The effectiveness of five strategies for the prevention of gastrointestinal toxicity induced by non-steroidal anti-inflammatory drugs: systematic review

CRD summary
This review assessed gastroprotective strategies for people taking non-steroidal anti-inflammatory drugs (NSAIDs). The authors concluded that misoprostol and cyclo-oxygenase-2 (COX-2) specific and selective NSAIDs significantly reduce symptomatic ulcers, while misoprostol and probably COX-2 specifics significantly reduce serious gastrointestinal complications, although the quality of the data was poor. This was a well-conducted review and the authors' conclusions appear reliable.

Authors' objectives
To assess the effectiveness of five specified gastroprotective strategies for people taking non-steroidal anti-inflammatory drugs (NSAIDs).

Searching
The Cochrane Library (Issue 2, 2002), MEDLINE (1966 to 2002), EMBASE (1980 to 2002), Current Controlled Trials (2002) and SIGLE (2002) were searched. The search terms were given on the BMJ website (accessed 25/06/2005). See Web Address at end of abstract. In addition, the reference lists of included studies and identified systematic reviews were checked and authors were contacted for additional studies. Non-English reports were eligible.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) of at least 21 days in duration were eligible for inclusion.

Specific interventions included in the review
Studies that compared one of the following gastroprotective strategies with non-selected NSAIDs alone were eligible for inclusion: non-selective NSAID plus H2 receptor antagonists; non-selective NSAID plus proton-pump inhibitors (PPIs); non-selective NSAID plus misoprostol; cyclo-oxygenase-2 (COX-2) selective NSAID only; or COX-2 specific NSAID only. The authors stated that some of the included studies used NSAIDs and gastroprotective agents at higher than recommended doses.

Participants included in the review
Studies that evaluated exclusively children or healthy volunteers were excluded. The baseline gastrointestinal status (based on a score of 1 to 6, and defined as the percentage of patients with history of ulcers or bleeds) varied across the included studies. Further details were reported.

Outcomes assessed in the review
The primary outcomes of interest were serious gastrointestinal complications, symptomatic ulcers, serious cardiovascular or renal illness, health-related quality of life (not measures of arthritis pain or disability) and mortality. Gastrointestinal complications included haemorrhage, haemorrhagic erosions, recurrent upper gastrointestinal bleeds, perforation, pyloric obstruction and melena. The secondary outcomes of interest included total gastrointestinal symptoms, endoscopic ulcers, anaemia, occult bleeding, the total number of drop-outs and drop-outs owing to gastrointestinal symptoms.

How were decisions on the relevance of primary studies made?
Two reviewers independently selected studies and resolved any disagreements through discussion.
Assessment of study quality
The studies were assessed for methods of randomisation, allocation concealment, baseline comparability, blinding of the participants, care providers and outcome assessors, and losses to follow-up. Studies were classified for risk of bias (low, medium or high) based on allocation concealment and baseline comparability. Two reviewers independently assessed validity and resolved any disagreements through discussion.

Data extraction
Two reviewers independently extracted the data and resolved any disagreements through discussion. For each comparison, data were on the number of people with each outcome were extracted for the longest follow-up point and used to derive a relative risk (RR).

Methods of synthesis
How were the studies combined?
The results from the individual studies were combined using a random-effects meta-analysis, where appropriate. A pooled RR with 95% confidence intervals (CIs) was calculated separately for each gastroprotective strategy for each outcome of interest. The number-needed-to-treat to prevent one symptomatic ulcer was calculated where data permitted. Publication bias was assessed using funnel plots and Egger's and Begg's tests.

How were differences between studies investigated?
Statistical heterogeneity was assessed using the Cochran test (with a significance level of P<0.1) and by visual assessment of forest plots. A random-effects meta-regression was used to examine the influence on symptomatic ulcers of length of follow-up, mean age of the participants, baseline gastrointestinal status and a number of initial risk factors for gastrointestinal harms. A sensitivity analysis was performed by omitting studies with a 'high' risk of bias, treatment arms with higher than recommended doses of NSAID or gastroprotective agent, and naproxen treatment arms (for deaths and serious cardiovascular and renal events).

Results of the review
One hundred and twelve RCTs (n=76,666) were included.

Five studies were considered to be at low risk for bias. Methodological flaws of the studies included lack of systematic reporting of important outcomes, overlapping of some outcomes, and lack of reporting allocation concealment and blinding of the outcomes assessment. The authors stated that few authors provided, or were able to provide, additional data when contacted and that few studies did not receive funding from pharmaceutical companies.

Non-selective NSAID plus H2 receptor antagonists versus placebo plus non-selective NSAID: 15 RCTs (2,621 patients) were identified, none of which were judged to be at low risk of bias. There were insufficient data to adequately compare H2 receptor antagonists with placebo on any of the primary outcomes. H2 receptor antagonists significantly reduced endoscopic ulcers compared with placebo (RR 0.55, 95% CI: 0.4, 0.7).

Non-selective NSAID plus PPIs versus placebo plus non-selective NSAID: 6 RCTs (1,358 patients) were identified, one of which was judged to be at low risk of bias. There were insufficient data to compare PPIs with placebo in terms of serious gastrointestinal complications, serious cardiovascular or renal conditions, quality of life, or death. The significant reduction in symptomatic ulcers with PPI versus placebo (RR 0.09, 95% CI: 0.0, 0.5) was lost on sensitivity analysis. The significant reduction in endoscopic ulcers with PPI versus placebo (RR 0.37, 95% CI: 0.3, 0.5) remained on sensitivity analysis.

Non-selective NSAID plus misoprostol versus placebo plus non-selective NSAID: 23 RCTs (16,945 patients) were identified, one of which was judged to be at low risk of bias. Misoprostol significantly reduced serious gastrointestinal complications (RR 0.57, 95% CI: 0.4, 0.9), symptomatic ulcers (RR 0.36, 95% CI: 0.2, 0.7) and endoscopic ulcers (RR 0.33, 95% CI: 0.3, 0.4). No statistically significant heterogeneity was detected and the results were stable to sensitivity analysis.
COX-2 selective NSAID only versus non-selective NSAIDs: 51 RCTs (28,178 patients) were identified, none of which were judged to be at low risk of bias. COX-2 selective NSAIDs significantly reduced symptomatic ulcers compared with placebo (RR 0.41, 95% CI: 0.3, 0.7). There were few events reported for the other primary outcomes.

COX-2 specific NSAID only versus non-selective NSAIDs: 17 RCTs (25,564 patients) were identified, three of which were judged to be at low risk of bias. COX-2 specific NSAIDs appeared to significantly reduce serious gastrointestinal complications (RR 0.55, 95% CI: 0.4, 0.8) and symptomatic ulcers (RR 0.49, 95% CI: 0.4, 0.6). No statistically significant heterogeneity was detected for either meta-analysis, but the results for serious gastrointestinal complications were not robust to sensitivity analysis. No significant difference was found in the occurrence of serious cardiovascular or renal illness, or total deaths. COX-2 specific NSAIDs were associated with significantly fewer endoscopic ulcers.

The meta-regression found no significant association between the RR of symptomatic ulcers (for COX-2 selectives and specifics) or endoscopic ulcers (for H2 receptor antagonists, PPIs and misoprostol) and length of follow-up, mean age, or baseline gastrointestinal status.

The number-needed-to-treat was infinite for H2 receptor antagonists and COX-2 specific NSAIDs and 14 (8 to 100) for PPIs.

**Authors' conclusions**

Misoprostol, COX-2 specific and selective NSAIDs, and possibly PPIs, significantly reduced the risk of symptomatic ulcers. Misoprostol and probably COX-2 specifics significantly reduced the risk of serious gastrointestinal complications, but the quality of the data was poor.

**CRD commentary**

The review question was clear in terms of the study design, participants, intervention and outcomes. Several relevant sources were searched and the search terms were stated. Attempts were made to minimise language and publication bias. Two reviewers independently selected studies, assessed validity and extracted the data, thus reducing the potential for bias and errors. Validity was assessed using established criteria. Adequate details on the results of the included studies were given, although information on the participants and interventions was limited. The methods used to combine the studies appeared appropriate. Differences between the studies were assessed and associations between treatment effect and several study characteristics were explored. The synthesis of the evidence took account of study quality. The authors' conclusions appear reliable.

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

**Practice:** The authors did not state any implications for practice.

**Research:** The authors stated that trials should report rare but important events (such as deaths, cardiovascular events or serious gastrointestinal bleeds) in papers so that data are available for independent meta-analysis or, at the very least, are available to named contact authors. They further stated that there is a need for a large multicentre, independently funded trial lasting at least 1 year into gastroprotective agents such as H2 receptor antagonists, PPIs, misoprostol, COX-2 selectives, COX-2 specifics and placebo.

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Other publications of related interest


This additional published commentary may also be of interest. Wong VW. Review: misoprostol or COX-2-specific or selective NSAIDs reduce gastrointestinal complications and symptomatic ulcers. ACP J Club 2005;142:75.

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