

trials, only five trials reported that blinding was successful, and of these, three did not present any quantitative data analysis to support their claim.

Only four trials assessed blinding in both the participants and either the outcome assessors or the investigators. Thus, the face validity of the double blinding was only reported in four of the 191 articles (2%). Furthermore, the quality of evidence in the few studies that reported on the success of blinding is weak on two fronts: the quality of the data and the evidence that blinding was successful.

We would like to see item 11(b) of CONSORT revised to require the assessment of blinding for all double blind randomised trials. Trialists have an ethical responsibility to justify the use of a placebo for blinding purposes in their research protocol and informed consent procedures. Thus, it seems reasonable to suggest that an assessment of the success of blinding is necessary. If blinding is not assessed, we may delude ourselves as to exactly what information we gain from incorporating a placebo comparison. The types of trials that will particularly benefit are trials with subjective outcomes or outcomes reported by patients (for example, quality of life instruments), or trials where the side effects are well known. The lack of successful blinding can bias observed estimates of effect. Although this bias is differential, its direction may not be easily ascertained.

We believe that trialists need to report a minimum set of information. This includes the counts of all patients allocated to each treatment; the counts of

patients who guess treatment assignment by the group to which they were allocated; the counts of correct guesses and of those who are undecided; the analytical methods and results used to assess success of blinding; and the author's interpretation of the efficacy of blinding and the effect on study results.

Trialists and editors need to make a concerted effort to incorporate, report, and publish information about the success of blinding and its potential effect on study results. We need evidence before we can assert that assay sensitivity exists in randomised, double blind, placebo controlled trials.

We thank Julie Comber and Jennifer Marshall for article retrieval and data collection.

Contributors: See bmj.com

Funding: This work was funded in part by the Canadian Institutes of Health Research.

Competing interests: None declared.

Ethical approval: Not required.

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(Accepted 11 November 2003)

doi 10.1136/bmj.37952.631667.EE

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

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Abstract

Objectives To reassess the prevalence of aspirin induced asthma and other issues related to the syndrome.

Data sources Biosis, SciSearch (1990 to March 2002), Embase (1974 to March 2002), Medline (1966 to March 2002), Toxline, Derwent Drug File (1964 to March 2002), Conference Papers Index and Inside Conferences, Int'l Pharmaceutical Abstracts, Pharma-Online (1978 to March 2002).

Selection criteria Study type, patient population, and outcome measures. Review was restricted to respiratory responses to analgesics available without prescription.

Results The prevalence of aspirin induced asthma was highest when determined by oral provocation testing (adults 21%, 95% confidence interval 14% to 29%; children 5%, 0% to 14%) than by verbal history (adults 3%, 2% to 4%; children 2%, 1% to 3%). Cross sensitivity to doses of over the counter non-steroidal anti-inflammatory drugs was present in most patients with aspirin induced asthma: ibuprofen, 98%;

naproxen, 100%; and diclofenac, 93%. The incidence of cross sensitivity to paracetamol among such patients was only 7%.

Conclusions Aspirin induced asthma in adults is more prevalent than previously suggested. When there is a clinical necessity to use aspirin or a non-steroidal anti-inflammatory drug and there is uncertainty about safety, oral provocation testing should be performed

Introduction

Aspirin induced asthma is characterised by the onset of asthma 30 minutes to three hours after the ingestion of aspirin. Affected patients are cross sensitive to all non-steroidal anti-inflammatory drugs (NSAIDs) that inhibit cyclo-oxygenase (COX) enzymes, but seldom cross sensitive to paracetamol (acetaminophen).^{1 2} Paracetamol may exert at least part of its analgesic

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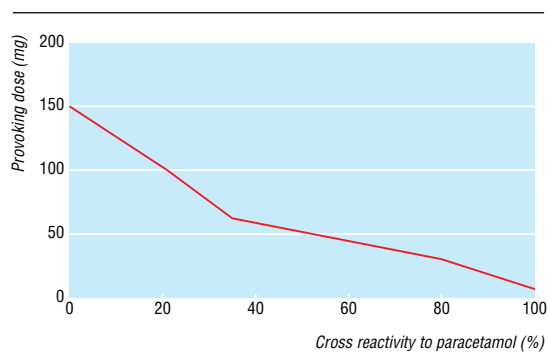
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BMJ 2004;328:434-7



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Relation between aspirin provoking dose and frequency of cross sensitivity to paracetamol (reproduced from Settignano et al 1995¹² with permission of Mosby)

effect through a newly identified COX-3 isoenzyme, whereas aspirin induced asthma is believed to involve inhibition of COX-1.³⁻⁵

Controversy remains as to the prevalence of aspirin induced asthma, with rates ranging from 4% to 44%. Differences in populations studied, methods used, definitions of outcomes, and criteria for defining sensitivity reactions may all be responsible for the variations in reported rates.⁶⁻⁸ A greater understanding of aspirin induced asthma is desirable, given the trend for consumers to self prescribe and the lack of association by many between asthma and some analgesics. We performed a systematic review to reassess the prevalence of aspirin induced asthma in the general asthma population and to understand better the cross sensitivity of these individuals to commonly used non-prescription analgesics.

Methods

On 3 March 2002 we identified articles with data on aspirin sensitivity among asthmatic patients and the use of paracetamol or NSAIDs. Additional articles were found through archives and the reference lists of identified articles. We excluded studies reporting non-respiratory responses to analgesics, such as urticaria.

Most studies recruited from asthma clinics or hospitals where patients had presented with acute exacerbations. To account for preselection bias, we subdivided the participants into three groups: group 1, all patients with asthma—with or without a history of aspirin induced asthma and with or without markers of an increased risk or likelihood of the syndrome; group 2, patients preselected on the basis that they had either a reliable history of aspirin induced asthma or markers of an increased risk or likelihood of the syndrome; and

group 3, patients with no markers of an increased risk or likelihood of aspirin induced asthma.

The primary outcome was whether the ingestion of aspirin triggered an asthmatic response, so we included in the main analysis only studies in which patients underwent provocation challenges. Our analysis defined a positive aspirin induced asthma response as a 20% or more reduction in forced expiratory volume in one second within three or four hours of the challenge.⁹

We conducted a subanalysis of studies in which authors had combined the results from patients with a history of aspirin sensitivity with patients showing a positive reaction to provocation challenge. We conducted a further subanalysis of papers in which history was the only means of determining aspirin sensitivity.

In the analysis of cross sensitivity we only included studies representing properly controlled, randomised, and single blinded or double blinded clinical trials. The primary outcome was whether the ingestion of NSAIDs (specifically ibuprofen, naproxen, and diclofenac) or paracetamol triggered an asthmatic response in patients who had been positively identified as having aspirin induced asthma by oral provocation testing, history, or both. Studies were only included for analysis if cross sensitivity to NSAIDs or paracetamol was determined by provocation challenge.

Using a weighted average of the incidence rates from individual studies, we calculated pooled incidence rates and 95% confidence intervals. The reciprocal of the variance in each study was calculated for weighting.

Results

Prevalence in adults

A total of 66 papers were identified that gave the prevalence for aspirin induced asthma. Only 21 (15 in adults and six in children) were eligible for inclusion in our analysis (see bmj.com). Owing to the risk of life threatening reactions, only four of the trials were double blind.

The pooled incidence of aspirin induced asthma was 21% (95% confidence interval 14% to 29%), regardless of whether the patients had a history of aspirin induced asthma or markers for an increased risk of the syndrome. Prevalence of aspirin induced asthma also seemed to depend on the method used to determine it, with history alone resulting in a much lower prevalence (2.7%). Four of the studies in adults gave data on the number of patients reacting to different doses of aspirin. Around half (57/113) of those who had positive reactions, reacted at low doses of aspirin (≥ 80 mg), indicating that they were highly sensitive.

Guidelines for use of analgesics in asthmatic patients

Patient characteristics	Recommendation
Anyone positively identified with aspirin induced asthma; or anyone who has ever experienced an asthmatic reaction to aspirin or NSAIDs (such as ibuprofen, diclofenac, naproxen sodium); or anyone with high risk features of aspirin induced asthma (severe asthma symptoms, nasal polyps, urticaria, or chronic rhinitis)	Patient should avoid all products that contain aspirin or NSAIDs indefinitely; paracetamol should be recommended, unless contraindicated
Younger than 40 years of age; or have not used aspirin or an NSAID recently without incident	Aspirin induced asthma may develop late in life, so patients should be informed of risks of aspirin and NSAIDs, and paracetamol should be recommended, unless contraindicated. If NSAIDs are necessary, the first dose may be taken under medical supervision
All other asthmatic patients	Any analgesic may be considered. If patients experience any respiratory reactions in response to therapy, they should be advised to stop treatment and visit a doctor

Prevalence in children

Aspirin induced asthma has been considered rare in children, yet we found the prevalence still to be around 5% (0% to 14%) when children are subject to oral provocation testing. Although only one of the studies was a double blind, randomised controlled trial, it accounted for almost half of the patients in our analysis. As with adults, the use of history alone gave a lower estimate of prevalence (2%, 1% to 3%) than that determined by oral provocation testing.

Incidence of cross sensitivity

Ten studies reported the incidence of cross sensitivity to three commonly used NSAIDs (ibuprofen, naproxen, diclofenac). Only three were eligible for inclusion. Based on these, the incidence of cross sensitivity was: ≤ 400 mg ibuprofen, 98% (95% confidence interval 90% to 100%); ≤ 100 mg naproxen, 100% (83% to 100); and ≤ 40 mg diclofenac, 93% (76% to 100%). See bmj.com for details.

Each article on cross sensitivity to paracetamol was classified according to its methods. Ten of 52 identified papers were eligible for inclusion. Of 268 adults and children with aspirin induced asthma who underwent oral challenge, only 32 had a positive respiratory reaction to paracetamol (pooled incidence 7%, 0% to 16%). See bmj.com for details.

Discussion

The prevalence of aspirin induced asthma is 21% for adults and 5% for children according to our systematic review. Our review is limited by the retrospective nature of the analysis and the heterogeneity of the patient population. We were unable to attain the clinical status of all the patients, there was a lack of uniformity with the challenge tests, and some studies included only a small number of patients. Clinical heterogeneity was overcome by analysing different patient populations separately, and the findings are strengthened by the distinction between adults and children and the types of testing involved (oral provocation testing, patient history, questionnaire).

Our value for the prevalence of aspirin induced asthma in adult asthmatic patients is higher than the 10% reported in recent reviews.⁷⁻¹⁰ Methods and patient bias provide one explanation for this, since studies assessing patient history only resulted in lower estimates than those based on oral provocation testing. Under-diagnosis of the syndrome may be due to the lack of routine testing by aspirin challenge in asthmatic patients who do not report a positive history of aspirin sensitivity.¹¹

Analyses based on the use of a questionnaire resulted in a higher prevalence rate (11-24%) than did retrospective analyses of medical records (2-3%). One explanation is that questionnaires are usually deployed within a set time frame and by a limited number of people, whereas medical records are likely to be completed by a larger number of different healthcare professionals. Retrospective analysis of medical records is therefore an insensitive means of detecting aspirin induced asthma.

Cross sensitivity to NSAIDs occurred in most of the patients with aspirin induced asthma. In contrast, the pooled incidence of cross sensitivity to paracetamol

What is already known on this topic

Aspirin induced asthma is a distinct syndrome that is potentially life threatening

The prevalence and cross reactivity to other analgesics has been difficult to assess due to differences in trial methods

Asthmatic patients sensitive to aspirin are usually cross reactive to NSAIDs, but seldom react to paracetamol

What this study adds

Aspirin induced asthma is more prevalent than previously suggested

Less than 2% of asthmatic patients are sensitive to both aspirin and paracetamol; reactions to paracetamol tend to be less severe

among patients with the syndrome was only 7%. Based on these data, less than 2% of asthmatic patients are likely to react to both paracetamol and aspirin. The available data indicate that patients who are highly sensitive to aspirin are more likely to be sensitive to paracetamol. The authors of one study found the mean provoking dose was only 47 mg of aspirin, compared with 1227 mg of paracetamol.¹² They also correlated aspirin dose and frequency of cross reactivity to paracetamol (figure). The reaction to paracetamol was also significantly shorter than that to aspirin and significantly milder.

We have simplified guidelines for the use of analgesics in asthmatic patients (table). Where history neither supports nor excludes aspirin induced asthma, and aspirin or NSAIDs are clinically indicated, formal provocation testing is warranted, but because of the risk of severe bronchoconstriction this must be conducted by specialised staff with facilities for emergency resuscitation.

Since aspirin and NSAIDs are often self prescribed, patients diagnosed with asthma should be alerted to the possibility of aspirin induced asthma by their healthcare professional. Our data justify the need to include simple, standardised warnings on packs of aspirin and NSAIDs, alerting asthmatic patients to the potential risks.

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Funding: CJ and LH are clinicians working partly in public hospital and private practice and in a research institute that receives funding from government, bequests, and many industry sources. Neither is directly funded by any manufacturer of non-steroidal anti-inflammatory drugs or paracetamol.

Competing interests: CJ has received payment from GlaxoSmithKline Consumer Healthcare Australia, the manufacturer of Panadol (paracetamol), for speaking at a conference. JC serves as a consultant on the Global Analgesics Advisory Board, which is funded by GlaxoSmithKline Consumer Healthcare.

Ethical approval: None required.

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Training for patients in a randomised controlled trial of self management of warfarin treatment

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Self management of warfarin treatment by patients, using a point of care coagulometer for testing international normalised ratios, is comparable to home glucose monitoring and may provide a robust model of service provision.^{1,2} Self management can lead to improvements in patients' self efficacy, closer adherence to treatment, and increased control of treatment with oral anticoagulants.³

We report data on the effectiveness of the training programme used for a clinical trial (self management of anticoagulation: a randomised trial, SMART) which aimed to evaluate clinical and cost effectiveness of self management compared with routine care. UK guidelines indicated that training to a standard acceptable is essential, although the nature of the training was not clearly defined.²

Participants, methods, and results

Patients aged over 18 with a long term indication for warfarin, from 48 general practices in the West Midlands, were eligible. After giving consent patients were randomly allocated to either self management or routine care. Data on demographics, age, ethnic origin, condition requiring warfarin treatment, and education were collected at consent. Nurses experienced in anticoagulation management, who had attended a course organised by the researchers to ensure standards and consistency, provided training. Patients randomised to self management attended at least two training sessions. Sessions were adapted from a German national programme,⁴ were practice based, and were held one week apart. The aims of training were to ensure that patients had a theoretical understanding of oral anticoagulation and INR monitoring, that they (or their carers) were able to measure the INR reliably by using a point of care system (Coaguchek S, Roche Diagnostics), and that they were able to interpret the INR in terms of appropriate warfarin dose. We assessed patients individually for competence in undertaking self management in terms of accurately performing an INR test (by using the point of care system), quality control issues, dosing algorithm and adjustment of dosage, and documenting INR results and adverse events. Capable patients were given equipment for home testing,

otherwise an additional session was arranged, and if they were still not considered capable of self management they were returned to usual care.

Of 2586 patients invited to participate 608 (24%) provided written consent, with central telephone randomisation to self management (n = 327) and usual care (n = 281). Of the patients randomised to self management 85/327 (26%) did not complete training (table). We defined reasons for dropout during training as either self exclusion of patients themselves or exclusion by the researcher. Of the patients 67/85 (79%) excluded themselves. The primary reason was manual difficulty with the procedure. Altogether 54/67 (81%) patients were generally unhappy with the procedure, and of those 30/54 (56%) gave the reason as trouble in obtaining sufficient capillary blood and placing the sample on to the test strip. In total 242/327 (74%) of patients passed the training assessment and started self management, and of those 212 (88%) completed 12 months of self management.

The participants who completed training were significantly younger than the group that did not complete training (61 v 71 years, P = 0.001). Significantly more patients were educated to GCSE or above standard among the patients who completed training (P = 0.003).

Comment

Although we used a training programme to train 242 unselected patients successfully in self management of warfarin treatment, 76% (1978/2586) of patients

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BMJ 2004;328:437-8

Details of patients enrolled in a randomised controlled trial of self management of warfarin treatment

	No of patients	Mean age (years)	Educated to GCSE or above
Patients invited	2586	69	—
Patients recruited	618 (24%)	65.2	—
Patients randomised to self management	327	64.1	—
Control	281	66.4	—
Patients randomised to self management who completed training	242 (74%)	61.2	120 (50%)
Patients randomised to self management who did not complete training	85 (26%)	71.4	30 (32%)