

Effects of the European restrictive actions concerning nimesulide prescription: a simulation study on hepatopathies and gastrointestinal bleedings in Italy

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Summary. In 2002 and 2007 the European Medicines Agency (EMA) examined the signals of a greater risk of hepatopathies related to nimesulide use. In 2007 restrictive actions were adopted in Europe. Moreover, EMA initiated a new referral in February 2010. The objective of this paper is to evaluate the effects of the 2007 regulatory measures concerning nimesulide and to estimate the potential effect of further actions. Specifically, we carried out a simulation on the expected number of hospitalisations for hepatopathies and upper gastrointestinal bleedings (UGIBs) in Italy before and after the regulatory measures (2006 vs. 2009), taking into account the shifting of nimesulide prescriptions on other non steroidal anti-inflammatory drugs (NSAIDs). The expected figures of hospitalisation for hepatopathies and UGIBs for all NSAIDs were calculated on the basis of risk estimates reported in two epidemiological studies. The result of the simulation suggests that the implementation of the restrictive actions might prevent 79 events of liver injuries, but might increase UGIBs by 859 events. The simulation helped to clarify the effects on hepatopathies and UGIBs as a consequence of nimesulide restriction of use. Analogous simulations might be conducted when assuming regulatory actions.

Key words: nimesulide, adverse drug reaction, hepatotoxicity, upper gastrointestinal bleeding.

Riassunto (*Effetti delle misure restrittive europee della prescrizione di nimesulide: una simulazione su epatopatie e sanguinamenti gastrointestinali in Italia*). Nel 2002 e nel 2007 l'Agenzia Europea dei Medicinali (EMA) ha valutato un segnale di rischio di epatopatie associate all'uso di nimesulide. Nel 2007 sono state adottate misure restrittive nella prescrizione del farmaco in Europa. Nel febbraio 2010 l'EMA ha aperto una nuova procedura di arbitrato. Obiettivo del lavoro è valutare l'effetto delle misure restrittive della prescrizione di nimesulide e di ulteriori possibili misure regolatorie. Attraverso una simulazione è stato stimato il numero atteso di ospedalizzazioni per epatopatie e per sanguinamenti gastroduodenali (UGIB) in Italia, nel 2006 e 2009, tenendo conto di un possibile spostamento delle prescrizioni di nimesulide verso altri farmaci antinfiammatori non steroidei (FANS). La frequenza attesa di ospedalizzazione, prima e dopo le misure restrittive, è stata calcolata in base ai dati di due studi epidemiologici. I risultati suggeriscono che l'implementazione delle azioni regolatorie riguardanti la nimesulide potrebbe avere evitato 79 ricoveri per danno epatico, ma avere incrementato i ricoveri per UGIB di 859 casi. La simulazione contribuisce a chiarire gli effetti su epatopatie e sanguinamenti gastroduodenali come conseguenza delle misure restrittive nella prescrizione di nimesulide. Valutazioni simili dovrebbero essere condotte quando si adottano misure limitative nell'uso di farmaci.

Parole chiave: nimesulide, reazioni avverse ai farmaci, epatotossicità, sanguinamenti gastroduodenali.

BACKGROUND

In 2002 the European Medicines Agency (EMA, now EMA) started a referral on nimesulide, after an alarm signal raised in Finland and subsequently in Spain. In these countries a greater risk of hepatopathies among users of nimesulide, in comparison

with other non steroidal anti-inflammatory drugs (NSAIDs), was observed (in Finland the risk was estimated to be around 100 times greater for nimesulide).

A retrospective cohort study conducted in Italy showed that the overall risk of hospitalisation for hepatopathy among current users of NSAIDs was

low (30 cases per 100 000 person/years). The estimated increased hepatotoxic risk of nimesulide in comparison with other NSAIDs ranged from 1.3 (95% CI: 0.7-2.3), when all the hepatopathies were taken into account, to 1.9 (95% CI: 1.1-3.8), for more severe events [1]. The study, even though supporting the hypothesis of an increased risk of nimesulide, did not confirm the magnitude of the signal reported by Finland and Spain. Moreover, it was also compatible with the spontaneous reporting data recorded in France, Portugal and Italy, where no specific risk of nimesulide was highlighted.

In May 2007, the Irish Medicines Board (IMB) was made aware of a retrospective review, performed by the Irish National Liver Transplant Unit, describing three new cases of fulminant hepatic failure among users of nimesulide (occurred from January 1994 to February 2007), requiring liver transplantation [2]. The IMB suspended the marketing authorisation of nimesulide systemic formulations in Ireland and opened at the EMA a procedure, according to the article 107 of the Directive 2001/83/EC.

In the absence of new studies aimed at comparing the hepatotoxicity of different NSAIDs, the debate mainly focused on a re-analysis of spontaneous reporting data. "The Committee for Human Medicinal Products (CHMP) concluded that the benefit-risk of nimesulide continues to be positive and recommended the maintenance of the marketing authorisation, but that there is a need to restrict its use" [3]. The CHMP also suggested that the maximum allowed duration of therapy for marketed packages should not exceed 15 days. The European Commission reinforced the restrictions by limiting nimesulide prescription as second line therapy.

In February 2010 the CHMP decided, upon request of the European Commission, a new referral procedure, with the aim to perform a full assessment of the benefits and risks of nimesulide containing products, "because of ongoing concerns over their gastrointestinal and hepatic safety" [4].

Regulatory measures, ranging from further restrictive actions to the withdrawal of nimesulide from the European market, can be foreseen as possible options. As in other therapeutic areas in which many alternative drugs share a similar efficacy profile, the switching of nimesulide prescriptions towards available alternatives is the expected effect. Different risk profiles need to be compared to estimate the expected effect of the regulatory actions. In case of nimesulide, the hepatotoxic risk should be analysed in the context of other potential risks, and in particular of gastroduodenal damage, which represent the most frequent adverse drug reaction (ADR) related to NSAIDs use. The need for a comprehensive evaluation is specifically relevant in Italy, where nimesulide is one of the most prescribed NSAIDs.

To evaluate the effects of the regulatory measures concerning nimesulide on the overall number of hospitalisations for hepatopathies and upper gastroin-

testinal bleedings (UGIBs) in Italy, we carried out a simulation.

The objective of this paper is to present the results of our simulation before and after the regulatory actions adopted in Europe as a consequence of the referral concluded in 2007, and to estimate the potential effect of further actions which may be adopted.

MATERIALS AND METHODS

The expected figures of hospitalisation for hepatopathies and UGIBs were calculated on the basis of risk estimates reported in two epidemiological studies [1, 5].

Total defined daily doses (DDD) and person-years of utilisation were calculated for each NSAID, using prescriptions issued in Italy in 2006 (the year preceding the restrictive regulatory measures) and in 2009. Overall sales data of all oral NSAIDs (public and private purchase) were obtained from the Italian National Observatory for Pharmaceutical Use (Osservatorio Nazionale sull'Impiego dei Medicinali, OsMed). Injective and topical formulations, as well as Over the Counter drugs, were not included in the analysis.

With regard to hepatopathies we considered the incidence data of a cohort study conducted in the Umbria Region, Italy [1]. Expected numbers of all hepatotoxic events, and of liver injuries (values of Alanine transaminase – ALT – or of total bilirubin >2 times upper normal value) were obtained by multiplying the person-years of NSAIDs use in Italy by the incidence rates observed in the study.

As for UGIBs we adopted the findings of the Laporte study, a multicenter case-control study conducted in Italy and Spain in the same years [5]. Expected numbers of events were obtained by multiplying the odds ratios estimated in the study by the baseline incidence rate in the population (100 per 100 000 person-years) by the person-years of NSAIDs use in Italy. The baseline incidence rate of UGIBs derived from literature data [6] and was in accordance with the Laporte study.

Since no risk data were available for some of the NSAIDs, only the substances with at least one estimate of hospitalisation risk for either hepatopathy or UGIB were included in the analysis. For the remaining NSAIDs, namely substances without specific risk estimates, we adopted the average risk of the NSAIDs included in the analysis (Coxibs were not included because in the Laporte study only rofecoxib, which was subsequently withdrawn, was evaluated). The total number of expected events among all users of NSAIDs was obtained by dividing the estimated number of hepatopathies and UGIBs of the NSAIDs, for which individual estimates were available, by the proportion of total person-years of marketed NSAIDs.

RESULTS

Around 2 300 000 person-years of NSAIDs use (39 DDDs per 1000 inhabitants-die), of which 1 066 000 of

nimesulide, were prescribed in Italy in 2006 (*Table 1*). In 2009, two years after the adoption of the restrictive actions, there was a decrease in the prescription of nimesulide (around 45%), whereas a 8% decrease of the overall prescription of NSAIDs was observed. The prescription of nimesulide mainly shifted towards ketoprofen (+ 93%).

For the NSAIDs for which individual risk data were available, 692 events of hepatopathy were estimated in 2006 and 627 in 2009. Taking into account that the individual NSAIDs included in the analysis represent a proportion of total NSAIDs use (87.8% and 88.6% in 2006 and 2009 respectively), the overall expected number of hospitalisations for hepatopathy in Italy could be estimated at 788 in 2006 and 708 in 2009 (*Table 2*).

The same procedures were adopted for calculating the expected number of liver injuries: a total of 673 events could be estimated in 2006 and 594 in 2009. As for UGIBs, the total number of events would be 12 315 in 2006 and 13 174 in 2009.

As a consequence, the result of the simulation suggests that the implementation of the restrictive actions adopted in 2007 might have caused the prevention of 79 events of liver injuries and the increase of 859 events of UGIBs.

DISCUSSION

This simulation was carried out to present and discuss the potential implication of regulatory actions on public health. Specifically, the simulation was intended to clarify the consequences in terms of safety of the regulatory restrictions concerning

nimesulide which were adopted on the basis of its potential greater hepatotoxicity in comparison with other NSAIDs.

The estimates were obtained adopting the risk figures of hepatopathy and of gastrointestinal bleeding associated with NSAIDs use, reported in two epidemiological studies [1, 5]. The findings suggest that the shifting of nimesulide prescription observed in Italy between 2006 and 2009 might have been associated with an increase of 11 events of UGIBs for each event of liver injury that was prevented.

Three reasons can explain our findings: 1) the “basal” incidence of UGIBs in the population is greater than that of hepatopathies; 2) nimesulide can be classified among the NSAIDs showing average-low risk of UGIBs; and 3) the prescription pattern of NSAIDs in Italy includes a high proportion of substances which can be considered among average-high risk profile of UGIBs.

In 2007, in contributing to the Italian position that was presented to the CHMP, we acknowledged that if the prescription of nimesulide shifted towards low-gastrotoxic NSAIDs, no (or limited) changes would be expected in the number of UGIB events. However, our assumption that the decrease in nimesulide use would be distributed proportionally among all the remaining NSAIDs, and not only among the less gastrotoxic ones was, as confirmed by the 2009 prescription, a reasonable assumption.

In our opinion, it is questionable to adopt a restrictive measure whose positive impact on the health of the population is conditional on the successful adoption of measures aiming at modifying the prescrip-

Table 1 | *Non steroidal anti-inflammatory drugs (NSAIDs) exposure in Italy and risk of hepatopathies and of upper gastrointestinal bleedings*

	Sales data 2006	Sales data 2009	All hepatopathies	Liver injuries ^(a)	Upper gastrointestinal bleedings
	Person-years	Person-years	Rates per 100 000 person-years [1]	Rates per 100 000 person-years [1]	Odds ratio [5]
Nimesulide	1 066 161	583 951	35.2	33.1	3.2
Ketoprofen	263 897	508 699	25.2	20.2	10.0
Diclofenac	240 659	286 596	39.2	22.4	3.7
Naproxen	114 782	125 225	25.5	12.8	10.0
Ibuprofen	106 873	203 597	44.6	44.6	3.1
Piroxicam	104 385	70 764	22.7	13.6	15.5
Meloxicam	81 099	57 895	23.6	-	5.7
Aceclofenac	74 280	73 747	-	-	1.4
Flurbiprofen	20 031	18 142	97.8	97.8	-
Ketorolac	15 709	14 053	66.8	33.4	24.7
Indometacine	13 830	14 033	-	-	10.0
Cinnoxicam	8 614	2 067	64.9	64.9	-
Dexketoprofen	3 012	1 185	-	-	4.9
Other NSAIDs	190 150	152 104	-	-	-
Total	2 303 481	2 112 059			

^(a)The rates of liver injuries are also included in the category of all hepatopathies.

Table 2 | Expected number of hospitalisations for hepatopathies and upper gastrointestinal bleedings associated to non steroidal anti-inflammatory drugs (NSAIDs) use in Italy (2006 and 2009)

	All hepatopathies		Liver injuries ^(a)		Upper gastrointestinal bleedings	
	2006	2009	2006	2009	2006	2009
Nimesulide	375	206	353	193	3 412	1 869
Ketoprofen	67	128	53	103	2 639	5 087
Diclofenac	94	112	54	64	890	1 060
Naproxen	29	32	15	16	1 148	1 252
Ibuprofen	48	91	48	91	331	631
Piroxicam	24	16	14	10	1 618	1 097
Meloxicam	19	14	-	-	462	330
Aceclofenac	-	-	-	-	104	103
Flurbiprofen	20	18	20	18	-	-
Ketorolac	10	9	5	5	388	347
Indometacine	-	-	-	-	138	140
Cinnoxamic	6	1	6	1	-	-
Dexketoprofen	-	-	-	-	15	6
NSAIDs with risk data n (% of total NSAIDs) ^(b)	692 (87.8)	627 (88.6)	568 (84.3)	501 (84.3)	11 145 (90.5)	11 922 (90.5)
Other NSAIDs	96	81	105	93	1 170	1 252
Total	788	708	673	594	12 315	13 174

^(a)The number of liver injuries is also included in the overall number of hepatopathies.

^(b)The proportion refers to the NSAIDs presenting risk data in Table 1.

tive behaviour of physicians (or on similar favourable circumstances). This “best scenario” approach has an even more critical implication: that the “average-case” scenario (not to mention the “worst-case” one) is assumed to carry an “average risk” of UGIB events which is greater after the implementation of the regulatory restrictions.

The simulation presents important limitations. In particular, it should be mentioned that our estimates are based on the findings of only two epidemiological studies: one for hepatotoxic risk (the only available study in which the hepatotoxicity of nimesulide has been compared with that of other NSAIDs), and one for gastrointestinal bleedings (a very large multicenter case-control study, conducted in the same period in Italy).

It is consequently possible that further epidemiological studies may provide different estimates of the relative toxicity of nimesulide in comparison with other NSAIDs. However, the Laporte study confirms a higher risk for some NSAIDs (*e.g.* ketorolac, piroxicam), and an average-high risk for others (*e.g.* ketoprofen). The estimates of the gastroduodenal toxicity observed in the Laporte study are coherent, at least with regard to the risk ranking of the different NSAIDs, with other epidemiological studies also conducted in Italy [7, 8] in different periods.

In 2007 a case-control study investigating the gastroduodenal toxicity of NSAIDs in Finland was published [9]. The semi-selective NSAIDs included in the analysis (mainly represented by meloxicam and nimesulide) appeared to carry a risk of GI

events greater than non-selective NSAIDs (mainly represented by diclofenac, ibuprofen, indomethacin, ketoprofen, naproxen and piroxicam). However, in order to reduce potential bias “caused by any NSAID use prior to current use, the analysis was repeated among patients whose only NSAID prescription during the year preceding the index date was the current one (new current users)” [9]. Among the six non-selective and semi-selective NSAIDs included in the analysis (ibuprofen, ketoprofen, naproxen, diclofenac, meloxicam and nimesulide), ibuprofen was the least gastrototoxic NSAID followed by nimesulide (with other NSAIDs showing higher odds ratios). Given the low level of exposure no comparison could be made with other non-selective NSAIDs such as piroxicam [9].

Again, even this study, conducted in a different population, supports the finding that nimesulide may carry a lower-than-average risk of gastroduodenal toxicity in comparison with other NSAIDs (as reported in the Laporte’s study), which explains the greater number of UGIB events that were potentially associated with the shifting of the prescription from nimesulide to other NSAIDs in the simulation.

With regard to patient safety, the comparison between liver injuries and digestive haemorrhages is an unquestionably complex task. Fulminant hepatitis is a very severe event, which may occur in a very small proportion of hepatopathies. In the cohort study conducted in the Umbria Region, the hospitalisation for hepatopathy among NSAIDs users in a population of more than 800 000 inhabitants,

followed during a five years period, was analysed. Out of a total of 780 000 person-years (current, recent and past use) included in the analysis, and 177 hospitalisations for hepatopathy, no cases of fulminant hepatitis were observed [1].

A survey related to the period 2001 – May 2007 was conducted on all Italian transplant centres by the Pharmacovigilance Unit of the Italian Medicines Agency (one of the authors, MV, was at the time the Head of the Pharmacovigilance Unit). Out of 21 centres that answered to the questionnaire, only one reported 3 cases of liver transplantation possibly associated to nimesulide use [10]. Since 2007, no fatal cases nor liver transplantations were reported to the Italian pharmacovigilance system.

The hospitalisation for gastrointestinal bleeding also represents a very severe event, potentially fatal. In two population-based studies, reported by Lanas *et al.*, the estimated proportion of fatal events among patients hospitalized for UGIB was around 5% [11]. Given the already higher incidence of hospitalisation for UGIBs in comparison with hepatopathies, the effect of a possible increase of UGIBs should not be underestimated.

The consequences of regulatory decisions should be considered in the light of the actual market, which for NSAIDs includes in Italy more than twenty different substances, rather than an ideal world where only a handful of first choice NSAIDs were available.

It is important to emphasise that the discussion does not concern the selection of first choice NSAIDs. If this were the case, we would share the common suggestion to consider substances such as diclofenac, ibuprofen, and naproxen, as reference NSAIDs in general practice. We are also aware that our simulation would be irrelevant in countries where the great majority of NSAID use is represented by less gastrototoxic NSAIDs.

However, whereas changing in prescription behaviour may be mainly promoted through audit initiatives, regulatory actions should not imply the concomitant diffusion of more appropriate practices. We deem that the simulation helped to clarify the effects on hepatopathies and UGIBs in Italy as a consequence of the regulatory restrictions concerning nimesulide. A similar exercise might be conducted in case further regulatory restrictive actions are expected to be adopted.

Acknowledgments

We thank Roberto Raschetti and Carmela Santuccio for their useful comments.

Conflict of interest statement

No conflict of interest to declare: all authors are employed by public institutions; no contribute of any kind was provided to the authors by any pharmaceutical companies.

Received on 12 March 2010.

Accepted on 8 April 2010.

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