Upper gastrointestinal complications among users of paracetamol
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CRD summary
The authors concluded that the use of paracetamol (acetaminophen) at commonly prescribed dosages is associated with small or no increased risk for upper gastrointestinal complications. The conclusions were in line with the evidence presented. However, the inclusion of only observational studies and lack of an assessment of validity make it difficult to be certain of the reliability of the authors' conclusions.

Authors' objectives
To determine the association between paracetamol (acetaminophen) and upper gastrointestinal complications in adult patients.

Searching
MEDLINE was searched for studies published from 1980 to 2004; the search terms were reported. Letters, commentaries, and abstracts were excluded. The reference lists of original articles and reviews reporting on paracetamol and upper gastrointestinal complications were reviewed.

Study selection
Study designs of evaluations included in the review
Case-control and cohort studies were eligible for inclusion. All of the included studies had a case-control design.

Specific interventions included in the review
Studies on paracetamol use and upper gastrointestinal complications were eligible for inclusion. Exposure was defined as any use in the previous week (8 studies), regular use in the previous week (1 study), regular use in the previous month (1 study), or any use in the previous month (1 study) or previous 3 months (1 study). Three of the included studies explored the association between daily dose of paracetamol and gastrointestinal complications.

Participants included in the review
Studies of adult users and non-users of paracetamol with (cases) and without (controls) upper gastrointestinal complications were included. Studies that included patients with uncomplicated peptic ulcer as controls were excluded. Seven studies used hospital controls, three used community controls, and two used hospital and community controls. Further details of the participants were not reported.

Outcomes assessed in the review
Studies that reported on upper gastrointestinal complications such as peptic ulcer bleeding and perforation were included.

How were decisions on the relevance of primary studies made?
The authors stated that relevant studies were determined by consensus.

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

Data extraction
Summary relative risks (RRs) and 95% confidence intervals (CIs) were calculated. Odds ratios from case-controlled studies were considered to provide a valid estimate of RR.

The authors did not state how many reviewers performed the data extraction.

Methods of synthesis
How were the studies combined?
A meta-analysis was used to estimate the pooled RR with 95% CI, weighting study estimates by the inverse of the variance and estimating linear predictors for the log effect measure. In addition to the fixed-effect estimate, the corresponding random-effects estimate was also calculated. Publication bias was assessed using a funnel plot.

How were differences between studies investigated?
The DerSimionan and Laird test statistic (Q) was used to investigate heterogeneity in effects between studies.

Results of the review
Twelve case-control studies (7,894 cases) were included.

Users of paracetamol had a small increased risk of gastrointestinal complications; the overall summary RRs were 1.3 (95% CI: 1.2, 1.5) (fixed effect) and 1.4 (95% CI: 1.1, 1.6) (random-effects). Estimates of RR from individual studies ranged from 0.2 to 1.95.

No significant statistical heterogeneity was detected among the pooled studies (p=0.12). The funnel plot did not provide evidence of publication bias.

In the 3 studies that explored the association of daily dose of paracetamol and gastrointestinal complications, there was a gradient dose-effect with higher doses associated with more gastrointestinal complications. In one study, the adjusted RR was 1.0 (95% CI: 0.8, 1.2) for users of at most 1,000 mg/day (n=752), 0.8 (95% CI: 0.6, 1.1) for users of 1,001 to 1,999 mg/day (n=301), 1.9 (95% CI: 1.4, 2.6) for users of 2,000 mg/day (n=211), 3.4 (95% CI: 2.4, 4.8) for users of 2,001 to 3,999 mg/day (n=78), and 6.5 (95% CI: 2.4, 17.6) for users of at least 4,000 mg/day (n=20). In the other 2 studies, users of more than 20 tablets in the past week had an RR of 2.4 compared with non-users and users of >1000 mg/day had an adjusted RR of 2.6.

Authors’ conclusions
The findings show that paracetamol at the doses most commonly used confers little or no increased risk of gastrointestinal complications.

CRD commentary
This review addressed a clearly defined question and was supported by clearly stated inclusion and exclusion criteria for the study design, intervention and outcome. The search involved one electronic database, so it is possible that relevant studies could have been missed. It is not clear if any language restrictions were applied and there were no attempts to search for unpublished literature. Publication bias was assessed. More than one author contributed to the study selection process, thereby reducing the risk of errors and bias, but other aspects of review methodology were not reported. No validity assessment was performed, thus it is difficult to assess the comprehensiveness and validity of the literature presented. Data about the participants in the included studies were limited, which makes it difficult to assess the generalisability of the review findings.

The methods used to pool the studies were appropriate and statistical heterogeneity was tested. Subgroup analyses were conducted to explore the gradient dose-effect, but the small group of studies included limits the evidence. The authors’ conclusions appear to be supported by the evidence; however, the lack of an assessment of the validity of the included studies, and their observational design, makes it difficult to confirm these conclusions.

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

Research: The authors stated that more research is needed to confirm or reject the hypothesis that high-dose paracetamol is associated with a risk of gastrointestinal complications of the same magnitude as that observed with traditional non-steroidal anti-inflammatory drugs.
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