Variability among nonsteroidal antiinflammatory drugs in risk of upper gastrointestinal bleeding
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CRD summary
The authors concluded that the risks of upper gastrointestinal bleeding/perforation for individual non-steroidal anti-inflammatory drugs varied between individual drugs; long half-life and slow-release formulations were associated with greater risks. The authors’ conclusions appeared to reflect the evidence, but a restricted search and limited assessment of study quality make it difficult to assess the reliability.

Authors’ objectives
To evaluate the risks of upper gastrointestinal bleeding or perforation for individual non-stereoidal anti-inflammatory drugs (NSAIDs).

The paper also reported results of a biochemistry study that evaluated the relationship between inhibitory effects on platelet COX-1 and monocyte COX-2 (using in vitro blood samples) of the various NSAIDs and the risk of upper gastrointestinal bleeding/perforation. The biochemistry study is referred to briefly in the result section of this abstract.

Searching
MEDLINE was searched for studies published in English between January 2000 and October 2008. Search terms were reported. Reference lists of selected articles and previous reviews were screened. Studies reported only as abstracts were excluded.

Study selection
Case-control and cohort studies that evaluated the effects of traditional NSAIDs or coxibs (selective inhibitors of cyclooxygenase 2 (COX-2)) on upper gastrointestinal bleeding or perforation in the general population were eligible for inclusion. Studies had to either provide the relative risk (RR) for NSAID users compared to non-users or sufficient data to permit its calculation.

The included studies evaluated coxibs (celecoxib and rofecoxib) and a range of traditional NSAIDs: ibuprofen, aceclofenac, ketorolac, piroxicam, naproxen, ketoprofen, indomethacin, meloxicam and diclofenac. All participants had been hospitalised or referred to a specialist for upper gastrointestinal bleeding/perforation. Studies defined NSAID exposure as at least one treatment or treatment in the previous seven to 90 days. Where reported, patients ranged in age from 16 to 105 years.

Two reviewers selected studies for inclusion. Decisions on included studies were reached by consensus.

Assessment of study quality
The authors stated that information on study methods and "objective quality-related characteristics" were extracted. Extracted information included source of cases and controls, definitions of outcome and exposure, sample size, methods used for validation of cases and control for confounding factors.

Two reviewers independently extracted data using a standardised form.

Data extraction
Two reviewers independently extracted adjusted relative risks (RRs) and 95% confidence intervals (CIs) using a standardised form. An author of a primary study was contacted for additional data. Odds ratios (ORs) from case-control studies were assumed to provide reliable estimates of relative risks.
Methods of synthesis
Data were pooled separately for all traditional NSAIDs combined and coxibs; data for individual NSAIDs were pooled only where there were more than five controls exposed. Pooled relative risks and 95% CIs were calculated using a fixed-effect inverse variance method. Summary estimates were calculated using a random-effects regression model. Heterogeneity was assessed using the DerSimonian and Laird Q statistic.

Subgroup analysis was used to examine the effect of study design, dosage (defined as low, medium or high), plasma-half life of drug (<12 hours and ≥12 hours) and formulation (slow-release versus shorter half-life). Where possible, relative risks for subgroups of interest were calculated from raw data.

Summary estimates were calculated including studies from a previously published review. The possibility of publication bias was explored using a funnel plot.

Results of the review
Nine studies were included (n=51,744 patients included 12,035 who were exposed to NSAIDs): two cohort studies, three nested case-control studies and four case-control studies. All of the nested case-control studies and cohort studies used computerised records to obtain data on exposure and outcomes. The case-control studies obtained data from field-based patient interviews. Confounders most commonly adjusted for were age, sex, prior ulcer history and concomitant medicines.

Cohort studies and nested case-control studies showed lower summary risks compared to field-based case-control studies.

Traditional NSAIDs were associated with a relative risk of bleeding or perforation of 4.50 (95% CI 3.82 to 5.31; significant heterogeneity). Coxibs were associated with a relative risk of 1.88 (95% CI 0.96 to 3.71).

A lower than the overall risk for NSAIDs was found for ibuprofen (RR 2.69, 95% CI 2.17 to 3.33), rofecoxib (RR 2.12, 95% CI 1.59 to 2.84), acetaminofen (RR 1.44, 95% CI 0.65 to 3.20) and celecoxib (RR 1.42, 95% CI 0.85 to 2.37). Relative risks were higher for ketorolac (RR 14.54, 95% CI 5.87 to 36.04) and piroxicam (RR 9.94, 95% CI 5.99 to 16.50).

Relative risks for other NSAIDs were: naproxen (RR 5.63, 95% CI 3.83 to 8.28), ketoprofen (RR 5.57, 95% CI 3.94 to 7.87), indomethacin (RR 5.40, 95% CI 4.16 to 7.00), meloxicam (RR 4.15, 95% CI 2.59 to 6.64) and diclofenac (RR 3.98, 95% CI 3.36 to 4.72).

Higher risks of gastrointestinal bleeding/perforation were found for NSAIDs with a long half-life (RR 5.74, 95% CI 3.58 to 9.21) and with slow-release formulations (RR 5.87, 95% CI 4.74 to 7.26).

Results were reported in tables for current and past use of NSAIDs and for treatment duration (from one to 30 days up to >365 days).

There was no evidence of publication bias from the funnel plot.

There was no significant correlation between the degree of inhibition of whole blood COX-1 and upper gastrointestinal bleeding or perforation. Profound and coincident inhibition (>80%) of both COX isoenzymes was associated with a higher risk.

Authors' conclusions
Risks of upper gastrointestinal bleeding/perforation varied between individual NSAIDs at doses commonly used in the general population. Higher risks of gastrointestinal bleeding/perforation were found for NSAIDs with a long half-life and for slow-release formulations.

CRD commentary
The review question was clearly stated. Inclusion criteria were appropriately defined. Limiting the search to studies
published in English and listed in one database plus references raised the potential for publication and language biases and may have resulted in the omission of other relevant studies. The funnel plot did not show evidence of publication bias, but was of limited value given the small number of studies. The authors stated that quality-related criteria were assessed, but this assessment appeared limited and it was difficult to judge the reliability of the findings. Methods were used to minimise reviewer errors during the review process. Appropriate methods were used for the meta-analyses. Heterogeneity was assessed. Various predefined subgroup analyses conducted.

The authors’ conclusions appeared to reflect the evidence, but the restricted search and limited assessment of study quality make it difficult to assess the reliability.

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

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