Pharmacological prevention of serious anaphylactic reactions due to iodinated contrast media: systematic review
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CRD summary
The review concluded that data supporting the use of premedication in patients with a history of allergic reactions was lacking. Given the limited evidence base this seemed reasonable, however, the conclusion that routine premedication should be abandoned may be somewhat strong given that the absence of evidence was not evidence of lack of effectiveness.

Authors' objectives
To determine the efficacy of pharmacological prevention of serious (potentially life threatening) reactions to iodinated contrast media.

Searching
MEDLINE/OldMEDLINE, EMBASE, HealthSTAR and CINAHL were searched without language restriction from 1950 to October 2005; search terms were reported. Cochrane Controlled trials register was also searched. References of relevant reviews and included studies were checked.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were included in the review.

Specific interventions included in the review
Studies that compared the use of premedication, alone or in combination, with a placebo or no treatment control group were eligible for inclusion. Five trials assessed H1 antihistamines (hydroxyzine, clemastine, chlorpheniramine, dimenhydrinate), five trials assessed corticosteroids (betamethasone, dexamethasone, methylprednisolone, prednisolone) and one trial assessed an H1-H1 combination (clemastine-cimetidine). In most trials, iodinated contrast medium was administered intravenously and in one trial intrathecally. Non-ionic low osmolar contrast media (ioxaglate, iohexol, ioversol) and ionic high osmolar contrast media (amidotrizoate sodium, meglumine, ioxithalamate) were used. One study reported only that the contrast media were ionic. One study did not specify the contrast medium used.

Participants included in the review
The authors did not pre-specify any inclusion criteria for participants. Adults undergoing a variety of radiological interventions were included in the primary studies (CT scan, venography, myelography, IV urography, IV injection, IV pyelography, arteriography and cholangiography). Some of the included studies excluded patients with previous reaction to the contrast medium or patients with a history of allergy, atrophy or drug hypersensitivity.

Outcomes assessed in the review
Studies that reported the presence or absence of allergic reactions were eligible for inclusion. Symptoms were regarded as potentially life threatening if they had the potential to deteriorate towards a status where ventilatory or haemodynamic support would be necessary. Outcomes reported in the trials included distinct allergy-related symptoms or combination of symptoms (haemodynamic, respiratory, cutaneous), arbitrary symptom combination (grades 1 to 3), non-specific symptoms or symptom combinations, and adverse drug reactions to the premedication.

How were decisions on the relevance of primary studies made?
The authors state neither how the papers were selected for the review nor how many reviewers performed the selection.

Assessment of study quality
Four criteria were used to evaluate the validity of the included trials: quality of randomisation; concealment of treatment allocation; blinding; and follow-up (including whether intention to treat analysis was performed). All the
investigators independently assessed the methodology of the included studies and any disagreements were resolved by discussion. A maximum score of seven was possible.

Data extraction
One investigator extracted data from the included studies, which were checked independently by the other investigators. Two investigators, an allergologist and an anaesthetist decided whether symptoms were allergy related and potentially life threatening. Where several similar outcomes were reported in one trial the reviewers selected the outcome with the most pronounced treatment effect in order to try and account for the possibility that more than one symptom could have occurred in the same patient. Peto odds ratios (ORs) and their 95% confidence intervals (CI) were calculated for all dichotomous data.

Methods of synthesis
How were the studies combined?
Trials were combined in a meta-analysis and efficacy estimates reported as summary ORs with 95% CI.

How were differences between studies investigated?
Statistical heterogeneity was assessed using the $\chi^2$ test (p<0.1 was considered significantly heterogeneous). The $I^2$ statistic was used to describe the degree of inconsistency between trials.

Results of the review
Nine RCTs were included in the review (n=9,251).

Quality
All nine studies reported randomisation, but none specified the method of randomisation. Only one study reported allocation concealment. Five studies reported blinding (although in one study this was deemed incomplete). Three studies reported incomplete follow-up. None of the included studies described a complete patient follow up to allow an intention to treat analysis.

Distinct allergy related symptoms
Premedication with steroids – intravenous betamethasone (8 mg) and oral methylprednisolone (2x32 mg) – did not significantly reduce the odds of hypotension compared to controls (OR 0.14; 95% CI: 0.01, 1.30, based on two trials). Intravenous dimenhydrinate 25 mg was also assessed, but the results were not reported. Premedication with antihistamines (OR 0.46; 95% CI: 0.15, 1.39, two trials) or corticosteroids (OR 0.31; 95% CI: 0.11, 0.88, two trials) did not significantly reduce the odds of serious respiratory symptoms. Premedication with antihistamines showed a significant reduction in cutaneous symptoms (OR 0.36; 95% CI: 0.22, 0.60, five trials), but significant statistical heterogeneity was shown. Two trials of premedication with corticosteroids showed a significant reduction in cutaneous symptoms compared to controls (OR 0.36; 95% CI: 0.15, 0.87).

Symptom categories
Only grade three symptoms were considered to be potentially life threatening. A double dose regimen of methylprednisolone (32 mg) was shown to significantly reduce grade three reactions compared with controls, OR 0.28 (95% CI: 0.13, 0.60, two trials). A single dose of methylprednisolone (32 mg) did not reduce grade three reactions, OR 2.00 (95% CI: 0.57, 7.00, one trial).

Non-specific symptoms
The symptoms in this category were considered not to be allergy related or life threatening and were not analysed further.

Adverse drug effects
Individuals receiving dexamethasone reported dyspepsia, insomnia, bitter taste, nausea and headaches. Individuals receiving hydroxyzine or clemastine reported bad taste, local skin reaction and somnolence.

Authors' conclusions
The authors concluded that serious anaphylactic reactions due to iodinated contrast media were rare. But, the usefulness
of premedication was questionable in unselected patients. Data supporting the use of premedication in patients with a history of allergic reactions were lacking. The efficacy of premedication should not be relied upon. Routine prophylaxis should be abandoned.

**CRD commentary**

The review addressed a clear question that was defined in terms of the participants, intervention, outcomes and study design. Several relevant electronic databases were searched without language restriction, reducing the risk of language bias. Procedures to extract data and assess validity were likely to have minimised reviewer error and bias, but similar methods were not reported for the selection of studies. Variation in the dose, type and administration of the premedication and contrast media, and the outcomes assessed, suggested that pooling estimates was not appropriate. In addition, as acknowledged by the authors, selecting outcomes with the most pronounced treatment effect may have led to an overestimation of the efficacy of the premedication. Given the diversity between the studies, multiple treatment elements and the questionable quality of the primary studies, there did not appear to be sufficient evidence to determine the efficacy of pharmacological prevention of serious reactions to iodinated contrast media. The authors’ conclusion that data supporting the use of premedication in patients with a history of allergic reactions were lacking seems reasonable, however, the conclusion that routine premedication should be abandoned may have been somewhat strong given that absence of evidence was not the evidence of a lack of effectiveness.

**Implications of the review for practice and research**

Practice: The authors stated that physicians dealing with patients who have received contrast media should not rely on the efficacy of premedication and that routine prophylaxis should be abandoned. They also stated that as only a small number of patients with serious reactions have a positive skin test for the administered contrast material, radiology departments should be trained to recognise and treat anaphylactic reactions appropriately and be staffed with the necessary resuscitation equipment.

Research: The authors stated that RCTs needed to formally assess whether steroid-antihistamine combinations improved the efficacy of premedication; studies estimating incremental cost effectiveness ratios, taking drug cost, prolonged hospital stay, delay in diagnosis and unplanned admission to the intensive care unit were needed for rational decision making, as were studies in patients with a history of allergic reactions.

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