Upper gastroduodenal ulceration in arthritis patients treated with celecoxib
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Authors' objectives
To evaluate the comparative incidence of endoscopic gastroduodenal ulcers in patients with rheumatoid arthritis or osteoarthritis, treated with celecoxib.

Searching
The Cochrane Controlled Trials Register, MEDLINE and EMBASE were searched from 1988 to July 2000. The search terms included 'antiinflammatory agents, nonsteroidal', 'celecoxib', cycloxygenase inhibitors' and 'SC-58635'. The websites of the Food and Drug Administration, and the European Agency for the Evaluation of Medicinal Products, were also searched, together with the reference lists of the retrieved articles. Studies reported in any language were considered.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials. All trials that met the inclusion criteria were of a double-blind parallel group design. Most were of 12 weeks' duration, but one was of 24 weeks.

Specific interventions included in the review
Trials of celecoxib were eligible for inclusion. The included trials tested doses ranging from 100 to 800 mg/day. Two trials compared celecoxib with placebo, and all made comparisons with other drugs: three with naproxen, two with diclofenac, and one with ibuprofen.

Participants included in the review
Patients with rheumatoid arthritis or osteoarthritis who had scheduled endoscopies, were included.

Outcomes assessed in the review
The primary outcome measure was the proportion of patients with endoscopically documented gastroduodenal ulcers, defined as any break in the mucosa of at least 3 mm in diameter with unequivocal depth.

How were decisions on the relevance of primary studies made?
Eligibility was determined independently by two authors; there were no differences in opinion between the two authors.

Assessment of study quality
The authors do not state that they assessed validity.

Data extraction
The authors do not state how the data were extracted for the review, or how many of the reviewers performed the data extraction. Data were extracted on the drug dosages, the duration of the trials, and the incidence of ulcers.

Methods of synthesis
How were the studies combined?
The rate ratio (also known as the relative risk; RR), rate difference (RD), and the number-needed-to-harm were calculated from the proportion of patients with gastroduodenal ulcers in the treatment group relative to the control group. These were calculated for all of the results from the individual studies, using an intention to treat analysis. The 95% confidence intervals (CIs) of the individual RR and RD were estimated using the Mantel-Haenszel method. The pooled effect sizes were calculated using a fixed-effect method. A sensitivity analysis was undertaken to compare
intention to treat with completers who undertook a final endoscopic evaluation.

**How were differences between studies investigated?**
The chi-squared test was used to assess heterogeneity between trials. The results from the studies were grouped for the following comparisons:

- celecoxib versus placebo, with subdivisions according to dose;
- different doses of celecoxib;
- celecoxib versus naproxen, with subdivisions according to dose;
- celecoxib versus diclofenac; and
- celecoxib versus ibuprofen.

**Results of the review**
Five randomised controlled trials (4,632 participants) were included.

The chi-squared tests did not indicate any significant heterogeneity between the results (using the criterion of p<0.1), because the test for heterogeneity was weak.

Using the intention to treat-analysis, the pooled RRs were calculated for ulcer incidence after 12 weeks, unless otherwise stated, along with the 95% CIs. For celecoxib (100 mg, twice daily) relative to placebo (2 trials), the RR was 1.96 (95% CI: 0.85, 4.55, p>0.05). For celecoxib (200 mg, twice daily) relative to placebo (2 trials), the RR was 2.35 (95% CI: 1.02, 5.38, p<0.05). This difference was statistically significant.

For 200 mg versus 100 mg celecoxib, both dosages twice daily (2 trials), the RR was 1.21 (95% CI: 0.62, 2.38, p>0.05).

For celecoxib (200 mg twice daily) versus naproxen (500 mg, twice daily) (3 trials), the RR was 0.24 (95% CI: 0.17, 0.33, p<0.05). This difference was statistically significant.

For celecoxib (200 mg, twice daily) versus diclofenac (75 mg, twice daily) at 24 weeks (1 trial), the RR was 0.24 (95% CI: 0.11, 0.52, p<0.05). This difference was statistically significant.

For celecoxib (200 mg, twice daily) versus ibuprofen (800 mg, 3 times daily) (1 trial), the RR was 0.30 (95% CI: 0.20, 0.48, p<0.05). This difference was statistically significant.

The sensitivity analysis, which only analysed results for those who undertook a final endoscopic evaluation, generally produced no qualitative difference in the results. The exception was that there were no significant differences between the rates of endoscopic ulcers with celecoxib, at all doses, compared with placebo. In addition, the comparison between celecoxib (200 mg, twice daily) and diclofenac (75 mg, twice daily) at 12 weeks became statistically significant, with a RR of 0.25 (95% CI: 0.16, 0.40); this was very similar to the result found for diclofenac at 24 weeks.

On average, for every seven patients treated with naproxen, one more had an ulcer than if they were treated with celecoxib.

**Authors’ conclusions**
Endoscopic studies have shown that over a period of 12 to 24 weeks, celecoxib at a wide range of doses is associated with a lower incidence of gastroduodenal ulcers than are diclofenac, ibuprofen or naproxen. Although celecoxib was associated with endoscopic ulcers, the incidence rates for celecoxib were similar, although not equivalent, to placebo. Head-to-head comparisons suggested that, at a wide range of doses(100 to 800 mg/day) there was no dose-related increase in endoscopic gastroduodenal ulcers with celecoxib. The results of longer-term comparative trials are needed to determine its ultimate risk-benefit profile.
CRD commentary
The review addressed a clearly defined question with clear criteria for selecting the trials. A wide-ranging search strategy enabled it to include unpublished trials. Double-blind, randomised controlled trials analysed on an intention-to-treat basis provide a good evidence base, provided that the trials are well-conducted, which we were not able to determine. There was no report of any further validity assessment beyond the stated study design. The methods used to determine the eligibility of the studies and to extract the data were not described. The individual studies included in the review were well described.

Tests for heterogeneity were carried out; since no significant heterogeneity was found, the statistical method used to pool the results was appropriate.

The authors’ conclusions appear justified, although it should be noted that many of the results are based on only one or two trials.

Implications of the review for practice and research
Practice: In line with the authors’ conclusion, celecoxib appears to offer an alternative to traditional non-steroidal anti-inflammatory drugs. There is a lower risk of gastroduodenal ulcers, at least over a period of 12 to 24 weeks.

Research: In line with the authors’ conclusion, longer-term trials are needed to fully assess its risks compared to those of the widely-used alternatives.

Bibliographic details

PubMedID
11485128

Indexing Status
Subject indexing assigned by NLM

MeSH
Anti-Inflammatory Agents, Non-Steroidal /adverse effects /therapeutic use; Arthritis, Rheumatoid /drug therapy; Celecoxib; Dose-Response Relationship, Drug; Humans; Incidence; Meta-Analysis as Topic; Osteoarthritis /drug therapy; Peptic Ulcer /chemically induced; Pyrazoles; Randomized Controlled Trials as Topic; Sulfonamides /adverse effects /therapeutic use

AccessionNumber
12001001848

Date bibliographic record published
30/06/2002

Date abstract record published
30/06/2002

Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.