Prevention of nonsteroidal anti-inflammatory drug-induced gastrointestinal mucosal injury:
a meta-analysis of randomised controlled clinical trials
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Authors' objectives
To examine the effectiveness of histamine type 2 (H2) blockers or misoprostol as co-therapy in the prevention of non-
steroidal anti-inflammatory drug (NSAID)-induced gastrointestinal mucosal injury.

Searching
MEDLINE was searched from January 1970 to December 1994, and bibliographies of review articles were examined. Only studies published in English were considered. The search strategy is given.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) where NSAIDs had been administered for at least 5 days, with patients included on an intention to treat basis. Studies on patients with osteoarthritis or rheumatoid arthritis, or on healthy patients, were considered to be eligible for data pooling if (1) an endoscopy had been performed before and during NSAID treatment; (2) individuals at admission had no evidence of an ulcer at the first endoscopy; (3) treatment regimens had been randomly allocated; (4) NSAID therapy had been given for at least 5 days; and (5) a placebo arm was included.

Specific interventions included in the review
H2 blockers (ranitidine, cimetidine, nizatidine) or misoprostol.

Participants included in the review
Patients with osteoarthritis or rheumatoid arthritis, or healthy patients, undergoing treatment with NSAIDs. The ages of the patients in the included studies ranged from 18 to 90 years.

Outcomes assessed in the review
The number of patients in whom a gastric ulcer (GU) developed; the number of patients in whom gastric lesions (GL) developed; the numbers of patients in whom a duodenal ulcer (DU) developed; and the number of patients in whom duodenal lesions (DL) developed.

How were decisions on the relevance of primary studies made?
Three authors assessed the papers for the review, although the authors do not state how the papers were selected.

Assessment of study quality
Each study was evaluated for quality using the criteria proposed by Chalmers et al. (see Other Publications of Related Interest no.1) and Liberati et al. (see Other Publications of Related Interest no.2). The quality of the included studies was expressed as a percentage of the total possible score. The median quality score for all trials was 52% (range: 31.5 - 76.5). The authors do not state how the quality assessment was performed; presumably, quality was also assessed by three independent blinded reviewers.

Data extraction
The data were extracted blindly and independently by three reviewers, with any disagreements resolved by consensus.

Methods of synthesis
How were the studies combined?
A baseline risk of lesions during NSAID therapy in the control groups was calculated by the methods of Coplen et al. (see Other Publications of Related Interest no.3). A meta-analysis was carried out using the method of DerSimonian and Laird (see Other Publications of Related Interest no. 4) to summarise the outcomes of the RCTs in terms of rate differences (RDs). Summary odds ratios (ORs) were also calculated using the method suggested by Yusuf et al. (see Other Publications of Related Interest no.5).

How were differences between studies investigated?
Differences between the studies were tested using the Q statistic (see Other Publications of Related Interest no.4), and a L’Abbe plot was used to investigate heterogeneity. Sensitivity analysis was also performed, by looking at subgroups of studies which included healthy participants only, or included patients only.

Results of the review
Twenty-four studies (4,325 patients and 680 healthy participants). (A total of 4,325 is reported in text of article though a total of 4,298 appear in Table 1).

Prevention of GUs: the weighted average baseline risks for GUs were found to be 3.6 and 6.8% with short- and long-term NSAID treatment, respectively. H2 blockers did not lead to a significant risk reduction of GUs either during the short term (pooled RD -0.9%, 95% confidence interval, CI:-4.0, 2.2) or long term (pooled RD -0.3%, 95% CI:-2.9, 2.2). A statistical benefit for these drugs was not shown in any of the included studies.

Misoprostol treatment resulted in a significant (P<0.05) risk reduction in the short term (pooled RD -13.3%, 95% CI: -25.7, -0.9) and in the long term (RD -8.4%, 95% CI: -17.7, -1.0, P<0.001).

The corresponding pooled ORs for short- and long-term treatment with H2 blockers were 0.51 (95% CI: 0.16, 1.66) and 0.86 (95% CI: 0.55, 1.34), respectively, and for treatment with misoprostol were 0.06 (95% CI: 0.03, 0.15) and 0.29 (95% CI: 0.20, 0.42).

Prevention of GLs: the weighted average baseline risks for GLs were found to be 53 and 27% with short- and long-term NSAID treatment, respectively. H2 blockers did not lead to a significant risk reduction with either short-term (RD -11.1%, 95% CI: -28.2, 6.0) or long-term (RD -0.6%, 95% CI: -7.0, 5.9) treatment. A statistical advantage of H2 blockers was shown in one study only. However, a statistical advantage of short-term treatment was shown when the approach of Yusuf et al. (see Other Publications of Related Interest no.5) was used (OR 0.56, 95% CI: 0.34, 0.94, P=0.03).

Misoprostol induced a significant RD in short-term (RD -59.8, 95% CI: -91.3, -28.3, P<0.001) and long-term (RD -13.3%, 95% CI: -20.8, -5.8, P<0.01) treatment. In 10 out of 11 studies, misoprostol showed a statistical advantage over placebo.

Prevention of DUs: the weighted average baseline risks for DUs were found to be 3 and 4% with short- and long-term NSAID treatment, respectively. H2 blockers did not lead to a significant risk reduction during short-term treatment (RD 1.1%, 95% CI: -2.7, 4.9), although a significant risk reduction was observed for long-term treatment (RD -2.4%, 95% CI: -4.6,-0.2, P=0.04). A statistical benefit was shown in 3 out of 5 long-term and none of the 4 short-term studies.

Misoprostol did not significantly reduce the risk of DUs with short-term treatment (RD -2.0%, 95% CI: -5.7, 1.6), although the approach of Yusuf et al. (see Other Publications of Related Interest no.5) found a significant pooled risk reduction (OR 0.11, 95% CI: 0.03, 0.44, P=0.004). Treatment was effective long-term (RD -3.4%, 95% CI: -5.8, -0.1, P<0.001). Treatment showed a statistically-significant advantage in 3 of 6 long-term trials.

Prevention of DLs: the weighted average baseline risks for DLs were found to be 1% and 12% with short-and long-term NSAID treatment, respectively. H2 blockers did not lead to a significant risk reduction with either short-term (RD -10.9%, 95% CI: -24.8, 2.9) or long-term (RD -6.4%, 95% CI: -14.6, 1.8) treatment, though the method of Yusuf et al. (see Other Publications of Related Interest no.5) showed a significant advantage (OR 0.4, 95% CI: 0.19, 0.84, P=0.02). Treatment showed a significant advantage in 1 out of 4 short-term trials and 1 out of 3 long-term trials.

Misoprostol resulted in a significant reduction in risk with short-term (RD -17.4%, 95% CI: -26.2, -8.5, P<0.001) and
long-term (RD -9.6%, 95% CI: -13.4, -5.8, P<0.01) treatment. In 6 out of 7 short-term and 3 out of 4 long-term studies, treatment showed a significant advantage over placebo. The sensitivity analysis showed that the results were generally not changed when the study focused on normal participants or patients. However, in the prevention of DLs with the use of H2 blockers, these drugs were found to result in a significant reduction in the risk of DLs in healthy participants during short-term prophylaxis when the study on patients was excluded (RD -16.7%, 95% CI: -24.8, -3.8, P<0.01). All of the long-term studies on the use of H2 blockers were performed on patients with arthritis, with the exception of 1 trial which found no advantage with ranitidine treatment in healthy participants. All of the long-term studies of misoprostol were performed on patients so no conclusions could be reached regarding the effectiveness of long-term prevention in healthy participants. Publication bias was also examined: no such bias was found for the studies examining misoprostol in prevention of GUs, though there appeared to be some publication bias in the area of misoprostol treatment in prevention of GLs. It was estimated that 21 short- and 45 long-term studies on GUs with negative results, and 199 short- and 14 long-term trials on GLs with negative results, would be required to offset the positive results of the meta-analysis regarding misoprostol.

Numbers-needed-to-treat (NNTs) were calculated for misoprostol and H2 blockers in prevention of GU or DU. The NNT to prevent 1 person from developing a GU within 2 weeks of NSAID therapy was found to range from 35 (95% CI: 34, 39) when the baseline risk was 3%, to 3 (95% CI: 3, 3) when the baseline risk was 40%. The corresponding NNTs for GU prevention in long-term studies ranged from 47 (95% CI: 41, 58) to 5 (95% CI: 4, 7). The NNTs for prevention of DU with misoprostol in short-term studies ranged from 36 (95% CI: 34, 60) with low baseline risk, to 4 (95% CI: 3, 7) with a high baseline risk. The NNTs for misoprostol treatment in long-term studies ranged from 47 (95% CI: 40, 65) for the lowest-risk patients, to 8 (95% CI: 4, 8) for the highest-risk patients. For long-term therapy with H2 blockers, the NNTs ranged from 54 (95% CI: 41, 136) in low-risk patients to 6 (95% CI: 4, 18) in high-risk patients.

Authors' conclusions
A rational approach to treat only high-risk patients is recommended. The treatment should be administered as soon as possible, as the risk of GLs and adverse events is higher in the first weeks of NSAID therapy.

CRD commentary
The quality assessment of the included trials is unfortunately limited. The studies were assessed, but this assessment was used simply as an overall description of the included studies. It would have been more useful to have differentiated between the lower- and higher-quality trials, e.g. by separate analysis of the latter group, as the lower-quality trials may overestimate the effectiveness of treatment; thus, the NNTs may need to be interpreted with caution. Generally, this was a thorough and detailed review.

Bibliographic details

PubMedID
8911239

Other publications of related interest
This additional published commentary may also be of interest. Scheiman J M. Meta-analysis: misoprostol reduces NSAID-induced gastrointestinal mucosal injury. ACP J Club 1997;126:36.

Indexing Status
Subject indexing assigned by NLM

MeSH
Adolescent; Adult; Aged; Aged, 80 and over; Anti-Inflammatory Agents, Non-Steroidal /adverse effects; Anti-Ulcer Agents /therapeutic use; Cost-Benefit Analysis; Drug Therapy, Combination; Duodenal Ulcer /chemically induced /prevention & control; Female; Histamine H2 Antagonists /therapeutic use; Humans; Male; Middle Aged; Randomized Controlled Trials as Topic; Research Design; Risk Factors; Stomach Ulcer /chemically induced /prevention & control; Time Factors

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