Nonsteroidal anti-inflammatory drugs and hepatic toxicity: a systematic review of randomized controlled trials in arthritis patients

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CRD summary
This review assessed the hepatic side-effects of non-steroidal anti-inflammatory drugs (NSAIDs) in patients with arthritis. The authors concluded that NSAIDs did not increase liver-related serious adverse effects, hospitalisation or death, but diclofenac and rofecoxib increased aminotransferase elevations compared with placebo and other NSAIDs examined. The conclusions were drawn from indirect comparisons, hence they may not be robust.

Authors' objectives
To assess the frequency of laboratory and clinical hepatic side-effects with non-steroidal anti-inflammatory drugs (NSAIDs) in patients with arthritis.

Searching
MEDLINE, EMBASE and the Cochrane Library were searched from inception to January 2004 for studies reported in the English language; the search terms were reported. The public archives of the U.S. Food and Drug Administration (FDA) were also searched.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) that lasted at least 4 weeks and had more than 40 patients in each NSAID treatment arm were eligible for inclusion. All but two of the included studies lasted at least 6 months.

Specific interventions included in the review
Studies of the NSAIDs celecoxib, rofecoxib, valdecoxib, meloxicam, diclofenac, naproxen and ibuprofen were eligible for inclusion.

Participants included in the review
Studies of adults (aged older than 18 years) with osteoarthritis and rheumatoid arthritis were eligible for inclusion. Most of the included studies were in patients with osteoarthritis.

Outcomes assessed in the review
Studies that explicitly reported the number of events for the following outcomes were eligible for inclusion: death due to hepatic cause; liver transplantation; hospitalisation due to acute liver disease; serious hepatic-related adverse event (SAE); discontinuation of drug due to elevated liver tests or clinical hepatic-related events; and aminotransferase (ALT/AST) more than three times the upper limit of normal. Studies that explicitly reported the absence of hepatic toxicity outcomes were also included.

How were decisions on the relevance of primary studies made?
Two reviewers independently selected studies and resolved any disagreements by consensus.

Assessment of study quality
Validity was assessed using the Jadad scale, which considers the reporting and handling of randomisation, blinding and handling of withdrawals.

Two reviewers independently assessed validity. Any disagreements were discussed and resolved by consensus.
Data extraction
Two reviewers independently extracted the data using a computer-based form. Any disagreements were discussed and resolved by consensus. Data extracted included hepatic events of interest, outcomes reported and not reported.

Methods of synthesis
How were the studies combined?
The studies were grouped by outcome. The overall percentage (weighted by sample size) of patients with 95% confidence interval (CIs) with hepatic events of interest was calculated separately for placebo and each type of NSAID. Treatments were compared by examining the degree of overlap between the 95% CIs for different NSAIDs and placebo.

How were differences between studies investigated?
A subgroup analysis was used to examine the effect of type of arthritis, study duration (13 weeks or shorter versus longer than 13 weeks) and NSAID dose (for diclofenac and rofecoxib).

Results of the review
One hundred and twenty-nine RCTs were included (n at least 51,942, exact number not reported or calculable). Sixty-four studies were identified from databases, while an additional 65 RCTs were identified from the FDA archives.

Sixty (96%) of the included studies identified in bibliographic databases were double-blind and 55 (86%) accounted for all randomised patients. The quality of the trials identified from the FDA website was not reported.

ALT/AST more than three times the upper limit of normal: this occurred in 0.29% (95% CI: 0.17, 0.51) of patients taking placebo. There was overlap between the 95% CIs for celecoxib, valdecoxib, meloxicam and naproxen and placebo. The highest rate of elevation was with diclofenac (3.55%, 95% CI: 3.12, 4.03), followed by rofecoxib (1.80%, 95% CI: 1.52, 2.13). There was no overlap between either diclofenac or rofecoxib and other NSAIDs or placebo.

Discontinuation due to hepatic-related adverse events: this occurred in 0.08% (95% CI: 0.02, 0.29) of patients taking placebo. Diclofenac was the only NSAID with higher non-overlapping 95% CI compared with placebo; the rate was 2.17% (95% CI: 1.78, 2.64).

Hepatic-related serious adverse events: these occurred very rarely. The highest rates were seen with naproxen (0.06%, 95% CI: 0.02, 0.15), followed by rofecoxib and diclofenac. All of these 95% CIs overlapped with placebo.

Hepatic-related hospitalisation, death and liver transplant: only 1 of 37,671 patients was hospitalised (with naproxen), giving an overall rate for all NSAIDs of 2.7 per 100,000 patients (95% CI: 0.5, 15). Only 1 of 51,942 patients had a liver-related death, giving an overall rate for all NSAIDs of 1.9 per 100,000 patients (95% CI: 0.3, 11). No liver transplants were reported. There was overlap amongst all treatment groups in the 95% CIs for liver-related hospitalisations and deaths.

The results were similar after analysing the data by type of arthritis. The studies showed a trend towards higher rates of aminotransferase elevations and liver-related discontinuations with longer term use of diclofenac compared with shorter term use, and for higher doses of diclofenac compared with lower doses (the data were reported).

Authors' conclusions
Diclofenac and rofecoxib were associated with higher rates of aminotransferase elevations than placebo and other NSAIDs examined. None of the NSAIDs examined increased liver-related serious adverse effects, hospitalisation or death.

CRD commentary
The review question was clear in terms of the study design, intervention, participants and outcomes. Several relevant
sources were searched and attempts were made to locate unpublished studies, thereby limiting the possibility of publication bias. No attempts were made to minimise language bias; this restriction to English language studies might have resulted in the loss of some relevant data. Two reviewers independently selected studies, assessed validity and extracted the data, thus reducing the potential for bias and errors. Only RCTs were included and validity was assessed using specified established criteria.

Details of the individual studies were not reported, but summary data were presented. Conclusions on the relative rates of adverse effects were drawn from indirect comparisons; a limitation which the authors acknowledged. A specific set of circumstances needs to be met for such a comparison to be valid. Some of these circumstances (e.g. comparability of placebo response rates) did not appear to have been met here. Direct comparisons of NSAIDs with each other and with placebo would be required to adequately assess the relative harms of these drugs.

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

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

Research: The authors stated that it is important to identify drugs that cause serious hepatic adverse effects, in particular, by using large clinical databases to systematically monitor outcomes in the post-marketing period.

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