

Pharmacological prevention of serious anaphylactic reactions due to iodinated contrast media: systematic review

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Abstract

Objective To review the efficacy of pharmacological prevention of serious reactions to iodinated contrast media.

Design Systematic review.

Data sources Systematic search (multiple databases, bibliographies, all languages, to October 2005) for randomised comparisons of pretreatment with placebo or no treatment (control) in patients receiving iodinated contrast media.

Review methods Trial quality was assessed by all investigators. Information on trial design, population, interventions, and outcomes was abstracted by one investigator and cross checked by the others. Data were combined by using Peto odds ratios with 95% confidence intervals.

Results Nine trials (1975-96, 10 011 adults) tested H₁ antihistamines, corticosteroids, and an H₁-H₂ combination. No trial included exclusively patients with a history of allergic reactions. Many outcomes were not allergy related, and only a few were potentially life threatening. No reports on death, cardiopulmonary resuscitation, irreversible neurological deficit, or prolonged hospital stays were found. In two trials, 3/778 (0.4%) patients who received oral methylprednisolone 2×32 mg or intravenous prednisolone 250 mg had laryngeal oedema compared with 11/769 (1.4%) controls (odds ratio 0.31, 95% confidence interval 0.11 to 0.88). In two trials, 7/3093 (0.2%) patients who received oral methylprednisolone 2×32 mg had a composite outcome (including shock, bronchospasm, and laryngospasm) compared with 20/2178 (0.9%) controls (odds ratio 0.28, 0.13 to 0.60). In one trial, 1/196 (0.5%) patients who received intravenous clemastine 0.03 mg/kg and cimetidine 2-5 mg/kg had angio-oedema compared with 8/194 (4.1%) controls (odds ratio 0.20, 0.05 to 0.76).

Conclusions Life threatening anaphylactic reactions due to iodinated contrast media are rare. In unselected patients, the usefulness of premedication is doubtful, as a large number of patients need to receive premedication to prevent one potentially serious reaction. Data supporting the use of premedication in patients with a history of allergic reactions are lacking.

Physicians who are dealing with these patients should not rely on the efficacy of premedication.

Introduction

Increased use of non-ionic iodinated contrast media has been associated with a decrease in the incidence of reactions to iodinated contrast media, but preventive prophylactic drug regimens are still widely used in clinical practice. In an observational study, Greenberger and Patterson concluded in 1991 that patients with a previous reaction to high osmolality iodinated contrast media should receive oral prednisone and diphenhydramine with or without ephedrine.¹ Since then, professional organisations have recommended a variety of pretreatment regimens.²⁻⁴ Published guidelines are based on observational data, and the efficacy of pre-treatment remains unclear. We set out to review the efficacy of pharmacological prevention of serious, potentially life threatening reactions to iodinated contrast media.

Material and methods

Search strategy—We searched trials (without language restrictions) from 1950 to October 2005 that tested premedication in patients who received iodinated contrast media. We searched Medline, Oldmedline, Embase, HealthSTAR, and CINAHL, by using generic and brand names of contrast media, steroids, antihistamines, and ephedrine, and key words for adverse drug reactions and prevention and prophylaxis. We searched the Cochrane controlled trials register and bibliographies.^{1 3 5} Inclusion criteria were random allocation of patients, use of premedication, a placebo or a no treatment control group, and reporting of presence or absence of allergic reactions.

Outcomes—We classified outcomes as “distinct allergy related symptoms,” “symptom categories,” “non-specific symptoms,” and “adverse drug reactions.” Two trials reported on arbitrary categories of symptom

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BMJ 2006;333:675-8



Extra references are on bmj.com



This is the abridged version of an article that was posted on bmj.com on 31 July 2006: <http://bmj.com/cgi/doi/10.1136/bmj.38905.634132.AE>

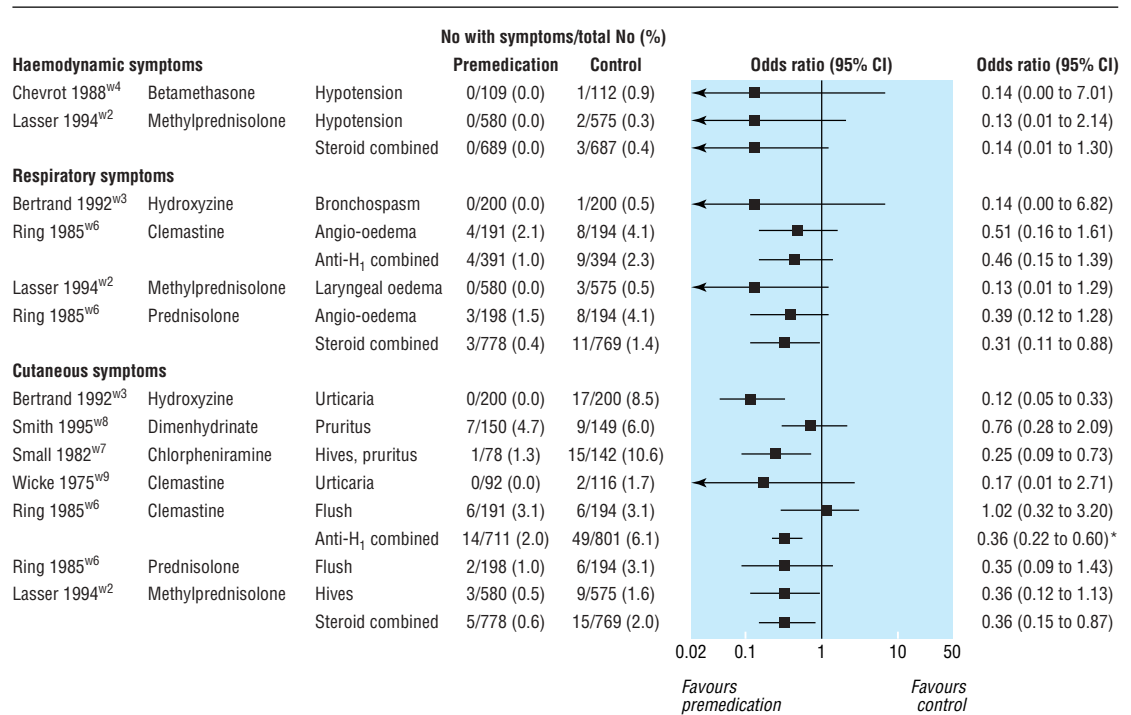


Fig 1 Distinct haemodynamic, respiratory, and cutaneous symptoms. Hypotension, bronchospasm, angio-oedema, and laryngeal oedema were considered to be potentially life threatening. Anti-H=antihistamine. *P for heterogeneity=0.03, I²=62%

combinations (grades).^{w1 w2} Grade 1 included a single episode of emesis, nausea, sneezing, and vertigo. Grade 2 consisted of hives, erythema, emesis, and fever or chills. Grade 3 comprised clinical shock, bronchospasm, laryngospasm, laryngeal oedema, loss of consciousness, convulsions, decrease or increase in blood pressure, cardiac arrhythmia, angina, angio-oedema, or pulmonary oedema.

Data extraction—On the basis of trial reports, an allergologist and an anaesthetist decided for each symptom whether it was allergy related and potentially life threatening. All investigators independently assessed the quality of the trials.

Data synthesis—We calculated dichotomous data as odds ratios; an odds ratio < 1 suggested efficacy with premedication. When we combined data from more than two trials, we did formal heterogeneity testing.

Results

Search results

Of 64 potentially relevant reports, we excluded 55; most compared different contrast media. Nine trials, published between 1975 and 1996, met our inclusion criteria (see bmj.com).^{w1-w9} The total number of participants was 10 011; 6108 received premedication. In no report was an adequate randomisation method described, and only in one was treatment allocation concealed.^{w1} In four reports, evidence existed of adequate blinding.^{w1-w3 w5} No report described a complete patient follow-up that enabled an intention to treat analysis.

Patients

Three trials excluded patients with a history of reaction to iodinated contrast media,^{w1 w3 w6} and one also excluded those with a history of allergy, atopy, or drug

hypersensitivity.^{w3} The other six did not specify exclusion criteria.

Premedications

Five trials tested H₁ antihistamines, five tested corticosteroids, and one tested an H₁-H₂ combination. None tested a steroid-antihistamine combination, and we found no reports on ephedrine.

Contrast media

In eight trials, iodinated contrast media were given intravenously, and in one it was given intrathecally. Trials used non-ionic low osmolar medium, ionic high osmolar medium, or a combination of both. In one trial, media were specified as ionic only,^{w1} and one trial did not specify the type or medium.^{w7}

Radiological interventions

Radiological interventions were urography,^{w2-w4 w6 w9} computed tomography scan,^{w2-w4} venography or arteriography,^{w3 w4 w8} and myelography,^{w5} pyelography,^{w7} or cholangiography.^{w9} In one trial, the imaging procedure was not specified.^{w1}

Outcomes

Distinct allergy related symptoms

Three trials reported on arterial hypotension. We regarded hypotension as potentially life threatening. None of the 689 patients who received steroids had hypotension compared with 3/687 (0.4%) controls (odds ratio 0.14, 95% confidence interval 0.01 to 1.30) (fig 1).

Three trials reported on respiratory symptoms. The outcomes were bronchospasm, angio-oedema (with urticaria), and laryngeal oedema; we regarded all as potentially life threatening. Four of 391 (1%) patients who received an antihistamine had a respiratory symptom compared with 9/394 (2.3%) controls (odds

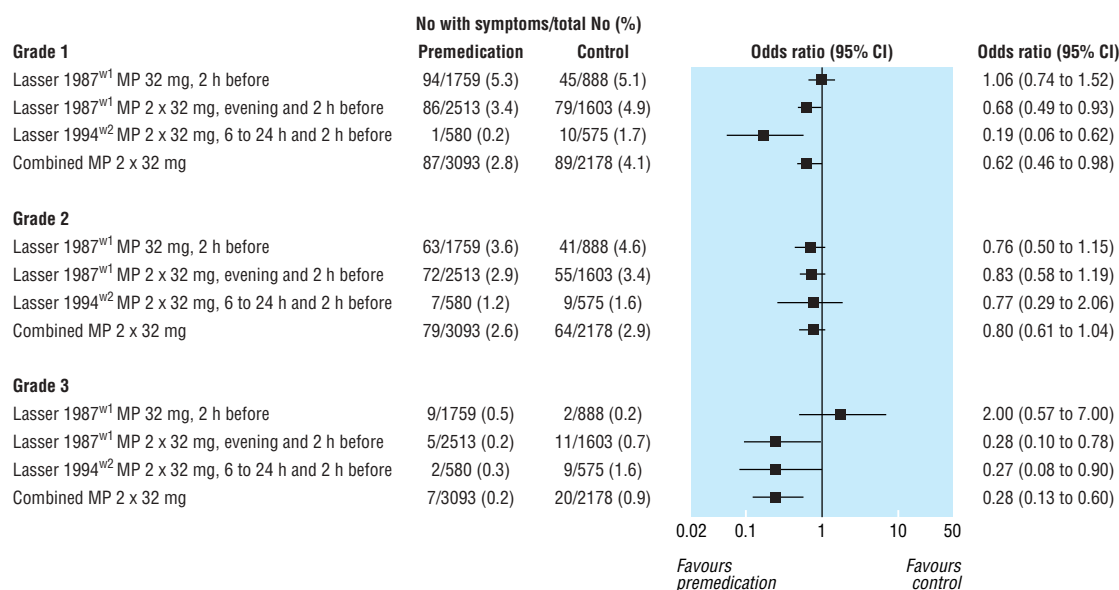


Fig 2 Arbitrary symptom combinations (“grades”) as defined in the original reports.^{w1 w2} Grade 1=single episode of emesis, nausea, sneezing, or vertigo; grade 2=hives, erythema, or emesis more than once or fever or chills (or both); grade 3=shock, bronchospasm, laryngospasm or laryngeal oedema, loss of consciousness, convulsions, fall or rise in blood pressure, cardiac arrhythmia, angina, angio-oedema, or pulmonary oedema. Grade 3 was considered to be potentially life threatening. MP=methylprednisolone (oral)

ratio 0.46, 0.15 to 1.39) (fig 1). Of patients who received a steroid, 3/778 (0.4%) had a respiratory symptom compared with 11/769 (1.4%) controls (odds ratio 0.31, 0.11 to 0.88). Finally, in one trial, 1/196 (0.5%) patients who received a clemastine-cimetidine combination had angio-oedema compared with 8/194 (4.1%) controls (odds ratio 0.20, 0.05 to 0.76).^{w6}

Six trials reported on cutaneous symptoms. The outcomes were urticaria, erythema, hives, pruritus, and flushing (all non-life threatening). Fourteen of 711 (2%) patients who received an antihistamine had cutaneous symptoms compared with 49/801 (6.1%) controls (odds ratio 0.36, 0.22 to 0.60; P for heterogeneity=0.03, $I^2=62\%$) (fig 1). With steroids, 5/778 (0.6%) patients had cutaneous symptoms compared with 15/769 (2%) controls (odds ratio 0.36, 0.15 to 0.87).

Symptom categories (grades)

Among the three grades of symptoms, we regarded grade 3 reactions as potentially life threatening (fig 2).^{w1 w2} Grade 1 reactions were significantly reduced with a double dose but not with the single dose methylprednisolone regimen: 87/3093 (2.8%) patients who received the double dose regimen had a grade 1 reaction compared with 89/2178 (4.1%) controls (odds ratio 0.62, 0.46 to 0.84) (fig 2). Grade 2 reactions were not significantly reduced. Grade 3 reactions were significantly reduced only with the double dose regimen: 7/3093 (0.2%) patients who received the double dose regimen had a grade 3 reaction compared with 20/2178 (0.9%) controls (odds ratio 0.28, 0.13 to 0.60).

Adverse drug reactions

Patients who received dexamethasone reported dyspepsia, insomnia, bitter taste, nausea, and headache.^{w2 w5} Patients who received hydroxyzine or clemastine reported bad taste, local skin reaction, and somnolence.^{w3 w9}

Discussion

With steroid premedication, the incidence of respiratory symptoms in patients who received iodinated contrast media was reduced from 1.4% to 0.4%, and the incidence of respiratory and haemodynamic symptoms was reduced from 0.9% to 0.2%. To prevent one episode of a potentially life threatening, iodinated contrast medium related reaction, 100 to 150 patients need to receive steroids prophylactically. Likewise, the clemastine-cimetidine combination showed statistically significant efficacy but for prevention of angio-oedema only and in a single trial with a limited number of patients. H₁ antihistamines and steroids reduced the risk of cutaneous symptoms, and a double dose methylprednisolone regimen reduced the risk of symptoms including sneezing, nausea, emesis, and vertigo. For other drugs (ephedrine) or drug combinations (steroid-antihistamine), we could retrieve no valid data.

Disastrous anaphylactic complications after administration of iodinated contrast media seem to be rare. In the analysed trials, more than 10 000 patients received an iodinated contrast medium; we found no reports of death, cardiopulmonary resuscitation, irreversible neurological deficit, or prolonged hospital stay. In more than 337 000 patients who received iodinated contrast media, two deaths occurred, but a causal relationship to the contrast medium could not be established.⁶

Potential limitations

None of the trials included only patients with a history of allergic reactions. Although three trials excluded patients with a history of a reaction to iodinated contrast media, six did not; we may thus assume that these trials represent daily clinical practice. Premedication may not necessarily be efficacious in a patient with a positive history.^{7 8} A large variety of symptoms were reported. The decision as to whether a symptom was allergy related or potentially life threatening was made on the basis of clinical features described in the

What is already known on this topic

Premedication with steroids, antihistamines, and other drugs, alone or in combination, is widely used before injection of iodinated contrast media

Premedication is thought to reduce the risk of life threatening anaphylactic reactions

What this study adds

Life threatening anaphylactic reactions due to iodinated contrast media are rare

In unselected patients, the usefulness of premedication is doubtful as a large number of patients need to receive premedication to prevent one potentially serious reaction

Data supporting the use of premedication in patients with a history of allergic reactions are lacking

original reports; we cannot rule out selection bias. Most of the reported symptoms were clinically of minor importance. Curiously, grade 1 and grade 3 reactions were significantly reduced but grade 2 reactions were not. However, use of arbitrarily defined composite outcomes may not be appropriate.⁹

Contrast media that are used today may have a more favourable risk profile than the tested iodinated contrast media. In a large scale survey,⁶ severe reactions occurred in about 0.2% of patients with high osmolar iodinated contrast media and in only about 0.04% with low osmolar non-ionic contrast media. Finally, the average quality of these trials was limited, and low quality trials are prone to bias, which could lead to an overestimation of the effect of a treatment.¹⁰

Arguments for and against premedication

An argument in favour of premedication is that serious non-fatal anaphylactic reactions may contribute to major morbidity, prolonged hospital stays, and excess cost. Arguments against premedication include the cost and the risk of doing more harm than good to the patients. Although an oral double dose steroid regimen may not be expensive, a large number of patients need to be treated for one to benefit. Radiological interventions may be delayed by prolonged drug prophylaxis. Pretreatment may create a sense of security among people who inject contrast media. Healthcare providers may neglect measures to survey patients and to treat anaphylaxis. Finally, the drugs used may cause harm.¹¹

Conclusions

A large number of patients need to receive an oral double dose of methylprednisolone to prevent a potentially life threatening, iodinated contrast medium related reaction in one of them. For antihistamines, limited evidence shows that they may prevent some reactions. Valid data supporting the efficacy of premedication in patients with a history of allergic reactions are completely lacking. Severe allergic reactions due to contrast media seem to be rare. Physicians using iodinated contrast media could be trained to recognise and treat anaphylactic reactions appropriately.^{12 13} Radiology departments should be staffed with equipment for resuscitation.¹⁴ Physicians dealing with patients receiving contrast media should not rely on the efficacy of premedication; routine prophylaxis should be abandoned.

We thank M Daniel Hake, Medical Library, Medical Faculty, Geneva University, for his help in searching electronic databases.

Contributors: See bmj.com.

Funding: MRT was a beneficiary of a PROSPER (Program for Social Medicine, Preventive and Epidemiological Research) grant from the Swiss National Research Foundation (No 3233-051939.97/2 and No 3200-064800.01/1).

Competing interests: None declared.

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doi 10.1136/bmj.38905.634132.AE

Corrections and clarifications

On a mission: how Cuba uses its doctors abroad

In this News article by Sara Carrillo de Albornoz we slipped up with the name of the editor of the Cuban public health journal *Revista Cubana de Salud Publica* (*BMJ* 2006;333:464, 2 Sep). We gave his name as Luis Carlos Da Silva, whereas it is in fact Luis Carlos Silva.

Waits for diagnostic tests threaten 18 week treatment target

We mixed up our royal colleges in this News article by Caroline White (*BMJ* 2006;333:463, 2 Sep). Dr Gill Markham is a vice president of the Royal College of Radiologists [not Pathologists] and also dean of its Faculty of Clinical Radiology.

Filler: bmjupdates+

The results given in *bmjupdates+* about black cohosh (*BMJ* 2006;333, 19 Aug. doi:10.1136/bmj.333.7564.0-e) were wrong owing to an author error in the original paper (*J Clin Oncol* 2006;24:2836-41). The correct mean reduction in hot flush scores was 15% (95% confidence interval 2% to 29%) for black cohosh and 31% (18% to 44%) for placebo.

Editor's choice: Whither medicine?

In this piece by Fiona Godlee we said that Roy Porter died "before the beginning of the new millennium" (*BMJ* 2006;333, 9 Sep, doi: 10.1136/bmj.333.7567.0-f). We were wrong; he died in 2002.