
Association between aspirin and upper gastrointestinal complications: systematic review of epidemiologic studies

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Authors' objectives

To systematically review the literature on serious upper gastrointestinal complications (UGIC) associated with aspirin use, and to evaluate the influence of dose and formulation of aspirin as well as the effect of study design.

Searching

MEDLINE was searched from 1990 to February 2001. The search terms used were 'anti-inflammatory nonsteroidal agents' (both overall and aspirin), 'adverse effects', and 'toxicity' combined with 'peptic ulcer', 'stomach ulcer', 'duodenal ulcer', or 'gastrointestinal diseases' (including haemorrhage and perforation). The references of previous reviews were also examined. When two articles reported results from the same study population, the most recent version was chosen. The earlier version was only considered if it provided additional sub-analyses.

Study selection

Study designs of evaluations included in the review

Observational epidemiological studies were included. The articles had to be case-control or cohort studies.

Specific interventions included in the review

The use of aspirin. Aspirin exposure was defined as during the last week, use in the last month, and use reaching the index date or prescriptions that would cover the index date. Aspirin was either the main exposure of interest, one among other anti-inflammatory drugs, or only considered as a potential confounder.

Participants included in the review

Adult aspirin users were eligible. Some studies restricted their sample to elderly populations. Some studies employed the following exclusion criteria: cancer, oesophageal varices, Mallory-Weiss disease, alcoholism, chronic liver disease, and coagulopathies.

Outcomes assessed in the review

The outcome assessed was UGIC, defined as bleeding, perforation, or any other serious upper gastrointestinal event resulting in hospitalisation or a visit to a specialist. Some studies specifically excluded oesophageal lesion and only considered lesions located in the stomach or duodenum. The exposure and outcome information was obtained from either computerised records or interviews. The articles had to provide valid relative risk (RR) estimates, or sufficient data for the authors to estimate a RR comparing aspirin users with non-users.

How were decisions on the relevance of primary studies made?

The inclusion criteria were applied independently by two of the authors, and any decisions regarding the inclusion of studies were reached by consensus.

Assessment of study quality

No systematic assessment of quality was undertaken.

Data extraction

Data from the articles were extracted in duplicate and entered into a database. Data on study methodology and objective quality-related characteristics were extracted. The list of characteristics was based on literature about the methods of epidemiological studies in general, and on previous meta-analyses on anti-inflammatory drugs and UGIC. The categories of data extracted from each study included: study reference details; period; location; the number of cases and

controls; the RR and 95% confidence interval (CI); exposure assessment; exposure window; and outcome.

Methods of synthesis

How were the studies combined?

A summary RR and 95% CI were calculated, weighting the study estimates by the inverse of the variance and estimating linear predictors for the log effect measure. In addition to these fixed-effect estimates, the corresponding random-effects models were also calculated. The odds ratio from case-control studies was assumed to provide a valid estimate of the RR. Potential publication bias was qualitatively explored using a funnel plot.

How were differences between studies investigated?

The heterogeneity in effects between studies was analysed using the DerSimonian and Laird test statistic (Q) for heterogeneity (see Other Publications of Related Interest).

Results of the review

Seventeen studies were included: 3 cohorts and 14 case-control studies. Three case-control studies were nested in a cohort. Ten case-control studies used matched designs. The total number of participants was not reported.

The pooled RR of UGIC associated with aspirin use was 2.6 (95% CI: 2.4, 2.7) when using a fixed-effect model, and 2.7 (95% CI: 2.2, 3.2) when using a random-effects model. However, the individual RR estimates were heterogeneous ($p < 0.001$) and varied from 1.4 to 11.2. The overall RR of UGIC associated with aspirin use was 2.2 (95% CI: 2.1, 2.4) for cohort studies and nested case-control studies, which was significantly lower than that for non-nested case-control studies (RR 3.1, 95% CI: 2.8, 3.3).

Five studies addressed the effect of different daily doses of aspirin in their analyses. All of them found greater risks of UGIC for aspirin doses above 300 mg/day than for lower doses. However, the risk was still elevated for doses up to 300 mg/day.

Four studies reported data on aspirin formulation. The pooled RRs were 2.4 (95% CI: 1.9, 2.9) for enteric-coated aspirin formulations and 2.6 (95% CI: 2.3, 2.9) for plain preparations. Two studies found buffered aspirin not to be associated with a lower UGIC risk than regular aspirin; the pooled RRs were 4.1 (95% CI: 3.2, 5.1) and 5.3 (95% CI: 3.0, 9.2) for plain and buffered aspirin, respectively, in those two studies.

When the frequency of exposure was investigated (2 studies), the RR was higher for patients using aspirin regularly (RR 3.2, 95% CI: 2.6, 3.9) than for those using aspirin occasionally (RR 2.1, 95% CI: 1.7, 2.6). When duration of use was investigated (3 studies), the risk of UGIC associated with aspirin was higher during the first month of use (RR 4.4, 95% CI: 3.2, 6.1) than in subsequent months of treatment (RR 2.6, 95% CI: 2.1, 3.1).

The funnel plot did not suggest the presence of publication bias.

Authors' conclusions

This systematic review confirms that aspirin, as used in the general population, increases the risk of UGIC. Aspirin was associated with UGIC even when used at low doses or in buffered or enteric-coated formulations. The latter findings may be partially explained by channelling of susceptible patients to these formulations.

CRD commentary

The review question was clearly set out and was well supported by pre-specified inclusion criteria. The literature search was limited as only MEDLINE was searched. Only published studies were considered and it was not stated whether any language restrictions were applied. Thus, important studies may have been missed. There was no systematic assessment of the quality of the included studies. Some details regarding the review process were provided, such as how many of the reviewers were involved and whether decisions were made independently. However, other details, such as whether the reviewers were blinded to the source and how disagreements were resolved, were not.

Both quantitative and qualitative syntheses were undertaken, and the data analysis used suitable methods for exploring heterogeneity. However, the statistical pooling of studies was inappropriate as there was significant heterogeneity. In addition, it was inappropriate to assume that the odds ratios from case-control studies were valid approximations of the RRs.

The findings of this review should be interpreted with extreme caution given the limitations highlighted. This review was supported in part by a research grant from Pharmacia.

Implications of the review for practice and research

The authors did not state any implications for further research and practice.

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Other publications of related interest

Takkouche B, Cadarso-Suarez C, Spiegelman D. An evaluation of old and new tests of heterogeneity in meta-analysis in epidemiologic research. *Am J Epidemiol* 1999;150:206-15.

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