Upper gastrointestinal bleeding among users of NSAIDs: a population-based cohort study in Denmark

Lene Mellemkjær,[1] William J. Blot,[2,3] Henrik Toft Sørensen,[4,5] Lars Thomassen,[1] Joseph K. McLaughlin,[2,3] Gunnar Lauge Nielsen[4,6,7] & Jørgen H. Olsen[1,3]

[1]*Institute of Cancer Epidemiology, Danish Cancer Society, Copenhagen, Denmark,* [2]*International Epidemiology Institute, Rockville, Maryland 20850, USA,* [3]*Department of Medicine, Vanderbilt University Medical Center and Vanderbilt-Ingram Comprehensive Cancer Center, Nashville, Tennessee, USA,* [4]*Department of Clinical Epidemiology, Aarhus University Hospital and Aalborg Hospital, Denmark,* [5]*Department of Medicine V, Aarhus University Hospital, Aarhus, Denmark,* [6]*Department of Medicine M, Aalborg Hospital, Aalborg, Denmark and* [7]*The Danish Epidemiology Science Center, Institute of Epidemiology, Aarhus University, Aarhus, Denmark*

Aims It is well-known that use of nonsteroidal anti-inflammatory drugs (NSAIDs) increases the risk of upper gastrointestinal bleeding (UGIB), but characteristics of the association and quantification of excess risk at the population level require clarification.

Methods All users of nonaspirin prescription NSAIDs in North Jutland County, Denmark during 1991–95 were identified in the regional Pharmaco-Epidemiologic Database. Using the Hospital Discharge Register, all hospitalizations for UGIBs were identified among the 156 138 users of NSAIDs and compared with the number of expected based on the North Jutland population who did not receive NSAID prescriptions.

Results During periods of NSAID use without use of other drugs associated with UGIB, we observed 365 UGIBs, a number 3.6 times higher than expected (95% CI = 3.3, 4.0). The excess risk varied by sex, type of NSAID and form and route of administration of the NSAID, but not by age at first NSAID prescription or number of prior prescriptions. Risk declined sharply following cessation of use. For ibuprofen and naproxen, there was a clear trend in rising risk by increasing dose, although the lowest doses were also associated with an excess of UGIB. Concurrent use of corticosteroids, anticoagulants and aspirin further increased the risk of UGIB.

Conclusions All types and formulations of NSAIDs appear to increase the risk of UGIBs, but the effect appear not to be cumulative and diminish rapidly with discontinue of use. Up to 15% of the UGIBs in the entire population of the North Jutland County may be explained by use of this drug.

Keywords: NSAIDs, pharmacoepidemiology, population-based cohort study, upper GI bleeding

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most commonly used drugs in many countries. Risk of upper gastrointestinal bleeding (UGIB) is known to be increased among persons prescribed NSAIDs, with the injury to the gastrointestinal mucosa thought to be caused by both systemic and topical effects of the drugs [1–3]. Systemic effects are likely related to inhibition of endogenous prostaglandin synthesis [3], while acute mucosal damage may be a result of direct toxic effects, depletion of mucosal prostaglandins and microcirculation disturbances due to interactions between leucocyte and endothelial cells [2].

There is uncertainty, however, concerning the magnitude of the absolute and relative risks among users and how they vary as a function of the amount and duration of use, form and route of administration, type

Correspondence: Dr L. Mellemkjaer, The Danish Cancer Society, Institute of Cancer Epidemiology, Strandboulevarden 49, DK-2100 Copenhagen Ø, Denmark. Tel.: +45 35 25 76 12; Fax: +45 35 25 77 31; E-mail: lene@cancer.dk

Received 19 June 2001, accepted 11 October 2001.

of NSAID and use of other drugs. Herein we describe a population-based cohort study in which all residents of a county in northern Denmark prescribed nonaspirin NSAIDs over a 5 year period were identified and followed for subsequent hospitalization for UGIB. The study affords the opportunity to determine rates of UGIB associated with NSAID use in a large population.

Methods

The study was carried out within the population of North Jutland in Denmark which comprised about 490 000 inhabitants, approximately 9% of the total Danish population, during the study period 1991–95. The National Health Service provides tax-supported health care for all inhabitants, guaranteeing free access to general practitioners, hospitals, and public clinics and refunding a variable proportion (usually 50–75%) of the costs of medications prescribed by physicians. The population-based Pharmaco-Epidemiologic Database of North Jutland [4], initiated on 1 January 1991, retains key information on prescriptions dispensed from all 33 pharmacies outside hospitals in the county. This includes the unique personal identification number of the customer, type of drug prescribed according to the anatomical therapeutical chemical (ATC) classification system [5], date of prescription (date of dispensing the drug), tablet size, number of tablets in the package and number of packages. Using the personal identification number, which encodes gender and date of birth, a complete prescription history can be established for each individual, and unambiguous linkages with other registers can be performed.

Exposure data

In the Pharmaco-Epidemiologic Database, we identified, during 1991–95, 171 092 users of nonaspirin NSAIDs (azapropazone ATC = M01A A04, diclofenac M01A B05, etodolac M01A B08, fenbufen M01A E05, fenoprofen M01A E04, flurbiprofen M01A E09, ibuprofen M01A E01, indomethacin M01A B01, ketoprofen M01A E03, ketorolac M01A B15, nabumetone M01A X01, naproxen M01A E02, phenylbutazone M01A A01, piroxicam M01A C01, proquazon M01A X13, sulindac M01A B02, tenoxicam M01A C02, tiaprofenic acid M01A E11, tolfenamic acid M01A G02, tolmetin M01A B03). Record linkage with the Danish mortality files resulted in the exclusion of 73 persons (0.04%) due to date of death before the date of NSAID prescription, or to an error in the identification number. We also excluded 696 users (0.4%) who were under the age of 16 or older than 105 years at date of NSAID prescription, and 5696 users (3.3%) who were not residents in the county.

UGIB and predisposing conditions

The remaining 164 627 persons were linked to the Regional Hospital Discharge Register (HDR), which retains key information at the individual level for all admissions to hospitals in the county from 1977 through 1995 [6]. For each hospitalization, the files of the HDR include information on the identification number of the patient, date of discharge, and up to 20 discharge diagnoses, coded according to the Danish version of the International Classification of Diseases, 8th revision [7], until the end of 1993, and 10th revision [8] thereafter. By use of the hospital discharge history from 1977, we subsequently excluded 722 (0.4%) persons who had an UGIB from 1977 until the first recorded NSAID prescription. These UGIBs were coded as oesophagitis (ICD-8, 530.98; ICD-10, no code), gastritis (535.01; K29.0), gastric (531.90, 531.92, 531.95; K25.0, K25.2, K25.4, K25.6), duodenal (532.90; K26.0, K26.2, K26.4, K26.6), gastroduodenal (533.90; K27.0, K27.2, K27.4, K27.6) or gastrojejunal ulcer (534.90; K28.0, K28.2, K28.4, K28.6), haematemesis (784.59; K92.0), melaena (785.79; K92.1) or GI haemorrhage without specification (K92.2). In addition, we excluded 3108 (2%) subjects with medical conditions predisposing to UGIB including alcoholism (303; F10), oesophageal varices (456.00–09; I85, I98.2), Mallory–Weiss syndrome (530.97; K22.6), or liver cirrhosis (571, 573; K70, K72–74, K76). Cancer is also a predisposing condition, so a further 4659 (3%) subjects were excluded after linkage with the Danish Cancer Registry, because they had a cancer diagnosis after 1980 and before the first recorded NSAID prescription. Persons with predisposing conditions were excluded to avoid possible effects of confounding and interaction with NSAIDs. Thus, a total of 156 138 (91.3%) users of NSAIDs were included in the study (Table 1).

Follow-up for UGIB

Follow-up for hospitalization for UGIB began on the date of the first recorded prescription for a NSAID, and ended on the date of first hospital admission for a UGIB, or on a censoring date due to hospital admission for one of the medical conditions that predispose to UGIB (alcoholism, oesophageal varices, Mallory–Weiss syndrome, liver cirrhosis or cancer), death, or 31 December 1995, whichever occurred first. The follow-up period was subdivided into periods of NSAID use (current exposure) lasting from the date of prescription until 90 days thereafter (or a censoring date), and periods of non use of NSAIDs (former exposure) extending from 90 days after a prescription to the date of next prescription (or a censoring date). Further, periods of use and non use were flagged if subjects received prescriptions at the same time

Table 1 Descriptive characteristics of NSAID users with one or more prescriptions and with three or more prescriptions recorded in North Jutland County Pharmaco-Epidemiologic Prescription Database, 1991–95.

	One or more NSAID prescriptions		*Three or more NSAID prescriptions*	
Characteristic	*Number of users*	*(%)*	*Number of users*	*(%)*
Total	156 138	(100)	58 708	(100)
Sex				
Men	70 141	(45)	23 230	(40)
Women	85 997	(55)	35 478	(60)
Age at first recorded prescription				
<60 years	110 062	(70)	33 834	(58)
60–69 years	19 307	(12)	9110	(16)
70+ years	26 769	(17)	15 764	(27)
Year of first recorded prescription				
1991	45 922	(29)	11 522	(20)
1992	31 647	(20)	11 145	(19)
1993	28 268	(18)	11 545	(20)
1994	26 569	(17)	12 035	(20)
1995	23 732	(15)	12 461	(21)

for one or more other drugs presumed to cause UGIB, i.e. low- and high-dose aspirin (ATC-codes B01AC06, N02BA01, N02BA51), anticoagulants (B01AA03, B01AA04) and corticosteroids (H02AB), again applying the 90 day rule. Then, periods of current exposure could be divided into periods of only NSAID use (88.5% of person-years for current use) and periods of combined use of NSAIDs and one or more of the other predisposing drugs (11.5%), e.g. NSAID + glucocorticoids (5.5%) and NSAID + anticoagulants (0.4%). Periods of former exposure were similarly divided into non use of any drug (93.8%) and use of one or more of the other drugs (6.2%). Periods when only NSAIDs were used were further classified according to sex, age, number of prior NSAID prescriptions, type of NSAID and form and route of administration.

For users of ibuprofen and naproxen, the most commonly prescribed NSAIDs in our population, the analysis was stratified according to sex, age, number of prior ibuprofen/naproxen prescriptions and used daily dose. Used daily dose was estimated for 13 444 users of ibuprofen and 3530 users of naproxen who had at least three consecutive time segments of drug use, i.e. there were less than 90 days between dates of prescriptions for ibuprofen/naproxen. The dose was calculated from tablet dose, number of tablets in the package and time interval between two consecutive prescriptions. For each new segment, the dose applied was an average of all doses previously prescribed in a continuous sequence. Follow-up started on the date of the third prescription and ended on the censoring dates described above.

In order to examine the risk of UGIB among persons likely to be continuous users of NSAIDs, we restricted the cohort of NSAID users to 58 708 (38%) subjects who had received at least three NSAID prescriptions during 1991–95 regardless of the time interval between prescriptions (Table 1). The date of entry was the date of the third prescription, while censoring dates and periods of current and former exposure were defined as described above.

Observed/expected (O/E) ratios of UGIB

The occurrence of UGIB during periods of use of NSAIDs was compared with that in the general population not exposed to NSAIDs by calculating O/E ratios as estimates for relative risk. The O/E ratio was calculated as the observed number of UGIBs divided by the expected number. The background population included all inhabitants of the North Jutland County who had not received an NSAID prescription or any of the other drugs presumed to cause UGIB, and who had not been hospitalized from 1977 to 1991 with an UGIB or a medical condition predisposing to UGIB (alcoholism, oesophageal varices, Mallory–Weiss syndrome, liver cirrhosis, or cancer) from 1977 on. For this population, rates of first time hospitalization for UGIB were computed according to sex, 5 year age group and 1 year calendar-period, and these rates were applied to the person-years of observation of current and former NSAID use to obtain the number of UGIBs expected if the users of NSAIDs had experienced the same hospitalization rates as nonusers. Confidence intervals (CI) for the O/E ratio were computed using Byar's approximation under the assumption that the observed number of UGIBs follows a Poisson distribution.

Under the assumption of an additive effect between NSAIDs and other risk factors for UGIB, the population attributable risk was calculated as the excess number of cases of UGIB per person-year among NSAID only users multiplied by the person-years accumulated among current users and divided by the total number of UGIBs during the study period among persons not predisposed to UGIB in North Jutland ($n = 2004$).

Results

Among the 156 138 persons who had at least one NSAID prescription, 107 305 person-years of NSAID use were accumulated during current use, with a mean cumulative duration of 0.7 years (range 0–5 years) (Table 2). There were 515 UGIBs observed against 124.9 expected yielding an O/E of 4.1 (95% CI = 3.8, 4.5). Most of the users (98%) had periods when only NSAIDs were used, and during 94 987 such person-years, 365 UGIBs were seen, which

Table 2 Observed (Obs) and expected (Exp) number and O/E ratios of UGIB associated with current and former NSAID use among persons with at least one NSAID prescription recorded in the North Jutland County Pharmaco-Epidemiologic Prescription Database, 1991–95. Exposure window is 90 days for all drugs considered.

Periods of drug use	*Number of persons*	*Person-years*	*UGIB Obs*	*Exp*	*O/E*	*95% CI*
Current use of NSAID	156 138	107 305	515	124.9	4.12	3.8, 4.5
NSAID only	152 882	94 987	365	101.2	3.61	3.3, 4.0
NSAID + glucocorticoids	17 875	5908	58	8.0	7.24	5.5, 9.4
NSAID + glucocorticoids + other drug (not anticoagulants)	1593	464	7	1.1	6.41	2.6, 13.2
NSAID + anticoagulants	1001	340	8	0.7	11.46	4.9, 22.6
NSAID + anticoagulants + other drug (not glucocorticoids)	178	35	0	0.1	–	–
NSAID + glucocorticoids + anticoagulants ± other drugs	154	29	1	0.1	18.74	0.2, 10.4
NSAID ± lowdose aspirin ± highdose aspirin	10 246	5542	76	13.8	5.52	4.3, 6.9
Former use of NSAID	145 877[1]	314 278	370	264.4	1.40	1.3, 1.5
Non use of any other drug[2]	144 584	294 676	267	224.9	1.19	1.0, 1.3
Current use of other drug[2] (not NSAID)	28 455	19 602	103	39.6	2.60	2.1, 3.2

[1]Among the 156 138 NSAID users, 145 877 were followed during periods of non use 90 or more days after a nonrenewed prescription.
[2]The category includes drugs suspected to predispose to UGIB (low- and high dose aspirin, anticoagulants and glucocorticoids).

was 3.6 times more than expected (95% CI = 3.3, 4.0). The population attributable risk was 15%. The risk was higher when NSAIDs were used in combination with other drugs such as glucocorticoids (O = 58; O/E = 7.2; 95% CI = 5.5, 9.4), anticoagulants (O = 8; O/E = 11.5; 95% CI = 4.9, 22.6) and aspirin (O = 76; O/E = 5.5; 95% CI = 4.3, 6.9).

There were 145 877 users of NSAIDs who had periods of non use at some time during follow-up (Table 2 lower panel). Of these, 144 584 were followed through periods of non use of any of the drugs considered, and during these periods 267 UGIBs were observed, which was slightly more than expected (O/E = 1.2; 95% CI = 1.0, 1.3). Former users of NSAIDs who had a prescription of one of the other drugs thought to increase risk had an O/E ratio of 2.6 for UGIB (O = 103; 95% CI = 2.1, 3.2).

The periods of NSAID only use were considered in more details (Table 3). The relative risk of UGIB was higher among women than among men, whereas there was no rising pattern in the O/E ratios according to age or number of prior NSAID prescriptions. The rate of hospitalization for UGIB, however, increased sharply with age ranging from 1.2 per 1000 person-years at ages below 60 years to 11.3 per 1000 person-years at ages above 70 years among NSAID only users. Analyses of risk of UGIB associated with use of the six most commonly used types of NSAIDs in Denmark showed the lowest risks associated with use of ibuprofen only (O/E = 2.4; 95% CI = 2.0, 2.9) and naproxen only (O/E = 3.0; 95% CI = 2.1, 4.2). The risk was highest for use of ketoprofen only (O/E = 6.3; 95% CI = 4.5, 8.5), while risk estimates for exclusive use of diclofenac, indomethacin, and piroxicam ranged between 4.3 and 5.0. The O/E ratios for UGIB were not lower for use of slow-release or enteric-coated tablets than the O/E ratio for plain tablets (Table 3). For use of suppositories, the risk was significantly higher, on the basis of 12 observed UGIBs, than that for use of plain tablets.

There were 89 415 persons who had periods of exclusive use of ibuprofen (Table 4). Among these, female users had a larger excess of UGIB than male users. There was no trend in risk by age or number of prior ibuprofen prescriptions. Of the total ibuprofen user group, 13 444 (15%) were regular users defined as those with at least three consecutive ibuprofen prescriptions. These users experienced an increasing risk of UGIB with increasing daily dose of ibuprofen, with use of less than 1000 mg per day of ibuprofen associated with a 2-fold increased risk of UGIB, and O/E ratios rising to 3.6 and 5.7 at 1000–1999 and 2000+ mg day^{-1}, respectively. Risk according to the above mentioned variables was also examined among 30 033 who used naproxen alone for specific periods (Table 5), and the results were similar to those found for ibuprofen. There was a dose–response relationship between naproxen and UGIB, with a three-fold increased risk for the lowest dose defined as less than 700 mg day^{-1}, and O/E ratios rising to 4.2 and 4.4 at higher doses.

The subcohort of persons with at least three NSAID prescriptions during 1991–95 was followed for a total of 59 609 person-years of use beginning with the third prescription, which gave a mean cumulative duration of use of 1.0 years (range 0–5 years). Risk estimates for periods of current and former use of NSAIDs for this subcohort were slightly higher than estimates found for the total cohort with at least one NSAID prescription.

Table 3 Observed (Obs) and expected (Exp) numbers and O/E ratios of UGIB in periods of use of NSAID only according to sex, age, number of prior prescriptions, type of NSAID, and route of administration. Exposure window is 90 days.

Periods of only use of NSAID	*Number of persons*	*Person-years*	*UGIB*			
			Obs	*Exp*	*O/E*	*95% CI*
Sex						
Men	68 551	37 447	135	46.5	2.90	2.4, 3.4
Women	84 331	57 540	230	54.7	4.21	3.7, 4.8
Age (years)						
<60	108 837	57 840	67	17.4	3.85	3.0, 4.9
60–69	18 573	14 253	40	13.6	2.93	2.1, 4.0
>69	25 472	22 894	258	70.2	3.68	3.2, 4.2
Number of prior NSAID prescriptions						
0	149 120	29 005	54	19.8	2.73	2.0, 3.6
1	82 424	14 880	50	12.8	3.99	3.0, 5.3
2	54 237	9252	43	9.1	4.72	3.4, 6.4
3	39 510	6444	25	7.1	3.50	2.3, 5.2
4	30 874	4899	21	5.9	3.57	2.2, 5.5
5+	26 898	30 509	172	46.8	3.68	3.1, 4.3
Type of NSAID						
Diclofenac	27 154	9854	43	8.8	4.87	3.5, 6.6
Ibuprofen	89 415	44 086	112	46.4	2.41	2.0, 2.9
Indomethacin	7420	5005	33	7.7	4.28	2.9, 6.0
Ketoprofen	18 634	6436	42	6.7	6.30	4.5, 8.5
Naproxen	30 033	12 812	35	11.5	3.03	2.1, 4.2
Piroxicam	10 399	4590	28	5.6	5.00	3.3, 7.2
Form and route of administration						
Tablets	131 139	73 313	253	77.8	3.25	2.9, 3.7
Slow-release tablets[1]	29 035	11 727	56	13.2	4.23	3.2, 5.5
Enteric-coated tablets[2]	14 297	5413	20	5.6	3.58	2.2, 5.5
Suppositories[3]	4659	1639	12	1.4	8.47	4.4, 14.8
Others (soluble tablets, mixture, etc.)	621	167	3	0.2	13.49	2.7, 39.4

[1]Indomethacin, diclofenac, ketoprofen, ibuprofen, tiaprofenic acid, flurbiprofen and tolfenamic acid.
[2]Diclofenac and naproxen.
[3]Indomethacin, diclofenac, ketoprofen, naproxen, piroxicam and tenoxicam.

All the results described above were derived using an exposure window for NSAIDs of 90 days (i.e. prescriptions were assumed to last 90 days). By changing the exposure window to 60 days, the O/E ratio of UGIB for current use of NSAIDs increased to 4.6 (95% CI = 4.2, 5.1) on the basis of 460 observed UGIBs, while an exposure window of 30 days increased the O/E ratio further to 5.6 (95% CI = 5.0, 6.2) on the basis of 333 observed UGIBs. Conversely, when risks of UGIB were calculated for periods 30–59 and 60–89 days after prescription, the O/E ratios declined to 3.2 (95% CI = 2.7, 3.9) and 2.1 (95% CI = 1.6, 2.8), respectively.

Discussion

This follow-up of a large general population in Denmark reveals that users of nonaspirin NSAIDs have on average received hospital diagnoses of UGIB at a rate approximately four times greater than persons of similar age and sex who have not been prescribed these products. The findings are consistent with emerging epidemiologic evidence from other countries showing elevations in risk of bleeding among groups of NSAID users [9–22]. Our data indicate that about 4.8 UGIB hospitalizations occurred per 1000 person-years of current NSAID use, compared with only about 1.2 per 1000 nonuser person-years. These incidence rates are very close to those reported among NSAID prescription recipients in the general populations of Saskatchewan, Canada [17], and somewhat lower than found among elderly persons prescribed NSAIDs in the United States [15] and Scotland [19]. UGIBs occur relatively commonly, the annual incidence of UGIB hospitalization in North Jutland exceeds the annual incidence for almost all individual cancers and for many serious diseases, and thus UGIB is an important public health issue [23]. Mortality from UGIB is non trivial with about 8–14% of patients hospitalized for UGIB not surviving [24, 25].

Table 4 Observed (Obs) and expected (Exp) numbers and O/E ratios of UGIB during periods of use of ibuprofen without use of other drugs according to sex, age, number of ibuprofen prescriptions and dose of ibuprofen. Exposure window is 90 days.

			UGIB			
Characteristics	*Number of persons*	*Person-years*	*Obs*	*Exp*	*O/E*	*95% CI*
Users with at least one ibuprofen prescription	89 415					
Sex						
Men	40 473	18 076	43	21.7	1.98	1.4, 2.7
Women	48 942	26 010	69	24.7	2.79	2.2, 3.5
Age (years)						
<60	64 639	27 204	20	8.1	2.48	1.5, 3.8
60–69	10 445	6487	12	6.2	1.92	1.0, 3.4
>69	14 331	10 395	80	32.1	2.49	2.0, 3.1
Number of prior ibuprofen prescriptions						
0	75 328	14 841	16	9.7	1.64	0.9, 2.7
1	38 176	6946	15	5.8	2.60	1.5, 4.3
2	24 238	4155	15	4.2	3.60	2.0, 5.9
3	17 424	2886	6	3.3	1.84	0.7, 4.0
4	13 418	2160	7	2.6	2.66	1.1, 5.5
5+	14 073	13 098	53	20.8	2.54	1.9, 3.3
Users with at least three consecutive ibuprofen prescriptions	13 444					
Dose of ibuprofen (mg day^{-1})						
<1000	7077	3692	12	5.7	2.10	1.1, 3.7
1000–1999	7776	5074	31	8.7	3.58	2.4, 5.1
≥2000	2325	1105	10	1.7	5.74	2.7, 10.6

Table 5 Observed (Obs) and expected (Exp) numbers and O/E ratios of UGIB during periods of use of naproxen without use of other drugs according to sex, age, number of naproxen prescriptions and dose of naproxen. Exposure window is 90 days.

			UGIB			
Characteristics	*Number of persons*	*Person-years*	*Obs*	*Exp*	*O/E*	*95% CI*
Users with at least one naproxen prescription	30 033					
Sex						
Men	12 298	4682	11	5.3	2.06	1.0, 3.7
Women	17 735	8130	24	6.2	3.86	2.5, 5.7
Age (years)						
<60	22 538	8625	8	2.3	3.45	1.5, 6.8
60–69	3255	1648	5	1.5	3.25	1.0, 7.6
>69	4240	2538	22	7.7	2.86	1.8, 4.3
Number of prior naproxen prescriptions						
0	22 984	4616	8	2.7	3.01	1.3, 5.9
1	11 347	2081	2	1.5	1.34	0.2, 4.8
2	6982	1235	4	1.0	3.85	1.0, 9.9
3	4819	822	3	0.8	3.86	0.8, 11.3
4	3643	604	1	0.6	1.63	0.0, 9.1
5+	4242	3455	17	5.0	3.43	2.0, 5.5
Users with at least three consecutive naproxen prescriptions	3530					
Dose of naproxen (mg day^{-1})						
<700	2208	1228	6	1.8	3.26	1.2, 7.1
700–1199	1538	962	6	1.4	4.18	1.5, 9.1
≥1200	608	279	2	0.5	4.37	0.5, 15.8

Women using NSAIDs tended to have higher UGIB risk than men, although no significant difference in risk by sex was observed. We found the relative increases in risk of UGIB among NSAID users across all age groups. These observations are consistent with a recent metaanalysis of 18 studies [22]. The underlying hospitalization rate for UGIB varied sharply with age, however, with UGIB rare among younger persons. Because of the link between

UGIB incidence and age, most of the NSAID-associated cases of UGIB in North Jutland occurred among persons over age 60 years. Taking into account the 3.6-fold increase in risk of UGIB associated with use of NSAIDs only, we estimate that about 15% of all cases of UGIB in the county over the 5 year study period were NSAID-related.

Information in the Pharmaco-Epidemiologic Prescription Database enabled examination of rates of UGIB according to type of NSAID. Others have reported fairly wide variation in UGIB rates among different NSAIDs, with ketoprofen and piroxicam generally associated with higher and ibuprofen with lower risks [2, 11, 13, 14, 16–20]. In our study, significant increases in risk of UGIB were associated with all types, although the magnitude of the increase varied by product. The risk estimates were largely in agreement with those in earlier reports, except for a higher risk confined to use of diclofenac in spite of similar recommended standard doses used in Denmark and other countries such as the US and the United Kingdom. The smallest increases were found for ibuprofen, followed by naproxen. The differences in risk by product type seem at least in part to be dose related. Ibuprofen is the medication most likely to be prescribed in lower (non anti-inflammatory) doses and is the only nonaspirin NSAID obtainable over the counter (OTC) in Denmark.

Although OTC purchases were not recorded, the North Jutland Prescription Database obtained data on all prescriptions of NSAIDs, including prescriptions on ibuprofen at or below maximum daily (1200 mg day^{-1}) OTC dose level. Our analyses revealed dose–response trends in risk of UGIB, with O/Es at the highest ibuprofen and naproxen doses being lower than, but beginning to approach, those associated with use of the prescription NSAIDs primarily used for treatment of rheumatoid arthritis and other inflammatory conditions. Others have also reported that risks of UGIB at high anti-inflammatory doses of ibuprofen and naproxen are similar to risks associated with other NSAIDs used for treatment of arthritis and other inflammatory diseases [16–18, 20] although in one study ibuprofen was associated with only half of the risk of GI toxicity as naproxen sodium [26]. However, our data show that even users prescribed less than 1000 mg day^{-1} of ibuprofen have an increased risk of UGIB, in accordance with other surveys assessing dose–response trends in UGIB among NSAID users, which tend to find increased risks at OTC doses. Indeed, our relative risk estimate of about a 2-fold increase corresponds closely with those found in eight studies for both aspirin and nonaspirin NSAIDs (including ibuprofen) at doses at or below maximum daily OTC levels [27].

Somewhat less than 40% of the NSAID users received three or more prescriptions over the entire study period. Risk of UGIB beginning with the third prescription was only slightly higher than risk across all uses, but there was an inconsistent pattern of rising risks with increasing prior use of NSAIDs assessed as number of prior prescriptions. Risk was shown to decrease substantially, however, following cessation of NSAID use. A significant residual effect was reported among former NSAID users in Scotland [19], but our findings of little trend in risk with increasing number of post prescriptions and a decline in risk following cessation of use suggest that the effects of NSAIDs upon UGIB are mainly acute, with little accumulated carry-over risk from prior use. We did observe small increases in UGIB risk among former users, but we could not rule out the possibility that some users continued use beyond 90 days postprescription and into periods we classified as non (former) use. Further indication of an acute effect is that the risk estimate increased with decreasing length of exposure window, with a greater than five-fold increase in risk of UGIB during NSAID use when prescriptions were assumed to last only 30 days. We chose 90 days as the prescription length to capture the main proportion of exposure to NSAID during current use, but this results in misclassification of exposure periods for some users and a resultant attenuation of the O/E ratio [28].

Risks of UGIB according to form and route of administration of NSAIDs have been sparsely investigated. A case-control study from Australia showed that rectal administration was associated with a higher risk than oral administration [11], while a Canadian nested case-control study found no marked difference between oral and rectal routes of administration or between enteric, slow-release or other oral forms of administration [17]. Our results show an increased risk associated with use of suppositories, and no beneficial effect of enteric coating or slow-release tablets. It must be mentioned that in Denmark suppositories involve NSAIDs generally associated with higher risk (see footnote of Table 3). Confounding by indication may also contribute to these results, since patients may have been prescribed these presumed low risk formulations because of previous gastrointestinal complications.

The highest risks of UGIB observed in this study were among persons who concurrently used NSAIDs and other drugs, such as corticosteroids and anticoagulants, known to increase risk of bleeding [1, 2]. Twenty percent of NSAID users in North Jutland had taken such drugs. The multiple users experienced a greater than 6-fold excess of UGIB compared with nondrug users, whereas the excess among those who used NSAIDs alone was 3.6-fold. We included both prophylactic (low-dose) and regular aspirin among these other medications (even though aspirin is also an NSAID). High doses of aspirin have long been known to increase bleeding risk. We and others

[11, 29–32] have previously reported that lower doses (100–150 mg) used primarily for protection against heart disease were linked to about a doubled risk of UGIB. Our findings thus indicate potential for an increase in risk of UGIB associated with the entire spectrum of NSAID medications.

Apart from use of corticosteroids and anticoagulants, established risk factors for UGIB include a history of ulcer and a serious systemic disorder, while *Helicobacter pylori* infection, smoking and alcohol consumption are possible risk factors [1]. The confounding and/or interactive effects of these factors could not be assessed in the present study. However, other studies have indicated that infection with *Helicobacter pylori* and smoking increase the risk of gastroduodenal mucosal injury associated with NSAID use at most minimally [1, 27, 33]. Use of alcohol does seem to increase this risk [27, 34] but in our study the potential effect of alcohol intake is likely to have been minimized, since we excluded all persons with alcoholism and liver cirrhosis from the study.

The present study has the advantage of considering the total population in one area of Denmark thus representing all socioeconomic groups. All hospitals in the county receiving emergency admissions report to the Regional Hospital Discharge Register, which secures complete follow-up for all UGIBs requiring admission to one of the hospitals in the county. In addition, utilization of the North Jutland Pharmaco-Epidemiologic Prescription Database ensured complete ascertainment of all use of prescription NSAIDs thus avoiding reliance upon self-reported analgesic use. NSAID users do make up a large proportion of the North Jutland population, but a substantial part of the users (62%) only received one or two prescriptions during the study period. These persons do contribute with observations and person-years but only during the short period of time when we assume that they take NSAIDs. Those with few prescriptions are also excluded from the background rates, and because numbers are high this does affect the statistical precision of the rates, but we judge that it will be most correct to exclude them since they did take NSAIDs at some point. However, our database could not assess OTC use of ibuprofen and aspirin. In general, the OTC use of nonaspirin NSAIDs in Denmark is 14% of the total NSAID use, but OTC use may be less common among persons with prescription use, so possible confounding by OTC analgesic use would lead to underestimation of the relative risk of UGIB associated with NSAIDs.

In conclusion, we were able to confirm earlier reports of about a four-fold increase in risk of UGIB among users of nonaspirin NSAIDs, which means that use of these drugs may explain approximately 15% of all UGIB in the North Jutland County of Denmark. Duration of use assessed as number of prior prescriptions had no systematic impact on the risk, and the risk declined sharply following cessation of use. Risk also varied according to type of NSAID. The lowest O/E ratio was found for users of ibuprofen and naproxen, among whom the risk depended strongly on daily dose, although all users including those taking doses below OTC levels were at increased risk of UGIB. Combining use of NSAIDs with use of glucocorticoids or anticoagulants increased the risk of UGIB even further, while no reductions in risk were associated with use of oral enteric-coated, oral slow-release or rectal formulations.

The staff at the Department of Health Insurance and Preventive Medicine and Hospital Discharge Registries in the County of North Jutland (Sygesikringen, Nordjyllands amt) are most gratefully thanked for excellent assistance in preparing the data for analyses.

The Pharmaco-Epidemiologic Prescription Database has been supported by grants from Speciallæge Heinrich Kopps Legat, Aalborg Stifts Julelotteri, The Medical Research Council of North Jutland, and The Danish Medical Research Council (grant no. 9700677). The activities of The Danish Epidemiology and Science Centre were funded by a grant from The Danish National Research Foundation, while the activities at the Institute of Cancer Epidemiology were supported by SmithKline Beecham and the International Epidemiology Institute.

References

1 Wolfe MM, Lichtenstein DR, Singh G. Gastrointestinal toxicity of nonsteroidal anti-inflammatory drugs. *N Engl J Med* 1999; **340**: 1888–1899.

2 Lanas A, Hirschowitz BI. Toxicity of NSAIDS in the stomach and duodenum. *Eur J Gastroenterol Hepatol* 1999; **11**: 375–381.

3 Schoen RT, Vender RT. Mechanisms of nonsteroidal anti-inflammatory drug-induced gastric damage. *Am J Med* 1989; **86**: 449–458.

4 Nielsen GL, Sørensen HT, Zhou W, Steffensen FH, Olsen J. Pharmacologic prescription database of North Jutland – a valid tool in pharmacoepidemiological research. *Int J Risk Safety Med* 1997; **10**: 203–205.

5 Capellá D. Descriptive tools and analysis. In *Drug Utilization Studies: Methods and Uses, European Series No. 45*, ed Dukes MNG. Copenhagen: WHO. Regional Publications, 1993: 55–78.

6 Andersen TF, Madsen M, Jørgensen J, Mellemkjær L, Olsen JH. The Danish National Hospital Register. A valuable source of data for modern health sciences. *Dan Med Bull* 1999; **46**: 263–268.

7 Danish National Board of Health. *Classification of Diseases, 8th Revision*. Copenhagen: National Board of Health, 1976.

8 Danish National Board of Health. *Classification of Diseases, 10th Revision*. Copenhagen: Munksgaard, 1992.

9 Gabriel SE, Jaakkimainen L, Bombardier C. Risk for serious gastrointestinal complications related to use of nonsteroidal anti-inflammatory drugs: a meta-analysis. *Ann Intern Med* 1991; **115**: 787–796.

10 Griffin MR, Piper JM, Daugherty JR, Snowden M, Ray WA. Nonsteroidal anti-inflammatory drug use and increased risk of peptic ulcer disease in elderly persons. *Ann Intern Med* 1991; **114**: 257–263.

11 Henry D, Dobson A, Turner C. Variability in the risk of major gastrointestinal complications from nonaspirin nonsteroidal anti-inflammatory drugs. *Gastroenterology* 1993; **105**: 1078–1088.

12 Kaufman DW, Kelly JP, Sheehan JE, *et al.* Nonsteroidal anti-inflammatory drug use in relation to major upper gastrointestinal bleeding. *Clin Pharmacol Ther* 1993; **53**: 485–494.

13 Garcia Rodriguez L, Jick H. Risk of upper gastrointestinal bleeding and perforation associated with individual nonsteroidal anti-inflammatory drugs. *Lancet* 1994; **343**: 769–772.

14 Langman MJ, Weil J, Wainwright P, *et al.* Risks of bleeding peptic ulcer associated with individual non-steroidal anti-inflammatory drugs. *Lancet* 1994; **343**: 1075–1078.

15 Smalley WE, Ray WA, Daughterty JR, Griffin MR. Nonsteroidal anti-inflammatory drugs and the incidence of hospitalizations for peptic ulcer disease in elderly persons. *Am J Epidemiol* 1995; **141**: 539–545.

16 Henry D, Lim LL, Garcia Rodriguez LA, *et al.* Variability in risk of gastrointestinal complications with individual non-steroidal anti-inflammatory drugs: results of a collaborative meta-analysis. *Br Med J* 1996; **312**: 1563–1566.

17 Perez Gutthann S, Garcia Rodriguez L, Raiford DS. Individual nonsteroidal anti-inflammatory drugs and other risk factors for upper gastrointestinal bleeding and perforation. *Epidemiology* 1997; **8**: 18–24.

18 Garcia Rodriguez L. Non-steroidal antiinflamatory drugs, ulcers and risk: a collaborative meta-analysis. *Semin Arthritis Rheum* 1997; **26**: 16–20.

19 MacDonald TM, Morant SV, Robinson GC, *et al.* Association of upper gastrointestinal toxicity of non-steroidal anti-inflammatory drugs with continued exposure: cohort study. *Br Med J* 1997; **315**: 1333–1337.

20 Garcia Rodriguez L. Variability in risk of gastrointestinal complications with different nonsteroidal anti-inflammatory drugs. *Am J Med* 1998; **104**: 30s–34s.

21 Singh G, Ramey DR. NSAID induced gastrointestinal complications: the ARAMIS perspective – 1997. *J Rheumatol Supplement* 1998; **51**: 8–16.

22 Hernández-Diaz S, Garcia Rodriguez L. Association between non-steroidal antiinflammatory drugs and upper gastrointestinal tract bleeding/perforation. An overview of epidemiologic studies published in the 1990s. *Arch Intern Med* 2000; **160**: 2093–2099.

23 Parkin DM, Muir CS, Whelan SL, Gao YT, Ferlay J, Powell J. *Cancer Incidence in Five Continents*, Vol. VI. Lyon: IARC Sci. Publications. 120, International Agency for Research on Cancer, 1992.

24 Rockall TA, Logan RFA, Devlin HB, Northfield TC. Incidence of and mortality from acute upper gastrointestinal haemorrhage in the United Kingdom. *Br Med J* 1995; **311**: 222–226.

25 Blatchford O, Davidson LA, Murray WR, Blatchford M, Pell J. Acute upper gastrointestinal haemorrhage in west of Scotland: case ascertainment study. *Br Med J* 1997; **315**: 510–514.

26 Strom BL, Schinnar R, Bilker WB, Feldman H, Farrar J, Carson J. Gastrointestinal tract bleeding associated with naproxen sodium vs ibuprofen. *Arch Intern Med* 1997; **157**: 2626–2631.

27 Blot WJ, McLaughlin JK. Over the counter non-steroidal anti-inflammatory drugs and risk of gastrointestinal bleeding. *J Epidemiol Biostatistics* 2000; **5**: 137–142.

28 Van Staa T-P, Abenhaim L, Leufkens H. A study of the effects of exposure misclassification due to the time-window design in pharmacoepidemiologic studies. *J Clin Epidemiol* 1994; **47**: 183–189.

29 Weil J, Colin-Jones D, Langman M, *et al.* Prophylactic aspirin and risk of peptic ulcer bleeding. *Br Med J* 1995; **310**: 827–830.

30 Kelly JP, Kaufman DW, Jurgelon JM, Sheehan J, Koff RS, Shapiro S. Risk of aspirin-associated major upper-gastrointestinal bleeding with enteric-coated or buffered product. *Lancet* 1996; **348**: 1413–1416.

31 Hansson L, Zanchetti A, Caruthers SG, *et al.* Effects of intensive blood pressure lowering and low-dose aspirin in patients with hypertension: principal results from the Hypertension Optimal Treatment (HOT) randomized trial. *Lancet* 1998; **351**: 1755–1762.

32 Sorensen HT, Mellemkjaer L, Blot WJ, *et al.* Risk of upper gastrointestinal bleeding associated with use of low-dose aspirin. *Am J Gastroenterol* 2000; **95**: 2218–2224.

33 Weil J, Langman MJS, Wainwright P, *et al.* Peptic ulcer bleeding. Accessory risk factors and interactions with non-steroidal anti-inflammatory drugs. *Gut* 2000; **46**: 27–31.

34 Neutel CN, Appel WC. The effect of alcohol abuse on the risk of NSAID-related gastrointestinal events. *Ann Epidemiol* 2000; **10**: 246–250.