenac	12.0	1.5	3.6	3.0	3.1	1.8	1925
Diclofenac	8.1	3.1	2.2	1.2	2.4	1.0	8807
Sulindac	6.1	0.4	3.3	0.5	2.0	0.4	4005
Meloxicam	3.8	1.0	0.8	0.1	1.8	0.5	800
Indomethacin	3.1	1.0	1.0	0.5	0.7	0.3	5995
Piroxicam	3.1	0.7	1.0	0.6	1.1	0.3	6854
Etodolac	3.0	1.3	1.1	0.5	0.6	0.4	3208
Celecoxib	2.3	0.8	0.9	0.3	0.4	0.2	12,499
Ibuprofen	2.0	0.7	0.7	0.2	0.5	0.2	27,440
Rofecoxib	1.8	0.7	0.5	0.2	0.5	0.2	16,599
Ketorolac	1.7	0.4	0.4	0.1	0.5	0.6	4755
Naproxen	1.3	0.4	0.4	0.2	0.4	0.1	22,108
Multiple NSAIDs†	9.2	3.0	2.8	1.5	2.2	1.2	3826

\*PRs of concomitant use of other hepatotoxic drugs excluded.

†Includes reports involving >1 COX-2 selective inhibitor and/or NSAID.

Table III. Proportion of reports (PRs) of various hepatic case definitions among cyclooxygenase (COX)-2 selective inhibitors and NSAIDs in the World Health Organization Uppsala Monitoring Centre data source, updated to the end of quarter 3 of 2003.\*<sup>29</sup> Values are %.

Drug	Overall Hepatic Disorders	Abnormal Hepatic Function	Jaundice	Hepatocellular Damage	Noninfectious Hepatitis	Hepatic Failure	Total No. of Reports
Bromfenac	20.7	10.8	3.2	3.5	4.3	2.2	2057
Nimesulide	14.4	7.2	2.0	1.0	5.7	0.4	1057
Sulindac	9.9	5.2	3.2	0.5	3.1	0.2	5777
Diclofenac	4.7	3.2	1.0	0.2	1.4	0.1	21,082
Etodolac	3.6	2.5	1.0	0.4	1.2	0.3	3553
Celecoxib	2.1	1.3	0.4	0.2	0.5	0.2	17,748
Piroxicam	2.0	1.2	0.4	0.1	0.6	0.1	13,973
Ibuprofen	1.8	1.1	0.4	0.2	0.5	0.1	32,786
Indomethacin	1.8	1.0	0.5	0.1	0.5	0.1	14,576
Rofecoxib	1.5	0.8	0.2	0.1	0.4	0.1	20,429
Naproxen	1.3	0.8	0.3	0.2	0.3	0.1	13,646
Meloxicam	0.8	0.4	0.1	0.0	0.4	0.0	3042
Ketorolac	0.6	0.4	0.1	0.1	0.1	0.2	1867
Multiple NSAIDs†	5.0	3.1	1.2	0.4	1.4	0.4	33,660

\*PRs of concomitant use of other hepatotoxic drugs excluded.

† Includes reports involving >1 COX-2 selective inhibitor and/or NSAID.

(95% CI, 1.10–1.27) in the WHO/UMC data source. Crude RORs for age and sex differed between data sources. The ROR for overall hepatic disorders in patients aged  $\geq 65$  years, compared with those aged <65 years, was not increased in the FDA/FOI data source (ROR 0.98; 95% CI, 0.92–1.03), but was moderately increased in the WHO/UMC data source (ROR 1.47; 95% CI, 1.39–1.55). Regarding sex, RORs for women compared with men were 1.17 (95% CI, 1.11–1.25) and 0.99 (95% CI, 0.93–1.05), in the FDA/FOI and WHO/UMC data sources, respectively.

Crude and adjusted RORs for overall hepatic disorders and hepatic failure comparing celecoxib and rofecoxib with nonselective NSAIDs are presented in Table IV. Both crude and adjusted RORs (adjustment 1) were <1 for celecoxib and rofecoxib in both data sources. When bromfenac, nimesulide, and sulindac were removed from the analysis (adjustment 2), all RORs remained <1.

## DISCUSSION

Based on a disproportionality analysis conducted in the FDA/FOI and WHO/UMC spontaneous reporting data sources, this study did not raise concerns about

the overall and specific hepatic profiles of celecoxib and rofecoxib compared with nonselective NSAIDs.

Adjustment of RORs by age and sex, and further exclusion of reports with bromfenac, nimesulide, and sulindac, did not modify these results. In addition, to further diminish the potential confounding effect of factors associated with spontaneous reporting of hepatic disorders, we restricted the analysis to those reports that did not include the concomitant use of other established hepatotoxic drugs.

The PR analysis of individual NSAIDs did not find differences in the profile of hepatic reports with celecoxib and rofecoxib versus that of ibuprofen and naproxen across different case definitions in either data source. The PRs of the 2 COX-2 inhibitors were consistently lower than those of bromfenac, nimesulide, sulindac, and diclofenac. The latter findings are consistent with results from previous epidemiologic studies.<sup>4–12</sup> The incidence of acute liver injury in the general population has been estimated at ~4 cases per 100,000 person-years.<sup>3</sup> The incidence among current users of NSAIDs is ~9 cases per 100,000 person-years, which translates to a 2-fold risk increase and ~5 extra cases per 100,000 users of NSAIDs per year.<sup>3</sup> To date,

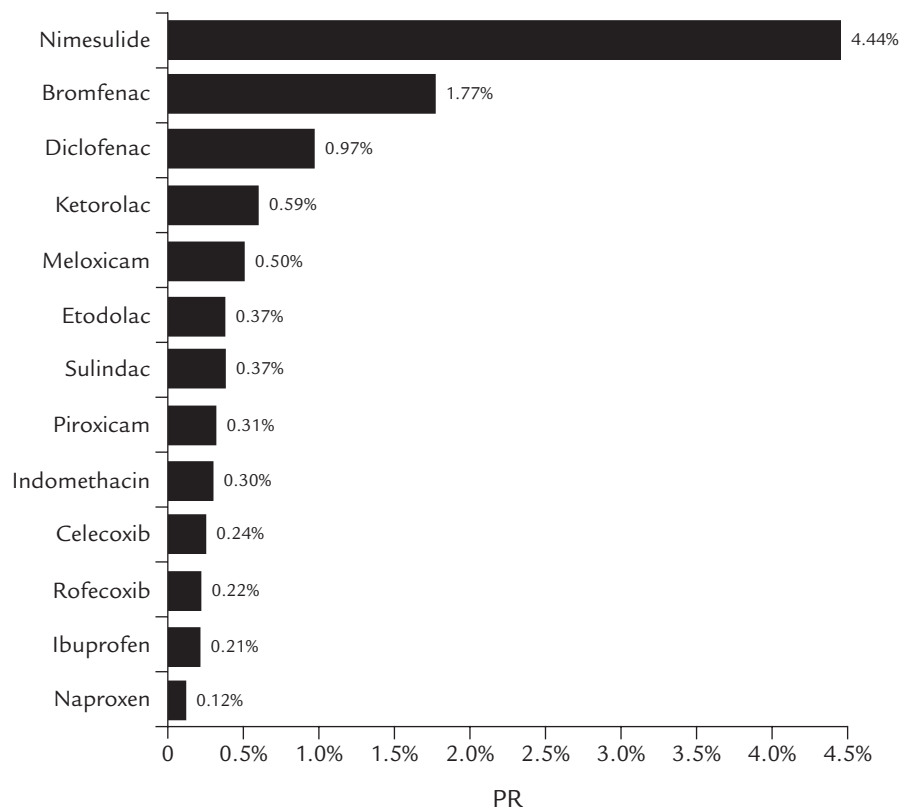


Figure 1. Proportion of reports (PRs) of liver failure with cyclooxygenase-2 selective inhibitors and NSAIDs in the US Food and Drug Administration Freedom of Information data source, updated to quarter 1 of 2003.<sup>28</sup>

epidemiologic studies have not shown major risk differences among individual NSAIDs except for sulindac, with risk estimates considerably higher than those of other NSAIDs.<sup>34</sup> However, 1 epidemiologic study, by de Abajo et al,<sup>35</sup> assessed the risk for acute liver injury in >1.6 million subjects aged 5 to 75 years in the UK-based General Practice Research Database (1994–1999) and found that the crude incidence rate of drug-induced liver injury was estimated as 2.4 per 100,000 person-years (95% CI, 2.0–2.8). Diclofenac was associated with a 4-fold increase compared with nonuse of NSAIDs. This estimate was based on a total of 10 cases of exposure to diclofenac. The functional injury patterns were cholestatic in 4 patients, hepatocellular in 2, mixed in 3, and undetermined in 1.

In general, the different results from disproportionality analysis for the FDA/FOI and WHO/UMC data sources could be explained by the different case definitions built for each data source. In the FDA/FOI data source, we used the definitions from the last available report of the CIOMS standardized search queries for

MedDRA preferred terms.<sup>31</sup> For the WHO/UMC analysis, we adapted WHO-ART preferred terms to build case definitions similar to those established in the FDA/FOI data source.

### Study Limitations and Future Direction

Limitations of analyses of spontaneous reports have been widely described.<sup>36–42</sup> There are discrepancies and variations in the approaches used to report, identify, define, and classify cases of hepatic disorders, as well as in the processes for evaluating and determining causality.<sup>36–38</sup> Underreporting is an important limitation of the analysis of spontaneous reports. Sgro et al<sup>39</sup> found that the annual incidence rate of drug-induced hepatic injury was 16-fold greater than the rate from spontaneous reporting. Other factors, such as the Weber effect (temporal pattern of adverse-event reports, increasing after launch and decreasing with time from launch), channeling effect (a type of allocation bias in which drugs with similar therapeutic indications are prescribed to groups of patients with prognostic dif-

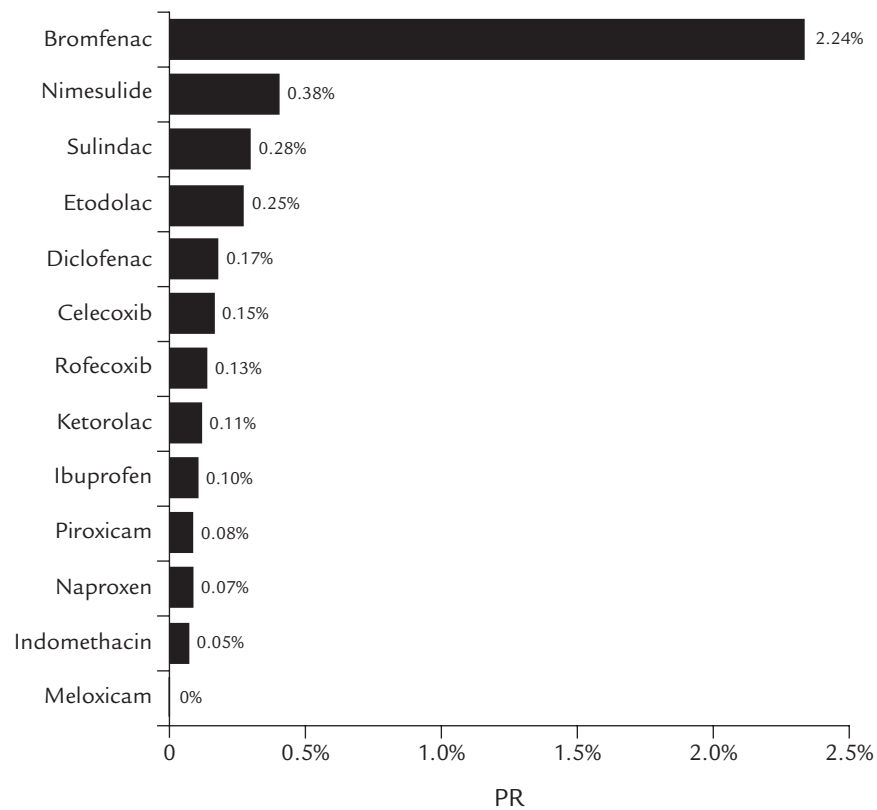


Figure 2. Proportion of reports (PRs) of liver failure with cyclooxygenase-2 selective inhibitors and NSAIDs in the World Health Organization Uppsala Monitoring Centre data source, updated to quarter 3 of 2003.<sup>29</sup>

Table IV. Crude and adjusted reporting odds ratios (95% CIs) of hepatic disorders and hepatic failure for celecoxib and rofecoxib compared with NSAIDs in the US Food and Drug Administration Freedom of Information (FDA/FOI) and World Health Organization Uppsala Monitoring Centre (WHO/UMC) data sources.<sup>28,29</sup>

Drug/Disorder	FDA/FOI			WHO/UMC		
	Crude	Adjustment 1*	Adjustment 2†	Crude	Adjustment 1*	Adjustment 2†
<b>Celecoxib</b>						
Hepatic disorders	0.72 (0.66–0.79)	0.69 (0.62–0.75)	0.75 (0.68–0.83)	0.63 (0.57–0.69)	0.49 (0.44–0.54)	0.62 (0.56–0.69)
Hepatic failure	0.75 (0.58–0.98)	0.70 (0.54–0.92)	0.76 (0.58–0.99)	0.87 (0.62–1.22)	0.76 (0.53–1.10)	0.95 (0.67–1.36)
<b>Rofecoxib</b>						
Hepatic disorders	0.56 (0.50–0.62)	0.58 (0.52–0.64)	0.63 (0.57–0.70)	0.43 (0.39–0.48)	0.39 (0.35–0.44)	0.51 (0.45–0.57)
Hepatic failure	0.49 (0.36–0.66)	0.52 (0.39–0.71)	0.57 (0.42–0.77)	0.63 (0.43–0.92)	0.59 (0.39–0.89)	0.76 (0.50–1.17)

\*Adjusted by age (< or ≥65 years), sex, and concomitant use of other hepatotoxic drugs.

†Adjusted by age (< or ≥65 years), sex, concomitant use of other hepatotoxic drugs, and exclusion of reports involving bromfenac, nimesulide, and sulindac.

ferences), physician awareness, time since launch, and media influence, have been described as modifiers of spontaneous reporting.<sup>37</sup> In addition, the reporting of some specific events associated with a drug might dilute the proportion of reports of other events reported with this same drug, thus limiting the value of the comparisons. The results must be interpreted with caution given the limitations inherent to these analyses.

The value of disproportionality analysis of spontaneous reports is debatable.<sup>40–43</sup> In our analysis, we estimated RORs using adjustment techniques in an attempt to control for confounding factors.<sup>18,21</sup> Although some authors have argued the limited value of disproportionality analysis from an epidemiologic perspective,<sup>40,41</sup> others consider the ROR as a mathematical approximation to relative risk.<sup>21,42</sup>

During the past 30 years, hepatotoxicity has been a cause of treatment discontinuation.<sup>44</sup> Most cases have occurred after a signal was detected in the analysis of spontaneous reports of ADRs.<sup>44</sup> Spontaneous reports are based on the judgment of health care practitioners, and despite the limitations of the reports (case confirmation, causality assessment), they have led to treatment discontinuation.<sup>44</sup> The value of the analysis of spontaneous reports is the early detection of potential safety signals associated with new drugs. Further clinical trials and/or well-designed epidemiologic studies are necessary to estimate risks.

## CONCLUSIONS

In this case/noncase analysis, bromfenac, nimesulide, sulindac, and diclofenac had higher proportions of reports of hepatic disorders compared with those of other NSAIDs in the FDA/FOI and WHO/UMC databases. The analysis did not raise a safety concern for celecoxib or rofecoxib versus NSAIDs for overall hepatic disorders and hepatic failure.

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Appendix. Preferred terms used in the US Food and Drug Administration Freedom of Information (FDA/FOI) and World Health Organization Uppsala Monitoring Centre (WHO/UMC) data sources to build broad and specific hepatic case definitions.

#### FDA/FOI DATA SOURCE

Abnormal hepatic function: 5-nucleotidase increased, alanine aminotransferase abnormal NOS, alanine aminotransferase increased, ammonia abnormal NOS, ammonia increased, aspartate aminotransferase abnormal NOS, aspartate aminotransferase increased, bile output abnormal, bile output decreased, bilirubin conjugated increased, biopsy bile duct abnormal, biopsy liver abnormal, blood alkaline phosphatase liver decreased, blood alkaline phosphatase liver increased, blood alkaline phosphatase NOS abnormal, blood alkaline phosphatase NOS increased, blood bilirubin abnormal, blood bilirubin increased, blood bilirubin unconjugated increased, bromosulphthalein test abnormal, cholangiogram abnormal, cholecystogram intravenous abnormal, cholecystogram oral abnormal, endoscopic retrograde cholangiopancreatography abnormal, endoscopy biliary tract abnormal,  $\gamma$ -glutamyltransferase increased, guanase increased, hepaplastin abnormal, hepaplastin increased, Kupffer cell decrease, leucine aminopeptidase increased, liver function tests NOS abnormal, retinol binding protein decreased, scan liver NOS abnormal, transaminases increased, ultrasound biliary tract abnormal, ultrasound liver abnormal, urine bilirubin increased, urobilin urine present, x-ray hepatobiliary abnormal.

Hepatic failure: coma hepatic, hepatic encephalopathy, hepatic failure, hepatorenal failure, hepatorenal syndrome.

Hepatitis: autoimmune hepatitis, cytolytic hepatitis, hepatitis acute, hepatitis alcoholic, hepatitis chronic active, hepatitis chronic active aggravated, hepatitis chronic NOS, hepatitis chronic persistent, hepatitis fulminant, hepatitis granulomatous NOS, hepatitis neonatal, hepatitis NOS, hepatitis toxic, ischemic hepatitis, radiation hepatitis.

Hepatocellular damage: acute fatty liver of pregnancy, alcoholic liver disease NOS, fatty liver alcoholic, hepatic necrosis, hepatocellular damage, hepatocellular damage aggravated, hepatocellular damage neonatal, hepatocellular foamy cell syndrome, hepatotoxicity aggravated, hepatotoxicity NOS, liver fatty, portal triaditis, Reyes syndrome, Zieve syndrome.

Jaundice: acholia, cholestasis, cholestasis of pregnancy, hepatitis cholestatic, jaundice cholestatic, jaundice extrahepatic obstructive NOS, jaundice hepatocellular, jaundice neonatal, jaundice NOS, Kernicterus, neonatal cholestasis, ocular icterus, postcholecystectomy syndrome.

Overall hepatic disorders: abnormal hepatic function, hepatic disorder aggravated, hepatic disorder NOS, hepatic failure, hepatic lesion NOS, hepatitis noninfectious, hepatobiliary disease NOS, hepatocellular damage, jaundice.

#### WHO/UMC DATA SOURCE

Abnormal hepatic function: BSP test abnormal, cephalin flocculation abnormal,  $\gamma$ -glutamyltransferase increased, hepatic enzymes increased, hepatic function abnormal, SGOT increased, SGPT increased, thymol turbidity abnormal.

Hepatic failure: coma hepatic, hepatic failure, hepatorenal syndrome.

Hepatitis: hepatitis, hepatitis chronic active.

Hepatocellular damage: hepatic necrosis, hepatocellular damage, liver fatty.

Jaundice: hepatitis cholestatic, jaundice.

Overall hepatic disorders: abnormal hepatic function, hepatic failure, hepatitis, hepatocellular damage, jaundice.

**Address correspondence to:** Jordi Castellsague, MD, MPH, Pfizer Global Epidemiology, Pl. Xavier Cugat 2, D, 08174 Sant Cugat del Vallès, Barcelona, Spain. E-mail: jordi.castellsague@pfizer.com