Association of upper gastrointestinal toxicity of non-steroidal anti-inflammatory drugs with continued exposure: cohort study

T M MacDonald, S V Morant, G C Robinson, M J Shield, M M McGilchrist, F E Murray, D G McDevitt

Abstract

Objectives: To determine the profile of risk of upper gastrointestinal toxicity during continuous treatment with, and after cessation of, non-steroidal anti-inflammatory drugs.

Design: Cohort study with a prospectively constructed, population based, record linkage database containing details of exposure to all community dispensed non-steroidal anti-inflammatory drugs and also all admissions to hospital for upper gastrointestinal diagnoses.

Setting: The population of Tayside, Scotland.

Subjects: 52 293 subjects aged 50 and over who received one or more non-steroidal anti-inflammatory between 1 January 1989 and 31 December 1991 and 73 792 subjects who did not receive one during the same period (controls).

Main outcome measures: Admission to hospital for upper gastrointestinal bleeding and perforation, and admission for other upper gastrointestinal diagnoses.

Results: About 2% of the non-steroidal anti-inflammatory cohort were admitted with an upper gastrointestinal event during the study period compared with 1.4% of controls. The risk of admission for upper gastrointestinal haemorrhage and perforation was constant during continuous non-steroidal anti-inflammatory exposure and carried over after the end of exposure. The results were similar for admissions for all upper gastrointestinal events.

Conclusion: This study provides evidence that non-steroidal anti-inflammatory toxicity persists with continuous exposure. There seems to be carryover toxicity after the end of prescribing. These findings have implications for the management of patients requiring non-steroidal anti-inflammatory drugs.

Introduction

Many studies have established the association between use of non-steroidal anti-inflammatory drugs and admission to hospital for upper gastrointestinal haemorrhage and perforation and other upper gastrointestinal events.[1–13] Data on the associations between duration of exposure to non-steroidal anti-inflammatory drugs and these events are limited. Previous studies have suggested that upper gastrointestinal toxicity shortly after exposure does not persist,[5 9 11 13 14] either because adaptation to the drugs takes place[15 16] or because there is a depletion of susceptible patients among long term users.[17] We carried out a population based cohort study in patients aged 50 years or over to test the hypothesis that upper gastrointestinal toxicity is constant during exposure to non-steroidal anti-inflammatory drugs.

Subjects and methods

The study was carried out with the record linkage database of the Tayside Medicines Monitoring Unit (MEMO).[18] Since 1989 all dispensed prescriptions for non-steroidal anti-inflammatory drugs other than aspirin for the population of Tayside who are registered with a Tayside general practitioner have been entered on a database. Each record includes a community health number which is unique to each patient and from which their date of birth and sex can be derived.

All discharges from Tayside hospitals are coded with up to six diagnostic codes from *International Classification of Diseases,* ninth revision (ICD-9)[19] and up to four operation or procedure codes from the Office of Population Census and Surveys (fourth revision).[20] These discharge diagnoses are entered on the Scottish Morbidity Record 1 (SMR1) database, which also includes each patient's community health number. Thus, dispensed prescriptions and admission to hospital can be temporally linked.

Study population and study cohorts

The study population consisted of all subjects resident in Tayside and registered with a Tayside general practitioner between 1 January 1989 and 31 December 1991. The non-steroidal anti-inflammatory cohort consisted of all subjects in the study population aged 50 or over on 1 January 1989 who redeemed one or more prescriptions for a non-steroidal anti-inflammatory during the study period, and the control cohort consisted of all other subjects aged 50 or over.

Events

Events with a broad range of upper gastrointestinal diagnostic codes (ICD-9 280, 530.1-536.9, 578.0-578.9, and 787.1) were extracted from the SMR1 database for

Medicines Monitoring Unit, Department of Clinical Pharmacology, University of Dundee, Ninewells Hospital and Medical School, Dundee DD1 9SY
T M MacDonald, *reader in clinical pharmacology*
M M McGilchrist, *senior computer programmer*
F E Murray, *consultant gastroenterologist*
D G McDevitt, *professor of clinical pharmacology*
Searle, PO Box 53, High Wycombe, Buckinghamshire HP12 4HL
S V Morant, *statistician*
G C Robinson, *clinical project manager*
M J Shield, *medical director*
Correspondence to: Dr MacDonald

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the study cohorts. The diagnoses were verified from original case records by medically qualified staff blinded to non-steroidal anti-inflammatory exposure and, in equivocal cases, were further reviewed by two consultant physicians, one of whom was a gastroenterologist.[21]

The highest ranking of the following diagnoses (in descending rank order) was ascribed to each event: (*a*) oesophageal varices; (*b*) gastric, duodenal, stomal, or small bowel ulcer; (*c*) oesophageal ulcer; (*d*) gastric or duodenal erosions; (*e*) gastritis or duodenitis; (*f*) gastric or duodenal erosions, or both; (*g*) oesophagitis; (*h*) other diagnoses—for instance, the Mallory Weiss syndrome; (*i*) investigated but no cause identified (for upper gastrointestinal haemorrhage only); and (*j*) a haemorrhage recorded in the case records but not investigated or an SMR1 diagnostic code indicating an upper gastrointestinal event in patients for whom the case records could not be located.

Two categories of diagnoses were used for analysis: complicated upper gastrointestinal events (upper gastrointestinal haemorrhage or upper gastrointestinal perforation) and any upper gastrointestinal event (any of diagnoses (*a*) to (*j*)).

Definition of drug exposure

There was no evidence that a substantial proportion of patients received regular repeat prescriptions for non-steroidal anti-inflammatories at intervals of other than

Table 1 Numbers of patients and dispensed prescriptions by age, sex, and history of admission to hospital for upper gastrointestinal event

	No history of admission to hospital			History of admission to hospital			Total		
	NSAID cohort			NSAID cohort			NSAID cohort		
Sex and age (years)	Prescriptions	No of patients	No of controls	Prescriptions	No of patients	No of controls	Prescriptions	No (%) of patients	No (%) of controls
Women									
50-59	48 346	9 616	11 517	1 714	299	258	50 060	9 915 (25.4)	11 775 (29.9)
60-69	59 136	9 594	12 007	2 327	313	347	61 463	9 907 (31.1)	12 354 (31.3)
70-79	53 369	7 528	8 720	2 743	395	396	56 112	7 923 (28.4)	9 116 (23.1)
80-89	24 594	3 387	4 838	1 940	257	346	26 534	3 644 (13.4)	5 184 (13.2)
⩾90	3 003	700	911	216	44	66	3 219	744 (1.6)	977 (2.5)
Total	188 448	30 825 (61.5*)	37 993 (53.6*)	8 940	1308 (60.9*)	1413 (49.2*)	197 388	32 133 (61.4*)	39 406 (53.4*)
Men									
50-59	27 156	6 972	12 550	1 175	246	442	28 331	7 218 (28.3)	12 992 (37.8)
60-69	35 904	6 726	11 148	1 411	276	491	37 315	7 002 (37.2)	11 639 (33.8)
70-79	24 568	4 003	6 683	1 183	224	339	25 751	4 227 (25.7)	7 022 (20.4)
80-89	7 301	1 139	2 326	410	90	169	7 711	1 229 (7.7)	2 495 (7.3)
⩾90	1 072	479	220	26	5	18	1 098	484 (1.1)	238 (0.7)
Total	96 001	19 319 (38.5*)	32 927 (46.4*)	4 205	841 (39.1*)	1459 (50.8*)	100 206	20 160 (38.6*)	34 386 (46.6*)
All subjects	284 449	50 144	70 920	13 145	2149	2872	297 594	52 293	73 792

NSAID=non-steroidal anti-inflammatory drug. *Percentage of total number of subjects (men and women).

Table 2 Numbers of complicated and uncomplicated events by age (years) in cohort given non-steroidal anti-inflammatory drugs and in control cohort

	50-59		60-69		70-79		80-89		⩾90		Total	
Type of event	Treatment	Control	Treatment	Control	Treatment	Control	Treatment	Control	Treatment	Control	Treatment	Control
Complicated events												
Haemorrhage:												
Varices	2	6	3	2	0	1	1	0	0	0	6	9
Duodenal ulcer	14	22	27	20	22	27	20	18	1	0	84	87
Gastric ulcer	5	17	11	20	17	13	14	7	1	0	48	57
Gastric and duodenal ulcers	1	0	3	3	0	3	3	0	1	0	8	6
Oesophageal ulcer	1	2	2	4	6	6	3	3	1	1	13	16
Gastric and duodenal erosions	5	3	3	7	10	6	2	1	1	1	21	18
Gastritis or duodenitis	12	11	14	14	28	11	9	7	0	2	63	45
Oesophagitis	5	3	7	18	13	16	7	7	0	0	32	44
Other diagnosis	1	4	1	1	2	0	0	3	0	0	4	8
Investigated but no cause identified	8	10	16	11	22	12	6	5	1	0	53	38
Not investigated	6	12	21	34	25	43	32	49	6	14	90	152
Perforation:												
Gastric ulcer	1	0	3	2	3	2	4	0	0	0	11	4
Duodenal ulcer	7	6	9	9	11	7	13	4	1	0	41	26
Total complicated events	68	96	120	145	159	147	114	104	13	18	474	510
Uncomplicated events												
Duodenal ulcer	13	13	20	23	20	12	8	5	0	0	61	53
Gastric ulcer	12	8	31	18	18	14	11	3	3	0	75	43
Gastric and duodenal ulcers	1	2	5	1	4	1	1	1	0	0	11	5
Oesophageal ulcer	5	14	4	13	13	11	1	1	0	0	23	39
Gastric or duodenal erosions	3	12	9	14	5	11	2	1	0	0	19	38
Gastritis or duodenitis	50	54	54	51	39	34	22	10	1	0	166	149
Oesophagitis	59	42	60	60	56	50	28	15	2	1	205	168
Total uncomplicated events	143	145	183	180	155	133	73	36	6	1	560	495
All events	211	241	303	325	314	280	187	140	19	19	1034	1005

Table 3 Patient years, events, and unadjusted event rates (per thousand patient years) in the two cohorts for patients with and without history of admission to hospital for any upper gastrointestinal event and who did or did not use ulcer healing drugs during study period

	No ulcer healing drug					Ulcer healing drug				
		Any event*		Complicated event†			Any event		Complicated event†	
Detail	Patient years	No of events	Rate (95% CI)	No of events	Rate (95% CI)	Patient years	No of events	Rate (95% CI)	No of events	Rate (95% CI)
NSAID cohort										
No history:										
Before first NSAID	41 749	82	2.0 (1.6 to 2.4)	26	0.6 (0.4 to 0.9)	8 669	54	6.2 (4.6 to 8.1)	13	1.5 (0.8 to 2.6)
During NSAID exposure	21 737	236	10.9 (9.5 to 12.3)	152	7.0 (5.9 to 8.2)	6 730	111	16.5 (13.6 to 19.8)	52	7.7 (5.8 to 10.1)
After NSAID exposure	56 656	244	4.3 (3.8 to 4.9)	118	2.1 (1.7 to 2.5)	13 618	169	12.4 (10.6 to 14.4)	58	4.3 (3.2 to 5.5)
Total	120 143	562	4.7 (4.3 to 5.1)	296	2.5 (2.2 to 2.8)	29 018	334	11.5 (10.3 to 12.8)	123	4.2 (3.5 to 5.1)
With history:										
Before first NSAID	790	17	21.5 (12.6 to 34.2)	8	10.1 (4.4 to 19.9)	1 121	19	16.9 (10.2 to 26.3)	7	6.2 (2.5 to 12.8)
During NSAID exposure	412	11	26.7 (13.4 to 47.3)	5	12.1 (4.0 to 28.1)	821	24	29.2 (18.8 to 43.2)	10	12.2 (5.9 to 22.3)
After NSAID exposure	1 224	17	13.9 (8.1 to 22.1)	6	4.9 (1.8 to 10.6)	1 858	50	26.9 (20.0 to 35.3)	19	10.2 (6.2 to 15.9)
Total	2 427	45	18.5 (13.6 to 24.7)	19	7.8 (4.7 to 12.2)	3 801	93	24.5 (19.8 to 29.9)	36	9.5 (6.6 to 13.1)
Control cohort										
No history	186 107	573	3.1 (2.8 to 3.3)	327	1.8 (1.6 to 2.0)	25 965	283	10.9 (9.7 to 12.2)	110	4.2 (3.5 to 5.1)
With history	4 025	44	10.9 (8.0 to 14.7)	25	6.2 (4.0 to 9.2)	4 443	105	23.6 (19.4 to 28.5)	48	10.8 (8.0 to 14.3)

NSAID=non-steroidal anti-inflammatory drug. *Any upper gastrointestinal event: any of diagnoses (*a*) to (*j*) (see text).
†Complicated gastrointestinal event: upper gastrointestinal haemorrhage or upper gastrointestinal perforation.

4 weeks. Sixty per cent of repeat prescriptions were filled within 45 days of the pervious prescription, and these were taken to imply continuous treatment. An interval between prescriptions of more than 45 days was taken to imply a new course of treatment. Exposure to a non-steroidal anti-inflammatory drug was assumed to last for 45 days after the final prescription in a continuous course of treatment.

Definition of risk factors

The potential risk factors examined were: age, sex, history of previous admission for an upper gastrointestinal event, current exposure to non-steroidal anti-inflammatory drug, type of drug, dose, duration of continuous exposure and non-exposure to non-steroidal anti-inflammatory drug, and the use of a drug for ulcer healing at any time during the study period.

All admissions for complicated or any upper gastrointestinal events in the nine years before 1 January 1989 were regarded as historical events.

Drug doses were categorised as low, medium, or high according to their data sheets. Ulcer healing drugs were those defined in section 1.3 of the *British National Formulary*.[22]

All courses of treatment were divided into the first, second, fourth to sixth, or subsequent months of exposure. The total exposure time and the total number of events in each of these periods were calculated. Non-exposure between courses of non-steroidal anti-inflammatory treatment were divided into similar consecutive periods. In the non-steroidal anti-inflammatory cohort a distinction was made between the period before first exposure and subsequent periods of non-exposure.

Analyses

Each patient's first admission for any upper gastrointestinal event in the study period was defined as the outcome event. All subsequent events and exposure were censored. All uncensored patient days of exposure and non-exposure to non-steroidal anti-inflammatory drugs were classified by the above risk factors and event rates for every combination of these factors were calculated. Events rates in the control cohort were also classified by the relevant risk factors.

Formal analyses were carried out by using a Poisson model for the number of events. The total number of days at risk to each combination of factors (in log units) was used as an offset variable.[23] Separate analyses were carried out for complicated and any events, and the results are presented as relative risks with 95% confidence intervals.

Results

Exposure to non-steroidal anti-inflammatory drugs

During the study period 52 293 subjects received 297 594 prescriptions for non-steroidal anti-inflammatories (table 1). Over half the subjects in the study received only one or two prescriptions, and only 7.9% received 20 or more prescriptions. The average was 5.7 prescriptions per subject over 3 years. The control group consisted of 73 792 subjects.

Table 4 Patient years of exposure and relative risks for complicated and any upper gastrointestinal events by age, use of ulcer healing drugs, and exposure to non-steroidal anti-inflammatory drugs

	Patient years of exposure	Relative risk (95% CI)	
Detail		Complicated event	Any event
Men	57 489	1.00	1.00
Women	91 671	0.94 (0.82 to 1.08)	0.92 (0.75 to 1.23)
Age (years):			
50-59	49 480	1.00	1.00
60-69	48 618	1.53 (1.10 to 2.12)	1.23 (1.02 to 1.50)
70-79	34 220	2.85 (2.10 to 3.88)	1.80 (1.49 to 2.18)
80-89	13 329	5.36 (3.88 to 7.41)	2.88 (2.33 to 3.56)
⩾90	3 512	3.04 (1.58 to 5.85)	1.43 (0.85 to 2.41)
Ulcer healing drug:			
No	120 143	1.00	1.00
Yes	29 018	1.54 (1.24 to 1.90)	2.45 (1.96 to 2.58)
NSAID exposure:			
Before current exposure	50 418	1.00	1.00
Exposed to NSAID	28 468	8.00 (5.63 to 11.4)*	3.94 (3.21 to 4.83)*
Carry over	70 274	3.02 (2.12 to 4.31)†	2.06 (1.69 to 2.51)†

NSAID=non-steroidal anti-inflammatory drug.
*Trend with duration of exposure: P=0.243 for complicated event and 0.403 for any event.
†Trend with time since last exposure: P=0.006 for complicated event and <0.001 for any event.

Table 5 Patient years of exposure to individual non-steroidal anti-inflammatory drugs and risks of any and complicated upper gastrointestinal events on each relative to ibuprofen

Drug	Patient years of exposure	Relative risk (95% CI)	
		Complicated event	Any event
Fenoprofen	79	4.74 (1.09 to 20.6)	3.08 (0.72 to 13.1)
Azapropazone	767	3.70 (1.85 to 7.42)	4.07 (2.45 to 6.74)
Piroxicam	2 199	3.31 (5.79 to 1.89)	2.82 (1.81 to 4.38)
Flurbiprofen	710	2.37 (1.04 to 5.40)	2.31 (1.22 to 4.38)
All others	1 607	1.85 (0.96 to 3.57)	1.91 (1.16 to 3.15)
Diclofenac retard	4 031	1.63 (0.91 to 2.93)	1.68 (1.08 to 2.62)
Diclofenac	1 351	1.35 (0.59 to 3.10)	1.35 (0.69 to 2.62)
Ketoprofen	1 078	1.40 (0.58 to 3.36)	1.29 (0.65 to 2.56)
Naproxen	4 789	1.38 (0.77 to 2.49)	1.44 (0.92 to 2.45)
Mefenamic acid	2 123	1.35 (0.67 to 2.75)	1.81 (1.11 to 2.95)
Ibuprofen	6 294	1.00	1.00
Indomethacin	1 798	0.98 (0.42 to 2.25)	1.25 (0.69 to 2.25)
Nabumetone	649	0.61 (0.14 to 2.69)	0.37 (0.09 to 1.57)
Fenbufen	987	0.43 (0.10 to 1.89)	0.50 (0.18 to 1.42)
Dose:			
Low	10 533	1.00	1.00
Medium	12 241	1.41 (1.03 to 1.93)	1.25 (0.98 to 1.58)
High	5 694	1.92 (1.18 to 3.14)	1.39 (0.93 to 2.07)

Gastrointestinal events

In the non-steroidal anti-inflammatory cohort there were 1034 events of which 474 were complicated (table 2). The unadjusted event rates (table 3) were substantially different in subjects with and without a history of admission for any upper gastrointestinal event, and a highly significant ($P < 0.001$) interaction existed between history of admission and exposure to non-steroidal anti-inflammatories which could not be accounted for by the other risk factors in the statistical model. Subsequent analyses were therefore confined to subjects without a history of admission.

In the control cohort there were 1005 events, of which 510 were complicated. The unadjusted event rates in the control cohort were higher for those with a history of admission and for those who took ulcer healing drugs. Event rates in the control cohort were higher than those in the non-steroidal anti-inflammatory cohort before those patients' first exposure to the drugs.

Age and use of ulcer healing drugs

In the non-steroidal anti-inflammatory cohort the risk of both any and complicated events increased with age and was higher among patients who used an ulcer healing drug during the study period (table 4). Similar relative risks for these factors were observed in the control cohort (1.63, 2.93, 4.78, and 5.05 in the 60-69, 70-79, 80-89, and ≥90 age bands, respectively, relative to the 50-59 age band and 2.10 for users of ulcer healing drugs for complicated events).

Duration of continuous exposure

The risk of a complicated event rose between five and 10-fold during exposure relative to the pre-exposure periods in the same subjects. There was no evidence of a trend during periods of continuous exposure (table 4, figure). The risk of any upper gastrointestinal event rose between threefold and fivefold and also did not show a trend with continuous exposure.

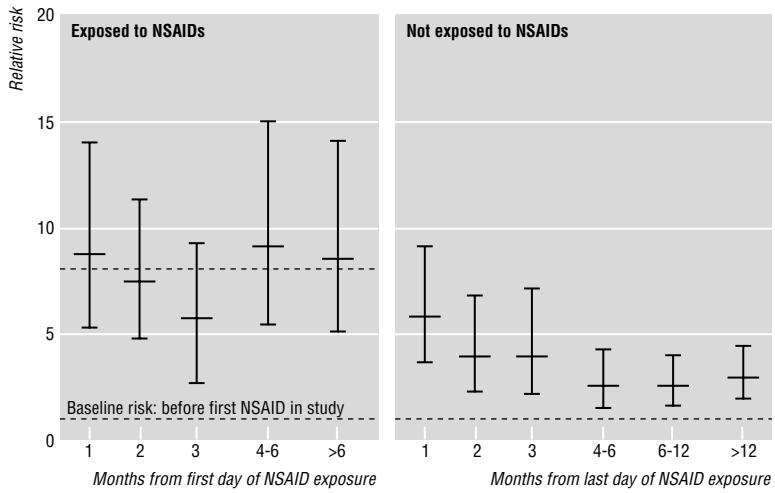
Duration of continuous non-exposure

After the discontinuation of treatment the risks of both complicated and any events remained higher than those observed in the periods before exposure in the same subjects. The risk decreased with increasing time since last exposure, but it remained higher than the baseline risk after a year of non-exposure (table 4, figure).

Dose and type of non-steroidal anti-inflammatory

There was evidence that both complicated and any events varied between drugs ($P = 0.005$ and $P < 0.001$, respectively, for the overall tests of significance). The risks during exposure to each drug relative to ibuprofen, the non-steroidal anti-inflammatory with the greatest exposure, are shown in table 5.

There was evidence of a greater risk of complicated events on medium and high doses of non-steroidal anti-inflammatory drugs relative to low doses.



Relative risks (95% confidence intervals) for risk of admission for complicated upper gastrointestinal events during each time period of continuous exposure (mean value shown as upper dotted line) and during each time period of subsequent continuous non-exposure to non-steroidal anti-inflammatory drugs (NSAIDs)

Discussion

The major finding in this study is that the increased risks of admission to hospital for both complicated and any upper gastrointestinal event associated with exposure to non-steroidal anti-inflammatory drugs are constant during continuous exposure. Furthermore, some excess risks seem to persist for at least a year after last exposure.

Our findings differ from those of case-control studies in which outcome events determine the duration of a course of treatment and which then use that duration as an explanatory variable in statistical analyses.[5 9 11 13 14] This can induce apparent relations which are arithmetic artefacts.

We found higher risks in the control cohort than in the period before exposure in the non-steroidal anti-inflammatory cohort. This suggests that general practitioners are taking account of risk factors not available in this analysis when prescribing non-steroidal anti-inflammatory drugs and that consequently the drug cohort is a lower risk population than the control group. The non-steroidal anti-inflammatory group have therefore been used as their own controls in our analysis.

We found that the risk of complicated and any events remained after exposure ceased. This may be due to subjects making their prescription last longer than intended. The effect of intermittent self treatment with leftover drug combined with the use of non-prescription use could account for the increased risks observed one year after last apparent exposure.

Our results agree closely with previous observations of the relative risks of complicated upper gastrointestinal events among different non-steroidal anti-inflammatory drugs and that the risk increases with age and dose.[12 13] Event rates were higher among subjects who used drugs for ulcer healing during the study period, perhaps because their use is a marker of previous or symptomatic upper gastrointestinal diseases.

A history of admission for an upper gastrointestinal event was a major risk factor. Risks attributable to non-steroidal anti-inflammatory exposure in patients with such a history were similar to those in patients with no history, but the relative risks were smaller because of the substantially higher baseline risk before exposure (table 3).

In this study, data on prescribed aspirin and over the counter drugs were unavailable, and the indications for the prescribed non-steroidal anti-inflammatory drugs were not known. We could not control for the confounding effects of smoking, alcohol consumption, and the use of anticoagulants or oral steroids, and we did not know which subjects had a history of upper gastrointestinal disease as outpatients. Any of these factors may confound the results of this study.

This study, however, is a cohort rather than a case-control study, with complete follow up over the study period. It used a population representing all socioeconomic groups and with universal healthcare coverage. Dispensed prescribing data was used thus eliminating primary non-compliance as a source of bias.[24] The wide range of diagnostic codes searched ensured a high probability that all admissions for the events of interest were captured, and primary hospital case records were used to validate the diagnoses.

The conclusions were robust to two sensitivity analyses. One confirmed that using a 45 day exposure period after a prescription for a non-steroidal anti-inflammatory drug was not a critical assumption. The second confirmed that excluding subjects not resident in the Tayside area for the entire study period had no material effect on the analyses.

Our findings have important implications for non-steroidal anti-inflammatory treatment. Such treatment seems to increase the risks of upper gastrointestinal events by similar proportions in all age groups over 50 years, but the attributable risk in elderly patients is substantially greater because their baseline risk is higher. The risk varies with type and dose, persists with continuing treatment, and seems also to carry over after the end of treatment. Patients at high risk should ideally avoid non-steroidal anti-inflammatory drugs altogether, but should such treatment be necessary, drugs known to carry least risk should be used and consideration given to the use of measures to reduce toxicity.

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Key messages

- The risk of upper gastrointestinal toxicity associated with non-steroidal anti-inflammatory drugs is constant with continuous exposure
- Gastrointestinal toxicity continues for some time after treatment stops
- Such toxicity is common in older patients and patients with a history of upper gastrointestinal disease
- Non-steroidal anti-inflammatory drugs should be avoided when possible; when they are used the lowest effective dose of the least toxic drug should be used for the shortest period possible

Conflict of interest: Searle, which funded the research, manufactures non-steroidal anti-inflammatory drugs.

1 Somerville K, Faulkner G, Langman M. Non-steroidal anti-inflammatory drugs and bleeding peptic ulcer. *Lancet* 1986;i:462-4.
2 Beard K, Walker AM, Perera DR, Jick H. Non-steroidal anti-inflammatory drugs and hospitalisation for gastroesophageal bleeding in the elderly. *Arch Intern Med* 1987;147:1621-3.
3 Carson JL, Strom BL, Morse ML, West SL, Soper KA, Stolley PD, et al. The association of non-steroidal anti-inflammatory drugs with upper gastrointestinal tract bleeding. *Arch Intern Med* 1987;147:1054-9.
4 Henry DA, Johnston A, Dobson A, Duggan J. Fatal peptic ulcer complications and the use of non-steroidal anti-inflammatory drugs, aspirin, and corticosteroids. *BMJ* 1987;295:1227-9.
5 Griffin MR, Ray WA, Schaffner W. Non-steroidal anti-inflammatory drug use and death from peptic ulcer in elderly persons. *Ann Intern Med* 1988;109:359-63.
6 Levy M, Miller DR, Kaufman DW, Siskind V, Schwingl P, Rosenberg L, et al. Major upper gastrointestinal tract bleeding. *Arch Intern Med* 1988;148:281-5.
7 Fries JF, Miller SR, Spitz PW, Williams CA, Hubert HB, Block DA. Toward an epidemiology of gastropathy associated with non-steroidal anti-inflammatory drug use. *Gastroenterology* 1989;96:647-55.
8 Beardon PHG, Brown SV, McDevitt DG. Gastrointestinal events in patients prescribed non-steroidal anti-inflammatory drugs: a controlled study using record linkage in Tayside. *Q J Med* 1989;71:497-505.
9 Griffin MR, Piper JM, Daughtery J, Snowden M, Ray WA. Non-steroidal anti-inflammatory drug use and increased risk for peptic ulcer disease in elderly persons. *Ann Intern Med* 1991;114:257-63.
10 Laporte J-R, Carne X, Vidal X, Moreno V, Juan J. Upper gastrointestinal bleeding in relation to previous use of analgesics and non-steroidal anti-inflammatory drugs. *Lancet* 1991;337:85-9.
11 Henry D, Dobson A, Turner C. Variability in the risk of major gastrointestinal complications from non-aspirin, non-steroidal anti-inflammatory drugs. *Gastroenterology* 1993;105:1078-8.
12 Garcia-Rodriguez LA, Jick H. Risk of upper gastrointestinal bleeding and perforation associated with individual non-steroidal anti-inflammatory drugs. *Lancet* 1994;343:769-72.
13 Langman MJS, Well J, Wainwright P, Lawson DH, Rawlins MD, Logan RFA, et al. Risk of bleeding peptic ulcer associated with individual non-steroidal anti-inflammatory drugs. *Lancet* 1994;343:1075-8.
14 Carson JL, Strom BL, Morse ML, West SL, Soper KA, Stolley PD, et al. The relative gastrointestinal toxicity of the non-steroidal anti-inflammatory drugs. *Arch Intern Med* 1987;147:1054-9.
15 Graham DY, Smith JL, Spjut HJ, Torres E. Gastric adaptation: studies in humans during continuous aspirin administration. *Gastroenterology* 1988;95:327-33.
16 Shorrock CJ, Prescott RJ, Rees WDW. The effects of indomethacin on gastroduodenal morphology and mucosal pH gradient in the healthy human stomach. *Gastroenterology* 1990;99:334-9.
17 Moride Y, Abenheim L. Evidence of the depletion of susceptibles effect in non-experimental pharmacoepidemiologic research. *J Clin Epidemiol* 1994;47:731-7.
18 MacDonald TM, McDevitt DG. The Tayside medicines monitoring unit (MEMO) In: Strom BL, ed. *Pharmacoepidemiology*. 2nd ed. Chichester: Wiley, 1994:245-55.
19 International Classification of Diseases. *Manual of the international statistical classification of diseases, injuries and causes of death*. Geneva: World Health Organisation, 1977.
20 Office of Population Census and Surveys. *Tabular list of the classification of surgical operations and procedures*. 4th rev. London: HMSO, 1990.
21 Dornan S, Murray FE, White G, McGilchrist MM, Evans JMM, MacDonald TM. Assessment of accuracy of upper gastrointestinal diagnoses in Scottish Morbidity Record 1 data in Tayside. *Health Bull (Edinb)* 1995;53:274-9.
22 British Medical Association and Royal Pharmaceutical Society of Great Britain. *British National Formulary*. London: Pharmaceutical Press, 1994:34-9. (No 28, September 1994.)
23 McCullagh P, Nelder JA. *Monographs on statistics and applied probability 37: general linear models*. 2nd ed. London: Chapman and Hall, 1989:193-244.
24 Beardon PHG, McGilchrist MM, McKendrick AD, McDevitt DG, MacDonald TM. Primary non-compliance with prescribed medication in primary care. *BMJ* 1993;307:846-8.

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