

Review article

Adrenaline for the treatment of anaphylaxis: cochrane systematic review

Background: Anaphylaxis is a serious allergic reaction that is rapid in onset and may cause death. Adrenaline is recommended as the initial treatment of choice for anaphylaxis.

Objectives: To assess the benefits and harms of adrenaline in the treatment of anaphylaxis.

Methods: We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2007, Issue 1), MEDLINE (1966 to March 2007), EMBASE (1966 to March 2007), CINAHL (1982 to March 2007), BIOSIS (to March 2007), ISI Web of Knowledge (to March 2007) and LILACS (to March 2007). We also searched websites listing ongoing trials: <http://www.clinicaltrials.gov/>, <http://www.controlledtrials.com> and <http://www.actr.org.au/> and contacted pharmaceutical companies and international experts in anaphylaxis in an attempt to locate unpublished material. Randomized and quasi-randomized controlled trials comparing adrenaline with no intervention, placebo or other adrenergic agonists were eligible for inclusion. Two authors independently assessed articles for inclusion.

Results: We found no studies that satisfied the inclusion criteria.

Conclusions: On the basis of this review, we are unable to make any new recommendations on the use of adrenaline for the treatment of anaphylaxis. In the absence of appropriate trials, we recommend, albeit on the basis of less than optimal evidence, that adrenaline administration by intramuscular injection should still be regarded as first-line treatment for the management of anaphylaxis.

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Anaphylaxis is a serious allergic reaction that is rapid in onset and may cause death (1). Trigger factors include foods, insect venoms, medications, including those used peri-operatively, natural rubber latex and exercise (2–9). Most anaphylactic episodes involve an immediate hypersensitivity reaction following allergen interaction with cell-bound immunoglobulin E (IgE). Less commonly, other immunological mechanisms, for example, autoimmune mechanisms are involved or no immune mechanism is involved, for example, when anaphylaxis is triggered by exposure to cold air or water. Some individuals have idiopathic anaphylaxis with no obvious trigger. Regardless of the inciting mechanism, the final common pathway involves release of histamine and other mediators from mast cells and basophils. Distinction between anaphylactic reactions and an anaphylactoid reaction is no longer recommended as the clinical picture and emergency treatment of anaphylaxis are similar regardless of the patho-physiological mechanism (1, 8, 10, 11).

Anaphylaxis is not a reportable disease and the true incidence remains unknown (12–18). An estimate of the

incidence in the general population is influenced by definitions, which differ from one investigator to another, as well as by coding issues and misclassification errors (19). A population-based study using data collected in the mid-1980s calculated an annual incidence of 30 per 100 000 person years, which raised concern that anaphylaxis was frequently not recognized (20). Other studies suggest the true incidence may be up to 590 per 100 000 person years. Anaphylaxis from the four most common triggers (foods, insect stings, medications and natural rubber latex) may affect more than 1% of the general population (16) with considerable variations in age (7) and in age-specific aetiology (21).

Skin symptoms and signs, including generalized urticaria, flushing, itching and angioedema [swelling of the subcutaneous tissues], are the most common manifestations of anaphylaxis (in 80%–90% of those affected) followed by respiratory (70%) and gastrointestinal (40%) symptoms; hypotension occurs in 10–30% of episodes (2, 4, 5, 22, 23). Symptoms often occur within 5–30 min of exposure to the trigger factor, although occasionally they

do not develop for several hours. Anaphylaxis may be fatal within minutes, usually through cardiovascular or respiratory compromise or both (24–27). Upper and lower respiratory tract obstruction is commonly reported in fatal cases (24, 25, 27). True mortality rates are unknown in anaphylaxis because of under-recognition and under-diagnosis of the disease (26).

The diagnosis of anaphylaxis is based largely on history and physical findings. Laboratory tests have proven to be disappointing in clinical practice. Plasma histamine may be elevated, but it is only reliable when measured within one hour of onset and the levels are not stable during routine handling and so the test is seldom used (28). Serum or plasma tryptase levels > 15 ng/ml within 12 h (preferably within three hours) of the onset of an episode is more widely used as a confirmatory test, but this test is usually negative in food-induced anaphylaxis. Serial total serum or plasma tryptase measurements may be more helpful than single measurements (3). Positive skin tests to allergens and elevated allergen-specific IgE levels in serum are not diagnostic of anaphylaxis. Rather, such tests confirm sensitization and provide clinically relevant information that directs risk reduction and the prevention of future episodes by avoidance of specific allergen or allergens or long-term immunomodulation where relevant, for example, with venom immunotherapy for insect sting anaphylaxis (8).

Adrenaline is widely advocated as the initial treatment of choice for anaphylaxis (29–31). This initial emergency management is supervised by a physician or other healthcare professional when anaphylaxis occurs in a healthcare setting. In this setting, intramuscular (i.m.) or intravenous (i.v.) infusion or both routes for adrenaline are preferred (32). When anaphylaxis occurs in the community, in a non-medical setting, the standard of first-aid treatment is the administration of self-injectable adrenaline into the anterolateral thigh using an EpiPen (also called Fastject), Anapen, AnaHelp, Fastject, Twinject or other adrenaline formulation (31, 33).

Adrenaline is an alpha- and beta-adrenergic agonist (i.e. it acts on two different important classes of receptors in the body) with bidirectional cyclic adenosine monophosphate-mediated pharmacological effects on target organs and a narrow therapeutic index (34). It results in vasoconstriction, increased peripheral vascular resistance, decreased mucosal oedema, inotropic and chronotropic effects (increased force and rate of cardiac action), bronchodilation and decreased mediator release from mast cells and basophils. The plasma and tissue concentrations of adrenaline needed for recovery from anaphylaxis have not yet been defined in humans (33). There have been no prospective human studies performed during the management of anaphylaxis to evaluate the bioavailability and optimal dose of adrenaline given i.m. or to assess the incidence of adverse effects. Case reports and large mortality reviews indicate that side-effects involving the myocardium can be serious, usually in the setting of inappropriate dosing (an overdose, an inadequately diluted i.v. dose or an overly

rapid rate of infusion) by medical staff (26). However, there is now increased awareness that the heart itself may be a target organ in anaphylaxis and that electrocardiographic changes suggesting ischaemia, myocardial infarction and dysrhythmias can occur even if adrenaline has not been given (35–37).

Only the i.v. route was used in the two studies in humans that indicate a beneficial treatment effect for reactions characterized by cardiovascular collapse (4, 38). In a canine model of fully-developed anaphylactic shock (defined as hypotension with the blood pressure contained at 50% of baseline blood pressure), adrenaline 0.01 mg/kg injected by the i.m. route was ineffective; an i.v. bolus of 0.01 mg/kg resulted in transient improvement and i.v. infusion at 0.19–0.45 μ g/kg/min was the only method to produce a sustained improvement (39, 40). The therapeutic effect in this model was from positive inotropy, with no increases in either systemic vascular resistance or pulmonary arterial wedge pressure. Thus, if a severe reaction develops and adrenaline is administered at the generally recommended initial doses for anaphylaxis, which are lower than the doses recommended for resuscitation, it might not adequately counteract the effects of vasodilation and distributive-hypovolaemic shock on its own, even when given as an i.v. infusion (35).

In summary, the use of adrenaline in anaphylaxis appears to be based largely on extrapolation from first principles, expert opinion and tradition. This review, the second in our series of Cochrane systematic reviews on the emergency management of anaphylaxis, sought to assess the benefits and harms of adrenaline in the treatment of anaphylaxis (41, 42).

Methods

Criteria for considering studies for this review

Types of studies. We planned to include randomized controlled trials comparing adrenaline with no intervention, placebo, or other adrenergic agonists. We also planned to include randomized controlled trials comparing different approaches to the administration of adrenaline and quasi-randomized controlled trials, i.e. trials where an attempt to approximate randomization was made (e.g. by alternate allocation). Controlled trials with little attempt to minimize bias during allocation were, however, not eligible for inclusion.

Types of participants. We were interested in all patients (infants, children and adults; community or hospital based) experiencing anaphylaxis caused by food, insect venom, medication, vaccination, latex or any other trigger.

Types of interventions. We were interested in studies involving any systemic (i.v. infusion or bolus injection, i.m., s.c. or inhaled from a metered-dose inhaler or a nebulizer) administration of adrenaline by the individual, a lay caregiver (of a child) or a medical professional. Adrenaline could have been administered anywhere in the community, including in a physician's office or in an ambulance or anywhere in the hospital, including emergency

departments, hospital clinics, dialysis units, wards, operating rooms and delivery rooms. It may also have been administered after another medication. The comparative treatments of interest were no intervention, placebo, other adrenergic agonists and different treatment approaches to the administration of adrenaline.

Types of outcome measures. Our primary outcome measure of interest was death and the secondary outcome measures are given below.

- 1 Resolution of upper airway obstruction.
- 2 Resolution of lower airway obstruction (symptomatic bronchospasm).
- 3 Improvement in arterial blood pressure (> 50 mmHg systolic).
- 4 Resolution of urticaria.
- 5 Requirement for second dose of adrenaline.
- 6 Admission to hospital.
- 7 Length of emergency department stay.
- 8 Length of hospital stay.
- 9 Re-presentation for therapy within 24 h.
- 10 Adverse events as a result of therapy in either treatment arm.

Search methods for identification of studies

Electronic searches. We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2007, Issue 1) (see Appendix 1); MEDLINE (1966 to March 2007) (see Appendix 2); EMBASE (1966 to March 2007) (see Appendix 3); CINAHL (1982 to March 2007) (see Appendix 4); BIOSIS (to March 2007) (see Appendix 5); ISI Web of Knowledge (to March 2007) (see Appendix 6) and LILACS (to March 2007) (see Appendix 7).

We searched MEDLINE using Ovid with the Cochrane randomized controlled trial filter (43) and the following key words: anaphyl* and adrenaline. We adopted our search terms for other databases. We did not apply any language restriction.

Searching other resources. In an attempt to uncover any additional relevant published data, grey literature, unpublished data and research in progress:

- 1 We contacted international experts in anaphylaxis (see Appendix 8).
- 2 We contacted relevant pharmaceutical companies (see Appendix 8).
- 3 We searched the UK's National Research Register: <https://portal.nihr.ac.uk/Pages/NRRArchive.aspx>.
- 4 We searched websites listing ongoing trials: <http://clinicaltrials.gov/>, <http://www.controlledtrials.com/> and <http://www.actr.org.au/>.

Data collection and analysis

Selection of studies. Two authors (YS and AS) independently reviewed titles and abstracts identified from literature searches for relevant trials and selected possibly relevant studies. We reviewed these studies using the full text and assessed them using the inclusion criteria detailed above.

We had agreed that we would resolve any disagreements by discussion between both of the authors; in the case of consensus not being reached, the third author (FERS) would become involved and, if necessary, arbitrate.

Data extraction. We stipulated that two authors (YS and AS) would independently extract data using a suitably adapted version of the data extraction form developed by the Cochrane Anaesthesia Review Group. We stated that we would resolve any disagreements by discussion between both of the authors; in the case of consensus not being reached, the third author (FERS) would be involved and, if necessary, arbitrate. This did not prove necessary.

Assessment of methodological quality of included studies. We planned to assess and document the methodological quality of included controlled trials following the Cochrane approach by using the methods detailed in Section 6 of the Cochrane Handbook for Systematic Reviews of Interventions (43). We proposed to concentrate on using the following five parameters to assess quality: allocation concealment, method of allocation to treatment, documentation of exclusions, completeness of follow up and methods of documentation of complications. We planned to grade each parameter of trial quality: A – low risk of bias; B – moderate risk of bias; C – high risk of bias and an overall assessment for each controlled trial using the same three criteria.

We also planned to subject quasi-randomized studies to methodological assessment, in which case, two authors (YS and AS) would independently assess study quality; review authors would not be masked to study details. We planned to assess the agreement of review authors on methodological quality assessment and to resolve disagreements by discussion and, if necessary, with the involvement of the third author (FERS).

Data analysis. We proposed to use Review Manager 5.0 for data analysis and quantitative data synthesis. For dichotomous data, we planned to calculate individual and pooled statistics as relative risks with 95% confidence intervals (95% CI). For continuous data, we planned to calculate individual and pooled statistics as mean differences or standardized means differences or both with 95% CI. We planned to consider the appropriateness of meta-analysis in the presence of significant clinical or statistical heterogeneity. We assumed significant heterogeneity if the I^2 statistic was >40% (i.e. more than 40% of the variability in outcome between trials could not be explained by sampling variation) (44). We planned to undertake meta-analysis using a fixed-effect model in the absence of statistical heterogeneity and a random-effects model, if such heterogeneity was likely. We planned to explore any statistical or clinical heterogeneity by using sensitivity or subgroup analysis (see below). We planned to undertake quantitative analyses of outcomes on an intention-to-treat basis, wherever possible. We planned to assess any evidence of publication bias graphically using funnel plots and statistically using Begg and Egger tests (45, 46).

Subgroup analysis. In the event of uncovering significant heterogeneity, we planned to investigate the heterogeneity by undertaking subgroup analyses. Our subgroups of interest were:

- 1 Presence or absence of shock.
- 2 Mild or more severe anaphylaxis (4).
- 3 Mode of administration of treatment (i.m. vs i.v.; administered by patient vs healthcare professional).
- 4 Time from onset of anaphylaxis to receiving treatment.
- 5 Age (infants, children and adults).
- 6 Trigger agents (iatrogenic vs community, antibiotic vs other drugs and muscle relaxants vs other agents).

Sensitivity analysis. We planned to undertake sensitivity analysis for the allocation of missing data by best and worst case analysis and also to undertake sensitivity analysis on the basis of only

including randomized studies. This would allow an assessment of the impact on the review conclusions of excluding quasi-randomized studies judged to be at increased risk of bias.

Results

Description of studies

Searching different databases up to March 2007 yielded 382 citations (see Fig. 1). After scrutiny of the abstracts of these studies, no studies fulfilled the inclusion criteria. We contacted context editors and pharmaceutical companies but this failed to contribute any relevant published or unpublished studies. The search of the UK National Research Register, Current Controlled Trials and Clinical Trials using anaphylaxis as a keyword identified no useful articles.

Discussion

This review failed to uncover any evidence from prospective, randomized or quasi-randomized trials on the

effectiveness of adrenaline for the emergency management of anaphylaxis. Given the relative infrequency of the condition, the speed of onset, the often unexpected occurrence and the established place of adrenaline in treatment guidelines internationally (29), this lack of evidence for a treatment that was introduced well before the evidence-based medicine era is perhaps unsurprising (9).

The optimal route of administration and the optimal dose of adrenaline have not yet been defined. In children, s.c. injection of adrenaline is associated with a significantly longer time to achieve peak of plasma adrenaline concentrations and pharmacological effects than the i.m. route (47). Other studies showed that the average maximum plasma adrenaline concentration was also significantly higher after i.m. route than after s.c. injection (48). Moreover, guidelines for the treatment of anaphylaxis have recommended against use of the s.c. route (49).

Some disagreement exists about the recommended intramuscular dose of adrenaline. Almost all of the literature agrees on 0.01 mg/kg in infants and children. Although North American, Australasian, and current UK guidelines suggest a maximum initial dose of 0.3–0.5 mg of adrenaline in adults, some older European literature suggests 0.5–1.0 mg as a maximum initial i.m. dose in adults (29, 50).

Delayed injection of adrenaline in anaphylaxis is reported to be associated with mortality (24–27). Given that current evidence supports the relative safety of i.m. adrenaline and early administration is believed to be associated with an improved survival, any patient with a serious allergic reaction that is rapid in onset should be a candidate for adrenaline by auto-injector.

Adrenaline has been associated with the induction of fatal cardiac arrhythmias and myocardial infarction. Major adverse events usually occur when adrenaline has been given in an excessive dose, an inadequately diluted i.v. dose or an overly rapid rate of infusion (26, 51–53). Historically, those individuals thought to be particularly at risk of adverse effects of adrenaline include elderly patients and patients with hypertension, arteriopathies or known ischaemic heart disease (26, 27); however, these patients may also be at increased risk for cardiac problems due to the anaphylaxis episode itself. It is difficult, particularly in retrospect, to dissect potential adverse effects of adrenaline from the known effects of anaphylaxis (26, 37, 51). Because of potential harm from the use of i.v. adrenaline in inexperienced hands, guidelines generally recommend that the i.v. route is reserved for cases that do not respond to initial treatment with i.m. adrenaline and where cardiovascular collapse and cardiac arrest is considered imminent (50). A controlled infusion is safer than bolus administration (50). It should be given in a resuscitation area that has electrocardiography and physiological monitoring by medical and nursing staff members who are trained in its use (54).

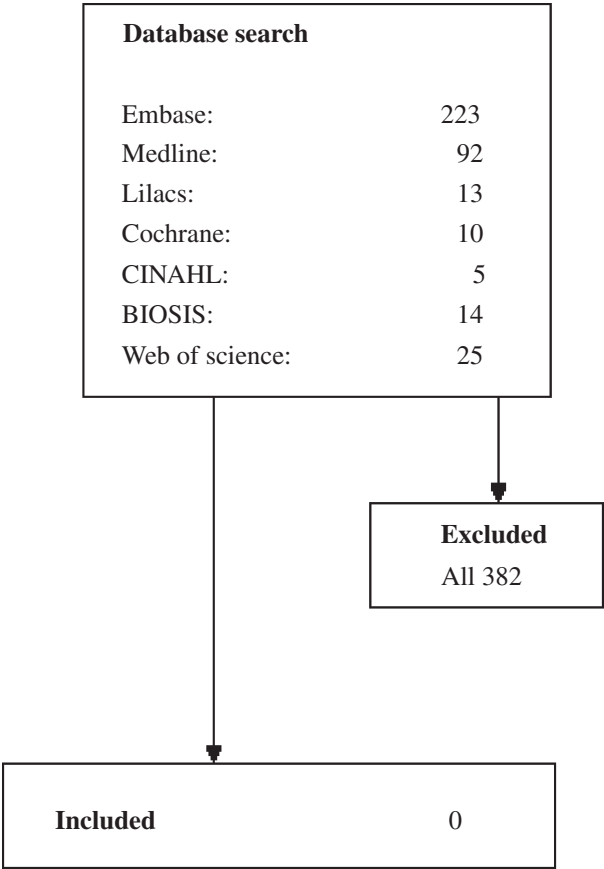


Figure 1. Search results.

In the past, adrenaline has been available worldwide in metered-dose inhaler formulations. These are no longer available in many countries because of their chlorofluorocarbon (CFC) propellant content and the phase out of CFC-containing medications. Inhalation of a few puffs of adrenaline from a pressurized metered-dose inhaler is not adequate for treatment of most of the symptoms in anaphylaxis. To achieve systemic effects, adults need to inhale 20–30 puffs and children need to inhale 10–20 puffs (55, 56). For an overview of the context in which adrenaline should be used in anaphylaxis: provide supplemental oxygen; place patient in the supine position, if tolerated; start volume resuscitation and prepare for intubation, the appropriate references should be consulted (50).

As there are no controlled trials, there is no way to estimate the risk in relation to benefit. On the basis of current evidence, we believe that the benefit of using appropriate doses of i.m. adrenaline is likely to far exceed the risk. Anaesthetists, who see anaphylaxis relatively commonly, usually have sophisticated monitoring in place before, during and after the event; they report a rapid and predictable response to adrenaline that is near universal. It should be stressed that adrenaline is not contraindicated in individuals with underlying ischaemic heart disease as the decrease in filling pressure caused by anaphylaxis is likely to result in further coronary ischaemia (53). However, careful monitoring and avoidance of an adrenaline overdose are necessary in these patients.

There is a strong clinical impression that prompt injection of adrenaline is life saving in anaphylaxis. Given the uncertainties surrounding its use, however, a firmer evidence base needs to be developed, if possible. Conducting research in this area is challenging for several reasons, including:

- 1 The established position of adrenaline treatment thereby making it difficult to argue for placebo-controlled trials.
- 2 The ethical issues involved in obtaining informed consent (or deferring consent) in emergency situations (57).
- 3 Difficulty in conducting double-blind, placebo-controlled studies because of the transient pharmacological effects (pallor, tachycardia, tremor) of adrenaline in standard doses that reverse airway obstruction and circulatory collapse.
- 4 Logistic issues: anaphylactic episodes usually occur without warning, often in a nonmedical setting; differ in severity from one individual to another and from one episode to another in the same individual.
- 5 Difficulty in obtaining baseline measurements.
- 6 The lack of any information on the pharmacokinetics and pharmacodynamics of adrenaline when given to humans during anaphylaxis and a lack of any prospectively collected information on clinical outcomes,

both of which are required to construct valid hypotheses and inform sample size calculations for a clinical trial.

Implications for practice

We found no relevant evidence for adrenaline use in the treatment of anaphylaxis. We are, therefore, unable to make any new recommendations based on the findings of this review. Guidelines on the management of anaphylaxis need to be more explicit about the basis of their recommendations regarding the use of adrenaline.

Implications for research

Given the routine use of adrenaline in the management of anaphylaxis, there is a need for academic debate about the ethics and practicality of mounting randomized trials to define the true extent, if any, of benefits from the administration of adrenaline in anaphylaxis. Specifically, more information is required on the subset of patients more likely to benefit from this therapy and the most appropriate preparations, route and dose of administration.

Although placebo-controlled trials of adrenaline in anaphylaxis would be unethical, it might be possible to conduct randomized controlled trials comparing two different doses of adrenaline or two different routes of administration of adrenaline, in addition to other standard-of-care treatments (58).

Any future trials would need to consider in particular:

- 1 Appropriate sample size with power to detect expected difference.
- 2 Careful definition and selection of target patients.
- 3 Appropriate comparator therapy.
- 4 Appropriate outcome measures.
- 5 Careful elucidation of any adverse effects.
- 6 The cost-effectiveness of the therapy.

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Conflicts of interest

None.

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Appendices

1. Search strategy for CENTRAL, *The Cochrane Library*

- #1 MeSH descriptor anaphylaxis explode all trees
- #2 anaphylact* near (react* or shock* or syndrom*)
- #3 acute near (allergic react*)
- #4 anaphylaxis
- #5 (#1 OR #2 OR #3 OR #4)
- #6 MeSH descriptor sympathomimetics explode all trees
- #7 MeSH descriptor Catecholamines explode all trees
- #8 MeSH descriptor Epinephrine explode all trees

- #9 MeSH descriptor Norepinephrine explode all trees
- #10 sympathomimetic* or Catecholamin* or Adrenalin* or Epinephrin* or Noradrenalin* or EpiPen or Anapen*
- #11 (#6 OR #7 OR #8 OR #9 OR #10)
- #12 (#5 AND #11)

2. Search strategy for MEDLINE (OVID)

- #1 randomized controlled trial.pt.
- #2 controlled clinical trial.pt.
- #3 randomized controlled trials.sh.

#4 random allocation.sh.
 #5 double blind method.sh.
 #6 single blind method.sh.
 #7 #1 or #2 or #3 or #4 or #5 or #6
 #8 (Animals not HUMAN).sh.
 #9 #7 not #8
 #10 clinical trial.pt.
 #11 exp clinical trials/
 #12 (clin\$ adj25 trial\$.ti,ab.
 #13 [(singl\$ or doubl\$ or trebl\$ or tripl\$) adj25 (blind\$ or mask\$)].ti,ab.
 #14 placebos.sh.
 #15 placebo\$.ti,ab.
 #16 random\$.ti,ab.
 #17 research design.sh.
 #18 #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17
 #19 #18 not #8
 #20 #19 not #9
 #21 comparative study.sh.
 #22 exp evaluation studies/
 #23 follow up studies.sh.
 #24 prospective studies.sh.
 #25 (control\$ or prospective\$ or volunteer\$).ti, ab.
 #26 #21 or #22 or #23 or #24 or #25
 #27 #26 not #8
 #28 #27 not (#9 or #20)
 #29 #9 or #20 or #28
 #30 ANAPHYLAXIS/
 #31 anaphylactic react\$.mp.
 #32 anaphylactic shock\$.mp.
 #33 anaphylactic syndrom\$.mp.
 #34 anaphylactoid react\$.mp.
 #35 anaphylactoid shock\$.mp.
 #36 anaphylactoid syndrom\$.mp.
 #37 acute near (allergic react*)
 #38 idiopathic anaphylaxis.mp.
 #39 systemic anaphylaxis.mp.
 #40 or/ 30-39
 #41 sympathomimetics
 #42 Catecholamines.mp. or CATECHOLAMINES/
 #43 Adrenaline.mp. or ADRENALINE/
 #44 Epinephrine.mp. or EPINEPHRINE/
 #45 Noradrenaline.mp. or NORADRENALINE/
 #46 Noradrenaline acid tartrate.mp.
 #47 Epinephrine bitartrate.mp.
 #48 Epinephrine hydrogentartrate.mp.
 #49 Adrenaline tartrate.mp.
 #50 EpiPen.mp. or EPIPEN/
 #51 Anapen.mp. or ANAPEN/
 #52 Miniject adrenaline.mp. or MINIJET ADRENALINE/
 #53 or/41-52
 #54 #41 or #52
 #55 #29 and #40 and #53

3. Search strategy for SilverPlatter EMBASE (WebSPIRS)

#31 #13 and #30r
 #30 #25 not #29
 #29 #27 not #28
 #28 #26 and #27
 #27 (ANIMAL or NONHUMAN) in DER
 #26 HUMAN in DER
 #25 #22 or #23 or #24
 #24 (SINGL* or DOUBL* or TREBL* or TRIPL*)
 near ((BLIND* or MASK*) in TI,AB)
 #23 (RANDOM* or CROSS?OVER* or FACTORIAL* or PLACEBO* or VOLUNTEER*) in TI,AB
 #22 #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21
 #21 'SINGLE-BLIND-PROCEDURE'/all subheadings
 #20 'DOUBLE-BLIND-PROCEDURE'/all subheadings
 #19 'PHASE-4-CLINICAL-TRIAL'/all subheadings
 #18 'PHASE-3-CLINICAL-TRIAL'/all subheadings
 #17 'MULTICENTER-STUDY'/all subheadings
 #16 'CONTROLLED-STUDY'/all subheadings
 #15 'RANDOMIZATION'/all subheadings
 #14 'RANDOMIZED-CONTROLLED-TRIAL'/all subheadings
 #13 #6 and #12
 #12 #7 or #8 or #9 or #10 or #11
 #11 sympathomimetic* or catecholamin* or adrenalin* or Epinephrin* or noradrenalin* or EpiPen or Anapen*
 #10 'noradrenalin-'/all SUBHEADINGS in DEM,-DER,DRM,DRR
 #9 'adrenalin-'/all SUBHEADINGS in DEM,-DER,DRM,DRR
 #8 'catecholamine-'/all SUBHEADINGS in DEM,-DER,DRM,DRR
 #7 explode 'adrenergic-receptor-stimulating-agent'/all SUBHEADINGS in DEM,DER,DRM,DRR
 #6 #1 or #2 or #3 or #4 or #5
 #5 anaphylaxis
 #4 acute near (allergic react*)
 #3 anaphylact* near (react* or shock* or syndrom*)
 #2 explode 'anaphylactic-shock' / all SUBHEADINGS in DEM,DER,DRM,DRR
 #1 explode 'anaphylaxis-' / all SUBHEADINGS in DEM,DER,DRM,DRR

4. Search strategy for CINAHL (EBSCO host)

[(anaphylax) or (MM 'Anaphylaxis') or anaphylact*) and ((MM 'Sympathomimetics') or (MM 'Catecholamins') or (MM 'Epinephrine') or sympathomimetic* or Catecholamin* or Adrenalin* or Epinephrin* or Noradrenalin* or EpiPen or Anapen*)]

5. Search strategy for BIOSIS Previews (WebSPIRS)

#7 #5 and #6
#6 random* or trial* or control* or placebo or multicenter
#5 #3 and #4
#4 sympathomimetic* or Catecholamin* or Adrenalin* or Epinephrin* or Noradrenalin* or EpiPen or Anapen*
#3 #1 or #2
#2 acute near (allergic react*)
#1 anaphylact* or anaphylax*

6. Search strategy for ISI Web of Science

(TS = anaphylax* OR TS = anaphylact*) AND
(TS = Sympathomimetic* OR TS = Catecholamin*
OR TS = Adrenalin* OR TS = Epinephrin* OR
TS = Noradrenalin* OR TS = EpiPen OR TS = Ana-
pen)

7. Search strategy for LILACS (BIREME)

‘ANAPHYLAXIA’ or ‘ANAPHYLAXIS’ or ‘ANAPHY-
LAXIS/’ or ‘ANAPHYLACTIC REACTION’ or ‘ANA-
PHYLACTIC REACTION/’ or ‘anaphylax\$’ or
‘anaphylact\$’ [Palavras]

8. List of experts and pharmaceutical companies contacted

Prof. H.A. Sampson
Prof. A.F. Brown
Prof. J.M. Negro-Alvarez
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Prof. U Muller
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Dr R.S. Pumphrey
Dr A. Helbling
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Dr S Clark
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Dr R Lockey
Dr S Kemp
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ALK-Abelló (UK) Ltd
Abbott Laboratories Ltd
UCB Pharma Ltd
Meridian Medical Technology Inc.
Cell Therapeutics (UK) Ltd
CSL Biotherapies
Lincoln Medical Ltd
Dey Laboratories
International Medication Systems (UK) Ltd