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. 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. Indeed, through their non-specific inhibition of the two cyclo-oxygenase isoenzymes, both aspirin and conventional NSAIDs induce gastroduodenal damage, and are now considered as a major cause of iatrogenic pathology. 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, 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.

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 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. 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, Bollini et al, and Gabriel et al, 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

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

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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>
<thead>
<tr>
<th>Table 1 RCTs included in the analysis</th>
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<tr>
<td>Ref Author NSAID Dose</td>
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<td>19</td>
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<td>50</td>
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<td>39</td>
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</tbody>
</table>
previous definition by our research group. Longitudinal studies we used a quality scoring algorithm performed using the Jadad score for RCTs, whereas for divergences were solved by consensus. Quality scoring was

given by experts in the fields of rheumatology, gastroenterology, specifically dedicated WHO meeting, which included leading
gastrointestinal standards and inclusion criteria compatibility during a

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 for RCTs, whereas for longitudinal studies we used a quality scoring algorithm previously defined by our research group.

Data extraction was performed by two independent 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 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 3325 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 simoprofen, 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.

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). 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 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 3325 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 simoprofen, 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.

Table 2 Longitudinal controlled cohort studies included in the analysis

<table>
<thead>
<tr>
<th>Ref Author</th>
<th>NSAID</th>
<th>Dose</th>
<th>Indication</th>
<th>Treated group size</th>
<th>Control group size</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>59 Kurata et al</td>
<td>Any</td>
<td>N/A</td>
<td>Gastrointestinal bleeding in patients with dyspepsia</td>
<td>282</td>
<td>263</td>
<td>GI-major</td>
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<tr>
<td>60 McMahon et al</td>
<td>Any</td>
<td>N/A</td>
<td>Gastrointestinal ulcers</td>
<td>249</td>
<td>464</td>
<td>GI-major</td>
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<tr>
<td>61 Carson et al</td>
<td>Any</td>
<td>N/A</td>
<td>Upper GI haemorrhage or perforation</td>
<td>25700</td>
<td>24550</td>
<td>GI-major</td>
</tr>
<tr>
<td>62 Bloom et al</td>
<td>Any</td>
<td>N/A</td>
<td>Gastrointestinal toxicity</td>
<td>47136</td>
<td>46434</td>
<td>GI-major</td>
</tr>
<tr>
<td>63 Smolley et al</td>
<td>Any</td>
<td>N/A</td>
<td>Incidence of hospitalisations for peptic ulcer disease in elderly people</td>
<td>52293</td>
<td>73792</td>
<td>GI-any</td>
</tr>
<tr>
<td>64 Garcia Rodríguez et al</td>
<td>Any</td>
<td>N/A</td>
<td>Serious GI events</td>
<td>1694</td>
<td>1053</td>
<td>GI-major</td>
</tr>
<tr>
<td>65 MacDonald et al</td>
<td>Any</td>
<td>N/A</td>
<td>Hospitalisation for upper GI bleeding</td>
<td>700000</td>
<td>5291</td>
<td>GI-major</td>
</tr>
<tr>
<td>66 Beard et al</td>
<td>Any</td>
<td>N/A</td>
<td>Hospitalisation for gastrointestinal events</td>
<td>6905000</td>
<td>3806000</td>
<td>GI-major</td>
</tr>
<tr>
<td>67 Mamdani et al</td>
<td>Any</td>
<td>N/A</td>
<td>Upper GI tract bleeding</td>
<td>2910</td>
<td>1000000</td>
<td>GI-major</td>
</tr>
</tbody>
</table>

p/d, person-day; p/y, person-year.
### 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 $\chi^2$, 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
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 \( t \) 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 osteoarthritic/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-2, \( p < 0.01 \)).

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
marked deleterious effect were retrieved compared with studies reporting no or a less marked adverse effect \( \text{ratio} = 1.29 \). 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.\(^{44}\) 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.\(^{15}\) 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.\(^{49}\) Another possible explanation relates to the fact that we restricted our survey 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.\(^{15–17}\) 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 osteoarticleral 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 osteoarthrosis 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.\(^{90,91–93}\) 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.\(^{85–84}\)

**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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