Systematic review of prevalence of aspirin induced asthma and its implications for clinical practice

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CRD summary
This review assessed the prevalence of aspirin-induced asthma in the general asthma population, and cross-sensitivity to paracetamol and non-prescription non-steroidal anti-inflammatory drugs. The authors' main conclusion was that aspirin-induced asthma in adults is more prevalent than previously suggested. Limitations in the review methodology and reporting mean that it is not possible to comment on the reliability of this conclusion.

Authors' objectives
To assess the prevalence of aspirin-induced asthma in the general asthma population, and the cross-sensitivity of these individuals to other commonly used non-prescription analgesics.

Searching
The following databases were searched to March 2002: BIOSIS Previews, SciSearch (from 1990), EMBASE (from 1974), MEDLINE (from 1966), TOXLINE, Derwent Drug File (from 1964), Conference Papers Index, Inside Conferences; International Pharmaceutical Abstracts, and Pharma-Online (from 1978); the search terms were not reported. Additional studies were located through searches of archives and the reference lists of identified articles. Publications in any language were eligible.

Study selection

Study designs of evaluations included in the review
It was unclear whether there were any inclusion criteria relating to study design for the primary analysis of aspirin-induced asthma. Randomised controlled trials (RCTs), controlled clinical trials, studies involving open challenge and patient reporting, retrospective reviews of medical records and surveys were included. In the secondary analyses of sensitivity to NSAIDs and paracetamol, only RCTs were included.

Specific interventions included in the review
Studies of analgesics available without prescription (aspirin, paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs)) were eligible for inclusion. The studies included in the review assessed aspirin (dose not reported), paracetamol (1,500 mg or less) and three NSAIDs (ibuprofen, 400 mg or less; naproxen, 100 mg or less; diclofenac, 40 mg or less).

Participants included in the review
Studies of people with asthma were eligible for inclusion. The populations in the included studies were either unselected or pre-selected to include those with a history of aspirin-induced asthma or those with no history of aspirin sensitivity.

Outcomes assessed in the review
To be eligible for inclusion, the studies had to report asthmatic response to provocation. A positive response was defined as a 20% or more reduction in forced expiratory volume in one second within 3 or 4 hours of the provocation challenge. Where the participants had an unequivocal history of aspirin-induced asthma, the provocation test was not necessary as it would be considered unethical.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

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

Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction. The numbers of people with positive responses to the drug were extracted separately for those who underwent oral provocation and those reporting a historical positive response verbally.

Methods of synthesis
How were the studies combined?
The studies were grouped by drug type. The studies of aspirin were further grouped into studies of adults and studies of children, and then subgrouped into population type (unselected, pre-selected with history of sensitivity or pre-selected without history). For each population type, the results were pooled separately for those based on oral provocation testing alone, verbal history alone, and provocation testing and verbal history combined. A weighted average, where studies were weighted by the inverse of the variance, was used. The results for the other drugs were pooled separately using the same method, and 95% confidence intervals (CIs) were calculated for each pooled estimate.

How were differences between studies investigated?
Some differences between the studies were investigated through the use of a subgroup analysis (as described above).

Results of the review
Twenty-seven studies, involving over 9,000 participants in total, were included in the review. Almost 8,000 participants were included in 6 retrospective studies of medical records and surveys with verbal history evidence only.

The pooled prevalence of aspirin-induced asthma in unselected populations of adults with asthma was 21% (95% CI: 14, 29) when using the results of oral provocation testing (5 studies), and 3% (95% CI: 2, 4) when using verbal history alone (6 studies). When using the results of oral provocation testing, prevalence was 30% (95% CI: 18, 41) for pre-selected populations with a history of aspirin-induced asthma (7 studies) and 9% (95% CI: 4, 14) for pre-selected populations with no history (2 studies).

In unselected populations of children with asthma, the prevalence of aspirin-induced asthma was 5% (95% CI: 0, 14) when using oral provocation test results (3 studies) and 2% (95% CI: 1, 3) when using verbal history alone (1 study). When using the results of oral provocation testing, prevalence was 16% (95% CI: 4, 27) for pre-selected populations with no history of sensitivity (2 studies).

The pooled incidences of cross sensitivity to NSAIDs were as follows: ibuprofen 98% (95% CI: 90, 100; 2 studies), naproxen 100% (95% CI: 83, 100; 2 studies), diclofenac 93% (95% CI: 76, 100; 2 studies). The pooled incidence of cross sensitivity to paracetamol was 7% (95% CI: 0, 16; 8 studies).

Authors' conclusions
Aspirin-induced asthma in adults is more prevalent than previously suggested (10% in recent reviews). Fewer than 2% of asthmatic patients are sensitive to both aspirin and paracetamol. Oral provocation testing should be performed when there is a clinical necessity to use either aspirin or an NSAID and there is uncertainty about safety.

CRD commentary
The review question was clear, as were the inclusion criteria for the participants, intervention and outcomes. Several relevant databases were searched, along with reference lists, thus reducing the likelihood that relevant studies were missed. It was unclear whether attempts were made to minimise publication bias or the introduction of bias and errors during the study selection and data extraction processes. The authors addressed some aspects of clinical heterogeneity by subgrouping by population and by the method of outcome assessment. However, study quality was not assessed, and the results from several study designs were combined in the analyses of aspirin-induced asthma. It is therefore to judge
whether this pooling was appropriate. In addition, the results for children and for NSAIDs were based on the pooling of small numbers of studies. These limitations in review methodology and reporting mean that, although the authors’ conclusions follow from the evidence presented, they may not be reliable.

Implications of the review for practice and research
Practice: The authors provided guidelines for the use of analgesics in asthmatic patients. They stated that asthmatic patients should be alerted to the risks of aspirin and NSAIDs. Where aspirin or NSAIDs are clinically indicated for asthmatic patients, formal provocation testing is warranted.

Research: The authors stated that prospective studies in the general asthma population are warranted to confirm the prevalence data derived in their review.

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