Cohort study of hepatotoxicity associated with nimesulide and other non-steroidal anti-inflammatory drugs

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Abstract

Objective To estimate the risk of acute hepatotoxicity associated with nimesulide compared with other non-steroidal anti-inflammatory drugs.
Design Retrospective cohort and nested case-control study.
Setting Umbria region, Italy.
Participants 400 000 current, recent, and past users (almost 2 million prescriptions) of non-steroidal anti-inflammatory drugs between 1 January 1997 and 31 December 2001.
Main outcome measures Admissions to hospital for acute non-viral hepatitis and incidence of all hepatopathies and liver injury among users of nimesulide and other non-steroidal anti-inflammatory drugs.
Results Current use of non-steroidal anti-inflammatory drugs was associated with a 1.4 (95% confidence interval 1.0 to 2.1) increased risk of hepatopathy compared with past use. In current users of nimesulide the rate ratio for all hepatopathies and more severe liver injury was 1.3 (0.7 to 2.3) and 1.9 (1.1 to 3.8), respectively.
Conclusion The risk of liver injury in patients taking nimesulide and other non-steroidal anti-inflammatory drugs is small.

Introduction

Nimesulide, a non-steroidal anti-inflammatory drug, is marketed in more than 50 countries. In March 2002, Finland suspended the marketing of nimesulide because of an associated high frequency of hepatotoxicity.[1] Spain followed in May 2002, but not other European countries, such as Italy and France.[2–5] Nimesulide is the most prescribed non-steroidal anti-inflammatory drug in Italy and Portugal, with Italy accounting for half the worldwide market. We compared the incidence of acute hepatotoxicity associated with nimesulide and other non-steroidal anti-inflammatory drugs.

Methods

During 1997-2001 we carried out a retrospective cohort study in the Umbria region of Italy, with a population of around 835 000. Patients were enrolled if they had received at least one prescription for a non-steroidal anti-inflammatory drug within the national health service between 1 January 1997 and 31 December 2001. (The monitoring system that provided the information on use included only prescriptions issued within the health service; private purchase is therefore not captured in the cohort). In Italy most commonly prescribed non-steroidal anti-inflammatory drugs are also available as over the counter products—for example, diclofenac, ketoprofen, piroxicam, naproxen, ibuprofen—but prescription only non-steroidal anti-inflammatory drugs are often purchased privately.

Drug use was defined as current according to the duration of the prescription (in defined daily doses) plus two weeks; recent for the 90 days after the end of the current period; and past use for the days up to 12 months after the prescription date. If a new prescription of the same drug occurred during the current period, time of use continued to accumulate in the particular category. When different non-steroidal anti-inflammatory drugs were dispensed in consecutive overlapping intervals of current use, time after the new prescription was allocated to the mixed use category.

Potential cases were all admissions to hospital for acute non-viral hepatitis. Codes were retrieved for main or secondary diagnoses according to ICD-9 (international classification of diseases, 9th revision) from the regional archive of hospital discharges: hepatitis, unspecified (573.3), acute and subacute necrosis of liver (570), other specified disorders of biliary tract (576.8), other specified disorders of liver (573.8), unspecified disorders of liver (573.9). No information was available on patients admitted to hospital outside the Umbria region.

Information on medical history, concomitant clinical conditions, drug use during the six weeks before admission, and laboratory data were collected from the clinical records, blinded to exposure status. Patients were excluded if they had malignancies, viral or chronic hepatitis, lithiasis of common biliary tract, a cholecystectomy performed during the admission to hospital included in the study, or normal liver function.

Abnormal liver function was defined as any increase between the upper limit of normal range and twice the upper limit of normal for alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, or total or conjugated bilirubin. Liver injury was defined as the increase over twice the upper limit of normal for alanine aminotransferase or conjugated bilirubin, or a combined increase of aspartate aminotransferase, alkaline phosphatase, and total bilirubin, provided one of them was above twice the upper limit of normal.[6–8] To also include more severe cases we restricted the analysis to increases over five times the upper limit of normal. Information on liver tests was available for all cases.

A nested case-control study was carried out to control for potential confounders: use of any other drug (different from non-steroidal anti-inflammatory drugs) during the 30 days before admission and number of prescriptions for non-steroidal anti-inflammatory drugs during the current period (one and more than one packet). For each case we randomly selected 20 controls from the cohort, matched for sex and age (difference of one year). The date of admission for cases was the index date for the matched controls. Use of

non-steroidal anti-inflammatory drugs at the index date for both cases and controls was defined as current, recent, or past, as in the cohort analysis.

Incidence was calculated by dividing the number of cases in each category of use by the corresponding person years of non-steroidal anti-inflammatory drug use. Poisson regression was used to control for the confounding effect of age and sex in the cohort study. Conditional logistic regression was used for the analysis of the case-control study. The analysis was performed with SAS (version 8.00) and SPSS (version 10.0.7) software.

Results

Between 1997 and 2001 around 2 million prescriptions for non-steroidal anti-inflammatory drugs were issued within the national health service in Italy and were included in our study. Nimesulide was the most prescribed drug (551 000 prescriptions). The characteristics of users of the different non-steroidal anti-inflammatory drugs were similar (table 1). Most of the prescriptions were related to short term treatment (1.2 packets per prescription for nimesulide and 1.3 for other non-steroidal anti-inflammatory drugs).

The 397 537 participants who received at least one prescription for a non-steroidal anti-inflammatory drug contributed to more than 770 000 person years (current use, 141 000 person years; recent use, 254 000 person years; past use, 378 000 person years; see table 1).

We excluded 168 of 819 (20.5%) potential cases because of hepatopathy as a secondary diagnosis and concomitant malignancy (figure). Of the remaining 651 clinical records, 568 (87.3%) were retrieved. Non-retrieved potential cases (12.7%) were proportionally distributed over the study drugs. In total, 392 patients were excluded.

Forty two of the 176 cases of hepatopathy included in the final analysis occurred during current use of a non-steroidal anti-inflammatory drug (incidence 29.8 per 100 000 person years). Compared with the incidence for past use (18.2), we estimated a rate ratio (adjusted for age and sex) of 1.4 (95% confidence interval 1.0 to 2.1). This ratio increased among elderly participants: after taking into account the effect of sex and current use of non-steroidal anti-inflammatory drugs, those aged over 75 had a 5.7-fold increase in the risk of hepatopathy compared with people under 45. The risk of hepatopathy in males was increased by 1.5 (1.2 to 2.2) compared with females (table 2).

The risk of hepatopathy among current users of nimesulide was slightly higher than for other non-steroidal anti-inflammatory drugs (rate ratio 1.3, 0.7 to 2.3). When the analysis was restricted to patients with liver injury this ratio was 1.7 (0.9 to 3.3). When only more severe diagnoses were included in the analysis, the rate ratio among users of nimesulide was 1.9 (1.1 to 3.8; table 3). For use of individual non-steroidal anti-inflammatory drugs compared with past use, the increase in the incidence of liver injury was 2.2 (1.3 to 3.9) for nimesulide and 1.5 (0.7 to 3.2) for diclofenac, the second most prescribed non-steroidal anti-inflammatory drug (table 4). The number of events for individual non-steroidal anti-inflammatory drugs was too small to allow for comparison of risks.

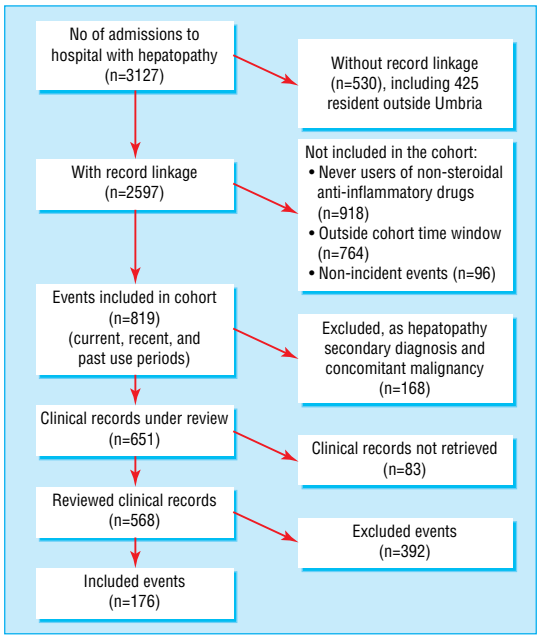
Table 1 Characteristics of users of non-steroidal anti-inflammatory drugs (NSAIDs) and details of prescriptions, Umbria region, 1997-2001

Characteristic	Nimesulide	Other NSAID	Any NSAID
No of users*	187 312	341 554	397 537
Median age	61	62	61
Male to female ratio†	0.7:1	0.8:1	0.8:1
No of prescriptions	551 000	1 400 000	1 951 000
No of packets	636 000	1 857 000	2 492 000
Defined daily dose	9 535 000	24 998 000	34 533 000
No of prescriptions per user	2.9	2.2	2.4
No of packets per prescription	1.2	1.3	1.2
Current use (person years):			
Single	38 300	84 411	122 711
Mixed	9 994	18 125	18 125
Total	48 294	102 536	140 836

*129 334 participants received a prescription for both nimesulide and other NSAID (concomitantly (mixed use) or in different time periods). Person time of mixed use of nimesulide also contributes to person time of mixed use of other NSAID.
†Ratios of users of single NSAIDs are similar. However, ratio is higher when NSAIDs are taken as group (with or without nimesulide) because females received more NSAIDs (different substances) than males and thus contribute less in total group than in partially overlapping subgroups.

The analysis carried out in the nested case-control study confirmed the risk estimates of the cohort analysis. The odds ratio of liver injury developing among users of nimesulide compared with users of other non-steroidal anti-inflammatory drugs was 1.9 (0.6 to 5.6), after controlling for prescriptions of other drugs received in the 30 days before admission to hospital (index date) and for number of prescriptions for non-steroidal anti-inflammatory drugs. Those who received drugs during the 30 days had a twofold increased risk (adjusted odds ratio 2.0, 0.6 to 6.6). No effect was associated with number of prescriptions for non-steroidal anti-inflammatory drugs during the current period (0.7, 0.3 to 1.9).

Among current users, the median interval between prescription for a non-steroidal anti-inflammatory drug and admission to hospital was 11 days, and only two of the 42 patients took the drugs for more than



Flow of participants through trial

Table 2 Incidence of admissions to hospital for hepatopathy, and rate ratios according to drug use, age, and sex

Characteristic	Person years	All hepatopathies			Liver injury		
		No of events	Rates per 100 000 person years	Adjusted rate ratio* (95% CI)	No of events	Rates per 100 000 person years	Adjusted rate ratio* (95% CI)
Category of use:							
Current	140 836	42	29.8	1.4 (1.0 to 2.1)	33	23.4	1.4 (0.9 to 2.1)
Recent	254 467	65	25.5	1.4 (1.0 to 2.0)	46	18.1	1.3 (0.9 to 1.9)
Past	378 433	69	18.2	1	56	14.8	1
Age (years):							
<45	150 849	11	7.3	1	9	6.0	1
45-54	127 284	14	11.0	1.5 (0.7 to 1.3)	10	7.9	1.3 (0.7 to 3.3)
55-64	156 046	41	26.3	3.6 (1.9 to 7.4)	29	18.6	3.1 (1.5 to 6.6)
65-74	192 993	45	23.3	3.2 (1.6 to 6.1)	34	17.6	2.9 (1.4 to 6.1)
⩾75	146 542	65	44.4	5.7 (3.0 to 11.0)	53	36.2	5.6 (2.8 to 11.0)
Sex:							
Male	311 531	88	28.2	1.5 (1.2 to 2.2)	68	21.8	1.7 (1.2 to 2.3)
Female	462 182	88	19.0	1	67	14.5	1

*Rate ratios for non-steroidal anti-inflammatory drug use adjusted for age and sex; rate ratios for age adjusted for sex and current use of non-steroidal anti-inflammatory drug; rate ratios for sex adjusted for age and current use of non-steroidal anti-inflammatory drug.

60 days. No fulminant hepatitis was observed. Among patients with liver injury a trend towards the normalisation of liver function (a positive dechallenge) could be assessed in 12 users of nimesulide (75%) and in 13 users of other non-steroidal anti-inflammatory drugs (65%). In the remaining patients there was either no follow up information or the length of stay was too small for comparisons (inconclusive dechallenge) (table 5).

Some patients admitted to hospital for liver injury received one or more prescriptions for the same drug after discharge: eight (50%) for current users of nimesulide (either alone or mixed use) and five (25%) for current users of other non-steroidal anti-inflammatory drugs. No participants were readmitted to hospital.

Three deaths occurred among current users (diclofenac, nimesulide, and piroxicam). Cause of death was considered unrelated to liver injury: one patient had normalisation of liver function and the other two had cardiac failure, but no worsening of hepatopathy.

Table 3 Incidence of admissions to hospital for hepatopathy, and rate ratios among current users of nimesulide and other non-steroidal anti-inflammatory drugs by severity of hepatopathy

Events	No of events*	Rate per 100 000 person years†	Adjusted rate ratio‡ (95% CI)
All hepatopathies (n=42)			
Nimesulide	17	35.2	1.3 (0.7 to 2.3)
Other non-steroidal anti-inflammatory drugs	29	28.3	1
Liver injury (n=33)§			
Nimesulide	16	33.1	1.7 (0.9 to 3.3)
Other non-steroidal anti-inflammatory drugs	20	19.5	1
More severe liver injury (n=28)¶			
Nimesulide	14	29.0	1.9 (1.1 to 3.8)
Other non-steroidal anti-inflammatory drugs	16	15.6	1

All hepatopathies includes abnormal liver function and liver injury.
*Patients who received both nimesulide and other non-steroidal anti-inflammatory drugs during current period (mixed use) are counted in both groups.
†Person years of exposure to nimesulide and other non-steroidal anti-inflammatory drugs are 48 294 and 102 536, respectively.
‡Adjusted for age and sex.
§Twice upper limit of normal range
¶Five times upper limit of normal range

Discussion

The risk of hepatopathy among patients taking non-steroidal anti-inflammatory drug is small. Despite its withdrawal in Finland and Spain because of reported hepatotoxicity, nimesulide was associated with only a small increased risk. The main risk factor for hepatotoxicity is age.

One strength of our study was that we followed a general population, in which almost 2 million prescriptions for non-steroidal anti-inflammatory drugs were issued during a five year period. Limitations of our study were that drug use was estimated through a prescription monitoring system, and no information was available on the actual use of the drugs, such as indications and dosage. A proxy for this information was the number of packets prescribed and the defined daily dose for each user. It seems that both nimesulide and other non-steroidal anti-inflammatory drugs are used as short term treatments. It is possible that confounding by indication may play a part in our study. The indications for prescription within the Italian national health service are the same for nimesulide and other non-steroidal anti-inflammatory drugs. Moreover, the users of both nimesulide and other non-steroidal anti-inflammatory drugs were similar, inferred from age, sex, expected duration of prescription, and concomitant prescriptions.

Our findings are consistent with available evidence. A cohort study in Canada concerned 1.5 million prescriptions for non-steroidal anti-inflammatory drugs.[9] In our study, 16 current users of non-steroidal anti-inflammatory drugs were admitted to hospital for acute liver injury, which corresponds to a rate of 9 per 100 000 person years and 1 per 100 000 prescriptions. We found a high incidence of hepatopathy, but if the number of prescriptions is taken as the denominator, the incidence of liver injury is 1.7 per 100 000 prescriptions, similar to the Canadian study.

The largest study to date is based on 2.1 million prescriptions for non-steroidal anti-inflammatory drugs from British general practitioners.[10] Out of the 23 patients with acute liver injury (1.1 per 100 000 prescriptions), eight were admitted to hospital (0.4 per 100 000). The age range of the 23 cases was between

Table 4 Incidence of admission to hospital for hepatopathies and for liver injury, and rate ratios, among current users of non-steroidal anti-inflammatory drugs*

Drug	Current use (person years)	All hepatopathies: No of events	All hepatopathies: Rates per 100 000 person years	All hepatopathies: Crude rate ratios (95% CI)	Liver injury: No of events	Liver injury: Rates per 100 000 person years	Liver injury: Crude rate ratios (95% CI)
Nimesulide	48 294	17	35.2	1.9 (1.1 to 3.3)	16	33.1	2.2 (1.3 to 3.9)
Diclofenac	35 760	14	39.2	2.1 (1.2 to 3.8)	8	22.4	1.5 (0.7 to 3.2)
Piroxicam	22 051	5	22.7	1.2 (0.5 to 3.1)	4	13.6	1.2 (0.4 to 3.4)
Ketoprofen	19 848	5	25.2	1.4 (0.6 to 3.4)	4	20.2	1.4 (0.5 to 3.8)
Ketorolac	5992	4	66.8	3.7 (1.3 to 10.0)	2	33.4	2.3 (0.6 to 9.2)
Ibuprofen	4482	2	44.6	2.4 (0.6 to 10.0)	2	44.6	3.0 (0.7 to 12.4)
Naproxen	7833	2	25.5	1.4 (0.3 to 5.7)	1	12.8	0.9 (0.1 to 6.2)
Celecoxib	6619	1	15.1	0.8 (0.1 to 6.6)	1	15.1	1.0 (0.1 to 7.3)
Meloxicam	4232	1	23.6	1.3 (0.2 to 8.1)	—	—	—
Cinnoxicam	1541	1	64.9	3.6 (0.2 to 12.5)	1	64.9	4.4 (0.3 to 13.7)
Flurbiprofen	1022	1	97.8	5.4 (0.3 to 14.9)	1	97.8	6.6 (0.3 to 13.4)
Past use	378 433	69	18.2	1.0	56	14.8	1.0

*Non-steroidal anti-inflammatory drugs with at least one event among current users shown.
Patients who received more than one non-steroidal anti-inflammatory drug during current period (mixed use) are included in counts of each subsequent drug.

26 and 80, whereas the age range of our patients was between 27 and 96, with almost 50% of the patients older than 80.

In Finland, spontaneous reporting of adverse effects associated with nimesulide reached more than 100 per 100 000 person years. The corresponding incidence for other non-steroidal anti-inflammatory drugs was less than 1 per 100 000 person years. In Spain, nimesulide was associated with the highest spontaneous reporting rate for hepatopathy (9.37 cases per million packets).[3] A large variability in reporting rates for other non-steroidal anti-inflammatory drugs has been observed, which is often the case with spontaneous reporting systems.

We found only a small increase in the risk associated with nimesulide, consistent with observations in other countries, such as Italy, France, and Portugal. In these countries the reporting of hepatotoxicity was similar for nimesulide and other non-steroidal anti-inflammatory drugs.

The potential mechanism of hepatotoxicity associated with nimesulide is unknown. It has been suggested that symptomatic hepatic effects of most non-steroidal anti-inflammatory drugs are usually mild.[11] In most of the patients in our study admitted to hospital because of liver injury, there was evidence of a trend towards the normalisation of liver function. As with two other studies, no fulminant hepatitis was observed.[4,5] This suggests that some of the spontaneously reported cases of fulminant hepatitis attributed to non-steroidal anti-inflammatory drugs are linked to concomitant conditions that would lead to exclusions in epidemiological studies.

A final consideration is the need to evaluate the overall risk profile of non-steroidal anti-inflammatory drugs, particularly the risk of serious gastroduodenal complications (bleeding and perforation), which are almost 10 times higher than hepatotoxicity. The incidence of admission to hospital for bleeding or perforation among non-users of non-steroidal anti-inflammatory drugs is around 100 events per 100 000 persons per year. Among users of non-steroidal anti-inflammatory drugs, assuming a relative risk of 4, around 400 events per 100 000 persons per year are expected, with around 300 extra cases per 100 000 persons per year.[12,13] In three observational studies in Italy, nimesulide was generally of average to low risk and other non-steroidal anti-inflammatory drugs, such as ketorolac and piroxicam, were more gastrotoxic.[14–16]

Table 5 Characteristics of patients with liver injury among current users of non-steroidal anti-inflammatory drugs (NSAIDs). Values are numbers (percentages) of patients unless stated otherwise

Characteristic	Nimesulide (n=16)	Other NSAIDs (n=20)
Median age	79	69
Male to female ratio	7:9	9:11
Other drugs (30 days before admission)	14 (87)	15 (75)
Median ratio*:		
Alanine aminotransferase	4.4	5.1
Median alkaline phosphatase	2.8	1.6
Dechallenge† (positive)	12 (75)	13 (65)
Dechallenge (inconclusive)	4 (25)	7 (35)
Rechallenge	8 (50)	5 (25)
Deaths	1 (6)	2 (8)

Three patients who received both nimesulide and other NSAIDs during the current period (mixed use) are counted in both groups. In six patients the liver injury was hepatocellular, in 13 it was cholestatic, and in 14 it was mixed.[6]
*Ratio between maximum value and upper normal limits.
†Normalisation of liver function before discharge.

What is already known on this topic

Liver injury is a rare class effect of non-steroidal anti-inflammatory drugs

An increased risk of hepatotoxicity with nimesulide was suggested by spontaneous reports

A procedure has been set up in Europe for the re-evaluation of the risk profile of nimesulide

What this study adds

The risk of hepatopathy among patients taking non-steroidal anti-inflammatory drugs, including nimesulide, is small

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Prospective observational cohort study of time saved by prehospital thrombolysis for ST elevation myocardial infarction delivered by paramedics

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Abstract

Objectives To evaluate a system of prehospital thrombolysis, delivered by paramedics, in meeting the national service framework's targets for the management of acute myocardial infarction.
Design Prospective observational cohort study comparing patients with suspected acute myocardial infarction considered for thrombolysis in the prehospital environment with patients treated in hospital.
Setting The catchment area of a large teaching hospital, including urban and rural areas.
Participants 201 patients presenting concurrently over a 12 month period who had changes to the electrocardiogram that were diagnostic of acute myocardial infarction or who received thrombolysis for suspected acute myocardial infarction.
Main outcome measures Time from first medical contact to initiation of thrombolysis (call to needle time), number of patients given thrombolysis appropriately, and all cause mortality in hospital.
Results The median call to needle time for patients treated before arriving in hospital (n=28) was 52 (95% confidence interval 41 to 62) minutes. Patients from similar rural areas who were treated in hospital (n=43) had a median time of 125 (104 to 140) minutes. This represents a median time saved of 73 minutes ($P < 0.001$). Sixty minutes after medical contact 64% of patients (18/28) treated before arrival in hospital had received thrombolysis; this compares with 4% of patients (2/43) in a cohort from similar areas. Median call to needle time for patients from urban areas (n=107) was 80 (78 to 93) minutes. Myocardial infarction was confirmed in 89% of patients (25/28) who had received prehospital thrombolysis; this compares with 92% (138/150) in the two groups of patients receiving thrombolysis in hospital.
Conclusions Thrombolysis delivered by paramedics with support from the base hospital can meet the national targets for early thrombolysis. The system has been shown to work well and can be introduced without delay.

Introduction

Evidence of the benefits of early thrombolysis in the context of an acute myocardial infarction is overwhelming.[1 2 3 4] This is reflected in the national service framework for coronary heart disease in the adoption of a challenging standard "call to needle time" (from the initial call for help to treatment) of less than 60 minutes.[5]