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Adverse Drug Reactions Related to the Use of NSAIDs with a Focus on Nimesulide

Results of Spontaneous Reporting from a Northern Italian Area

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Abstract

Objective: To analyse and compare the adverse drug reactions (ADRs) associated with the use of nimesulide with those associated with diclofenac, ketoprofen, and piroxicam, reported spontaneously in a northern Italian area (Veneto and Trentino).

Methods: Data were obtained from the spontaneous reporting system database of Veneto-Trentino, the principal contributor to the Italian spontaneous surveillance system. All case reports that occurred in association with all formulations of the nonsteroidal anti-inflammatory drugs (NSAIDs) under investigation during the period from January 1988 to December 2000, were analysed in detail.

Sales data from June 1996 to May 1999 and prescription data, from 1997 to 2000 from the Veneto region were utilised to select the most widely used NSAIDs to be included in the study. The prescription data were also used to look at the drug use in relation to age.

Results: During the study period, 10 608 reports describing 16 571 adverse reactions were entered into the surveillance system. We found 207 case reports for nimesulide, 187 for diclofenac, 174 for ketoprofen, and 137 for piroxicam. Analysis of sales and prescription data revealed that in the Veneto region nimesulide was the most widely prescribed drug followed at a long distance by diclofenac, piroxicam and ketoprofen.

No age-related difference in the use of the four drugs was found. Analysis of the case reports revealed significantly different toxicity profiles for the four drugs. In particular, nimesulide was associated with fewer and less severe gastrointestinal (GI) ADRs compared with the other NSAIDs. Nimesulide was associated with about half the number of GI reactions (10.4%) than the other three NSAIDs (21.2% for diclofenac, 21.7% for ketoprofen, 18.6% for piroxicam). Two previously unreported reactions were also found for piroxicam and ketoprofen.

Conclusions: Nimesulide is the most frequently used NSAID in Italy. Spontaneous reporting data suggest that nimesulide has the most favourable GI tolerability profile of the NSAIDs investigated, with few reports of severe GI reactions. A few reports of hepatic and renal impairment associated with nimesulide suggest caution in patients at risk. Age-related reporting analysis suggests a higher tox-

icity for diclofenac and piroxicam in the elderly compared with nimesulide and ketoprofen.

This analysis of the Veneto-Trentino database on spontaneous reporting confirms that NSAIDs differ in their tolerability profile, and this fact should be taken into account in the choice of drugs in relation to patient characteristics.

Objectives

It is well known that data emerging during the clinical development of a new drug are not sufficient to fully assess its potential toxicity when this drug is used in a larger patient population. Therefore, the post-marketing period assumes a role of great importance in consolidating the safety profile of drugs or in detecting previously unobserved adverse effects.

Spontaneous reporting of adverse drug reactions (ADRs) has proven to be a valuable tool in providing information about new adverse effects and in early signal generation. It plays a primary role among pharmacovigilance methods.[1,2]

Moreover, when adequate reporting rates and consumption data are available, it is possible to utilise the spontaneous reporting data to give a useful impression of the frequency of ADRs.[3] Some studies comparing the safety of different drugs, based on spontaneous reporting data, have been published to date.[4-8] In addition, calculation methods relative to risks with confidence intervals and odds ratios for detecting possible drug interactions in the context of spontaneous reporting have been published.[9,10] However, potential confounding factors and reporting bias should be considered and the spontaneous reporting data have to be confirmed by other *ad hoc* studies. In some reports, the involvement of a drug is uncertain and further evidence is needed to confirm the causality relationship between drug and adverse reaction. Furthermore, there is a substantial under-reporting, that generally increases with the length of time that a drug has been on the market. A cluster of reports, following a drug alarm, may introduce a further confounding factor. Spontaneous reporting is generally considered as a source of signals and its success depends on the reporting rate and on the quality of reports.[11]

Nimesulide is the most commonly used nonsteroidal anti-inflammatory drug (NSAID) in Italy, where it has been available since 1985. The drug is also marketed in other European and Latin American countries and ranks fifth in the worldwide NSAIDs market even though it is not sold in the US or UK.[12]

Many studies have been published on the safety of NSAIDs and the most frequent adverse events reported are gastrointestinal (GI) and dermatological reactions.[13,14] It has been estimated that during 1997 in the US, 16 500 patients with rheumatoid arthritis or osteoarthritis died as a result of GI adverse effects of NSAIDs, a number similar to the AIDS-related deaths.[15] Not all the NSAIDs, however, have the same risk for inducing severe GI ADRs and alot of data on this subject has been published. In a recent meta-analysis,[15] epidemiological studies related to the use of NSAIDs and upper GI tract bleeding/perforation published between 1990 and 1999 were reviewed. Pooled relative risk estimates were calculated. Among the drugs considered in this analysis, ibuprofen was associated with the lowest risk, followed by diclofenac, sulindac, naproxen sodium, indomethacin, ketoprofen and piroxicam.[16] A similar ranking based on spontaneous reporting data had been observed in the UK.[17]

Few studies have tried to define the risk of developing severe GI reactions with nimesulide compared with other NSAIDs, and epidemiological data are limited. A meta-analysis of controlled studies showed that the benefit-risk ratio was better for nimesulide than other NSAIDs (diclofenac, piroxicam, ketoprofen, naproxen, etodolac), since the tolerability of nimesulide 100mg twice daily was approximately equal to that of placebo, espe-

cially regarding GI effects.[18] On the other hand, a recent epidemiological study from Italy found that upper GI tract bleeding was as common in nimesulide users as in nonselective NSAIDs consumers (i.e. ketoprofen, naproxen, tenoxicam, indomethacin).[19]

Large post-marketing studies on the tolerability of nimesulide reported an overall incidence of adverse reactions of about 8%, and a withdrawal rate of approximately 2%.[20,21] The adverse events mainly involved the GI tract (epigastric pain, heartburn, nausea, diarrhoea and vomiting), skin (rash, pruritus) and CNS (headache, dizziness and somnolence). An evaluation of the adverse events with nimesulide reported in clinical trials since 1991 has shown an 8.9% incidence of these events, mainly GI, in the 4224 patients receiving oral nimesulide for various inflammatory and painful conditions versus a 16.7% incidence in the 1017 patients treated with reference drugs.[22]

NSAIDs have been related to serious adverse reactions mainly involving skin and liver, and several drugs of this class have been withdrawn from the market for safety issues, such as bromofenac, the latest example. The pattern of serious nimesulide skin and liver reactions which have emerged from clinical trials and from spontaneous reporting is mainly comparable with that of other NSAIDs.[23] In the last 3 years, some case reports of serious hepatic injury associated with nimesulide have been published,[24-27] although the risk of developing liver diseases seems to be small and no different to other NSAIDs.[28] Renal impairment associated with nimesulide has also been reported, mostly in patients with risk factors.[29]

Finally, data from a large number of clinical studies suggest that nimesulide can be considered a reliable alternative drug in patients with aspirin (acetylsalicylic acid)/NSAID intolerance or bronchial asthma.[30]

The aim of this study was to assess the safety profile of nimesulide and of the other most commonly used NSAIDs in Italy (diclofenac, ketoprofen and piroxicam) by analysing the data reported to the Veneto-Trentino spontaneous surveillance system over a 13-year period from 1988 to 2000. At the beginning of the observation period all the investigated drugs had a market life of at least 3 years and were widely used. We can presumably exclude a differential reporting rate due to the different length of time on the market. The rate of reporting for NSAIDs increases usually towards the end of the second year of marketing and thereafter declines to reach a stable figure.[31]

Methods

The safety data were obtained from a database that collects all spontaneous case reports of ADRs from Veneto and Trentino. This area had an estimated population of 4 830 649 inhabitants in December 1996 (about 8% of the Italian population) and is the principal contributor to the Italian spontaneous surveillance system, accounting for about 25% of all Italian reports. The Veneto-Trentino pharmacovigilance database, developed in 1988, has an annual input of 270 reports per million inhabitants, which is comparable to that recorded for the UK (294 in 1997).[32] During the last 4 years there has been a substantial increase in the number of ADRs submitted to this system, which is probably due to the reinforcement of compulsory reporting after the introduction in Italy of a new pharmacovigilance law in February 1997.

We analysed the spontaneous case reports collected between January 1988 and December 2000. The following information was taken into consideration: reporter's category; patient's age and gender; reporter's diagnosis of the ADR; characteristics of the underlying diseases; drug exposure (indication, treatment duration and dosage); time of event onset and outcome. Reports were classified according to the WHO criteria for causality assessment.[33] Reports with certain, probable or possible causality assessment were included.

The drugs were categorised following the Italian System Codifa and the Anatomical Therapeutic Chemical classification. The reactions were classified according to the WHO Adverse Reaction Terminology, and classified as serious or nonserious events on the basis of the WHO Critical Term List.[34]

All reports of ADRs that occurred in association with nimesulide during the study period were selected and analysed in detail. On the basis of both IMS and regional prescription data, diclofenac, piroxicam, and ketoprofen were selected for comparison as the most frequently used NSAIDs. Diclofenac and ketoprofen have been marketed in Italy since 1975, prioxicam since 1981 and nimesulide since 1985. Drug sales data from the Veneto and Trentino region were supplied by IMS for the period June 1996 to May 1999 (table I). The data included both prescription and nonprescription (self-medication) drug use. However, even though (of the NSAID class) only ketoprofen and diclofenac have oral over-the-counter pharmaceutical formulations, the so-called under-the-counter market, i.e. the sale of 'prescription only' drugs without a prescription, is a common phenomena in Italy for the NSAID class.

Annual prescription data for the Veneto Region were also evaluated. These data only refer to drugs which were reimbursed by the Italian health system in the years 1997 to 2000. Prescription data were analysed in relation to the following age ranges: 0 to 18, 19 to 45, 46 to 65, >65 years.

Figure 1 shows the number of defined daily doses per million inhabitants for the four most frequently prescribed NSAIDs in the period 1997 to 2000. In both drug-use analyses nimesulide is the most widely prescribed drug, followed at a long distance by diclofenac, piroxicam and ketoprofen.

Age of the patients, severity of the reactions and route of administration of drugs have been analysed. For each drug the female/male reporting ratio was calculated on the basis of gender distribution in Veneto region. The toxicity profiles of the individual NSAIDs were compared using the χ^2 test for statistical analyses.

Table I. Consumption of the four most frequently used nonsteroidal anti-inflammatory drugs in the Veneto and Trentino regions during the period June 1996 to May 1999[a]

Drug	Total units sold	Total DDD	DDD/ inhabitants
Nimesulide	3 985 264	59 778 960	12.37
Diclofenac	1 869 720	27 313 716	5.65
Piroxicam	687 684	16 366 775	3.39
Ketoprofen	966 789	11 354 164	2.35

a Source: IMS data from the Veneto and Trentino regions in Northern Italy.

DDD = daily defined dose.

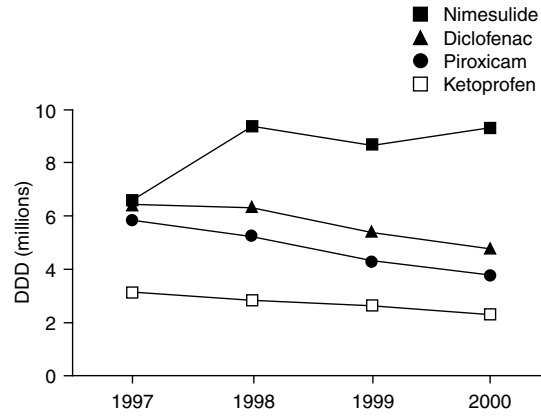

Fig. 1. Prescriptions of the four most frequently used nonsteroidal anti-inflammatory drugs in the Veneto region in Italy during the period 1997 to 2000. Prescription figures, in millions of defined daily doses (DDD), derived from the Veneto region data for drugs reimbursed by the Italian National Health System.

Results

During the 13-year period under consideration, 10 608 reports (33% of which were serious) were entered into the system, corresponding to a mean annual reporting rate of approximately 183 per million inhabitants. The reported reactions were 16 571 (35% of which were serious). The number of reports and reactions related to nimesulide, diclofenac, piroxicam, and ketoprofen are shown in table II. The female/male reporting rate ratio was lower for ketoprofen and higher for nimesulide, diclofenac, and piroxicam compared with the ratio for the total database (1.54). The percentage of serious reactions was higher for ketoprofen compared with the other three drugs, with similar percentages for nimesulide, diclofenac and piroxicam.

About 68% of reports involved outpatients and 32% involved inpatients, and complete recovery was reported in more than 70% of cases. In 1% of outpatients, the adverse reaction led to hospitalisation, with no significant differences among the four

Table II. Adverse drug reactions attributed to nimesulide, diclofenac, ketoprofen and piroxicam during a 13-year period (January 1988 to December 2000)

Drug	No. of reports (% of serious reports)	Female/male reporting rate ratio	No. of reactions (% of serious reactions)
Nimesulide	207 (35.3)	1.79	279 (25.8)
Diclofenac	187 (42.2)	1.93	288 (26.0)
Ketoprofen	174 (55.2)	1.21	249 (32.5)
Piroxicam	137 (37.2)	2.16	194 (26.8)

NSAIDs. Nimesulide was the only drug suspected to cause the adverse reaction in 65% of its reports, while diclofenac, ketoprofen and piroxicam were indicated as the only suspected drug in 75% of their own reports.

Figure 2 shows the percentage of reports by the route of administration for each of the drugs considered in the study. In Italy ketoprofen, piroxicam and diclofenac are available as parenteral, rectal, topical and oral formulations while nimesulide is available only as a rectal and oral formulations. No ADR reports associated to nimesulide rectal formulations were sent by doctors. Piroxicam, ketoprofen and diclofenac were administered orally in 68, 45 and 49% of patients. Ketoprofen was administered topically in 28% of patients, whereas piroxicam and diclofenac were administered topically in 2 and 3% of patients respectively. Figures are too low to analyse the ADR profile in relation to this administration route.

Figure 3 shows the percentage of ADR reports for each agent on the basis of patient age. More than 50% of reports associated with the use of nimesulide and ketoprofen involved patients aged <46 years, whereas this percentage was lower than 30% for diclofenac and piroxicam. No age-related differences in the use among the four drugs were found from the prescription data.

Table III shows the observed ADRs according to the involved organ systems. For all drugs, the highest percentage of reactions (ranging from 37.5% for diclofenac to 50.2% for ketoprofen) involved the skin as the target organ. We noted a significantly lower percentage of GI reactions for nimesulide than for the other NSAIDs. No differences were observed among the four drugs in the reactions involving the body as a whole, while the percentage of kidney reactions was slightly higher for

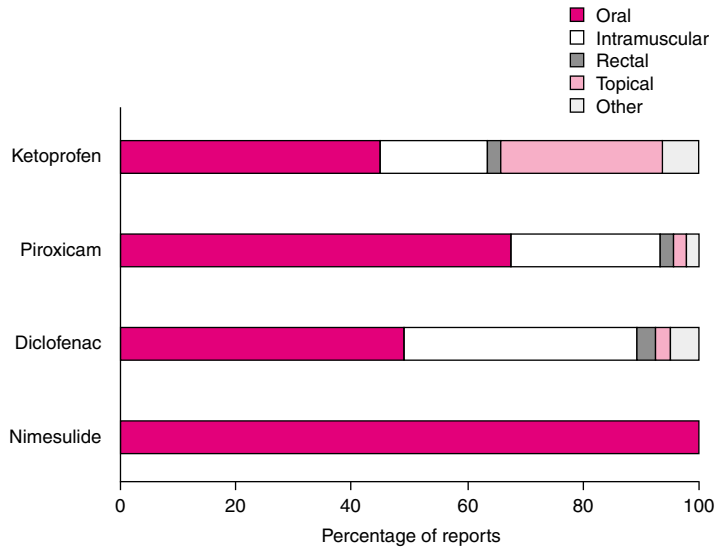

Fig. 2. Percentage of reports by the route of administration for each of the drugs considered in the study.

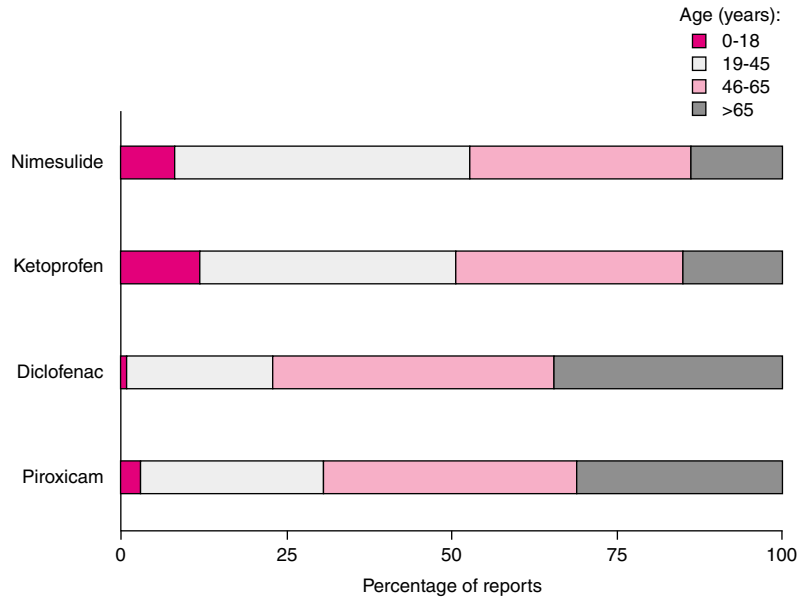

Fig. 3. Percentage of adverse drug reaction reports in relation to the patient's age for each of the drugs considered in the study.

nimesulide and the percentage of respiratory reactions was significantly higher for ketoprofen.

For the most frequently involved organ systems, the percentage of serious reactions are shown in figure 4. The most frequently reported serious reactions for nimesulide were: acute renal impairment (9 reports), erythema multiforme (8), and angioedema (7). Four cases of hepatitis (one of which referred to a patient also taking other NSAIDs), and 3 cases of Stevens-Johnson syndrome in patients aged 21 to 30 years were also reported with nimesulide.

GI bleeding (16 reports), anaphylactic reactions (9), and nonbleeding GI ulcers (5) were the most frequently reported serious reactions associated with diclofenac. Five cases of acute renal failure in patients with risk factors for renal disorders were also reported.

The serious skin reactions to ketoprofen included 10 reports of photosensitivity reactions (9 of which related to topical application), 8 of bullous eruptions, 6 of erythema multiforme, and 5 of angioedema. Among serious GI reactions, 10 reports of bleeding and 4 of colitis were collected. Finally, 4 cases of allergic asthma, each occurring after a single dose of ketoprofen, were reported.

GI bleeding (12 reports), bullous eruptions (6), angioedema (5), and nonbleeding GI ulcers (5) were the most frequently reported serious reactions to piroxicam. No serious general disorders (body as a whole) were notified.

We found only 2 reports of serious reactions not actually included in the package leaflet of the referred drug. One of them described a 49-year-old patient who developed chorioretinitis after receiving piroxicam and thiocolchicoside for 5 days. The patient had experienced a similar reaction to the same drugs 6 years earlier. The other report was a 68-year-old patient who developed acute myelosuppression, leading to hospital admission, after receiving intramuscular ketoprofen for 1 week.

Discussion

Signal generation and identification of new ADRs are among the strengths of the spontaneous reporting system, described by Professor Sir Michael Rawlins from the University of Newcastle-upon-

Tyne, England, as 'the sentinel safety monitoring system'.[35] This system does not allow accurate quantification of the risk associated with a given drug, due to possible confounding bias and the under-reporting of ADRs. However, the comparison of the benefit-risk profiles of drugs within the same therapeutic class and with similar indications, marketed in the same country in a comparable period of time is generally acceptable.[4,7,36] In these conditions the under-reporting can be assumed to be more or less of the same magnitude for the reference drugs.[7,37]

This study presents the ADR spontaneous reports of the most commonly prescribed and used NSAIDs as they occurred in a 13-year period of 'real world' medical practice in a northern Italian region which covers a population of approximately 5 million inhabitants. The four drugs have the same indications and have all been available on the Italian market for more than 15 years. The analysis of the reports associated with the use of nimesulide substantially confirms the safety profile derived from available clinical and epidemiological data.[18,23,38]

For all the drugs investigated, adverse reactions were more frequent in women. This is also observed when analysing an Italian interregional database, and it is in accordance with the findings of other surveillance systems.[39-41] The greater consumption of medications by women and the unbalanced gender ratio in the elderly population may at least partially account for the excess of reports in the female population. The female/male reporting rate ration was lower than the mean value of the whole database only for ketoprofen. In this case, it is impossible to explain this difference due to the lack of gender-related drug consumption data.

Since no age-related difference among the four drugs was found analysing prescription data for the period 1997 to 2000, a higher percentage of ADRs for diclofenac and piroxicam in the elderly in comparison with nimesulide and ketoprofen suggests an age-related toxicity for the former compounds. This fact is not confirmed by strong evidence; however, some data suggest an age-related safety profile for the different NSAIDs. For example, among 180 reports of diclofenac-induced hepatotoxicity to the US Food and Drug Administration, 71% involved patients aged 60 years or over.[42] However, in absence of US prescription data we cannot ex-

Table III. Toxicity profiles of nimesulide, diclofenac, ketoprofen and piroxicam: number of reports (%) according to body system

Organ or system	Nimesulide	Diclofenac	Ketoprofen	Piroxicam
Skin and appendages[a]	136 (48.7)	108 (37.5)	125 (50.2)	92 (47.4)
Gastrointestinal system[a]	29 (10.4)	61 (21.2)	54 (21.7)	36 (18.6)
Body as a whole (general disorders)	27 (9.7)	31 (10.8)	22 (8.8)	17 (8.8)
Urinary system	21 (7.5)	14 (4.9)	6 (2.4)	10 (5.2)
Respiratory system[a]	5 (1.8)	12 (4.2)	17 (6.8)	2 (1.0)
Cardiovascular system	9 (3.2)	11 (3.8)	7 (2.8)	5 (2.6)
Central and peripheral nervous system	10 (3.6)	12 (4.2)	2 (0.8)	7 (3.6)
Psychiatric	9 (3.2)	10 (3.5)	2 (0.8)	8 (4.1)
Haematological	8 (2.9)	8 (2.8)	4 (1.6)	5 (2.6)
Metabolic and nutritional	8 (2.9)	6 (2.1)	1 (0.4)	3 (1.5)
Vision	5 (1.8)	4 (1.4)	1 (0.4)	5 (2.6)
Liver and biliary system	8 (2.9)	4 (1.4)	1 (0.4)	1 (0.5)
Application site		3 (1.0)	4 (1.6)	
Musculoskeletal system	2 (0.7)	1 (0.3)	2 (0.8)	2 (1.0)
Reproductive	1 (0.4)	3 (1.0)		1 (0.5)
Collagen	1 (0.4)		1 (0.4)	
Total	**279 (100)**	**288 (100)**	**249 (100)**	**194 (100)**

a Significant differences (χ^2 test, $p < 0.02$) among the drugs in the reports implicating this organ system versus the other reports.

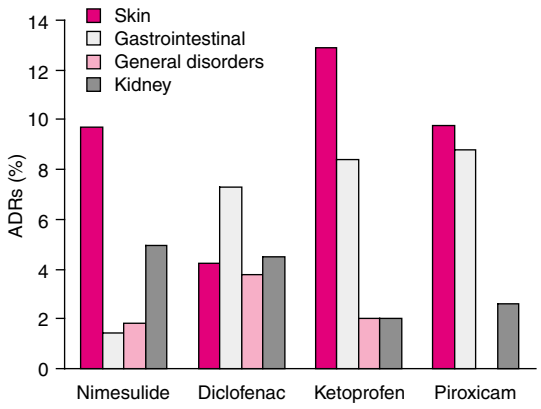

Fig. 4. Serious reactions as a percentage of the total number of adverse drug reactions (ADRs) reported in the Veneto-Trentino during the 1988 to 2000 period. The most frequently involved organ systems are shown.

clude that the large number of reports in the elderly was due to an age-related difference in diclofenac use. The pharmacokinetic profile of nimesulide was no different in patients aged >80 years than in younger patients, furthermore, it has shown good tolerability in a clinical trial in elderly patients.[43,44]

Results of this study showed that, in comparison with diclofenac, piroxicam and ketoprofen, nimesulide had the best GI tolerability, with few reports of severe GI reactions. The other three agents were associated with a higher incidence of GI toxicity with more severe events (about 8% of the total reactions for each comparator drug and less than 2% for nimesulide).

Nimesulide was available in Italy before the discovery of the two cyclo-oxygenase (COX) isoenzymes (the constitutive form COX-1 and the inducible form COX-2), and before the development of the new COX-2 selective NSAIDs. Based on *in vitro* and *in vivo* studies, nimesulide can be classified as a preferential COX-2 inhibitor, with a 1.3- to 2.5-fold higher selectivity towards COX-2 than COX-1 (according to the assay preparation).[45] The effects of nimesulide could also be related to other mechanisms, including free radical scavenging and effects on histamine release and on the neutrophil myeloperoxidase pathway.[46] This pharmacodynamic profile could explain the reduced potential of nimesulide to cause adverse GI effects when compared with the other NSAIDs, even if this hypothesis has to be confirmed by further epidemiological studies.

Although the number of severe hepatic, renal and cutaneous reactions appears to be very low in relation to the large use of nimesulide in Italy, our analysis confirms the previous observations of possibly serious reactions involving these organ systems.[23-27,29] In particular, these data suggest caution in patients at risk for renal or hepatic impairment or with other concomitant predisposing factors. As clearly stated in the patient's leaflet and data sheet, nimesulide is contraindicated in patients with hepatic or severe renal impairment.

The 10 case reports of phototoxicity associated with ketoprofen found in this study are suggestive of a specific toxicity and are confirmed by epidemiological and pharmacodynamic data. Among the NSAIDs, ketoprofen was previously found to be the main drug involved in photosensitivity reactions. These adverse reactions are related to the drug's chemical structure and seem to be more commonly reported with the use of the topical formulation, probably because of the higher concentration of drug in the skin.[47] A study conducted by the French drug surveillance system detected 337 cutaneous adverse reactions following the introduction to the market of the ketoprofen gel. Reactions were severe in 40% of cases (essentially photosensitisation and contact eczema) and hospitalisation was required in 10% of them.[48] In Italy, the label of the topical formulation of ketoprofen has recently been updated to include a warning about photosensitivity reactions.

Conclusions

Epidemiological data show a comparable efficacy, but differential toxicity, for the most frequently used NSAIDs in Italy, suggesting that the tolerability profile should be taken into account when selecting one of these drugs. This analysis of the Veneto-Trentino database for spontaneous reporting of ADRs confirms that individual NSAIDs differ in their tolerability profiles. Age-related report-

ing analysis suggests a higher toxicity for diclofenac and piroxicam in the elderly compared with nimesulide and ketoprofen. A better GI tolerability for nimesulide as well as the rare occurrence of severe renal and hepatic reactions emerged from the spontaneous reporting data. These findings should be verified by *ad hoc* investigations, such as case-control studies, that could be easily performed in Italy due to the wide use of this drug.

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