Use of Nimesulide, Other NSAIDs, and the Risk of Upper Gastrointestinal Complications in Friuli Venezia Giulia, Italy

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BACKGROUND AND OBJECTIVE

- Few epidemiological studies have evaluated the risk of upper gastrointestinal complications (UGICs) in users of nimesulide
- The objective of this study was to estimate the risk of UGIC in users of nimesulide and other individual nonsteroidal anti-inflammatory drugs (NSAIDs) in the population of Friuli Venezia Giulia (FVG), Italy

METHODS

Source Population

- General population in the region of FVG in northern Italy with 1.2 million inhabitants
- Regional database system with information on the individual use of health care resources
- Key databases: Patient Identification, Outpatient Prescription, and Hospital Service

Study Design

- Retrospective cohort and nested case-control study of users of NSAIDs

Study Cohort

- All residents in FVG for at least 1 year who were prescribed an NSAID between January 1, 2001, and December 31, 2008
- No exclusion criteria applied

Follow-up

- From the first NSAID prescription to the earliest of the following: (1) hospital admission for UGIC, (2) emigration or disenrollment from health system, (3) end of study period, or (4) death

Case Definition

- Patient with hospital admission 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

Case Identification

- Through primary and/or secondary hospital discharge International Classification of Disease 9th Revision Clinical Modification (ICD-9-CM) codes:
  - Site- and lesion-specific: gastric ulcer (code 531), duodenal ulcer (532), peptic ulcer site unspecified (533), and gastrojejunal ulcer (534)
  - Nonspecific: hematemesis (578.0), melena (578.1), and unspecified bleeding of intestinal tract (578.9)

Case Validation

- Review of hospital medical charts for the following:
  - Random sample of cases identified with primary discharge codes 531 and 532 (n = 108)
  - All potential cases identified with primary discharge codes 533 (n = 40), 534 (n = 137), and 578 (n = 1,770)
  - Random sample of potential cases identified with secondary codes 531, 532, 533, 534, and 578 (n = 458)
- Data abstracted from hospital medical records by trained personnel using a standardized abstraction form
  - Final confirmation of cases conducted blindly to exposure to NSAIDs
- Positive predictive values (PPVs)
  - Primary codes: 96.6% for gastric ulcer, 91.5% for duodenal ulcer, 79.5% for peptic ulcer, 83.1% gastrojejunal ulcer, and 40.2% gastrointestinal hemorrhage
  - Secondary codes: 34.7%
  - Combination of secondary codes with a primary code for peritonitis (567.2 and 567.8) or acute posthemorrhagic anemia (285.1): 83.3%
  - See poster by Pisa et al. for full details of validation.

Selection of Controls

- Density-based sampling of 10 controls from the set of members of the cohort that were at risk at the date of hospitalization for UGIC of each case (risk set)

Exposure Assessment

- Exposure to NSAIDs estimated assuming 15 days of supply for oral formulations and 7 days of supply for injectable formulations
- Sensitivity analysis conducted assuming (1) 30 days for oral formulations and 15 days for injectables, (2) 7 days for both oral and injectable formulations, and (3) days of supply estimated from the quantity dispensed expressed in defined daily doses
- Exposure to NSAIDs classified in four mutually exclusive exposure categories:
  - Current use: supply of the most recent dispensing for a specific NSAID ended on or overlapped the index date
  - Recent use: supply ended within 60 days before the index date
  - Past use: supply ended between 61 and 150 days before the index date
  - Nonuse: supply ended more than 150 days before the index date (reference category for all analyses)

Confounding Factors

- Potential confounding factors measured at the index date and their effect evaluated in the analysis
- Risk factors evaluated: age, male sex, prior peptic ulcer disease, severe comorbidity and life-threatening conditions, and concurrent use of other medications

Analysis

Cohort

- Crude age- and sex-specific incidence rates (IRs) and 95% confidence intervals (CIs) of UGICs estimated for each exposure category and stratified by history of peptic ulcer and calendar year

Case-Control

- Conditional logistic regression used to estimate crude and adjusted relative risks (RR) and 95% CIs
- First analysis restricted cases to those with primary hospital discharge codes with a high PPV: 531 gastric ulcer and 532 duodenal ulcer
- Full analysis included all cases identified with codes 531 and 532 and all cases identified with the rest of codes that were confirmed in the review of the hospital medical charts

RESULTS

- The study cohort included 588,827 subjects who received 3,623,341 prescriptions for NSAIDs and contributed to 2,959,555 person-years of follow-up, including 173,248 person-years of current use of NSAIDs and 1,994,419 person-years of nonuse.
  - The cohort included 251,013 users of nimesulide who received 831,074 prescriptions.
- A total of 3,031 cases of UGICs were confirmed (Table 1).
  - Site-specific codes for gastric and duodenal ulcer contributed to 67.4% of the total number of final cases.
  - Validation of specific codes (533 peptic ulcer and 534 gastrojejunal ulcer) and nonspecific codes (578 GI hemorrhage) contributed to 27.7% of final cases.

Table 1. Number and Distribution of Confirmed Cases of UCIG by Identification Code, FVG, Italy, 2001-2008

ICD-9-CM Code	Code Description	Final Cases All Ages n	(%)	Final Cases Aged 20-89 Years n	(%)
531	Gastric ulcer	1,079	(35.6)	975	(35.7)
532	Duodenal ulcer	963	(31.8)	893	(32.7)
533[a]	Peptic ulcer	31	(1.0)	29	(1.1)
534[a]	Gastrojejunal ulcer	112	(3.7)	103	(3.8)
578.0[a]	Hematemesis	221	(7.3)	193	(7.1)
578.1[a]	Blood in stool (melena)	233	(7.7)	205	(7.5)
578.9[a]	Hemorrhage of gastrointestinal tract, unspecified	243	(8.0)	213	(7.8)
567.2[b]	Other suppurative peritonitis	37	(1.2)	33	(1.2)
567.8[b]	Other specified peritonitis	8	(0.3)	6	(0.2)
285.1[b]	Acute posthemorrhagic anemia	104	(3.4)	85	(3.1)
Total		**3,031**	**(100)**	**2,735**	**(100.0)**

[a] Cases confirmed through review of hospital medical charts.
[b] Cases with a diagnosis for UGIC in the secondary position.

Cohort

- The overall crude IR of UGIC was 1.02 cases (95% CI, 0.99-1.06) per 1,000 person-years.
  - The crude IR of UGIC was 0.76 cases (95% CI, 0.72-0.80) per 1,000 person-years during nonuse of NSAIDs and 3.28 cases (95% CI, 3.01-3.55) per 1,000 person-years during current use of NSAIDs. IRs increased by increasing age, particularly after age 65 (Figure 1).
  - Among patients with history of UGIC, the IRs were 6.26 (95% CI, 5.09-7.43) per 1,000 person-years during nonuse of NSAIDs and 28.22 (95% CI, 20.48-35.97) per 1,000 person-years during current use of NSAIDs (Figure 2). Among patients without history of UGIC, IRs were 3.02 (95% CI, 2.76-3.28) for nonusers and 0.71 (95% CI, 0.67-0.75) for current users.
- The overall IR in the study cohort decreased from 1.93 cases per 1,000 person-years in 2001 to 0.74 per 1,000 person-years in 2008 (Figure 3).
  - For current use of NSAIDs, IRs per 1,000 person-years decreased from 4.45 cases in 2001 to 2.21 cases in 2008.
  - The use of antiulcer drugs (defined daily dose [DDD] 1,000 inhabitants per day) increased from 17.5 DDD in 2001 to 43.2 DDD in 2008.

Figure 1. Age- and Sex-Specific IRs of Hospitalization for UGICs During Current Use and Nonuse of NSAIDs, FVG, 2001-2008

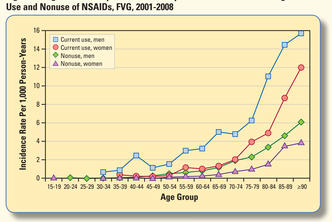


Figure 2. Age-Specific IRs of Hospitalization for UGICs During Current Use and Nonuse of NSAIDs, by History of Peptic Ulcer Disease, FVG, 2001-2008

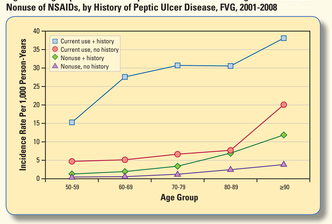
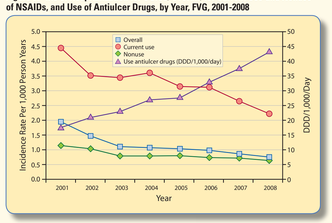


Figure 3. IRs of Hospitalization for UGICs, Overall, for Current Use and Nonuse of NSAIDs, and Use of Antiulcer Drugs, by Year, FVG, 2001-2008



Source for use of antiulcer drugs in FVG: Gruppo di lavoro OsMed, 2008.[2]

- Restricting the analysis to cases of UGICs identified with specific codes with high PPV (531 gastric ulcer and 532 duodenal ulcer), underestimated the true IR by approximately 33%.
  - Inclusion of all potential cases identified prior to validation (n = 4,014) overestimated the IR of UGICs by 33%.
  - Based on the sample validation of cases identified with codes in secondary discharge position, the IR estimated in this study underestimated the true incidence by approximately 17%

Case-Control

- A total of 2,735 cases and 27,011 controls aged 20 to 89 years old were included.
  - Adjusted RR for current single use of nimesulide: 1.53 (95% CI, 1.08-2.18) (Table 2, Figure 4).
- When the analysis was restricted to cases identified with primary hospital discharge codes with a high PPV (1,582 cases and 15,338 controls), the adjusted RR for current single use was 2.46 (95% CI, 2.11-2.87) (Table 2).
  - The adjusted RR for current single use of nimesulide was 1.60 (95% CI, 1.17-2.17).
- The ranking of RR for individual NSAIDs is presented in Figure 4.
  - RRs were below 2 for current single use of rofecoxib, celecoxib, and nimesulide; between 2 and 4 for naproxen, ibuprofen, diclofenac, and etoricoxib; and above 4 for meloxicam, ketoprofen, piroxicam, and ketorolac. Sensitivity analyses assuming different days of supply for exposure led to similar results.

Figure 4. Adjusted RR of UGICs Associated With Current Single Use of Individual NSAIDs

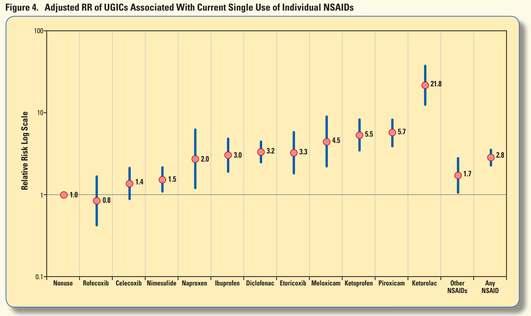


Table 2. Crude and Adjusted Relative Risk of UGICs Associated With the Use of NSAIDs

Use of NSAIDs	Full Analysis With All Confirmed Cases										Analysis of Cases With High PPV		
	Cases (n = 2,735)		Controls (n = 27,011)		Crude RR (95% CI)			Adjusted RR (95% CI)			Adjusted RR (95% CI)		
	n	%	n	%	RR	LL	UL	RR	LL	UL	RR	LL	UL
Nonuse	1,357	49.6	17,215	63.7	1.00	—	—	1.00	—	—	1.00	—	—
Current	506	18.5	1,837	6.8	4.00	3.55	4.51	3.28	2.86	3.76	2.80	2.43	3.22
Current single	353	12.9	1,510	5.6	3.39	2.96	3.87	2.83	2.43	3.29	2.46	2.11	2.87
Rofecoxib	10	0.4	109	0.4	1.47	0.76	2.83	0.84	0.41	1.74	—	—	—
Celecoxib	24	0.9	170	0.6	2.24	1.45	3.47	1.38	0.85	2.24	1.42	0.89	2.27
Nimesulide	42	1.5	412	1.5	1.45	1.05	2.00	1.53	1.08	2.18	1.60	1.17	2.17
Naproxen	8	0.3	39	0.1	3.10	1.43	6.71	2.74	1.14	6.59	2.83	1.23	6.50
Ibuprofen	24	0.9	84	0.3	3.78	2.39	5.99	3.04	1.81	5.12	1.98	1.16	3.36
Diclofenac	81	3.0	271	1.0	4.28	3.31	5.55	3.24	2.40	4.36	2.97	2.24	3.93
Etoricoxib	16	0.6	55	0.2	3.44	1.97	6.02	3.27	1.72	6.19	—	—	—
Meloxicam	13	0.5	36	0.1	5.47	2.87	10.45	4.47	2.16	9.27	—	—	—
Ketoprofen	30	1.1	72	0.3	5.92	3.84	9.15	5.45	3.29	9.05	4.26	2.69	6.75
Piroxicam	37	1.4	100	0.4	5.56	3.77	8.20	5.70	3.65	8.89	4.26	2.93	6.21
Ketorolac	47	1.7	26	0.1	24.42	15.04	39.66	21.76	11.93	39.70	15.8	(8.5	29.67
Other NSAIDs	21	0.8	136	0.5	2.20	1.38	3.51	1.72	1.02	2.90	1.77	1.31	2.40
Current switcher	116	4.2	262	1	6.52	5.17	8.22	4.92	3.77	6.42	3.57	2.66	4.79
Current multiple	37	1.4	65	0.2	8.57	5.64	13.01	6.23	3.81	10.18	5.59	4.02	7.78
Recent use	546	20.0	4,057	15.0	1.88	1.69	2.10	1.68	1.48	1.89	1.36	1.14	1.63
Past use	326	11.9	3,902	14.5	1.13	0.99	1.29	1.00	0.87	1.16	1.08	0.89	1.31

LL = lower limit of confidence interval; UL = upper limit of confidence interval.

CONCLUSIONS

- The results are overall in line with prior studies regarding age and sex incidence rates of UGICs, and the NSAIDs associated with higher, medium, and lower relative risks.
- The incidence rate of UGICs decreased by approximately 60% between 2001 and 2008.
- The risk associated with nimesulide appears to be comparable to that of NSAIDs in the medium or lower range of relative risk for UGICs.
- The validation of the specific hospital discharge codes for peptic ulcer and gastrojejunal ulcer, and nonspecific codes for GI hemorrhage, contributed to approximately 28% of final cases of UGICs.
- The results of the analysis with cases identified with discharge codes with high PPV were in line with the full analysis of confirmed cases. However, restricting the analysis to these codes underestimates estimations of absolute risk by approximately 33%.
- Estimation of incidence rates including all potential cases identified prior to validation overestimates the rates by 33%.
- The sample validation of cases identified with codes in secondary discharge position indicates that the incidence rate of UGIC can be underestimated by approximately 17% if these codes are not used in the case identification and validation.

Ethical and Scientific Review and Funding Source

The study was approved by the RTI International institutional review board. The study protocol was reviewed by the ethics committees of all hospitals in the FVG region that were asked for permission to access medical records for case validation.

The study was conducted under Good Pharmacoepidemiology Practices (International Society for Pharmacoepidemiology [ISPE]). The study complied with the definition of a noninterventional (observational) study provided in Article 2(c) of Directive 2001/20/EC and its refinement provided in Chapter I.7 Section 1 of Volume 9A of the Rules Governing Medicinal Products in the European Union and in Determinazione AIFA 20/03/08 (GU n. 76 del 31-3-2008). The study protocol was shared with the Italian Medicines Agency (AIFA), together with the notification for the start of the study, and with the European Medicines Agency. The study was registered in the Register of Observational Studies of the AIFA (study FVG2011_NSAIDUGIB).

The financial sponsor of this study was Helsinn Healthcare S.A., manufacturer of original nimesulide. Helsinn committed to maintain its role as financial sponsor, while giving the research partners scientific independence, including publication of manuscripts.

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