REVIEW

Time dependent risk of gastrointestinal complications induced by non-steroidal anti-inflammatory drug use: a consensus statement using a meta-analytic approach

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Objectives: To provide an updated document assessing the global, NSAID-specific, and time dependent risk of gastrointestinal (GI) complications through meta-analyses of high quality studies.

Methods: An exhaustive systematic search was performed. Inclusion criteria were: RCT or controlled study, duration of 5 days at least, inactive control, assessment of minor or major NSAID adverse effects, publication range January 1985 to January 2003. The publications retrieved were assessed during a specifically dedicated WHO meeting including leading experts in all related fields. Statistics were performed conservatively. Meta-regression was performed by regressing NSAID adjusted estimates against study duration categories.

Results: Among RCT data, indolic derivates provided a significantly higher risk of GI complications related to NSAID use than for non-users: RR = 2.25 (1.00; 5.08) than did other compounds: naproxen: RR = 1.83 (1.25; 2.68); diclofenac: RR = 1.73 (1.21; 2.46); piroxicam: RR = 1.66 (1.14; 2.44); tenoxicam: RR = 1.43 (0.40; 5.14); meloxicam: RR = 1.24 (0.98; 1.56), and ibuprofen: RR = 1.19 (0.93; 1.54). Indometacin users had a maximum relative risk for complication at 14 days. The other compounds presented a better profile, with a maximum risk at 50 days. Significant additional risk factors included age, dose, and underlying disease. The controlled cohort studies provided higher estimates: RR = 2.22 (1.7; 2.9). Publication bias testing was significant, towards a selective publication of deleterious effects of NSAIDs from small sized studies.

Conclusion: This meta-analysis characterised the ''compound'' and ''time'' aspects of the GI toxicity of non-selective NSAIDs. The risk/benefit ratio of such compounds should thus be carefully and individually evaluated at the start of long term treatment.

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used for the treatment of pain, fever, and inflammation. The worldwide NSAID market for both occasional and chronic users has been conservatively estimated at over 60 million people, and some NSAIDs (aspirin, naproxen, ibuprofen, etc) are among the most popular over the counter drugs.[1][2] Chronic NSAID treatment effectively reduces the symptoms of many painful arthritic syndromes, but induces adverse gastrointestinal (GI) complications, ranging from abdominal discomfort to life threatening GI ulceration, bleeding, and perforation.[3][4] Indeed, through their non-specific inhibition of the two cyclo-oxygenase isoenzymes, both aspirin and conventional NSAIDs induce gastroduodenal damage,[5][6] and are now considered as a major cause of iatrogenic pathology.[7] The most common clinical manifestations of NSAID related GI damage to tissue are a combination of gastroduodenal erosions and ulcerations, often called NSAID induced gastropathy,[4] affecting 25–50% of chronic NSAID users. NSAID induced gastropathy may limit long term NSAID treatment and causes a significant financial burden to the healthcare system.[4][8][9]

In the late 1980s and 1990s, drug related adverse reactions observed with NSAIDs were assessed in epidemiological studies, mostly cross sectional and case controlled. Their results were pooled in several quantitative systematic reviews[10–12] aiming at clarifying the relationship between NSAID use and GI complications. They concluded that exposure to NSAIDs resulted in a threefold increase in the risk of perforation, ulcers, or bleeding in comparison with the risk for non-users. Additional risk factors were shown to be an age greater than 60 years, a previous history of GI events, concomitant corticosteroid and anticoagulant use, and the presence of *Helicobacter pylori*. This latter risk factor has been extensively explored in a recent meta-analysis.[12] A synergism was found between NSAIDs and *H pylori* infection in the risk of peptic ulcers, despite the presence of still unknown sources of heterogeneity in this relation. The odds ratio of developing an ulcer when exposed to NSAIDs in the presence of *H pylori* was evaluated as greater than 2.

However, despite the highest level of sophistication of these quantitative systematic reviews, the studies included might not be relaying the best level of evidence. As noted by Hawkey,[7] Bollini *et al*,[9] and Gabriel *et al*,[10] most of the meta-analyses focused on cross sectional and retrospective trials, but such designs have been shown to induce overestimated results compared with randomised controlled trials (RCTs) and/or controlled longitudinal cohort studies. The reasons are that RCTs provide a more accurate way to control for confounding factors and bias, and the odds ratios in this

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Abbreviations: ANOVA, analysis of variance; GI, gastrointestinal; NSAIDs, non-steroidal anti-inflammatory drugs; RCT, randomised controlled trial; RR, relative risk

setting are less conservative estimates than relative risk. A meta-analysis of a high quality RCT is thus, according to the Cochrane Collaboration, the best source of medical evidence. Few attempts have been made to characterise the complex time-effect relationship between NSAID intake and GI side effects. The gaps in the available publications reflect the need for further large epidemiological studies examining these important questions. The need for additional research is supported by the widespread use of conventional, non-specific NSAIDs, despite the better GI safety profile of cyclo-oxygenase-2 inhibitors or the combination of NSAIDs and prostaglandins or proton pump inhibitors.[13]

Our goal was to provide an updated document accurately assessing the risk of GI complications induced by the most commonly used non-selective NSAIDs and to characterise the relationship between the duration of exposure and the relative risk of GI complications.

METHODS

An exhaustive search of all potentially appropriate publications was performed, following a predefined protocol. Electronic sources included Medline and Premedline, Biosis Preview, Healthstar, Embase, Cochrane Library of Randomised Controlled Trials, Current Contents, EBM reviews, and the internet. Because all reports are not indexed in these databases, we conducted a hand search of the reference section. The strategy was derived from the sensitive search strategy currently recommended by the Cochrane Collaboration Musculoskeletal Group, and the results were added to those provided by another validated method.[14]

We retrieved any RCT and controlled cohort study assessing the relationship between exposure to NSAIDs and adverse GI events. Seven NSAIDs were individually investigated: indometacin, naproxen, diclofenac, piroxicam, tenoxicam, meloxicam, and ibuprofen. Other compounds

Table 1 RCTs included in the analysis

Ref	Author	NSAID	Dose	Indication	Treated group size	Placebo group size	Outcomes
19	Laerum et al	Diclofenac	150 mg/day	Recurrent renal colic	41	39	GI-minor
25	Wahlström et al	Diclofenac	150 mg/day	Heterotopic ossification after hip arthroplasty	46	50	GI system disorders
37	Laurent et al	Diclofenac	100 mg/day	Proteinuria in glomerular diseases	14	12	GI-minor
43	Bassotti et al	Diclofenac Indometacin	150 mg/day 150 mg/day	Healthy volunteers	8 8	8	GI-minor
27	Reis et al	Diclofenac	150 mg/day	Heterotopic ossification after hip arthroplasty	90	90	GI-minor
34	Schnitzer et al	Etodolac Nabumetone	800 mg/day 1500 mg/day	Knee osteoarthritis	91 89	90	GI-minor
40	Laine et al	Etodolac Naproxen	400 mg bid 500 mg bid	Gastrointestinal tolerability	18	16	GI-major
22	Hoikka et al	Flurbiprofen	200 mg/day	Heterotopic ossification after hip arthroplasty	34	34	GI-minor
30	Elmstedt et al	Ibuprofen	1200 mg/day	Heterotopic ossification after hip arthroplasty	21	22	GI-minor
45	Langman et al	Ibuprofen Diclofenac Ibuprofen Diclofenac	2400 mg/day 150 mg/day	Osteoarthritis	1564	514	GI system disorders
41	Persson et al	Ibuprofen	1200 mg/day	Heterotopic ossification after hip arthroplasty	48	47	GI-minor
48	Doyle et al	Ibuprofen	1200 mg/day	Gastrointestinal tolerability	833	413	GI-minor
26	Schmidt et al	Indometacin	75 mg/day	Heterotopic ossification after hip arthroplasty	102	99	GI system disorders
20	Kjaersgaard et al	Indometacin	75 mg/day	Heterotopic ossification after hip arthroplasty	19	22	Any GI adverse event
42	Scott et al	Indometacin	25 mg/day	Knee osteoarthritis	202	303	GI-minor
47	Eliakim et al	Indometacin	150 mg/day	Acute musculoskeletal disorders	65	513	GI-major
38	Berry et al	Lornoxicam	12 mg/day	Knee and hip osteoarthritis	44	42	GI-minor
21	Lemmel et al	Meloxicam	15 mg/day 7.5 mg/day	Rheumatoid arthritis	162 159	147	GI system disorders
46	Yocum et al	Meloxicam Diclofenac	3.75-15 mg/day 100 mg/day	Osteoarthritis	464 153	157	Any GI adverse event
33	Lipscomb et al	Meloxicam Piroxicam	15 mg/day 20 mg/day	Gastrointestinal tolerability	15 14	15	GI-minor
35	Patoia et al	Meloxicam Piroxicam	15 mg/day 20 mg/day	Gastrointestinal tolerability	13 13	13	GI-severe
36	Lund et al	Meloxicam	15 mg/day	Knee osteoarthritis	134	137	GI-minor
44	Dougados et al	Meloxicam Piroxicam	15/22.5 mg/day 20 mg/day	Ankylosing spondylitis	120 108	121	GI-major
29	Simon et al	Naproxen	500 mg/day	Rheumatoid arthritis	138	101	GI ulcers
18	Gebuhr et al	Naproxen	750 mg/day	Heterotopic ossification after hip arthroplasty	28	27	GI system disorders
49	Schiff et al	Naproxen	1000 mg/day	Knee osteoarthritis	116	116	GI-minor
31	Bono et al	Oxaprozin	1200 mg/day	Tendinitis and bursitis	43	43	GI-major
24	Prupas et al	Tenidap	40-200 mg/day	Rheumatoid arthritis	131	67	GI-minor
23	Gebuhr et al (2)	Tenoxicam	40 mg/day	Heterotopic ossification after hip arthroplasty	35	35	GI system disorders
28	Burssens et al	Tenoxicam	20 mg/day 10 mg/day	Heterotopic ossification after hip arthroplasty	26 29	29	GI-minor
50	Szpalski et al	Tenoxicam	20 mg/day	Low back pain	37	36	GI-minor
39	Dougados et al (2)	Ximoprofen	30 mg/day	Ankylosing spondylitis	50	95	GI-minor

Table 2 Longitudinal controlled cohort studies included in the analysis

Ref	Author	NSAID	Dose	Indication	Treated group size	Control group size	Outcomes
59	Kurata et al	Any	N/A	Gastrointestinal bleeding in patients with dyspepsia	282	263	GI-major
56	Allison et al	Any	N/A	Gastrointestinal ulcers	249	464	GI-major
51	Guess et al	Any	N/A	Fatal upper GI haemorrhage or perforation	134060 p/y	834051 p/y	GI-major
60	McMahon et al	Any	N/A	Upper GI haemorrhage and perforation	25700	24550	GI-major
53	Carson et al	Any	N/A	Upper tract bleeding	47136	44634	GI-major
55	Beardon et al	Any	N/A	Gastrointestinal events	Events per 1000 subjects	Events per 1000 subjects	GI-any
57	MacDonald et al	Any	N/A	Gastrointestinal toxicity	52293	73792	GI-major GI-minor
52	Bloom et al	Any	N/A	Gastrointestinal toxicity Cost	33880	36200	GI-major GI-minor
61	Smalley et al	Any	N/A	Incidence of hospitalisations for peptic ulcer disease in elderly people	1000 p/y	1000 p/y	GI-major
58	Fries et al	Any	N/A	Serious GI events	1694	1053	GI-major
62	Garcia Rodriguez et al	Any	N/A	Hospitalisation for upper GI bleeding	700000		GI-major
63	Beard et al	Any	N/A	Hospitalisation for gastro-oesophageal bleeding	6095000 p/d	38006000	GI-major
13	Mamdani et al	Any	N/A	Upper GI tract bleeding	5291	100000	GI-major

p/d, person-day; p/y, person-year.

(etodolac, nabumetone, flurbiprofen, lornoxicam, oxaprozin, tenidap, ximoprofen) were considered as comparators because data available for each compound were too sparse. NSAIDs had to be compared with an inactive control (placebo or non-exposed group). Drugs had to be orally given. In RCTs, both groups had to be matched at inclusion for age, sex, and history of GI events. Treatment duration had to be at least 5 days. The study purposes had to be: safety trials, osteoarticular disorders, or prevention of heterotopic ossification after major orthopaedic surgery. The studies had to be published between January 1985 and January 2003. We focused on English publications or reports

The publications retrieved were discussed for methodological standards and inclusion criteria compatibility during a specifically dedicated WHO meeting, which included leading experts in the fields of rheumatology, gastroenterology, endocrinology, public health, and quantitative epidemiology. Divergences were solved by consensus. Quality scoring was performed using the Jadad score[15] for RCTs, whereas for longitudinal studies we used a quality scoring algorithm previously defined by our research group.[16]

Data extraction was performed by two independent authors (FR, OB) to ensure accuracy in data encoding. Values from intention to treat analyses were systematically used when available; otherwise we considered per-protocol results. Heterogeneity was assessed before choosing the combination model among the subgroups and in the summary assessment.

The meta-regression process was done in several steps. Firstly, all RCTs were combined to obtain a summary estimate. Thereafter, a subdivision was made according to drug. Finally, the individual estimates were regressed against the respective study durations. Sensitivity analyses were set to explore the confounding effects of age (under versus over 60 years), study purpose (rheumatic diseases versus heterotopic ossification versus tolerability), dose and outcomes, which were categorised in two classes. Minor GI events included abdominal pain, nausea, constipation, diarrhoea, and dyspepsia. Major events included any duodenal, gastric, or intestinal ulcers, bleeding, perforation, hospitalisation, and related death.

The α risks were set at 5% for association and 10% for heterogeneity tests. The global and individual estimators were surrounded by their 95% confidence intervals.

Publication bias was statistically explored by funnel plot drawing (log of the relative risks against their precision, symmetrical if no publication bias is present) and by regressing standard normal deviates of the effects against their precision (no difference from 0 on the y axis if no publication bias is present).[17] Statistical operations were performed using registered copies of Comprehensive Meta-analysis, version 1.0.25 (Biostat, Englewood NJ 07631, USA), and Statistica 6.0 (Statsoft, France).

RESULTS

At the end of the bibliographic research, 1893 publications were found. Among them, 527 were selected and reviewed for minimal methodological quality requirements by two authors (FR, OE). After excluding articles solely or predominantly dealing with the tertiary prevention of NSAID-induced complications by prostaglandins (misoprostol) or other agents, and studies providing insufficient data for subsequent meta-analysis, 32 RCTs on NSAIDs[18–31 33–50] and 13 major cohort studies on NSAIDs[13 51–53 55–66] were included after review by a specifically dedicated group of experts (see tables 1 and 2). The duration of the included RCTs ranged from 5 days to 1825 days. Among them, 15 studies investigated the anti-inflammatory properties of the drugs in rheumatic diseases, 10 focused on the prevention of heterotopic ossification after major orthopaedic surgery, 5 were GI tolerability trials, 1 was on the improvement of recurrent renal colic, and 1 was on the effect of diclofenac on proteinuria in glomerular diseases. The total number of patients was 5325 receiving active drugs and 3453 receiving placebo in the RCT section. The trials were of good quality according to the classification of Jadad, with a median score of 70% (range 20–100). Most of the cohort studies were matched for age and sex to enhance comparability between groups, while almost all RCTs assessed homogeneity between groups at inclusion for the major confounding variables. The median daily doses were 1200 mg ibuprofen, 875 mg naproxen, 200 mg flurbiprofen, 30 mg ximoprofen, 1200 mg oxaprozin, 150 mg diclofenac, 800 mg etodolac, 75 mg indometacin, 120 mg tenidap, 15 mg meloxicam, 20 mg tenoxicam and 20 mg piroxicam.
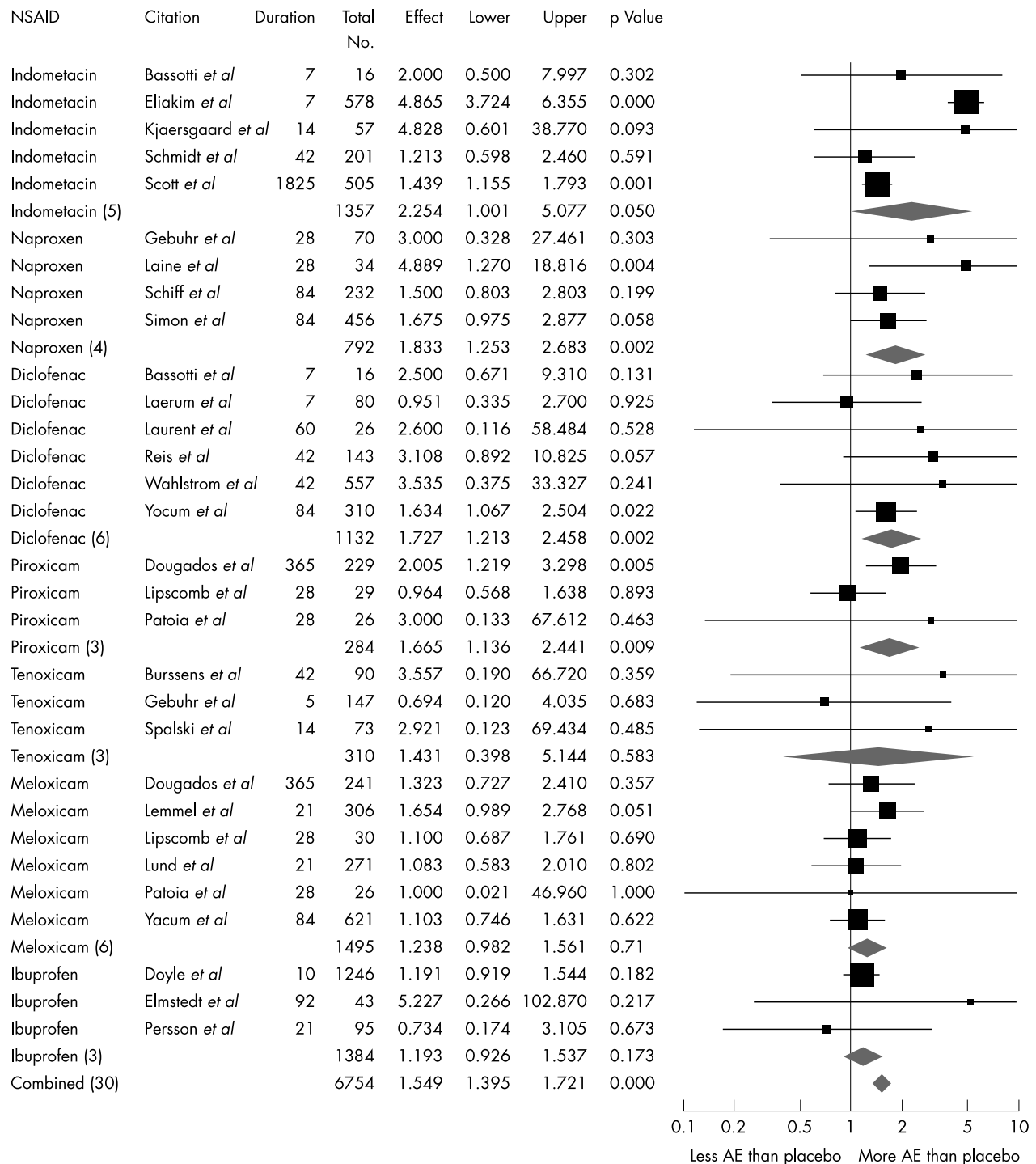
NSAID	Citation	Duration	Total No.	Effect	Lower	Upper	p Value
Indometacin	Bassotti et al	7	16	2.000	0.500	7.997	0.302
Indometacin	Eliakim et al	7	578	4.865	3.724	6.355	0.000
Indometacin	Kjaersgaard et al	14	57	4.828	0.601	38.770	0.093
Indometacin	Schmidt et al	42	201	1.213	0.598	2.460	0.591
Indometacin	Scott et al	1825	505	1.439	1.155	1.793	0.001
Indometacin (5)			1357	2.254	1.001	5.077	0.050
Naproxen	Gebuhr et al	28	70	3.000	0.328	27.461	0.303
Naproxen	Laine et al	28	34	4.889	1.270	18.816	0.004
Naproxen	Schiff et al	84	232	1.500	0.803	2.803	0.199
Naproxen	Simon et al	84	456	1.675	0.975	2.877	0.058
Naproxen (4)			792	1.833	1.253	2.683	0.002
Diclofenac	Bassotti et al	7	16	2.500	0.671	9.310	0.131
Diclofenac	Laerum et al	7	80	0.951	0.335	2.700	0.925
Diclofenac	Laurent et al	60	26	2.600	0.116	58.484	0.528
Diclofenac	Reis et al	42	143	3.108	0.892	10.825	0.057
Diclofenac	Wahlstrom et al	42	557	3.535	0.375	33.327	0.241
Diclofenac	Yocum et al	84	310	1.634	1.067	2.504	0.022
Diclofenac (6)			1132	1.727	1.213	2.458	0.002
Piroxicam	Dougados et al	365	229	2.005	1.219	3.298	0.005
Piroxicam	Lipscomb et al	28	29	0.964	0.568	1.638	0.893
Piroxicam	Patoia et al	28	26	3.000	0.133	67.612	0.463
Piroxicam (3)			284	1.665	1.136	2.441	0.009
Tenoxicam	Burssens et al	42	90	3.557	0.190	66.720	0.359
Tenoxicam	Gebuhr et al	5	147	0.694	0.120	4.035	0.683
Tenoxicam	Spalski et al	14	73	2.921	0.123	69.434	0.485
Tenoxicam (3)			310	1.431	0.398	5.144	0.583
Meloxicam	Dougados et al	365	241	1.323	0.727	2.410	0.357
Meloxicam	Lemmel et al	21	306	1.654	0.989	2.768	0.051
Meloxicam	Lipscomb et al	28	30	1.100	0.687	1.761	0.690
Meloxicam	Lund et al	21	271	1.083	0.583	2.010	0.802
Meloxicam	Patoia et al	28	26	1.000	0.021	46.960	1.000
Meloxicam	Yacum et al	84	621	1.103	0.746	1.631	0.622
Meloxicam (6)			1495	1.238	0.982	1.561	0.71
Ibuprofen	Doyle et al	10	1246	1.191	0.919	1.544	0.182
Ibuprofen	Elmstedt et al	92	43	5.227	0.266	102.870	0.217
Ibuprofen	Persson et al	21	95	0.734	0.174	3.105	0.673
Ibuprofen (3)			1384	1.193	0.926	1.537	0.173
Combined (30)			6754	1.549	1.395	1.721	0.000

Figure 1 Relative risk of GI complications depending on NSAID (RCT).

Summary of effects

Among the seven primary NSAIDs investigated, the risk of GI complications due to NSAIDs compared with the risk for non-users was estimated at 1.54 (1.4; 1.7) at a median exposure time of 28 days in the RCTs (fig 1). Cohort studies provided a global relative risk of 2.2 (1.7; 2.9) and a median duration of 365 days (fig 4).

Subgroup analyses

Among the RCT of the seven mainly investigated NSAIDs (fig 1), indometacin provided a significantly higher risk for GI complication: RR = 2.25 (1.01; 5.07), followed by naproxen: RR = 1.83 (1.25; 2.68), diclofenac: RR = 1.73 (1.21; 2.46), piroxicam: RR = 1.66 (1.14; 2.44), tenoxicam: RR = 1.43 (0.40; 5.14), meloxicam: RR = 1.24 (0.98; 1.56), and ibuprofen: RR = 1.19 (0.93; 1.54). The other NSAIDs (etodolac, flurbiprofen, lornoxicam, nabumetone, oxaprozin, tenidap, and ximoprofen) provided RR = 1.64 (1.2; 2.26). The proportion of minor and major GI events studied among those trials was significantly homogeneous among the seven primary NSAIDs investigated (Pearson's χ^2, p>0.05). The meta-regression for non-indometacin NSAIDs, grouped together, provided a duration of treatment of 84 days as threshold for a significant risk of GI effects (fig 2). At seven
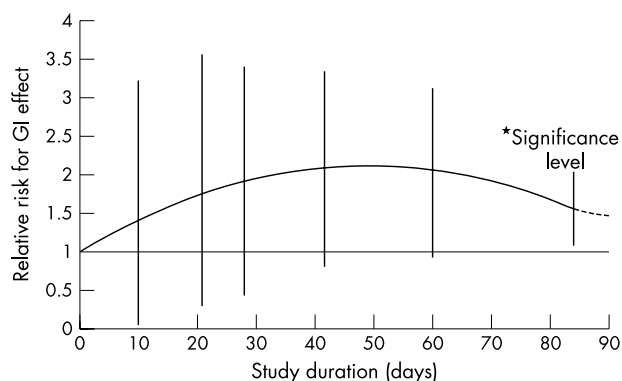
Figure 2 Meta-regression of relative risk against study duration (non-indometacin compounds).
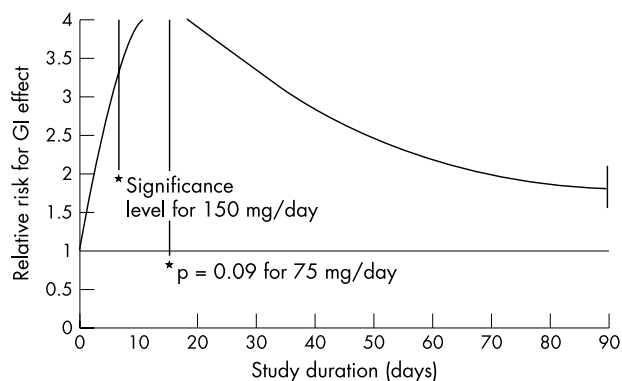

Figure 3 Meta-regression of relative risk against study duration (indometacin).

days of exposure, indometacin at 150 mg daily significantly increased the risk (fig 3) Both categories of compounds displayed a non-linear response of reported risks against study durations.

Sensitivity analyses

The mean age of patients included in these studies had no significant influence on the reported relative risks: RR = 1.67 (1.02; 2.7) for studies in patients over 60 and RR = 1.82 (1.15; 2.87) for patients under 60 (analysis of variance (ANOVA), $p = 0.84$). The relative risk for GI complications was significantly affected by increasing the daily dose of indometacin (Kendall's τ test, $p < 0.05$), while this covariant remained non-significant for the other compounds. For non-indometacin compounds, we found a significant difference in risk between patients enrolled in tolerability trials: RR = 1.28 (1.04; 1.59) and patients with osteoarthritis/rheumatoid arthritis or taking NSAIDs after hip arthroplasty: RR = 1.54 (1.38; 1.7). The risk for minor events was RR = 1.35 (1.14; 1.59) and RR = 1.74 (1.26; 2.41) (ANOVA−1, $p = 0.49$) for major events. For indometacin trials, insufficient data were present to assess the role of the study purpose. The relative risks for minor and major events were RR = 1.45 (1.18; 1.78) and RR = 2.97 (1.03; 8.5) (ANOVA−1, $p < 0.01$).

The cohort studies assessing various NSAIDs (fig 4) reported slightly higher estimates: RR = 2.17 (1.76; 2.67) for 1 year and below, and RR = 1.45 (1.19; 1.75) for studies between 2 and 3 years. Four studies assessed the GI adverse effects in cohorts during more than 3 years, and reported RR = 2.87 (1.4; 5.9). It was noted that, in this analysis, both intra- and intervariability were high (Cochrane's Q, $p < 0.01$), reflecting the lower level of selection of patients and control for bias.

Funnel plots appeared to be asymmetric for the RCT on NSAIDs (fig 5). Indeed more small sized studies reporting a

| Citation	Effect name	Duration	Effect	Lower	Upper	p Value
Bloom et al	GI-minor	90	2.464	2.202	2.757	0.000
Bloom et al	GI-major	90	3.271	1.398	7.657	0.004
Carson et al	GI-major	180	1.529	1.186	1.971	0.001
Mamdani et al	GI-major	365	3.846	2.283	6.479	0.000
Kurata et al	GI-major	365	1.632	1.017	2.618	0.039
Guess et al	GI-major	365	3.660	2.107	6.358	0.000
Allison et al	GI-major	365	1.765	1.258	2.477	0.001
Beardon et al	PUB-women <60	365	1.000	0.202	4.943	1.000
Beardon et al	PUB-men >60	365	2.143	1.143	4.017	0.015
Beardon et al	PUB-women >60	365	1.933	1.043	3.584	0.033
Beardon et al	PUB-men <60	365	1.750	0.514	5.959	0.364
Smalley et al	GI-major	730	3.200	1.177	8.702	0.016
McDonald et al	GI-major	1095	1.312	1.158	1.485	0.000
McDonald et al	GI-minor	1095	1.596	1.415	1.801	0.000
McMahon et al	GI-major	1230	2.266	1.635	3.142	0.000
Garcia Rodriguez et al	GI-major	1460	4.837	4.260	5.493	0.000
Fries et al	GI-major	1460	5.594	1.701	18.395	0.001
Beard et al	GI-major	2190	1.391	0.930	2.080	0.106
Combined (18)			2.218	1.699	2.895	0.000

Less AE than placebo   More AE than placebo
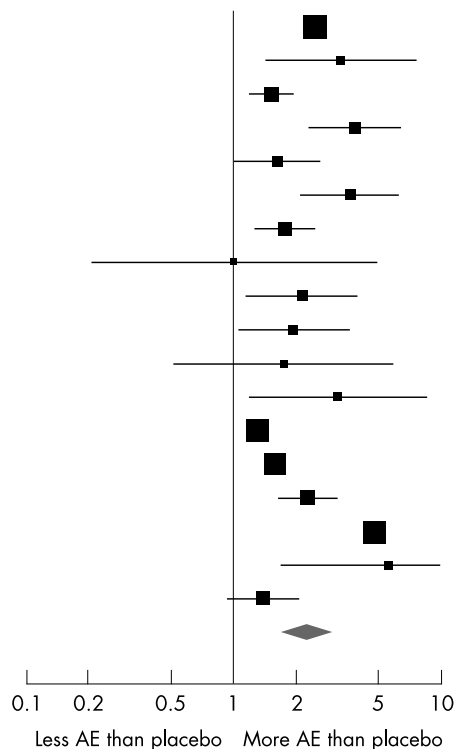
Figure 4 Relative risk of GI complications provided by longitudinal controlled cohort studies. PUB, perforation, ulcers, or bleeding.
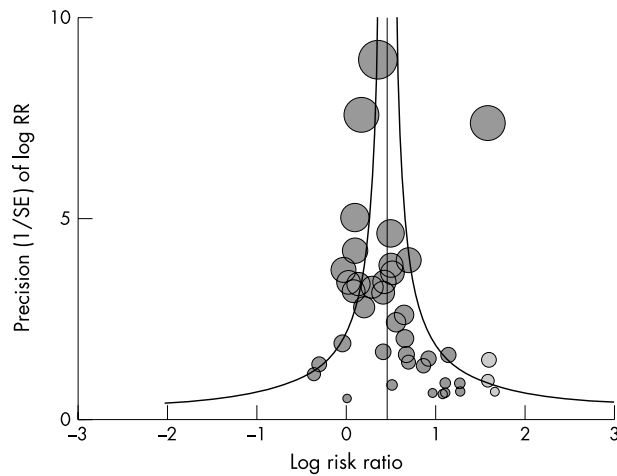
Figure 5 Funnel plot.

marked deleterious effect were retrieved compared with studies reporting no or a less marked adverse effect (ratio = 1.29). The statistical method confirmed this preliminary inspection (p<0.05). This means that, in reality, a higher proportion of trials showing lower risks for adverse effects due to NSAIDs have been performed compared with the fraction of published papers showing marked effects.

DISCUSSION

Throughout the history of NSAIDs we have seen an overall increase in their potency and this has been accompanied, on the whole, by attempts and refinements to improve their tolerability.[64] Despite this trend, however, the classic GI side effects of NSAIDs are just as much a feature of treatment with contemporary drugs as they were with aspirin itself, and in this context it is amazing that aspirin was thought initially to be a better tolerated drug in the stomach than the salicylic acid from which it was derived. Nevertheless, currently, NSAIDs are the best recognised cause of iatrogenic pathology. They have been estimated to cause as many as 16 500 deaths a year in the America.[65] These drugs exhibit a wide range of actions resulting from local and systemic mechanisms, or a combination of both, which contribute to their overall toxicity.[66]

In this quantitative review of English publications, which focused on RCTs and cohort studies, we found deleterious effects of NSAIDs as soon as 1 week after the start of treatment with indometacin. Nevertheless, the magnitude of the risk shown by our results seems to be consistently less alarming than that previously published.[10 67–73] This can be partially explained by the conservative approach we used. For instance, relative risk was used to assess causality instead of an odds ratio. Using odds ratios can lead to overestimated global estimates compared with relative risk, in the analysis of prospective data.[74] Another possible explanation relates to the fact that our survey was restricted to articles published after 1985. Prior studies might differ because they no longer reflect current practice, and may be of smaller size. We decided to include RCTs and cohort studies. The rationale for this approach was that while we expect the risk estimate to be less biased when derived from RCTs, the populations being studied in such trials are usually highly selected groups and, therefore, are not always fully representative of the patients seen in clinical practice. On the other hand, the analysis performed using non-RCT longitudinal trials provide estimates that may be more representative of daily clinical practice, despite a lack of precision about the NSAIDs used.

Furthermore, there is evidence that case-control studies yield exaggerated estimates of effect compared with cohort studies.[75 76]

In this meta-analysis, we found that indometacin induces a significant risk of GI side effects after less than 1 week of treatment, whereas other non-specific NSAIDs ''required'' more than 1 month to induce deleterious effects. Ibuprofen was the safest drug, while naproxen and diclofenac exhibited a higher risk than the investigated oxicams (piroxicam, tenoxicam, and meloxicam), which is consistent with previous findings.[5]

Conflicting results have been reported on the relationship between the risk of GI events and the duration of exposure to NSAIDs. A number of epidemiological studies have suggested that the risk of GI complications is higher at the onset of long term NSAID treatment.[13 77] The findings of this meta-analysis support this claim. The use of meta-regression showed that the maximum risk appeared at 14 days for indometacin, and at 50 days for other NSAIDs. However, prospective experimental studies suggest a steady increase in the rate of GI complications over time.[78] These differences may be explained by the fact that patients who have not been taking NSAIDs appear to have an increased risk of developing ulcers and clinical events after starting NSAID treatment compared with those who have already been taking NSAIDs. This is related to a selection process of NSAID tolerant patients.

Our data come from studies with various purposes—for example, safety trials versus efficacy trials in patients requiring NSAIDs. Most of the RCTs focused on patients with osteoarticular diseases, mostly osteoarthritis and rheumatoid arthritis (75%). We found a significant difference in risk between patients without disease (RR = 1.3, NS) and patients with osteoarthritis or rheumatoid arthritis (RR = 1.7, p = 0.035). These findings support the claim that the underlying disease requiring NSAID treatment may have a role in the development of GI damage. More studies are needed to assess this point clearly.

This meta-analysis showed a higher risk for major than for minor GI side effects. The explanation is that most of the studies in the first subgroup assessed preclinical erosion of the gastric mucosa as an end point. It has been known for more than 10 years that ulcers defined as breaches in the mucosa may develop within 1 week of regular NSAID use.[79] Furthermore, the mean age of patients in whom perforation, ulcers, or bleeding were assessed was significantly higher than that of patients in whom minor discomforts were reported (Mann-Whitney U, p = 0.04), and they were exposed for a non-significantly longer period to NSAIDs (Mann-Whitney U, p = 0.29).

Selective inhibitors of the isoenzyme II of cyclo-oxygenase are now marketed in most North American and European countries for the symptomatic management of osteoarthritis and rheumatoid arthritis. These compounds have, repeatedly, demonstrated that they induce a lower incidence of GI side effects than conventional NSAIDs.[80] Other studies have also reported a decrease in the GI toxicity of NSAIDs when combined with prostaglandin analogues (misoprostol).[81 82] However, coxibs and prostaglandin analogues are significantly more expensive than conventional NSAIDs and are not yet widely available to every patient requesting treatment with NSAIDs, which means that the use of non-selective NSAIDs as first line treatment is high and is increasing.[83 84]

CONCLUSION

The appearance of GI side effects induced by NSAIDs is time dependent but depends less on the drug used. Indometacin at 150 mg daily can exhibit significant deleterious effects as soon as 7 days after initiation of treatment, whereas other NSAIDs, at their recommended therapeutic dose, usually

induce GI effects after 2–3 months. Depending on the study design, exposure time, compound, and underlying disease, the relative risks of GI adverse reactions compared with untreated controls vary from 1.2 to 5.6. This meta-analysis demonstrates that NSAIDs should be given cautiously to patients requiring long term management of chronic disease. The risk/benefits ratio of such compounds should be carefully and individually evaluated.

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