Adverse drug reactions associated with the use of NSAIDs: a case/noncase analysis of spontaneous reports from the French pharmacovigilance database 2002–2006

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\textbf{INTRODUCTION}

Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used to treat a large number of common acute and chronic inflammatory conditions. These drugs possess different chemical and clinical profiles but essentially exert the same therapeutic properties and are associated with similar adverse effects. Gastrointestinal injuries, which range from dyspepsia to fatal upper gastrointestinal tract bleeding and perforation, are

\textbf{ABSTRACT}

To evaluate the safety profile of eight oral nonsteroidal anti-inflammatory drugs (NSAIDs) available in France, using data reported through the French pharmacovigilance system. Data (from 2002 to 2006) were analysed for aceclofenac, diclofenac, ketoprofen, meloxicam, naproxen, nimesulide, piroxicam and tenoxicam, focusing on the reported rates of serious adverse drug reactions (ADRs) in the following system organ classes: gastrointestinal, hepatic, cutaneous, renal and cardiovascular. A total of 42 389 serious ADR reports were identified, and 38 506 were included in a case/noncase analysis. Ketoprofen was associated with the highest cumulative reported rate of serious ADRs (0.78 cases per million defined daily doses), followed by diclofenac (0.58), nimesulide (0.52), naproxen (0.50), piroxicam (0.47), tenoxicam (0.42), meloxicam (0.41) and aceclofenac (0.30). The most frequently reported serious ADRs were cutaneous, followed by gastrointestinal, hepatic, renal and rarely, cardiovascular events. In the case/noncase analysis, ketoprofen, piroxicam and naproxen were associated with the highest risk of serious gastrointestinal ADRs (odds ratios [ORs] of 6.87, 6.54 and 5.07, respectively). Nimesulide and aceclofenac were associated with the highest risk of liver ADRs (adjusted ORs of 4.53 and 3.67, respectively), as was meloxicam for cutaneous ADRs (adjusted OR of 3.15) and tenoxicam for renal ADRs (adjusted OR of 3.17). The most frequent serious ADRs reported with the selected oral NSAIDs are cutaneous, followed by gastrointestinal, hepatic, cutaneous and renal adverse events were linked, respectively, with ketoprofen, nimesulide, meloxicam and tenoxicam compared with the other NSAIDs.
among the most common adverse drug reactions (ADRs) associated with the use of NSAID [1–3]. Other important ADRs include skin reactions, renal complications, allergic reactions, alteration in hepatic enzyme levels and, rarely, hepatopathies [4–7]. Hepatic ADRs associated with NSAIDs are quite uncommon when compared with other pharmacological classes such as antibiotics [6,8]. Epidemiological studies have reported the incidence of acute liver injury to be 1–9 cases per 100 000 NSAID users [6,7].

As recommended by the European Medicine Agency (EMA) [9], NSAIDs should be prescribed at the lowest effective dose and for the shortest time necessary to control symptoms. Moreover, other factors such as the overall safety profile of each compound (e.g. potential gastrointestinal and other concerns) and individual risk factors must be considered for improved patient management [10].

Differences in safety profiles between NSAIDs are a key discriminator for choosing between one NSAID and another, and not all NSAIDs have the same level of risk for inducing gastrointestinal ADRs. First-generation NSAIDs are nonselective and block the activity of both COX-1 and COX-2. Second-generation agents, the COX-2 inhibitors, were developed with the aim of reducing the incidence of gastrointestinal adverse effects by sparing the gastrointestinal protective functions of COX-1 while still inhibiting inflammation [11,12]. However, it was clear reasonably soon after their commercialization that the use of these COX-2 inhibitors (i.e. rofecoxib and valdecoxib) was associated with an increase in cardiovascular risk, leading to their withdrawal from the market [13,14]. These events led to a revision of the overall safety profile of all NSAIDs, particularly in regard to their renal and cardiovascular risk profile. Moreover, a number of studies evaluating the gastrointestinal tolerability of COX-2 inhibitors did not demonstrate a lower risk of upper or lower gastrointestinal events [15,16].

Several factors influence a patient’s risk of developing different ADRs while receiving NSAIDs; for example, elderly patients or those with cardiovascular disorders, chronic renal disease, rheumatoid arthritis or chronic obstructive pulmonary disease are at greater risk of cardiovascular ADRs [15]. Gastrointestinal ADRs are important indicators when evaluating the overall risk profile of NSAIDs because of the risk of gastrointestinal bleeding and perforation. Risk factors for gastrointestinal complications, according to the National Institute for Clinical Excellence, include age over 65 years, the use of corticosteroids, aspirin or anticoagulants, serious comorbidity or a history of upper gastrointestinal events [10].

The aim of this pharmacoepidemiological study was to compare the safety profile of eight-first-generation NSAIDs available in France, by assessing the reporting of serious ADRs in several system organ classes [SOCs] from data in the French pharmacovigilance system from 2002 to 2006.

METHODS

This study analysed serious ADRs spontaneously reported to the French pharmacovigilance system between 1st January 2002 and 31st December 2006 for NSAIDs available in France. It has been compulsory since 1995 for all prescribers in France to report any ADR defined as ‘serious’ and/or ‘unexpected’ [16]. ‘Serious’ ADRs are defined as those being fatal, life-threatening, causing hospitalization, resulting in persistent or significant disability or incapacity, requiring intervention to prevent permanent damage or causing a congenital anomaly [16]. This study focused on serious ADRs associated with gastrointestinal, hepatic, cutaneous, renal and cardiovascular systems.

Serious ADRs of interest were identified from specific codes of the World Health Organisation Adverse Reactions Terminology (WHO-ART) classification of selected organ class disorders (Table I).

Study design

The data collected were analysed for the reporting of serious ADRs in the population treated with the selected NSAIDs and to calculate the odd ratios (ORs) of the association of these ADRs with the NSAIDs in this population, using a case/noncase analysis.

For the estimation of ADR reporting, data were analysed and compared for eight oral formulations of NSAIDs: aceclofenac, diclofenac, ketoprofen, meloxicam, naproxen, nimesulide, piroxicam and tenoxicam.

Case/noncase analysis has been widely used in the last decade in several spontaneous reporting databases, including the French pharmacovigilance database [17,18]. For example, this analytical method was applied to data from the French and Spanish pharmacovigilance national databases to compare the risk of hepatic damage with the administration of different NSAIDs [19]. In this method, ‘cases’ are the ADRs of interest and the ‘noncase’ control group corresponds to all other ADRs recorded in the database. The principle is to
compare drug exposure (i.e. all drugs taken before the drug-related event) among cases and noncase controls.

Statistical analysis

Reporting rate of ADRs

The reporting rate of the total number of serious ADRs and the reporting of serious ADRs related to the selected system organ class (SOC) was computed for each NSAID by dividing the number of ADRs reported by the total number of defined daily doses (TDDDs) consumed in the same period and multiplying by $10^6$ (reporting rates are expressed as number of adverse reactions per million DDD). For each reporting rate, a 95% confidence interval (CI) was also computed using the exact method based on the Poisson distribution.

The TDDDs of each NSAID considered in the study were estimated from the sales figures in standard units obtained from the IMS-Health, while the DDD for each compound was obtained from the WHO Collaborating Centre for Drug Statistics Methodology. The DDDs for oral formulations of the drugs of interest, checked on 29th June 2007 (http://www.whocc.no/atcddd/), were: aceclofenac, 200 mg; diclofenac, 100 mg; ketoprofen, 150 mg; naproxen, 500 mg; nimesulide, 200 mg; piroxicam, 20 mg; tenoxicam, 20 mg; and meloxicam, 15 mg.

Case/noncase analysis

The case/noncase method was used to determine whether there is a statistically significant association between the event and the NSAIDs’ exposure. In this study, the case/noncase method was applied to compare the reports corresponding to specific ADRs in different SOCs, defined as ‘cases’, with the other reports in the database, called ‘noncases’, for each NSAID examined. The association between each ADR and the selected NSAIDs was quantified by calculating an OR of exposure to each drug with its 95% CI, adjusted on age and gender, to minimize the risk of confounding. All analyses and calculations were executed using SAS® Version 9.2 of the SAS System for Windows (SAS Institute Inc., Cary, NC, USA).

RESULTS

Reporting rate of ADRs

Of the 42 389 ‘serious’ ADRs that were recorded in the French pharmacovigilance database between 1st January 2002 and 31st December 2006, 34 748 (81.9% of the total number) involved hospitalization; 1067 (2.5%) led to disability or sequelae, 5152 (12.2%) were life-threatening, and 1422 (3.4%) resulted in death.

In terms of serious ADRs overall reporting rate (number of adverse reactions per million DDD), ketoprofen had the highest reporting rate of NSAIDs (0.78), followed by diclofenac (0.58), nimesulide (0.52), naproxen (0.50), piroxicam (0.47), tenoxicam (0.42), meloxicam (0.41) and aceclofenac (0.30) (Table II).

Of the eight NSAIDs examined, nimesulide, tenoxicam and piroxicam had the lowest proportions of reported ADRs that were life-threatening or resulted in death (9.6%, 8.0% and 6.6%, respectively) compared with aceclofenac (22.7%), naproxen (16.1%), diclofenac (14.5%), meloxicam (13.0%) and ketoprofen (11.9%).

Reporting of ADRs by SOCs

The cumulative reporting rates of ADRs according to the SOCs for the eight NSAIDs evaluated are summarized in Table III.

Gastrointestinal ADRs

Ketoprofen had the highest cumulative reporting rate for gastrointestinal ADRs (0.17 cases per million DDDs), followed by piroxicam (0.10), diclofenac (0.10), naproxen (0.09), nimesulide and tenoxicam (both 0.05), aceclofenac (0.04) and meloxicam (0.04).
Liver ADRs
For liver ADRs, nimesulide had the highest cumulative reporting rate (0.16), followed by diclofenac (0.09) and ketoprofen (0.09); tenoxicam exhibited the lowest rate (0.03).

Skin ADRs
Meloxicam had the highest reporting of skin ADRs over the entire period (0.16), followed by piroxicam (0.14) and ketoprofen (0.14); aceclofenac had the lowest reporting rate (0.06).

Renal ADRs
Ketoprofen was associated with the highest reporting rate of renal ADRs (0.12), followed by diclofenac (0.08) and tenoxicam (0.07); aceclofenac had the lowest rate (0.01).

Cardiovascular ADRs
For arterial thrombosis (cardiac and peripheral), a very small number of cases were reported with diclofenac, ketoprofen and naproxen over the entire period covered by the study. No case associated with aceclofenac, nimesulide, meloxicam, piroxicam and tenoxicam was reported during the study period.

Case/noncase analysis
Of the original 42,389 serious ADR reports examined, 476 cases (1.12%) were excluded because of missing data concerning age and/or gender (required to calculate adjusted odds ratios); 3407 reports (8.04%) were discarded because patients were under 15 years of age. Reports included in the case/noncase analysis totalled 38,506 (90.84%) (Figure 1).

Cases were then stratified by each single SOC according to gender and age (15–45, 46–65, 66–80 and >80 years). Results of the analysis for each NSAID according to the different SOC are presented in Table IV.

Gastrointestinal ADRs
The case/noncase comparison showed that ketoprofen and piroxicam were associated with the highest risk of

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### Table II

Annual reporting rates [with the 95% CI] of serious adverse reactions (ADRs); the number of ADRs per million defined daily doses (DDDs) for each of the eight nonsteroidal anti-inflammatory drugs (NSAIDs), as reported in the French pharmacovigilance database from 2002 to 2006.

<table>
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<tbody>
<tr>
<td>Aceclofenac</td>
<td>0.16 [0.02–0.64]</td>
<td>0.52 [0.28–0.88]</td>
<td>0.18 [0.07–0.42]</td>
<td>0.30 [0.19–0.46]</td>
<td></td>
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</tr>
<tr>
<td>Diclofenac</td>
<td>0.65 [0.51–0.82]</td>
<td>0.56 [0.28–0.88]</td>
<td>0.47 [0.36–0.61]</td>
<td>0.58 [0.52–0.64]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ketoprofen</td>
<td>0.70 [0.55–0.87]</td>
<td>0.71 [0.58–0.86]</td>
<td>0.65 [0.53–0.79]</td>
<td>0.78 [0.72–0.85]</td>
<td></td>
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<tr>
<td>Naproxen</td>
<td>0.61 [0.44–0.83]</td>
<td>0.58 [0.40–0.80]</td>
<td>0.29 [0.17–0.47]</td>
<td>0.50 [0.42–0.58]</td>
<td></td>
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<tr>
<td>Nimesulide</td>
<td>0.71 [0.45–1.07]</td>
<td>0.56 [0.34–0.87]</td>
<td>0.40 [0.22–0.66]</td>
<td>0.52 [0.41–0.64]</td>
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</tr>
<tr>
<td>Meloxicam</td>
<td>0.31 [0.08–1.01]</td>
<td>0.39 [0.12–0.91]</td>
<td>0.24 [0.06–0.78]</td>
<td>0.41 [0.26–0.62]</td>
<td></td>
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</tr>
<tr>
<td>Piroxicam</td>
<td>0.47 [0.35–0.62]</td>
<td>0.55 [0.42–0.71]</td>
<td>0.39 [0.28–0.53]</td>
<td>0.47 [0.42–0.53]</td>
<td></td>
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<tr>
<td>Tenoxicam</td>
<td>0.33 [0.10–0.93]</td>
<td>0.26 [0.06–0.85]</td>
<td>0.53 [0.17–1.25]</td>
<td>0.42 [0.27–0.61]</td>
<td></td>
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</tbody>
</table>

*Drug became available in 2004.

### Table III

Cumulative reporting rate [95% CI] of serious adverse drug reactions (ADRs) per million defined daily doses (DDDs) according to selected system organ class (SOCs) for each of eight nonsteroidal anti-inflammatory drugs (NSAIDs) as reported in the French pharmacovigilance database from 2002 to 2006.

<table>
<thead>
<tr>
<th></th>
<th>Gastrointestinal</th>
<th>Liver</th>
<th>Skin</th>
<th>Renal</th>
<th>Cardiovascular</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aceclofenac</td>
<td>0.04 [0.009–0.12]</td>
<td>0.08 [0.03–0.18]</td>
<td>0.05 [0.01–0.14]</td>
<td>0.01 [0.000–0.14]</td>
<td>0.000 [0.000–0.05]</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>0.10 [0.07–0.13]</td>
<td>0.09 [0.06–0.11]</td>
<td>0.10 [0.07–0.13]</td>
<td>0.08 [0.05–0.10]</td>
<td>0.003 [0.000–0.012]</td>
</tr>
<tr>
<td>Ketoprofen</td>
<td>0.17 [0.14–0.20]</td>
<td>0.09 [0.06–0.11]</td>
<td>0.13 [0.10–0.16]</td>
<td>0.11 [0.07–0.08]</td>
<td>0.002 [0.000–0.009]</td>
</tr>
<tr>
<td>Naproxen</td>
<td>0.08 [0.05–0.12]</td>
<td>0.04 [0.02–0.07]</td>
<td>0.08 [0.05–0.11]</td>
<td>0.03 [0.01–0.06]</td>
<td>0.003 [0.000–0.017]</td>
</tr>
<tr>
<td>Nimesulide</td>
<td>0.05 [0.02–0.09]</td>
<td>0.15 [0.10–0.23]</td>
<td>0.12 [0.07–0.19]</td>
<td>0.05 [0.02–0.09]</td>
<td>0.000 [0.000–0.023]</td>
</tr>
<tr>
<td>Meloxicam</td>
<td>0.03 [0.004–0.13]</td>
<td>0.03 [0.004–0.13]</td>
<td>0.16 [0.07–0.31]</td>
<td>0.03 [0.004–0.13]</td>
<td>0.000 [0.000–0.067]</td>
</tr>
<tr>
<td>Piroxicam</td>
<td>0.10 [0.07–0.13]</td>
<td>0.06 [0.04–0.08]</td>
<td>0.14 [0.11–0.17]</td>
<td>0.03 [0.02–0.05]</td>
<td>0.000 [0.000–0.007]</td>
</tr>
<tr>
<td>Tenoxicam</td>
<td>0.05 [0.01–0.14]</td>
<td>0.03 [0.004–0.12]</td>
<td>0.13 [0.05–0.26]</td>
<td>0.06 [0.01–0.17]</td>
<td>0.000 [0.000–0.062]</td>
</tr>
</tbody>
</table>
gastrointestinal ADRs, followed by naproxen, diclofenac, aceclofenac and nimesulide. Meloxicam and tenoxicam were not significantly associated with gastrointestinal ADRs, and few cases were reported with these drugs.

Liver ADRs
Nimesulide, aceclofenac, diclofenac and piroxicam were significantly associated with liver ADRs.

Skin ADRs
The level of risk for skin ADRs was lower than those observed for liver or gastrointestinal disorders. Meloxicam, piroxicam and nimesulide were significantly associated with skin ADRs.

Renal ADRs
Tenoxicam, diclofenac and ketoprofen were significantly associated with renal ADRs.

Table IV A case/noncase analysis showing age- and gender-adjusted odds ratios (OR) for association of nonsteroidal anti-inflammatory drugs (NSAIDs) with serious gastrointestinal, liver, skin, renal and cardiovascular adverse reactions (ADRs) as reported in the French pharmacovigilance database from 2002 to 2006. For each ADR, the comparator for the exposure to each NSAID is the whole database (among 38 506 cases with age and gender). Values in boldface indicate a level of significance <0.05.

<table>
<thead>
<tr>
<th>NSAID</th>
<th>Gastrointestinal</th>
<th>Liver</th>
<th>Skin</th>
<th>Renal</th>
<th>Cardiovascular</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total n</td>
<td>OR [95% CI]</td>
<td>n</td>
<td>OR [95% CI]</td>
<td>n</td>
</tr>
<tr>
<td>Aceclofenac</td>
<td>22</td>
<td>3.74 [1.10–12.7]</td>
<td>6</td>
<td>3.67 [1.43–9.41]</td>
<td>4</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>338</td>
<td>4.55 [3.40–6.08]</td>
<td>53</td>
<td>1.93 [1.44–2.60]</td>
<td>60</td>
</tr>
<tr>
<td>Ketoprofen</td>
<td>506</td>
<td>6.87 [5.51–8.57]</td>
<td>58</td>
<td>1.27 [0.96–1.67]</td>
<td>87</td>
</tr>
<tr>
<td>Meloxicam</td>
<td>23</td>
<td>2.26 [0.53–9.66]</td>
<td>2</td>
<td>0.89 [0.21–3.80]</td>
<td>9</td>
</tr>
<tr>
<td>Naproxen</td>
<td>162</td>
<td>5.07 [3.33–7.73]</td>
<td>14</td>
<td>0.82 [0.46–1.49]</td>
<td>26</td>
</tr>
<tr>
<td>Nimesulide</td>
<td>83</td>
<td>2.33 [1.12–4.86]</td>
<td>25</td>
<td>4.53 [2.83–7.27]</td>
<td>20</td>
</tr>
<tr>
<td>Piroxicam</td>
<td>257</td>
<td>6.54 [4.84–8.84]</td>
<td>35</td>
<td>1.54 [1.07–2.20]</td>
<td>77</td>
</tr>
<tr>
<td>Tenoxicam</td>
<td>25</td>
<td>2.94 [0.87–9.92]</td>
<td>2</td>
<td>0.86 [0.20–3.68]</td>
<td>8</td>
</tr>
</tbody>
</table>

Figure 1 Population of the case/noncase analysis. ADRs, adverse drug reactions; CV, cardiovascular; DB, database; GI, gastrointestinal.
Cardiovascular ADRs
The majority of NSAIDs (aceclofenac, meloxicam, nimesulide, piroxicam and tenoxicam) did not have reports of cardiovascular ADRs during the period of the study. Two cases of thrombosis were reported for diclofenac, and one case each for ketoprofen and naproxen.

DISCUSSION
This analysis of the French Pharmacovigilance database evaluated and compared the overall safety profile of eight widely used NSAIDs, in terms of the overall reporting rate of serious ADRs, as well as the reporting rate of specific classes of serious ADRs. As far as we know, this is the first study providing data on the safety profile of eight different NSAIDs under real conditions of use in France.

The main strength of the present study was the use of a national database, which collected standardized information on adverse reactions related to drug use in a ‘real-world’ population. However, the study presents several limitations resulting from the spontaneous reporting of ADRs, which include the inability to accurately identify drug-related events (particularly cardiovascular ones), bias owing to media coverage, the time elapsed since the marketing of a drug and the fact that some ADRs are better known than others (resulting in under-reporting).

The overall reporting rates of serious ADRs were similar for the selected NSAIDs (0.31–0.58 cases per million DDDS) in this French context, with the exception of ketoprofen (0.78), which was associated with a higher reporting rate of serious ADRs. Annual reporting rates in France were similar for the years 2002–2006, although the rates of ADRs were high in 2004, which may be explained by increasing reporting because of the increased media coverage of the COX-2 inhibitors and conventional NSAID safety following the withdrawal of rofecoxib [13–15]. These reporting rates must be interpreted with caution, because not all reactions have a constant risk over time, and if the reaction occurs early, there may be large difference between long-term and short-term users. A recent study in France using data from the Health Insurance system indicated that the median duration of NSAIDs’ prescription should be estimated 30 days (Fournier JP, Lapeyre-Mestre M, Sommet A, Pathak A, Oustric S, Montastruc JL unpublished data). The number of adverse event reports for a drug may be influenced by advertising and may depend on expectations and the degree of awareness of health professionals. Although there is no reliable way to measure the contribution of these types of factors, it can be surmised that reporting rates of some ADRs may be overestimated or erroneously attributed to NSAIDs. Nevertheless, despite the well-known limits of spontaneous reporting systems, the results of this analysis are in agreement in many ways with the scientific literature.

Of the serious ADRs attributed to the oral NSAIDs examined in this study, the most frequently reported involved the skin, followed by the gastrointestinal system, liver and the renal system, with far fewer reports involving the cardiovascular system. It is well known that cutaneous adverse reactions are frequently observed with NSAIDs, with cross-reactive reactions between co-administered drugs. Oxicams and ketoprofen seem to present the highest cutaneous risk, as observed in studies investigating rare but serious ADRs such as Stevens–Johnson syndrome or toxic epidermolysis [20]: nimesulide and diclofenac present an intermediate risk, and aceclofenac and naproxen the lowest risk.

The second highest reporting of ADRs concerns gastrointestinal reactions. The rank of the studied NSAIDs investigated, in term of serious gastrointestinal ADRs, reveals that ketoprofen and piroxicam exhibited the highest levels of risk, whereas nimesulide exhibited the lowest [2,18]. In a case–control study, Laporte et al. compared the gastrointestinal bleeding risk associated with first- and second-generation NSAIDs, and the rank of risk was very similar to that obtained in our study [21].

The reporting of hepatic ADRs for a number of NSAIDs assessed in this study confirms that the liver is one of the potential organ targets of ADRs when NSAIDs are used [5–7,22], even though the reporting of these ADRs is lower when compared with the reporting of cutaneous or gastrointestinal ADRs. Nimesulide presented the highest reporting of hepatic ADRs in terms of cases per million DDDS (0.157). A comparative analysis of the French and Spanish pharmacovigilance databases conducted in the period 1982–2001 had shown a nonsignificant OR for liver injuries and nimesulide in France, whereas it was statistically significant in Spain [19]. Actually, nimesulide was withdrawn from the Spanish and the Finnish markets in 2002 because of an unfavourable benefit–risk balance related to liver injuries [23–25]. In the present study, it was found that nimesulide and aceclofenac were associated with the highest risk of liver ADRs, followed by diclofenac and piroxicam, which is in agreement with the literature [6,7,26,27].

Study results revealed that serious renal ADRs are significantly associated with the use of tenoxicam,
ketoprofen and diclofenac. Despite these results needing to be interpreted with caution because of the low number of reported cases, they may suggest that the expected pharmacological impact of NSAID on renal function is not always taken into account when treating in particular old patients. Indeed, NSAIDs may affect arterial blood pressure via the renin–angiotensin system and alterations in sodium levels and water retention in the kidneys [9].

The last type of serious ADR investigated, thrombotic cardiovascular events, was very rarely reported to the French pharmacovigilance system, as in other systems [26].

CONCLUSION

This study shows that the most frequent serious ADRs reported for oral NSAIDs were cutaneous, followed by gastrointestinal, hepatic and renal events and rarely, cardiovascular ones. Overall, the highest risk for serious ADRs was linked to ketoprofen, the lowest to acetylrafenac, with the other drugs presenting intermediate risks. The risks differed for the specific drug and system involved: the greatest gastrointestinal, hepatic, cutaneous and renal risks were observed, respectively, with ketoprofen, nimesulide, meloxicam and tenoxicam. This emphasizes the importance of evaluating the risks of specific NSAIDs in relation to the patient’s history, in order to accurately determine their benefit–risk profiles and improve patient safety.

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