Epidemiology overview of gastrointestinal and renal toxicity of NSAIDs

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CRD summary
This review assessed the risk of serious gastrointestinal complications with non-steroidal anti-inflammatory drugs (NSAIDs). The authors concluded that, at low doses, the risk is lower with ibuprofen than with other NSAIDs. Wide variation in the estimate of risk between different studies of the same drugs, which the authors were unable to explain, casts doubt on the reliability of the conclusion.

Authors’ objectives
The objectives were three-fold: to update previous systematic reviews; to determine the effects of non-steroidal anti-inflammatory drugs (NSAIDs) on the risk of serious gastrointestinal complications; and to examine the place of drug dose in explaining the variation in this risk.

Searching
MEDLINE, EMBASE, the Cochrane Library, HealthSTAR, CINAHL, IDIS were searched from 1985 using a predefined list of search terms. In addition, the reference lists in identified studies were checked and some published journals were handsearched. The authors stated that the review included studies that were either published or notified to the authors before June 2001.

Study selection
Study designs of evaluations included in the review
Cohort studies with a concurrent or historical control group and case-control studies were eligible for inclusion. In the cohort studies, NSAID use had to be determined through routine medical care. In case-control studies, patients were included based on study outcomes and not through exposure to the drug. Most of the case-control studies were hospital-based and most used direct or frequency matching of cases and controls, or clearly described methods of adjusting for age, gender and other possible confounders. Most of the case-control studies assessed NSAID use 7 to 30 days before the adverse event.

Specific interventions included in the review
Studies of NSAIDs were eligible for inclusion. The included studies determined NSAID usage from prescription databases, structured interviews, medical records, record linkage, ICD-9 diagnostic codes (without validation), or other sources. The NSAIDs used in the included studies were, for example, aspirin (used in low dose as cardiovascular prophylaxis), ibuprofen, naproxen, ketoprofen, diclofenac, piroxicam and indomethacin. The included studies used high and low doses of drugs and the classification of dose category varied among the studies.

Participants included in the review
The inclusion criteria were not specified in terms of participants. No details of the participants in the included studies were presented.

Outcomes assessed in the review
Studies that reported serious upper gastrointestinal complications were eligible for inclusion. The review defined this as bleeding or perforation of gastric, duodenal or oesophageal lesions. The authors stated that the review focused on complications requiring hospital treatment, but this was not explicitly stated to be one of the inclusion criteria for studies.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.
Assessment of study quality

Validity was assessed using an instrument known to the authors, which provided a quality score. The criteria appear to have included the selection of the control, definition of control, comparability of cases and controls with respect to confounders, and ascertainment of exposure. Two reviewers independently assessed validity. Inter-rater agreement was measured using the kappa statistic.

Data extraction

Two reviewers extracted the data. The data extracted appear to have included raw data for the calculation of odds ratios (ORs) and ORs adjusted by the investigators for study-level confounding.

Methods of synthesis

How were the studies combined?
The studies were grouped by study design (cohort or case-control study) and combined using a meta-analysis. Pooled ORs and 95% confidence intervals (CIs) for serious gastrointestinal complications in NSAID users, compared with non-users, were calculated using a random-effects model in which weights were assigned to individual studies using the inverse of the variance. The data were also analysed using ibuprofen instead of non-use of NSAIDs as the reference. The authors stated that the terms OR and relative risk (RR) were used interchangeably in the review. Individual NSAIDs were compared by ranking the size of the unadjusted and adjusted pooled estimates of risk.

How were differences between studies investigated?
Statistical heterogeneity in the meta-analyses was assessed using the chi-squared statistic. The meta-analysis of case-control studies was repeated after excluding studies using aspirin. Meta-analyses of individual NSAIDs were shown for ibuprofen, indomethacin and piroxicam. For each individual NSAID, the adjusted point estimate of risk in each study was shown graphically. Risks with high and low doses of specified NSAIDs were compared by plotting the log ORs against high and low doses, as defined by the original investigators.

The influence of study quality score on the risk was explored for criteria with an adequate spread of scores and significant variation between the studies. The RRs and 95% CIs were compared for studies with low and high quality scores (no details were given of what constituted a low or a high score).

Results of the review

Thirty-six case-control studies (19,648 cases and 105,373 controls) and 8 cohort studies (approximately 400,000 exposed people and 1 million non-exposed people) were included.

The overall quality score was not associated with marked differences in ORs. However, low scores for the selection of controls, definitions of controls, comparability of cases and controls, and ascertainment of exposure tended to inflate the estimated risk of complications.

Case-control studies.

The use of NSAIDs significantly increased the risk of serious gastrointestinal complications compared with non-use. The unadjusted pooled OR was 4.06 (95% CI: 3.47, 4.75). Significant heterogeneity was detected (P<0.00001). After excluding studies using aspirin, the pooled OR (25 studies) was 3.81 (95% CI: 3.17, 4.58), still with significant heterogeneity (P<0.00001).

Cohort studies.

The use of NSAIDs in cohort studies significantly increased the risk of serious gastrointestinal complications compared with non-use. The unadjusted pooled OR was 2.29 (95% CI: 1.50, 3.51). Significant heterogeneity was detected (P<0.00001). None of the cohort studies used aspirin.

Different NSAIDs.
Studies showed that ibuprofen was associated with a significantly lower risk than non-aspirin NSAIDs.

The unadjusted ORs for individual NSAIDs ranged from 1.81 (95% CI: 1.3, 2.4) with ibuprofen (16 studies) to 7.46 (95% CI: 5.1, 10.9) for piroxicam (15 studies). The adjusted ORs were slightly higher but the rank order was the same (ibuprofen, aspirin, naproxen, diclofenac, indomethacin, ketoprofen and piroxicam).

Comparisons of the individual drugs with ibuprofen showed that aspirin was not significantly different, but the other NSAIDs were associated with an increased risk of complications. The RR was 1.63 (95% CI: 0.64, 4.2) for aspirin, 1.78 (95% CI: 1.6, 2.2) for naproxen, 1.73 (95% CI: 1.4, 2.1) for diclofenac. 1.88 (95% CI: 1.6, 2.3) for indomethacin, 2.45 (95% CI: 1.8, 3.3) for ketoprofen, and 3.21 (95% CI: 2.6, 4.0) for piroxicam.

Drug dosage.

There appeared to be a rank order of NSAIDs at low doses but the ORs (except for piroxicam) tended to converge at high doses.

**Authors' conclusions**

The risk of serious gastrointestinal complications varies by class and by individual drug between studies, and the reasons for this are not readily explained. Ibuprofen is associated with a lower risk of serious gastrointestinal complications than other NSAIDs, but probably not at higher doses (greater than 1,800 mg/day ibuprofen).

**CRD commentary**

The review addressed a clear question in terms of the intervention, outcomes and study design. Several relevant sources were searched and the authors stated that published and unpublished studies were eligible. However, no details of the search strategy or specific journals searched were given, and it was unclear whether any language limitations were applied. The methods used to select the studies were not explicitly described, although the authors stated that they used standard Cochrane Collaboration methods. Two reviewers independently assessed validity to reduce the potential for bias and errors, but it was unclear whether the two reviewers who extracted the data did so independently. The validity assessment for potential bias in the included studies was not transparent. The characteristics of the participants were not discussed and so it could not be determined whether the populations were comparable across studies.

Meta-analyses for all NSAIDs combined were performed despite finding significant statistical heterogeneity, suggesting that a meta-analysis was inappropriate. The exploration of differences between the studies was limited to the influence of individual NSAIDs, study quality and drug dose. The data presented show that ibuprofen is associated with a lower risk of gastrointestinal complications than other NSAIDs, but the unexplained variability across the studies gives cause for uncertainty.

**Implications of the review for practice and research**

The authors did not state any implications for practice or further research.

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