PHARMACOEPIDEMIOLOGY AND DRUG SAFETY 2012
Published online in Wiley Online Library (wileyonlinelibrary.com) **DOI**: 10.1002/pds.3385

ORIGINAL REPORT

Risk of upper gastrointestinal complications in a cohort of users of nimesulide and other nonsteroidal anti-inflammatory drugs in Friuli Venezia Giulia, Italy[†‡]

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ABSTRACT

Purpose Information on the risk of upper gastrointestinal complications (UGIC) in users of nimesulide, the most used nonsteroidal anti-inflammatory drug (NSAID) in Italy, is scarce. In the context of the European regulatory review on nimesulide, we estimated and compared the risk associated with nimesulide and other individual NSAIDs with the risk in nonusers.

Methods We used 2001–2008 data from regional health databases in Friuli Venezia Giulia (FVG), Italy, to conduct a cohort and nested case–control study of users of NSAIDs. Cases were identified by specific and nonspecific hospital discharge diagnoses in primary and secondary position and validated through hospital records. Ten controls per case were selected using density-based sampling from the cohort. Conditional logistic regression was used to estimate adjusted relative risks (RRs) and 95% confidence intervals (CIs).

Results The cohort included 588 827 NSAIDs users and 3031 UGIC cases. Nonspecific codes contributed to 23% of cases and secondary codes to 5%. Among current users, IR per 1000 person-years decreased from 4.45 cases in 2001 to 2.21 cases in 2008. The RR (95%CI) for current use of NSAIDs was 3.28 (2.86, 3.76). RR was <2 for rofecoxib, celecoxib, and nimesulide; 2 to <5 for naproxen, ibuprofen, diclofenac, etoricoxib, and meloxicam; and ≥ 5 for ketoprofen, piroxicam, and ketorolac.

Conclusions IRs of UGIC in FVG decreased about 50% between 2001 and 2008. Nimesulide was in the low–medium range of RR. A complete ascertainment of UGIC cases in databases may require validation of nonspecific codes, secondary codes, and additional codes such as peritonitis and acute posthemorrhagic anemia. Copyright © 2012 John Wiley & Sons, Ltd.

KEY WORDS—nonsteroidal anti-inflammatory drugs; NSAIDs; selective COX-2 inhibitors; upper gastrointestinal complications; epidemiology; cohort studies; case–control studies; Friuli Venezia Giulia; pharmacoepidemiology

Received 13 March 2012; Revised 21 September 2012; Accepted 29 October 2012

INTRODUCTION

Nimesulide, a nonsteroidal anti-inflammatory drug (NSAID), is the most prescribed NSAID in Italy.[1] Nimesulide was subject of referrals by the European Medicine Agency, in 2002 and 2007, further to withdrawal of the marketing authorization in some countries due to concerns regarding its hepatic toxicity. The overall benefit/risk profile of nimesulide was evaluated in another referral initiated in 2010, where specific focus was requested to its gastrointestinal (GI) profile. These referrals resulted in restrictions of the indications and duration of treatment with nimesulide.

Although the GI safety of NSAIDs has been evaluated in many epidemiologic studies across numerous populations, data on nimesulide are scarce and dated. The most recent data come from two case–control

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[†]Preliminary results of this study have been presented at the ICPE 2011 (Castellsague et al., Pharmacoepidemiol & Drug Saf 2011; 20: S178; Pisa et al., Pharmacoepidemiol Drug Saf 2011; 20: S172) and are posted at the RTI-Health Solutions Web site (http://www.rtihs.org/request/index.cfm?fuseaction=display&PID=17608; http://www.rtihs.org/request/index.cfm?fuseaction=display&PID=17613).

[‡]All authors contributed in conceiving and planning their study or played an important role in the acquisition, analysis, and interpretation of the data; drafted or made substantive suggestions for revision of the manuscript; and approved the final submitted version.

studies, one conducted in Finland between 2000 and 2004[2] and the other in Italy and Spain between 1998 and 2001.[3] Three other studies were conducted in Italy in the 1990s.[4–6] Overall, for upper GI complications (upper gastrointestinal complication [UGIC]), the relative risk (RR) comparing current use of nimesulide with nonuse of any NSAID ranged from 2.5 (95% confidence interval [CI]: 1.2, 5.3) to 4.4 (95%CI: 2.5, 7.7).

Within the context of the European regulatory review on nimesulide, we conducted a retrospective cohort and nested case–control study in the region of Friuli Venezia Giulia (FVG), in Italy, to estimate incidence rates of UGIC in users and nonusers of NSAIDs and to compare the risk associated with the use of nimesulide and other NSAIDs with the risk in nonusers.

METHODS

Data source

The region of FVG maintains computerized information on the use of health services for its approximately 1.2 million residents. Information is recorded in several databases linked by a unique personal identifier. The Hospital Service Database contains data on hospitalizations in all public and private hospitals of the region since 1986. The information includes dates of admission and discharge, vital status at discharge, one primary diagnosis, and up to five secondary diagnoses. Diagnoses are recorded using the *Internal Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM). The Outpatient Prescription Database includes data from reimbursed prescription medications dispensed in the pharmacies of the region since 1995. The Patient Identification Database includes demographic and vital status information of all residents in FVG since 1970.

Study cohort

The study cohort included all residents in the FVG region with at least 1 year of permanent residence who were prescribed systemic NSAIDs between 1 January 2001 and 31 December 2008. We applied no exclusions to the study cohort to estimate incidence rates of UGIC in the general population. Each eligible member of the study cohort was followed from the first date the patient was prescribed an NSAID during the study period (the start date) to the earliest of the following dates: (i) hospitalization for UGIC, (ii) emigration from the region or disenrollment from database, (iii) end of study period, or (iv) death.

Case definition and identification

A case of UGIC was defined as a patient requiring hospitalization for hemorrhage, perforation, and/or obstruction located in the stomach and/or duodenum or a peptic ulcer causing bleeding, perforation, and/or obstruction confirmed by clinical evidence of hematemesis, melena, endoscopy, radiology, surgery, or autopsy. The index date was defined as the date of hospital admission. Potential cases were identified by primary and secondary discharge diagnoses. Both site- and lesion-specific ICD-9-CM codes and nonspecific codes were used. Specific codes were 531, gastric ulcer; 532, duodenal ulcer; 533, peptic ulcer; and 534, gastrojejunal ulcer. Nonspecific codes were 578.0, hematemesis; 578.1, blood in stool (melena); and 578.9, hemorrhage of GI tract, unspecified. A total of 4014 potential cases were identified using the primary discharge diagnosis and 6123 using the primary and secondary discharge diagnoses.

Case validation

Validation of potential cases was conducted through the review of hospital medical charts. Based on the results of a prior validation study,[7] we requested medical charts for a random sample of primary discharge codes 531 and 532 ($n = 108$) and all primary discharge codes 533, 534, and 578 ($n = 1947$ charts). In addition, we validated a random sample of charts with secondary codes for UGIC ($n = 458$). The data abstraction was conducted by seven trained abstractors using a computerized abstraction form. Review of the abstracted information involved five epidemiologists blinded to exposure status.

Of the 2513 charts requested, 2473 (98.4%) were obtained and reviewed. The positive predictive value (PPV) for primary discharge codes was 96.6% for code 531, 91.5% for code 532, 79.5% for code 533, 83.1% for code 534, and 40.2% for code 578. For secondary codes, the PPV was 34.7%. For the combination of secondary codes with a primary code for peritonitis (code 567.2 and 567.8) or acute posthemorrhagic anemia (code 285.1), the PPV was 83.3%. Further details on the validation of cases have been published elsewhere.[8] Based on these results, we included as final cases all cases identified with primary specific codes 531 ($n = 1079$) and 532 ($n = 963$); all cases identified with primary codes 533 ($n = 31$), 534 ($n = 112$), and 578 ($n = 697$) that were confirmed in the validation process; and all cases identified with the combination of a primary code for peritonitis ($n = 45$) or acute posthemorrhagic anemia ($n = 104$) and a secondary code for UGIC. A total of 3031 cases

DOI: 10.1002/pds

were considered final cases of UGIC. For the case–control analysis, we excluded cases and controls aged over 89 years ($n = 296$) to minimize the effect of potential outcome and exposure misclassification derived from increased fragility of elderly patients and potentially inaccurate or incomplete capture of individual prescriptions for residents of nursing homes.

Exposure definition

Time at risk for the effect of NSAIDs was classified in four mutually exclusive categories: current use, defined as the days of supply of a prescription (intended duration of treatment associated with a prescription); recent use, the 60 days following current use; past use, the 90 days following recent use; and nonuse, the remaining time after past use. Current use of each individual NSAID was further classified in three mutually exclusive categories: current single use, current use of only one individual NSAID without recent use of a different NSAID; current switching use, current use of only one NSAID with recent use of a different NSAID; and current multiple use, current use of more than one NSAID.

The days of supply of each prescription were estimated from descriptive analysis of consecutive prescriptions. We assumed a total of 15 days of supply for oral formulations and 7 days of supply for injectable formulations. We conducted sensitivity analyses using other estimates for days of supply: (i) 30 days for oral formulations and 15 days for injectable formulations, (ii) 7 days for both oral and injectable formulations, and (iii) quantity dispensed expressed in defined daily doses (DDDs).[5]

In the nested case–control analysis, exposure to NSAIDs was ascertained at the index date according to the days of supply of the last prescription as defined earlier. We defined the following exposure categories: (i) current use, when days of supply of the last prescription before the index date overlapped the index date; (ii) recent use, when days of supply ended within 60 days before the index date; (iii) past use, when days of supply ended between 61 and 150 days before the index date; and (iv) nonuse, when days of supply ended more than 150 days before the index date. We assessed the effect of dose and duration of use of NSAIDs among current single users. Dose was estimated as cumulative and daily dose. Cumulative dose was calculated as the total number of DDDs prescribed for each NSAID in the 3 months prior to the index date and was categorized as low–medium and high with the cut-off median number of DDDs (30 DDDs) for all NSAIDs aggregated. Daily dose was estimated as the total supply of the most recent prescription before the index date divided by 15 days (oral formulations) and by 7 days (injectables) of estimated supply. Daily dose was categorized as low–medium and high according to cut-off values used in prior studies. Duration of use was estimated as the total days of continuous treatment, allowing for a maximum gap of 60 days between the dispensing of prescriptions.

Nested case–control study

We conducted a nested case–control analysis to address the effect of confounding factors. We used density-based sampling to select 10 controls for each case identified in the study cohort.[9] Selected controls were eligible to become cases if they experienced UGIC during follow-up. The nested case–control analysis included 2735 cases of UGIC and 27 011 controls aged 20–89 years.

We used the hospitalization and the prescription databases to identify factors associated with the risk of UGIC, potential selective prescribing of individual NSAIDs, and general medical frailty.[10] Risk factors for UGIC included age; sex; history of peptic ulcer, other upper GI diseases, chronic liver diseases, and chronic alcoholism; and concurrent use of medications associated with the risk of UGIC. General medical frailty was assessed by a history of malignancy and severe chronic disease before the index date.

Analysis

Age- and sex-specific incidence rates and 95%CIs of UGIC were estimated for current use and nonuse of NSAIDs. Incidence rates were stratified by history of peptic ulcer and by calendar year. In the nested case–control analysis, we used conditional logistic regression to estimate crude and adjusted odds ratios for UGIC comparing current, recent, and past use of NSAIDs with nonuse. We report odds ratios as RRs because odds ratios are considered unbiased estimates of the incidence rate ratio when controls are selected independently of exposure status.[11]

We conducted subgroup analysis for new users of NSAIDs defined as those without any NSAID prescribed in the 365 days before the start date and for individuals without history of risk factors for UGIC. Effect measure modification was evaluated for the concurrent use of prescription aspirin, anticoagulants, and oral corticosteroids. Departure from additive models was evaluated by computing the relative excess risk due to interaction (RERI) and the synergy index.[12]

DOI: 10.1002/pds

The study was approved by the RTI International (North Carolina, United States) institutional review board and reviewed by the ethics committees of all hospitals in the FVG region that were asked for permission to access medical records for case validation.

RESULTS

The study cohort included 588 827 subjects who received 3 623 341 prescriptions for NSAIDs between 2001 and 2008. Nimesulide was the most frequently used NSAID (Table 1). The overall person-time of follow-up was 2 959 555 person-years, including 173 248 person-years of current use of NSAIDs, 398 385 person-years of recent use, 393 504 person-years of past use, and 1 994 419 person-years of nonuse. A total of 3031 cases of UGIC were included in the cohort analysis (Table 2). The most frequent type of complication was bleeding (86.9%), and the site of the lesion was gastric or duodenal in 83.5% of cases. The type of lesion was peptic ulcer in 79.0% of cases, erosions and inflammatory disorders in 7.6%, other lesions in 2.8%, and unknown in 10.7%. For validated cases ($n = 840$), 81.8% were confirmed by endoscopy, surgery, radiology, and/or autopsy. Among the cases confirmed by endoscopy ($n = 663$), 37.5% had evidence of bleeding (Forest I or Forest II lesions). A total of 153 cases (18.2%) were confirmed only by clinical evidence of melena and/or hematemesis. The overall 30-day case-fatality rate was 9.1%.

Incidence rates of UGIC

Incidence rates increased by age in users and nonusers of NSAIDs for both men and women (Figure 1). Among nonusers, the IR per 1000 person-years was 0.60 (95%CI: 0.55, 0.64) in women and 0.97 (95% CI: 0.90, 1.03) in men; among current users, the IR was 2.71 (95%CI: 2.41, 3.01) in women and 4.47 (95%CI: 3.92, 5.02) in men. Among patients without a history of peptic ulcer complications, the crude IR per 1000 person-years was 0.71 (95%CI: 0.67, 0.75) in nonusers and 3.02 (95%CI: 2.76, 3.28) in current users; among patients with history of UGIC, the IR was 6.26 (95%CI: 5.09, 7.43) in nonusers and 28.22 (95%CI: 20.48, 35.97) in current users (Figure S1). The overall IR per 1000 person-years decreased from 1.93 cases in 2001 to 0.74 case in 2008 (Figure 2). For current users, the IR per 1000 person-years decreased from 4.45 cases in 2001 to 2.21 cases in 2008.

Nested case-control analysis

The distribution of comorbidity and comedication in cases and controls at the index date and the corresponding crude and adjusted RRs for UGIC are summarized in Table 3. Cases were older than controls, a higher proportion of cases than controls were male, and cases had more frequent comorbidity and more concurrent use of medications than controls. The strongest factors independently associated with the risk of UGIC were age, sex, prior UGIC, other UGIC, liver diseases, and conditions related to alcohol abuse.

The adjusted RR of UGIC for current use of NSAIDs versus nonuse was 3.28 (95%CI: 2.86, 3.76), and the adjusted RR for current single use was 2.83 (95%CI: 2.43, 3.29; Table 4). RRs for current use of NSAIDs were stable during the study period. RR were 3.31 (95%CI: 2.47, 4.45) for the period 2001–2002, 3.27 (95%CI: 2.51,4.26) for 2003–2004, 3.54 (95%CI: 2.69, 4.66) for 2005–2006, and 3.14 (95%CI: 2.33, 4.23) for the period 2007–2008. For individual NSAIDs, the lowest RR was for rofecoxib, and the highest was for ketorolac. The adjusted RR was less than 2 for rofecoxib, celecoxib, and nimesulide; from 2 to less than 5 for naproxen, ibuprofen, diclofenac, etoricoxib, and meloxicam; and 5 or higher for ketoprofen, piroxicam, and ketorolac. The adjusted RR for nimesulide was 1.53 (95%CI: 1.08, 2.18). For cases and controls who were new users at cohort entry, adjusted RRs increased between 11% and 34% for piroxicam, ibuprofen, nimesulide, rofecoxib, and diclofenac (Table S1).

We did not observe a consistent dose response for the overall current single use of any NSAID. For individual NSAIDs, a consistent dose response for daily dose was observed for rofecoxib, diclofenac, etoricoxib, and ketoprofen (Table S2). The effect of daily dose could not be estimated for celecoxib, naproxen, ibuprofen, meloxicam, and nimesulide because of lack of variability. A dose response for cumulative dose was observed for rofecoxib, nimesulide, diclofenac, etoricoxib, ketoprofen, piroxicam, and ketorolac.

For current single use of any NSAID, the adjusted RR of UGIC was slightly higher during the first 15 days of treatment, 3.29 (95%CI: 2.70, 4.00), and was maintained during treatment. The adjusted RR was 2.42 (95%CI: 1.64, 3.58) for a duration of use of 16–30 days, 2.16 (95%CI: 1.61, 2.91) for a duration of use of 31–180 days, and 2.86 (95%CI: 1.95, 4.20) for a duration of use longer than 180 days.

Adjusted RR from analyses restricted to cases and controls without history risk factors for UGIC increased

DOI: 10.1002/pds

Table 1. Characteristics and utilization patterns of NSAIDs in Friuli Venezia Giulia, Italy, 2001–2008

NSAID	Number of users	New users* (%)	Age <45/>65 years (%)	Female (%)	Number of prescriptions	Number of boxes	Number of DDDs	Number of boxes/DDDs per prescription†	Number of prescriptions/ DDDs per user†
Nimesulide	251 013	65.7	22.1/39.1	60.3	831 074	1 087 448	17 486 435	1.3/21.0	3.3/69.7
Diclofenac	226 805	61.3	21.8/40.5	57.7	661 387	945 042	13 456 372	1.4/20.3	2.9/59.3
Ketoprofen	150 062	55.5	22.9/40.3	60.6	312 149	435 508	5 971 265	1.4/19.1	2.1/39.8
Piroxicam	121 117	46.5	20.8/41.3	61.5	285 638	397 767	6 370 348	1.4/22.3	2.4/52.6
Celecoxib	97 527	57.8	9.3/56.8	68.7	295 711	448 750	8 975 000	1.5/30.4	3.0/92.0
Ibuprofen	94 148	56.3	16.4/48.6	63.6	233 581	304 022	4 244 357	1.3/18.2	1.3/45.1
Etoricoxib	67 705	43.6	10.9/54.7	67.1	158 106	214 785	5 607 090	1.4/35.5	1.4/82.8
Ketorolac	61 759	49.2	21.8/42.0	59.1	146 494	259 394	779 259	1.8/5.3	1.8/12.6
Rofecoxib	57 242	46.4	9.7/56.8	68.6	144 578	222 112	3 789 408	1.5/26.2	1.5/66.2
Aceclofenac	56 289	50.7	16.5/46.1	62.7	112 964	140 236	2 443 620	1.2/21.6	1.2/43.4
Meloxicam	48 498	47.7	12.0/52.6	67.2	104 122	138 415	3 621 710	1.3/34.8	2.1/74.7
Indomethacin	37 216	44.6	15.7/47.0	51.8	85 676	129 207	960 556	1.5/11.2	1.3/25.8
Naproxen	31 207	50.6	24.2/36.9	64.1	74 315	98 721	3 139 993	1.3/42.3	2.4/100.6
Diclofenac + misoprostol	22 266	47.4	13.8/50.5	63.5	60 148	86 691	1 716 956	1.4/28.5	2.7/77.1
Other NSAIDs‡	58 222	20.9	13.7/50.5	66.4	117 398	154 929	3 189 721	1.3/27.2	2.0/54.8
Any NSAID	588 827	86.9§	26.9/35.4	56.7	3 623 341	5 063 027	81 752 090	1.4/22.7	6.2/138.8

DDD = defined daily dose; NSAID = nonsteroidal anti-inflammatory drug.
*Percentage of new users at the first prescription of each NSAID.
†Average number.
‡"Other NSAIDs" includes tenoxicam, oxaprozin, lornoxicam, amtolmetin, nabumetone, flurbiprofen, dexibuprofen, valdecoxib, proglumetacin, tiaprofenic acid, mefenamic acid, sulindac, acetametacin, fentiazac, niflumic acid, dexketoprofen, meclofenamic acid, and morniflumate.
§Percentage of new users at the start date.

DOI: 10.1002/pds

Table 2. Number and distribution of confirmed cases of upper gastrointestinal complications by type and site of complication, transfusion requirements, and 30-day case fatality

Site	Total number of cases	Bleeding	Perforation	Bleeding and perforation	Obstruction	Transfusion*	Fatal cases
Gastric	1336 (44.1)	1167 (44.3)	127 (43.8)	34 (52.3)	8 (19.0)	156 (61.2)	108 (8.1)
Prepyloric/Pyloric	102 (3.4)	95 (3.6)	7 (2.4)	0 (0)	0 (0)	65 (63.7)	7 (6.9)
Duodenal	1092 (36.0)	919 (34.9)	110 (37.9)	30 (46.2)	33 (78.6)	86 (66.7)	87 (8.0)
Gastrojejunal	84 (2.8)	82 (3.1)	1 (0.3)	0 (0)	1 (2.4)	57 (67.9)	6 (7.1)
Multiple	114 (3.8)	113 (4.3)	0 (0)	1 (1.5)	0 (0)	80 (70.2)	10 (8.8)
Upper GI	303 (10.0)	258 (9.8)	45 (15.5)	0 (0)	0 (0)	126 (80.8)	59 (19.5)
Total	3031	2634 (86.9)	290 (9.6)	65 (2.1)	42 (1.4)	570 (67.9)	
Fatal	277 (9.1)	204 (7.7)	53 (18.3)	18 (27.7)	2 (4.8)		277 (9.1)

Values are presented as *n* (%). GI = gastrointestinal.
*Percentage was calculated from the number of cases confirmed through validation.

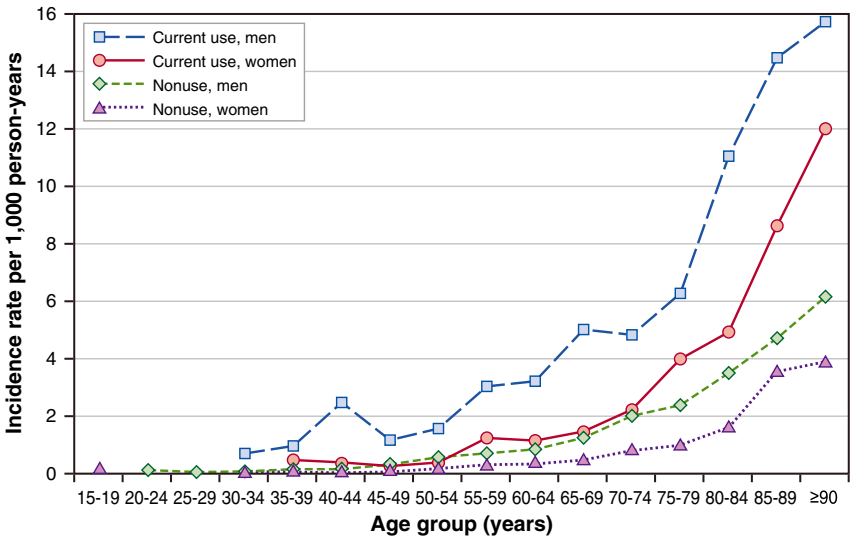

Figure 1. Age- and sex-specific incidence rates of upper gastrointestinal complications in current users and nonusers of NSAIDs

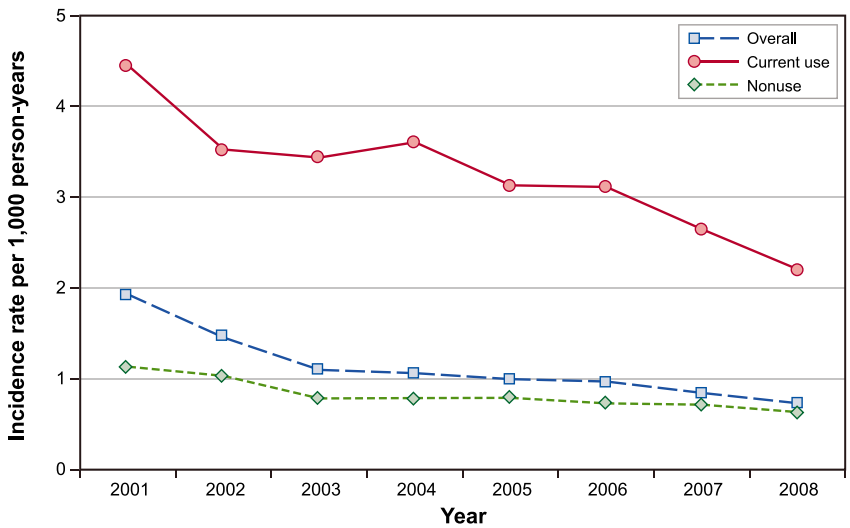

Figure 2. Time trends of incidence rates for upper gastrointestinal complications, overall, and in current users and nonusers of NSAIDs

DOI: 10.1002/pds

Table 3. Characteristics of cases and controls and relative risks for upper gastrointestinal complications

	Cases ($n = 2735$)		Controls ($n = 27\,011$)		Crude RR	Age- and sex-adjusted RR	Adjusted RR*
Variable	*n*	%	*n*	%	(95%CI)	(95%CI)	(95%CI)
Age (years)							
20–49	105	3.8	7534	27.9	1.00	1.00	1.00
50–64	477	17.4	8182	30.3	4.22 (3.40–5.22)	4.36 (3.52–5.40)	3.18 (2.55–3.97)
65–74	706	25.8	5915	21.9	8.59 (6.97–10.58)	9.08 (7.37–11.19)	5.20 (4.17–6.49)
75–84	1033	37.8	4457	16.5	16.80 (13.68–20.62)	19.24 (15.65–23.66)	9.84 (7.88–12.29)
85–89	414	15.1	923	3.4	32.68 (26.04–41.01)	40.75 (32.37–51.32)	19.72 (15.36–25.32)
Sex							
Female	1274	46.6	15 875	58.8	1.00	1.00	1.00
Male	1461	53.4	11 136	41.2	1.64 (1.51–1.77)	2.20 (2.02–2.40)	2.05 (1.87–2.25)
Prior hospitalization[†]							
Upper gastrointestinal complications	260	9.5	293	1.1	9.65 (8.10–11.49)	6.53 (5.40–7.91)	4.59 (3.73–5.65)
Uncomplicated peptic ulcer disease	122	4.5	251	0.9	9.40 (7.84–11.27)	6.63 (5.44–8.08)	1.64 (1.26–2.14)
Esophageal, liver and alcohol abuse-related diseases[‡]	409	15.0	1262	4.7	3.57 (3.17–4.02)	3.17 (2.78–3.61)	2.40 (2.08–2.77)
Cardiovascular disease[§]	2001	73.2	10 721	39.7	4.12 (3.77–4.50)	1.95 (1.77–2.15)	1.40 (1.26–1.56)
Musculoskeletal disorders[¶]	904	33.1	7231	26.8	1.35 (1.24–1.47)	1.10 (1.00–1.20)	0.81 (0.73–0.89)
Other chronic disease[>]	1224	44.8	5706	21.1	3.02 (2.79–3.28)	2.19 (2.01–2.39)	1.68 (1.53–1.85)
Concurrent use of medications[<]							
Proton pump inhibitors	491	18.0	2008	7.4	2.74 (2.46–3.06)	1.90 (1.69–2.14)	1.10 (0.97–1.25)
H2-receptor antagonists and antacids	231	8.5	790	2.9	3.11 (2.66–3.62)	2.48 (2.11–2.93)	1.82 (1.52–2.18)
Aspirin, platelet aggregation inhibitors, and anticoagulants	864	31.6	3027	11.2	3.67 (3.35–4.02)	1.84 (1.67–2.03)	1.54 (1.38–1.71)
Oral corticosteroids	164	6.0	639	2.4	2.64 (2.21–3.15)	2.20 (1.82–2.66)	1.70 (1.38–2.09)
Bisphosphonates	50	1.8	187	0.7	2.66 (1.94–3.65)	2.04 (1.46–2.84)	1.51 (1.06–2.16)
Selective serotonin reuptake inhibitors	142	5.2	803	3.0	1.80 (1.50–2.16)	1.63 (1.33–1.98)	1.38 (1.11–1.70)

CI = confidence interval; NSAIDs = nonsteroidal anti-inflammatory drugs; RR = relative risk.
*Adjusted by all the variables in the table and use of NSAIDs.
[†]Hospitalization with a primary or secondary discharge ICD-9-CM code of interest any time before the index date.
[‡]Includes esophageal varices, Mallory–Weiss syndrome, alcohol-abuse-related diseases, and liver diseases.
[§]Includes hypertensive disease, ischemic heart disease, heart failure, cerebrovascular disease, peripheral vascular disease, other cardiovascular diseases, and prescription for cardiovascular medications dispensed within 60 days before the index date. Cardiovascular medications include antihypertensives, vasodilators, antiarrhythmics, diuretics, beta-blocking agents, calcium channel blockers, angiotensin agents, peripheral vasodilators, and lipid-modifying agents.
[¶]Musculoskeletal disorders include rheumatoid arthritis, osteoarthritis, diffuse connective tissue diseases, polymyalgia rheumatica, and other arthropathies.
[>]Includes malignancy, diabetes with complications, renal failure, blood disorders, and hospitalization within 365 days before the index date.
[<]Prescription dispensed within 60 days before the index date.

between 15% and 66% for all NSAIDs except for naproxen, etoricoxib, and ketorolac (Table S3). The adjusted RR after excluding cases that were confirmed only by clinical evidence of melena and/or hematemesis was 3.41 (95%CI: 2.97, 3.92) for current use of NSAIDs and 2.92 (95%CI: 2.50, 3.40) for current single use.

The adjusted RRs of UGIC for the interaction between current use of any NSAID and medications known to increase the risk of UGICs are presented in Table 5. Small to moderate departures from additivity were observed for the concurrent use of any NSAID and aspirin, RERI, 1.58; any NSAID and anticoagulants, RERI, 1.12; and any NSAID and oral corticosteroids, RERI, 3.91. The synergy index for concurrent use of NSAIDs was 1.61 for aspirin, 1.35 for anticoagulants, and 2.35 for oral corticosteroids.

Results from the sensitivity analysis for the definition of exposure show that, in general, adjusted RRs of UGIC were higher when shorter days of supply were used in the estimation of days of supply; this scenario led to the highest RR for recent use of any NSAID (Table S4). The adjusted RR of UGIC for nimesulide ranged from 1.41 (95%CI: 107, 1.86) in the model using 30 and 15 days of supply to 2.21 (95%CI: 1.37, 3.57) in the model using 7 days of supply.

DISCUSSION

We estimated the incidence rates of UGIC in users and nonusers of NSAIDs and the risk associated with the use of overall and individual NSAIDs relative to the risk during nonuse of NSAIDs. The study was conducted in a large cohort of users identified in a well-defined and stable population in southern Europe without applying any exclusions to cohort entry. Cases of UGIC were identified using hospital discharge diagnosis in both primary and secondary position and

DOI: 10.1002/pds

Table 4. Crude and adjusted relative risk of upper gastrointestinal complications associated with the use of NSAIDs

Use of NSAIDs	Cases ($n = 2735$)		Controls ($n = 27{,}011$)		Crude RR (95%CI)	Age- and sex-adjusted RR (95%CI)	Adjusted RR* (95%CI)
	n	%	*n*	%			
Nonuse	1357	49.6	17 215	63.7	1.00	1.00	1.00
Current	506	18.5	1837	6.8	4.00 (3.55-4.51)	3.32 (2.92-3.78)	3.28 (2.86-3.76)
Current single	353	12.9	1510	5.6	3.39 (2.96-3.87)	2.85 (2.47-3.29)	2.83 (2.43-3.29)
Rofecoxib	10	0.4	109	0.4	1.47 (0.76-2.83)	1.03 (0.52-2.03)	0.84 (0.41-1.74)
Celecoxib	24	0.9	170	0.6	2.24 (1.45-3.47)	1.57 (1.00-2.47)	1.38 (0.85-2.24)
Nimesulide	42	1.5	412	1.5	1.45 (1.05-2.00)	1.41 (1.00-1.98)	1.53 (1.08-2.18)
Naproxen	8	0.3	39	0.1	3.10 (1.43-6.71)	2.97 (1.30-6.81)	2.74 (1.14-6.59)
Ibuprofen	24	0.9	84	0.3	3.78 (2.39-5.99)	3.11 (1.90-5.10)	3.04 (1.81-5.12)
Diclofenac	81	3.0	271	1.0	4.28 (3.31-5.55)	3.26 (2.47-4.32)	3.24 (2.40-4.36)
Etoricoxib	16	0.6	55	0.2	3.44 (1.97-6.02)	2.98 (1.63-5.46)	3.27 (1.72-6.19)
Meloxicam	13	0.5	36	0.1	5.47 (2.87-10.45)	4.23 (2.14-8.37)	4.47 (2.16-9.27)
Ketoprofen	30	1.1	72	0.3	5.92 (3.84-9.15)	5.49 (3.40-8.87)	5.45 (3.29-9.05)
Piroxicam	37	1.4	100	0.4	5.56 (3.77-8.20)	4.96 (3.23-7.62)	5.70 (3.65-8.89)
Ketorolac	47	1.7	26	0.1	24.42 (15.04-39.66)	25.63 (14.51-45.28)	21.76 (11.93-39.70)
Other NSAIDs	21	0.8	136	0.5	2.20 (1.38-3.51)	1.83 (1.11-3.03)	1.72 (1.02-2.90)
Current switching†	116	4.2	262	1.0	6.52 (5.17-8.22)	5.12 (3.97-6.61)	4.92 (3.77-6.42)
Current multiple‡	37	1.4	65	0.2	8.57 (5.64-13.01)	6.72 (4.25-10.63)	6.23 (3.81-10.18)
Recent use	546	20.0	4057	15.0	1.88 (1.69-2.10)	1.62 (1.44-1.82)	1.68 (1.48-1.89)
Past use	326	11.9	3902	14.5	1.13 (0.99-1.29)	1.03 (0.90-1.18)	1.00 (0.87-1.16)

CI = confidence interval; NSAIDs = nonsteroidal anti-inflammatory drugs; RR = relative risk.

*Adjusted for age, sex, history of complicated and uncomplicated peptic ulcer disease, esophageal varices, Mallory–Weiss syndrome, alcohol-abuse-related diseases, liver diseases, cardiovascular diseases, musculoskeletal disorders, other chronic disease, and use of medications within 60 days before the index date. Use of medications included proton pump inhibitors, H2-receptor antagonists and antacids, aspirin, platelet aggregation inhibitors and anticoagulants, oral corticosteroids, bisphosphonates, and selective serotonin reuptake inhibitors.

†Current switching use defined as current use of only one individual NSAID with recent use of a different NSAID.

‡Current multiple use defined as current use of more than one NSAID with or without recent use of other NSAIDs.

Table 5. Adjusted relative risk of upper gastrointestinal complications for current use of NSAIDs by use of medications that increase the risk of gastrointestinal bleeding

Medication use	Cases		Controls		Adjusted RR*
	n	%	*n*	%	(95%CI)
Aspirin					
Nonuse, aspirin or NSAIDs	1076	57.8	15 925	83.6	1.00†
Current use, aspirin only	281	15.1	1290	6.8	1.44 (1.21-1.71)
Current use, NSAIDs only	400	21.5	1657	8.7	3.17 (2.68-3.75)
Current use, aspirin and NSAIDs	106	5.7	180	0.9	5.19 (3.74-7.18)
Anticoagulants					
Nonuse, anticoagulants or NSAIDs	1224	65.7	16 816	88.3	1.00†
Current use, anticoagulants only	133	7.1	399	2.1	1.91 (1.48-2.46)
Current use, NSAIDs only	462	24.8	1786	9.4	3.28 (2.79-3.84)
Current use, anticoagulants and NSAIDs	44	2.4	51	0.3	5.31 (3.20-8.82)
Oral corticosteroids					
Nonuse, oral corticosteroids or NSAIDs	1296	69.6	16 918	88.8	1.00†
Current use, corticosteroids only	61	3.3	297	1.6	1.73 (1.23-2.43)
Current use, NSAIDs only	455	24.4	1747	9.2	3.18 (2.71-3.72)
Current use, corticosteroids and NSAIDs	51	2.7	90	0.5	7.83 (4.79-12.79)

CI = confidence interval; NSAIDs = nonsteroidal anti-inflammatory drugs; RR = relative risk.

*Adjusted for age, sex, history of complicated and uncomplicated peptic ulcer disease, esophageal varices, Mallory–Weiss syndrome, alcohol-abuse-related diseases, liver diseases, cardiovascular diseases, musculoskeletal disorders, other chronic disease, and use of medications within 60 days before the index date. Use of medications included proton pump inhibitors, H2-receptor antagonists and antacids, aspirin, platelet aggregation inhibitors and anticoagulants, oral corticosteroids, bisphosphonates, and selective serotonin reuptake inhibitors.

†Reference category.

validated through the review of medical records, achieving a very high chart retrieval rate. In general, age- and sex-specific incidence rates for UGIC were in line with prior studies. Rates decreased over time during the study period in both users and nonusers of NSAIDs. For individual NSAIDs, the RR of UGIC

DOI: 10.1002/pds

was consistent with that from other studies; nimesulide appears to be in the low–medium range of RR.

One of the strengths of our study is the comprehensive validation of potential cases identified with both primary and secondary hospital discharge diagnoses. The validation confirmed the quality of hospital records and the high, almost complete, chart retrieval rate in the FVG region. The full validation of cases identified with nonspecific codes (GI hemorrhage), which had a low PPV, led to confirmation of 697 cases, about 23% of the total number of cases included. Validation of the random sample of potential cases identified with secondary codes confirmed 34.7% to be cases of UGIC. A full validation of potential cases identified with secondary codes could have contributed approximately 617 cases. This indicates that studies restricting the identification and validation of cases of UGIC to those with primary codes could underestimate the incidence of UGIC up to about 17.6%. Although prior studies did not use secondary codes to identify cases of UGIC, the partial validation we conducted allowed us to include 149 additional cases and to reduce the underestimation of the incidence rate of UGIC to 13.5%.

A number of confirmed cases identified with secondary diagnoses for UGIC had a primary diagnosis for peritonitis (ICD-9-CM 567.1 and 567.8) or acute hemorrhagic anemia (ICD-9-CM 285.1). The PPV for these cases was high (83.3%), and we included them in the analysis. However, as in most published studies conducted in databases using ICD-9-CM coding, we did not use the codes for peritonitis and anemia to identify potential cases. Although the PPV for these codes in primary position without a secondary code for UGIC is unknown, we could have missed some cases of UGIC. Overall, there were 617 patients with a primary code for peritonitis and 375 with a primary code for anemia. Validation of these potential cases could provide useful information for future studies to improve the ascertainment of cases and the estimation of incidence rates of UGIC.

One of the main findings of this study was the decrease of IRs of UGIC by approximately 50% to 60% between 2001 and 2008. This decrease is consistent with the increase in the use of proton pump inhibitors (PPI) in the study cohort during the study period. The prevalence of users of PPI in the study cohort increased from 22.8% for the period 2001–2002 to 50.7% for the period 2007–2008. A report from the Italian Medicines Agency indicated that the use of PPIs in Italy increased from 13.3 DDDs per 1000 persons per day in 2001 to 44.8 DDDs per 1000 persons per day in 2008.[1] An increase in *Helicobacter pylori* eradication therapy could also explain the decrease of incidence rates over time. However, eradication therapy in our cohort of users of NSAIDs was below 2% during the study period. The decrease of IRs of UGIC observed in this study is similar to that observed in some countries.[13–15] A population-based study conducted in Spain found a decrease of rates for upper GI bleeding from 0.55 case per 1000 person-years in 1996 to 0.26 case per 1000 person-years in 2005.[13] However, other studies have reported no change in incidence rates for UGIC over time.[16]

Although RRs for current use of NSAIDs remained stable during the study period, the population attributable risk for current use of NSAIDs decreased from 20.6% for the period 2001–2002 to 8.7% for the period 2007–2008. This decrease is also consistent with the observed increase of the use of PPIs. Alternatively, an increase of the use of non-reimbursed NSAIDs, not captured in the database, could contribute to these time trends. The percentage of private expenditure for NSAIDs or for medications indicated for the musculoskeletal system in Italy increased during the study period. According to the annual reports of the Gruppo di lavoro OsMed, the percentage of private expenditure was 15% in 2001, around 40% between 2002 and 2004, and increased from 49% in 2005 to 54% in 2008 (http://www.agenziafarmaco.gov.it/it/content/rapporti-osmed-luso-dei-farmaci-italia, accessed September 2012).

In our study, the RR associated with nimesulide ranged from 1.53% (overall) to 1.81% (new users). These RRs for nimesulide are lower than those published in other studies, in which RRs ranged from 2.5 to 4.4. One of these studies was conducted in FVG between 1991 and 1995,[4] and another study was conducted in the region of Umbria in Italy between 1993 and 1994.[5] Both studies validated the cases identified in the hospital databases. Changes over time in the indications of use (from chronic to acute conditions) and patterns of use (shorter duration of continuous use) could partly explain the lower RR obtained in our study.

One of the limitations of this study is that the intended duration of use of each NSAID prescription was not available in the prescription database. Our estimation of days of supply of each prescription was based on descriptive analyses of consecutive prescriptions and could have led to misclassification of exposure. However, the sensitivity analysis found no major variations in the magnitude of effect estimates according to the different scenarios of days of supply. The lack of information on days of supply also impacted the estimation of the effect of dose. This was estimated through several approaches used in prior studies. However, the cut-offs did not result in a consistent dose–response relationship for overall NSAIDs or for

DOI: 10.1002/pds

some individual NSAIDs. Our ability to refine and check assumptions about days of supply and dose estimation was limited by the low number of repeated prescriptions in the study population. On the other hand, our results for total duration of use of NSAIDs (continuous treatment) were consistent with those from other studies.

A limitation of most studies using information from computerized prescriptions is the lack of information on the use of over-the-counter medications. In FVG, aspirin is the only NSAID available without prescription. However, as in the rest of Italy, it is estimated that approximately 50% of prescriptions for NSAIDs, mostly for acute and off-label indications, are not reimbursed and therefore are not captured in the prescription database. This could lead to a potential misclassification of exposure and a lowering of the RR estimates for those NSAIDs with a high percentage of unreimbursed prescriptions. The findings in the Italian Medicines Agency reports for 2007 and 2008 indicate important variability in the level of unreimbursed prescription of NSAIDs in Italy.[1,17] The proportion of unreimbursed prescription costs was 10% or less for selective COX-2 inhibitors, 30% for piroxicam, 42% for diclofenac, 50% for ketoprofen, 60% for ketorolac, and 85% for ibuprofen. For nimesulide, this proportion was 58% in 2007 and 44% in 2008.

In conclusion, this study indicates that the IRs of UGIC in the region of FVG decreased by about 50% between 2001 and 2008. Our findings suggest that the RR for nimesulide is comparable with that of NSAIDs in the low–medium range of RR for UGICs. This study indicates that a complete ascertainment of cases of UGIC in databases may require the validation of potential cases identified with nonspecific GI codes and with codes in secondary position and the inclusion of additional codes such as those for peritonitis and acute posthemorrhagic anemia.

CONFLICT OF INTEREST

J.C., N.R.G., and S.P.G. are employees of RTI-Health Solutions. J.C., N.R.G., and S.P. conducted research on NSAIDs sponsored by the European Community's Seventh Framework Programme. S.P.G. conducted research activities funded by NicOx S.A., a developer of NSAIDs. S.P.G. has served on advisory boards, provided consultation to pharmaceutical companies including NSAID manufacturers/developers such as Helsinn and NicOx S.A, and serves as a member of the scientific committee of a study on the safety of NSAIDs sponsored by Dundee University. F.P., V.R., D.D., N.R.G., M.A., E.C., F.T., and L.Z. do not have conflict of interest.

KEY POINTS

- Incidence rates of hospitalization for UGIC decreased by approximately 50% between 2001 and 2008 in a cohort of users of NSAIDs identified in FVG, Italy.
- Nimesulide, the most used NSAID in Italy, is among the NSAIDs with a low–medium increase in the risk of UGIC.
- Complete ascertainment of cases of UGIC in databases requires the validation of potential cases identified with nonspecific GI codes, codes in secondary position, and additional codes such as those for peritonitis and acute posthemorrhagic anemia.
- The health database system of FVG provides access to hospital medical records with a very high chart retrieval rate and is a reliable source of information for conducting population-based studies.

GOOD PHARMACOEPIDEMIOLOGY PRACTICE

The study adhered to the *Guidelines for Good Pharmacoepidemiology Practices* (*GPP*) (International Society for Pharmacoepidemiology, 2008). The study was a noninterventional postauthorization safety study according to Volume 9A of the *Rules Governing Medicinal Products in the European Union: Guidelines on Pharmacovigilance for Medicinal Products for Human Use* (European Commission, 2008). We used STROBE (http://www.strobe-statement.org) as a guideline for the reporting of observational studies (checklist included at the end of the manuscript). The study protocol was shared with the Italian Medicines Agency and with the European Medicines Agency. This study was registered in the Register of Observational Studies of the Italian Medicines Agency with the identification number FVG2011_NSAIDUGIB and in the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance Register of Studies (http://www.encepp.eu).

ACKNOWLEDGEMENTS

The financial sponsor of this study was Helsinn Healthcare S.A., a privately owned pharmaceutical group with headquarters in Switzerland and the manufacturer of original nimesulide. The sponsor of

DOI: 10.1002/pds

the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

We acknowledge Professor Angel Lanas, Department of Gastroenterology, Hospital Clínico Universitario of Zaragoza, Spain, for his guidance on and assistance with the validation of cases of UGIC and for his comments on the study report; Professor Kenneth J Rothman, RTI Health Solutions, Waltham, MA, USA, for his advice on the study methods, protocol, and statistical analysis plan and for his comments on the study report; and Jaume Aguado, BStat, Barcelona, Spain, for his contribution in the data programming and analysis.

We are indebted to the directors and staff of the hospitals in the FVG region and the central archive department that supported access to and retrieval of the charts for the case validation: Central Archive of the FVG region and hospitals AOUD Udine, San Daniele del Friuli, Casa di cura Città di Udine, Latisana, Palmanova, Gemona, Tolmezzo, AOUTS Ospedali Riuniti Trieste, Pineta del Carso, Salus, Sanatorio Triestino, Gorizia, Monfalcone, Pordenone, Sacile, Spilimbergo, San Vito al Tagliamento, Maniago, Casa di cura San Giorgio. We thank Viviana Antonutti, MD; Rossella Cimarosti, MD (candidate); Elena Finotto, MD (candidate); Anna Gnoni, MD; Giorgia Gregoraci, MD; and Laura Papais, MD, for conducting the abstraction of hospital charts for case validation. We also thank Carla Franzoni, BSc (Biol), RTI-HS, Barcelona, Spain; Vittoria Tosolini, BA, Udine University, Udine, Italy; María Florencia Miniello, RTI-HS, Barcelona, Spain; and Adele Monroe, DVM, MSPH, ELS, medical editor, RTI-HS, Research Triangle Park, NC, USA, for their support in project management, administration, and editorial review.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of this article.

Figure S1. Age-specific incidence rates of upper gastrointestinal complications in current users and nonusers of NSAIDs by history of peptic ulcer

Table S1. Adjusted relative risk of upper gastrointestinal complications in new users of NSAIDs

Table S2. Adjusted relative risk of upper gastrointestinal complications by dose in current single users of NSAIDs

Table S3. Adjusted relative risk of upper gastrointestinal complications in cases and controls without history of peptic ulcer and other risk factors

Table S4. Sensitivity analysis for definition of exposure—adjusted[a] relative risk of upper gastrointestinal complications.

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DOI: 10.1002/pds