Meta-analysis of dyspepsia and nonsteroidal antiinflammatory drugs

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CRD summary
This review of oral nonsteroidal antiinflammatory drugs (NSAIDs) concluded that high doses of any NSAID and any dose of indomethacin, meclofenamate or piroxicam increased dyspepsia. Short study durations and a tendency to select healthy people for placebo-controlled trials limited the generalisability of the results and no evidence was presented for individual drugs. Hence the conclusions may not be reliable.

Authors' objectives
To assess the effect of non-steroidal anti-inflammatory drugs (NSAIDs) on dyspepsia.

Searching
MEDLINE, BIOSIS Previews, EMBASE, HealthSTAR were searched from 1966 to 1998; the search strategy was presented. Reference lists from systematic reviews, articles in previous reviews and personal files were also checked. Reviews of new drug applications (NDA) were obtained from the Food and Drug Administration (FDA) for five NSAIDs that, together, represented 69.5% of the 1998 US prescription NSAID market (diclofenac, etodolac, ibuprofen, nabumetone and naproxen). Each NDA review was scanned for unpublished studies. Studies in any language were eligible, but 20 studies in predominantly Eastern European languages were subsequently excluded due to the lack of interpreters.

Study selection
Study designs of evaluations included in the review
Reviews, clinical practice guidelines, consensus statements, case reports and case series were excluded. The studies were not otherwise restricted by design. The included studies were randomised controlled trials (RCTs), case-control studies, cohort studies and exposure studies (defined as uncontrolled studies reporting dyspepsia over time). Some of the studies were crossover studies. A post hoc decision was made only to include studies that compared NSAIDs with each other if they had 50 patients or more (reasons for this decision were stated).

Specific interventions included in the review
Studies of oral NSAIDs used for more than 4 days were eligible for inclusion. Studies that were not of oral NSAIDs, and studies that were predominantly about aspirin or prophylaxis of NSAID complications, were excluded. The included controlled studies compared NSAIDs with placebo or each other, and used low, medium and high daily doses.

Participants included in the review
Studies of patients aged 18 years or older were eligible for inclusion.

Outcomes assessed in the review
Studies that assessed defined upper gastrointestinal (GI) complications were eligible for inclusion. Studies that assessed dyspepsia were also included. The review defined 'dyspepsia' as 'any outcome term relating to epigastric or upper abdominal pain or discomfort but not including nausea, vomiting or heartburn'.

How were decisions on the relevance of primary studies made?
Two reviewers independently screened identified papers for inclusion and resolved any disagreements by reaching a consensus.

Assessment of study quality
Validity was assessed on the basis of comparability among treatment groups (randomisation for clinical trials), blinding and the handling of withdrawals or missing data. The validity of controlled clinical trials was assessed using the Jadad Database of Abstracts of Reviews of Effects (DARE)
scale, which considers randomisation, blinding and withdrawals. Two unblinded reviewers independently assessed validity using a standardised form.

**Data extraction**
Two reviewers independently extracted the data using a standardised form and resolved any disagreements through consensus. Studies that were not published in English were not reviewed in duplicate. The reviewers classified the total daily dose of each NSAID as a low, medium or high dose. The percentage of patients with dyspepsia was calculated for each treatment group in each RCT and for each exposure study. The risk difference (RD) and risk ratio (RR) were calculated for RCTs. Most crossover studies did not report the data separately for the pre crossover period, so the data were analysed in three different ways. Since the results were similar, they were averaged before and after the crossover period. A value of 0.5 was added to the outcomes for those studies reporting zero outcomes in the control group.

**Methods of synthesis**
How were the studies combined?
The studies were grouped according to the following study designs and combined in a meta-analysis: RCT comparing NSAID with placebo; RCT comparing NSAIDs with each other; case-control study; cohort study; and exposure study. The percentage of patients with dyspepsia in the NSAID and placebo groups was calculated for RCTs. The pooled RD and the pooled RR with their respective 95% confidence intervals (CIs) were calculated from RCT data using a random-effects model. The number of unpublished studies required to alter significant findings (fail-safe N) was also calculated. The percentage of patients with dyspepsia was calculated separately for data from studies comparing NSAIDs with each other and data from large exposure studies.

How were differences between studies investigated?
The data on dyspepsia were analysed in three different ways:

assuming the number of patients with dyspepsia was the same as the largest number of reported outcomes and either selecting the outcome that minimised the risk ratio between treatment groups (conservative estimate), or selecting the outcome that maximised the risk ratio (liberal estimate); and

assuming the number of patients with dyspepsia was equal to the sum of all reported ‘dyspepsia’.

The results obtained were similar and only the results using the conservative estimate were reported.

Statistical heterogeneity of the treatment and control arms was tested using the chi-squared statistic. A meta-regression was used to explore the influence on the study results of the following: dose of NSAID, age and type of patient, whether the study excluded patients with prior GI complaints, study quality and study duration. The regression was weighted by the number of patients in each 2x2 cell. Indomethacin, meclofenemate and piroxicam were classified a priori as ‘high dyspepsia’ drugs on the basis of the authors’ clinical experience, and data for these NSAIDs were analysed separately. An adjusted odds ratio (OR) and 95% CIs were calculated for high doses of high dyspepsia drugs, not high doses of high dyspepsia drugs, and not high doses of other NSAIDs. The authors discussed possible reasons for the different rates of dyspepsia across study types.

**Results of the review**
The review included 55 published RCTs, 37 unpublished RCTs (FDA studies) that compared NSAIDs with placebo, 86 RCTs that compared NSAIDs with each other, and 103 observational studies. However, only 48 RCTs that compared NSAIDs with placebo assessed dyspepsia (approximately 12,000 patients).

The quality of the studies was generally good: 82% of the RCTs comparing NSAIDs with placebo, and 80% of the RCTs comparing NSAIDs with each other, scored 3 or more on the Jadad scale.

NSAID use increased the rate of dyspepsia compared with placebo (4.8% versus 2.3%). The RD was 1.4% (95% CI: 0.6, 2.2) and the pooled RR was 1.4% (95% CI: 1.1, 1.8).
High doses of 'high dyspepsia' NSAIDs increased dyspepsia, whereas other NSAIDs and other dosages were not associated with increased dyspepsia. The adjusted OR for a high dose of high dyspepsia NSAIDs (5 RCTs, 1,729 patients) was 2.8 (95% CI: 1.4, 5.7); significant heterogeneity was detected among the treatment groups (P<0.05). The adjusted OR for a high dose of other NSAIDs (5 RCTs, 327 patients) was 3.1 (95% CI: 1.6, 5.9). The adjusted OR for not high dose of high dyspepsia NSAIDs (8 RCTs, 1,514 patients) was 2.8 (95% CI: 1.7, 4.5); significant heterogeneity was detected among the control groups (P<0.05). The adjusted OR for not high dose of other NSAIDs (36 RCTs, 8,593 patients) was 1.1 (95% CI: 0.9, 1.3); significant heterogeneity was detected among the treatment groups (P<0.05).

The meta-regression showed significant interactions for NSAID dosage (P=0.002) and type of drug (P<0.001).

The fail-safe N was 70 studies.

Dyspepsia was reported in 4.8% of patients in studies of NSAIDs versus placebo (48 studies, 11,996 patients), compared with a rate of 7.1% in studies comparing NSAIDs with each other (66 studies, 11,299 patients) and a rate of 11.0% in large exposure studies (8 studies, 79,571 patients).

Authors’ conclusions
High doses of any NSAID and any dose of indomethacin, meclofenamate or piroxicam increased dyspepsia. Lower doses of other NSAIDs did not increase dyspepsia.

CRD commentary
The review question was clear in terms of the intervention, participants and outcomes. Several relevant sources were searched, the search terms were stated and attempts were made to locate unpublished studies. No language restrictions were applied initially, but studies in some languages were subsequently excluded. Two reviewers independently selected the studies, assessed validity and extracted the data; this reduces the potential for bias and errors in the review process. Validity was assessed using established criteria.

No information on the individual studies was presented in the review, although the authors stated that a complete evidence table was available on request. Classifying some NSAIDs a priori as 'high dyspepsia drugs' appears to have been a subjective undertaking and may have biased the results. No evidence was presented supporting this classification and the drugs were not examined individually. The authors explored the influence of various factors on the results and discussed some of the limitations of the review. For example, the studies generally appeared to be short-term (only two were longer than 12 weeks) and this, as the authors acknowledged, may have led to an underestimation of the dyspepsia rates. The short duration of most of the studies and the tendency to select healthy patients for placebo-controlled trials (reported by the review authors) may limit the generalisability of these results. No evidence was presented on the risks of dyspepsia for individual NSAIDs.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated that a standardised validated measurement tool for dyspepsia in NSAID trials needs to be developed. In addition, research into patient characteristics associated with an increased risk of NSAID-related dyspepsia is required.

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