

**Suspected Anaphylactic Reactions
Associated with Anaesthesia**

Revised Edition 1995

2

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CONTENTS

	Page	
Summary	1	
Section 1	Introduction	2
Section 2	Objectives	3
Section 3	Definition of Terms	4
Section 4	Incidence and Recognition	7
Section 5	Investigation	10
Section 6	Tests to Identify Causative Agent	11
Section 7	Reporting	12
Section 8	Screening	13
Appendix A	Anaphylaxis Drill	14
Appendix B	Investigations	16
Appendix C	Yellow Card	19
References		20
Acknowledgements		22

SUMMARY

1. This report is a follow up to the first report published in September 1990. Attention has been given to recent information about the investigation of suspected anaphylactic reactions during anaesthesia.
2. Anaphylactic reactions are rare during anaesthesia: even severe reactions show a prompt and successful response to appropriate treatment in most patients.
3. Every anaesthetist should know an 'anaphylaxis drill'.
4. Anaesthetists should rehearse a simulated 'anaphylaxis drill' at regular intervals.
5. Treatment normally should include adrenaline at an early stage.
6. Any patient who has a suspected anaphylactic reaction associated with anaesthesia should be investigated fully.
7. Measurement of serum tryptase may confirm that a reaction was anaphylactic or anaphylactoid.
8. Skin tests are the most readily available and useful tests for allergy to anaesthetic drugs. The working party continues to recommend the skin prick test in the investigation of suspected anaphylaxis associated with anaesthesia.
9. All suspected adverse reactions should be reported to the Committee on the Safety of Medicines.
10. There is no valid predictor of drug anaphylaxis at present. Claims that any form of screening will predict anaphylaxis are without foundation.

SECTION 1 - INTRODUCTION

- 1.1 In 1990, the Association of Anaesthetists of Great Britain and Ireland published its first report on suspected anaphylactic reactions associated with anaesthesia. However, concern has continued about the role and the responsibilities of individual anaesthetists in the investigation and subsequent management of patients suspected of having suffered an anaphylactic reaction associated with anaesthesia.
- 1.2 At times, individual anaesthetists and departments of anaesthesia have experienced difficulty in obtaining advice from clinical immunologists and have failed to make the prospective arrangements with local immunology departments which were recommended in the first report.
- 1.3 There remains uncertainty about which laboratory investigations should be undertaken following a reaction, their interpretation and significance.
- 1.4 The role of the anaesthetist in undertaking skin tests and the source of training in the procedure has been a cause for concern.
- 1.5 The incidence of anaphylactic reactions and the associated morbidity/mortality in the UK is still unclear.
- 1.6 A second working party was established to give particular attention to the results of recent research on the value of investigations and their availability to anaesthetists in Great Britain and Ireland. To increase the value of the report, members of the British Society of Allergy and Clinical Immunology joined the working party. This report summarises its findings.

SECTION 2 - OBJECTIVES

- 2.1 To review the incidence of anaphylactic reactions associated with anaesthesia.
- 2.2 To consider the recognition and treatment of anaphylactic reactions.
- 2.3 To make recommendations about the investigation of anaphylactic reactions.
- 2.4 To consider the role of screening for anaphylactic reactions before anaesthesia.
- 2.5 To make recommendations about the reporting and collection of data on anaphylactic reactions.

SECTION 3 - DEFINITION OF TERMS [1-4]

- 3.1 An **adverse drug reaction** is the occurrence of any drug effect that is not of therapeutic, diagnostic or prophylactic benefit to the patient. Adverse reactions may be classified as follows:

Type A	Type B
Dose related	Not dose related - may be precipitated by a tiny dose. More severe on re-exposure.
Extension of pharmacological response	Symptoms and signs unlike normal pharmacological response. Typical of drug allergy.
Common	Uncommon

- 3.2 An **anaphylactic reaction (anaphylaxis)** is an exaggerated response to a substance to which an individual has become sensitised, in which histamine, serotonin and other vasoactive substances are released from basophils and mast cells in response to an IgE mediated reaction. This causes systemic symptoms which can include pruritus, erythema, flushing, urticaria, angio-odema, nausea, diarrhoea, vomiting, laryngeal oedema, bronchospasm, hypotension, cardiovascular collapse and death, Anaphylactic reactions are Type B adverse reactions.
- 3.3 **Anaphylactoid reactions** are clinically indistinguishable from anaphylaxis, but are not mediated by sensitising IgE antibody. Examples include urticaria, pruritus and hypotension following opioid anaesthesia, resulting from direct release of histamine by opioids.

Whether a reaction is called **anaphylactic** or **anaphylactoid** may depend on whether it is investigated, the means by which it is investigated and how the results are interpreted.

- 3.4 An **antigen** is any substance that is capable of inducing a specific immune response and of reacting with the products of that response.
- 3.5 **Allergy** is a hypersensitive state acquired through exposure to a specific antigen, re-exposure bringing to light an altered capacity to react.
- 3.6 **Hypersensitivity** is a state of altered reactivity in which the body exhibits an exaggerated immune response to a foreign agent.
- 3.7 **IgE** is one of a series of proteins with known antibody activity, synthesised by lymphocytes and plasma cells and found in serum as well as other body tissues. It is involved in immediate hypersensitivity reactions. Antigen or drug-specific IgE antibodies sensitise mast cells and basophils by binding to their high-affinity cell-surface receptors for IgE. Cross-linking of two or more cell surface bound IgE molecules produces cell activation and mediator release.
- 3.8 **Radio-allergosorbent test (RAST)** is a technique for measurement of antigen specific IgE antibodies in serum. The CAP system (Pharmacia) is an alternative to RAST. It is a fluoro-immunoassay for measurement of antigen specific antibodies and is usually more sensitive than RAST.
- 3.9 **Atopy** is defined as the production of specific IgE antibodies to one or more of the common allergens. In the UK, these are house dust mite, grass pollen and an animal dander, either cat or dog. Hayfever, allergic asthma and eczema are atopic disorders. Patients with drug allergy are often not atopic, ie. do not have specific IgE antibodies to the common allergens, but have drug specific IgE antibodies.
- 3.10 **Mast cell tryptase** is the principal protein content of mast cell granules and is released, together with histamine and other amines, in anaphylactic and anaphylactoid reactions. Its concentration in the plasma or the serum is raised between 1 and 6 h after reactions which involve mast cell degranulation [5,6].

Approximately 99% of the body's total enzyme is located within the mast cell. It is not present in red or white cells and therefore plasma concentrations are not affected by haemolysis. Thus, post-mortem analysis of plasma tryptase may yield meaningful results. The basal plasma tryptase concentration is 0.8 to 1.5 ng/ml with the normal value usually < 1 ng/ml. The half life of the analyte is approximately 2.5 h with maximum concentrations at approximately 1 hour. Thus, elevated concentrations can be detected for 12 to 14 h even in the event of death. Plasma tryptase concentrations of >20 ng/ml may be seen after

anaphylactic reactions. *In vitro*, tryptase is a stable protein. Plasma or serum may be stored at -20°C for long periods before laboratory analysis.

In reactions to anaesthetic drugs, the analysis of mast cell tryptase in plasma or serum appears to be a specific and sensitive diagnostic test for anaphylactic and anaphylactoid reactions. It is the most useful acute test available at present but requires further validation in mild/moderate reactions.

Some agents may release histamine without tryptase, eg. agents acting through neuropeptide receptors.

- 3.11 **Methylhistamine** is the principal metabolite of histamine and is excreted in the urine. Raised urinary concentrations occur after reactions which involve systemic histamine release. Methylhistamine concentrations are corrected for urinary creatinine. The normal range is 15-20 ng/ml/mmol creatinine/l but there may be difficulties in interpreting values outwith this range.

SECTION 4 - INCIDENCE AND RECOGNITION.

- 4.1 Estimation of the frequency of these reactions remains difficult. Between 1991 and 1994, 90 (4 fatal) suspected anaphylactic reactions associated with anaesthesia have been reported by British anaesthetists to the Medicines Control Agency (MCA) on yellow cards. In 1992, 51 suspected anaphylactic reactions were assessed by a single centre in London [7]. However, the reactions did not necessarily occur in 1992 and the data were collected actively by direct approaches to anaesthetists all over the UK.
- 4.2 In France, it is estimated that a suspected anaphylactic reaction occurs in 1 in 3,500 anaesthetics with true anaphylaxis seen in 1 in 6,000 [8,9]. The incidence has not increased between 1989 and 1993.

In Australia [10,11], the incidence is reported to be between 1 in 10,000 to 1 in 20,000 anaesthetics.
- 4.3 By extrapolating these data to the UK, there may be 175 to 1,000 reactions in the UK each year.
- 4.4 Reactions are more common in female patients. In France, 3 times as many women as men had reactions. In anaphylactic shock after neuromuscular blocking drugs, the ratio of women to men was between 5 and 10 to 1. In Australia, the ratio of females to males having reactions was 4:1 for neuromuscular blocking drugs and 3:1 for thiopentone.
- 4.5 A previous history of specific drug exposure does not seem necessary, particularly for neuromuscular blocking drugs where there may be no history of previous exposure in as many as 80% of reactions.
- 4.6 Latex hypersensitivity is increasingly being recognised as a cause of anaphylaxis, especially in abdominal and gynaecological surgery. Typically the reaction begins 30-60 minutes after the start of the procedure rather than at induction. Patients with latex allergy may show cross-reactivity with certain foods, especially banana, chestnuts and avocado.
- 4.7 Anaphylactic reactions are more common when drugs are given intravenously.
- 4.8 The working party knows of no suspected anaphylactic reaction being reported to inhaled anaesthetic agents.

- 4.9 It is essential that every doctor who gives drugs, particularly intravenously, is able to recognise and treat such reactions. The clinical features of anaphylaxis are [5,10,11]:

Clinical features of anaphylaxis (n=460)	Frequency
Cardiovascular collapse	88%
Bronchospasm	36%
Angio-oedema - commonly of the face, eg. periorbital and perioral	24%
Generalised oedema	7%
Cutaneous signs such as:	
rash	13%
erythema	45%
urticaria	8.5%

The first clinical features in severe reactions have been reported [10]:

First clinical features (n=458)	Frequency
no pulse detected, decrease in arterial pressure	28%
difficult to inflate lungs	26%
flush	21%
coughing	6%
rash	4%
desaturation	3%
cyanosis	3%
others (eg. ECG changes, uricaria, swelling)	9%

The response to treatment may depend on the severity of the reaction. Even severe anaphylaxis is associated with a prompt and successful response to appropriate treatment in most patients.

- 4.10 Every anaesthetist should know an 'anaphylaxis drill'. This should be agreed by departments of anaesthesia as a standard operating procedure and

be available immediately in all rooms where anaesthetics are given. An example of an 'anaphylaxis drill' is given in Appendix A.

- 4.11 Anaesthetists should rehearse a simulated 'anaphylaxis drill' at regular intervals. These rehearsals should include members of staff who would be called upon to assist.
- 4.12 Treatment of severe cases normally should include adrenaline at an early stage.
- 4.13 The standard procedure should include advice about investigation of the reaction and advice to be given to the patient.

SECTION 5 - INVESTIGATION

- 5.1 Any patient who has a suspected anaphylactic reaction associated with anaesthesia should be investigated fully (Appendix B).
- 5.2 The anaesthetist who administers the drugs which were associated with the suspected anaphylactic reaction must be responsible for ensuring that these tests are performed and interpreted adequately. He may seek help from a colleague who is experienced in skin testing or from a specialist in allergy and clinical immunology, but the anaesthetist remains responsible for providing further advice to the patient. Trainee anaesthetists should always inform a consultant and record this in the case notes.
- 5.3 The investigation should be conducted in consultation with an allergist or a clinical immunologist. The British Society of Allergy and Clinical Immunology (BSACI) publishes a list of names and addresses of members able to advise. This list is available from the Association of Anaesthetists or from the BSACI.
- 5.4 Departments of anaesthesia should make prospective arrangements with an appropriate allergy or immunology department to enable investigations to be undertaken when the need arises.
- 5.5 No tests that can be performed at the time of the reaction have been shown to provide useful information for immediate clinical management.
- 5.6 Approximately one hour after the beginning of the reaction, 10ml of venous blood should be taken into a glass tube. The serum should be separated and stored at -20°C until the sample can be sent to a reference laboratory for estimation of serum tryptase concentration. Elevated serum tryptase indicates that the reaction was associated with mast cell degranulation. This may occur in both anaphylactic and anaphylactoid reactions. However, a negative test does not completely exclude anaphylaxis.
- 5.7 No blood test identifies confidently the causative agent.

SECTION 6 - TESTS TO IDENTIFY THE CAUSATIVE AGENT

- 6.1 A detailed analysis of events surrounding the suspected anaphylactic reaction must be undertaken. All drugs given before and during the anaesthetic as well as their timing in relation to the reaction must be noted. After the patient has recovered, a detailed history including concurrent illness, previous anaesthetic history and any known allergies should be taken.
- 6.2 We recommend that skin prick tests be used in the investigation of suspected anaphylaxis associated with anaesthesia. Ideally the tests should be performed by a person experienced in performing skin prick tests both with common allergens and anaesthetic agents.
- 6.3 Specific antibodies may be detected for a limited range of anaesthetic drugs by serological tests [8]. Until recently, radioallergosorbent testing (RAST) was available for suxamethonium, thiopentone and alcuronium. These RAST tests are being withdrawn (probably because of low sensitivity) with only the test for suxamethonium being still available.
- 6.4 Appropriate skin testing concentrations of anaesthetic drugs for intradermal testing have been published and are 1,000 to 10,000 times more dilute than those advised for skin prick testing [12].
- 6.5 Non-anaesthetic drugs given during surgery may need to be considered as possible causes. Appropriate investigation will depend on the drug in question and the severity of the reaction.
- 6.6 Latex sensitivity can be assessed by skin testing, RAST or the CAP system.

SECTION 7 - REPORTING [13]

- 7.1 Accurate reporting requires careful record keeping at the time of the event.
- 7.2 All adverse drug reactions which are potentially dangerous, incapacitating or lethal should be reported to the Committee on the Safety of Medicines. Thus, all suspected anaphylactic reactions associated with anaesthesia should be reported.
- 7.3 All reactions should be reported on a yellow form (Appendix C) even if the reaction is reported elsewhere (eg. at a morbidity meeting, as a case report, to an immunologist, or to the drug company). The doctor who administers the drug is responsible for ensuring that the reaction is reported appropriately.
- 7.4 The 'anaesthetic yellow card' is available for this report. Departments of anaesthesia are responsible for ensuring that supplies of Anaesthetic Yellow Forms are available in all rooms where anaesthetics are given. Supplies are available from hospital pharmacies, the Association of Anaesthetists and the Committee on the Safety of Medicines, Freepost, London SW8 5BR.
- 7.5 The anaesthetist is responsible for the advice given to patients about future anaesthesia. This responsibility cannot be delegated. This must include a full explanation to the patient, parent or guardian. There must be a full record in the case notes with a copy to the general practitioner. The patient should be given a written record of the reaction and be encouraged to carry an anaesthetic hazard card or a Medic-alert bracelet.

SECTION 8 - SCREENING

- 8.1 There is no support at present for routine screening of patients for specific drug antibodies before anaesthesia.
- 8.2 There is no valid predictor of drug anaphylaxis. Claims that any form of screening will predict anaphylaxis are without foundation.
- 8.3 A history of previous exposure is not necessary for an anaphylactic reaction. Routine testing is not indicated before a first or subsequent exposure to drugs used previously without incident.
- 8.4 The use of test doses of intravenous drugs is not an appropriate method of testing for anaphylaxis. Anaphylaxis has resulted from very small doses.

APPENDIX A

MANAGEMENT OF A PATIENT WITH SUSPECTED ANAPHYLAXIS DURING ANAESTHESIA

SAMPLE OPERATING PROCEDURE/GUIDELINE

Statement of Intent

This guideline is not to be construed as a standard of medical care. Standards of medical care are determined on the basis of all clinical data available for an individual case and are subject to change as knowledge advances.

The ultimate judgement with regard to a particular clinical procedure or treatment plan must be made by the clinician in light of the clinical data presented and the diagnostic and treatment options available.

Initial Therapy

1. Stop administration of drug(s) likely to have caused the anaphylaxis.
2. Maintain airway: give 100% oxygen.
3. Lay patient flat with feet elevated.
4. Give adrenaline. This may be given intramuscularly in a dose of 0.5 mg to 1 mg (0.5 to 1 ml of 1:1,000) and may be repeated every 10 minutes according to the arterial pressure and pulse until improvement occurs.

Alternatively, 50 to 100 µg intravenously over 1 minute has been recommended (0.5 to 1 ml of 1:10,000) for hypotension with titration of further doses as required.

In a patient with cardiovascular collapse, 0.5 to 1 mg (5 to 10 ml of 1:10,000) may be required intravenously in divided doses by titration. This should be given at a rate of 0.1 mg/minute stopping when a response has been obtained.

5. Start intravascular volume expansion with crystalloid or colloid.

Secondary Therapy

1. Antihistamines (chlorpheniramine 10-20 mg by slow intravenous infusion).

2. Corticosteroids (100-300 mg hydrocortisone iv).
3. Catecholamine infusions (starting doses: adrenaline 4-8 $\mu\text{g}/\text{min}$ [0.05-0.1 $\mu\text{g}/\text{kg}/\text{min}$]; noradrenaline 4-8 $\mu\text{g}/\text{min}$ [0.05-0.1 $\mu\text{g}/\text{kg}/\text{min}$]; isoprenaline 0.05-1 $\mu\text{g}/\text{min}$).
4. Consider bicarbonate (0.5-1.0 mmol/kg iv) for acidosis.
5. Airway evaluation (before extubation).
6. Bronchodilators may be required for persistent bronchospasm.

APPENDIX B

INVESTIGATION OF A PATIENT WITH SUSPECTED ANAPHYLACTIC REACTION ASSOCIATED WITH ANAESTHESIA

IMMEDIATE

1. Do not attempt any investigation until the immediate treatment of the emergency has been completed.
2. Diagnosis is made on clinical grounds. It is important to make a detailed written record of events, including timing of administration of all drugs in relation to onset of reaction.
3. Approximately 1 hour after the beginning of the reaction, take 10 ml venous blood into a plain glass tube. Separate serum and store at -20°C until the sample can be sent to a reference laboratory for estimation of serum tryptase concentration.

LATER

4. The anaesthetist is responsible for ensuring adequate investigation and providing advice to the patient.
5. After the patient has recovered, a detailed history including concurrent illness, previous anaesthetic history and any known allergies should be taken.
6. Skin tests should be performed with all anaesthetic drugs (except inhalation agents) used in the procedure associated with the suspected anaphylaxis and with other anaesthetic agents which might be used in future procedures. These should be performed by someone with experience in performing and interpreting skin tests.
7. Some anaesthetists will feel competent to conduct and interpret such tests: others will wish to obtain specialist advice either from a more expert colleague or from a specialist in allergy and clinical immunology. A list of specialists able to advise and investigate these reactions may be obtained from either the Association of Anaesthetists or the British Society for Allergy and Clinical Immunology.

SKIN PRICK TESTS FOR ANAESTHETIC AGENTS

1. Before skin tests are performed, it is essential to document events at the time of the reaction in detail, and to note all drugs given and their timing.

This includes pre-medication, the anaesthetic drugs and any other drugs given, eg. iv antibiotics or analgesics. The hospital notes must be obtained and anaesthetic and operative records and drug charts examined. This history is vital, as it may give an indication of the cause. As well as allergy to anaesthetic drugs, it is important to consider the possibility of reactions to other drugs (eg. antibiotics), iv fluids (eg. Haemaccel or Gelofusine) or latex, as well as operative causes or technical anaesthetic problems.

2. Skin prick tests should be performed with a wide range of anaesthetic drugs (except inhalational agents), including all those used at the time of the reaction. In addition other agents should be studied, with the aim of identifying not only the cause of the reaction and other drugs to be avoided but also drugs likely to be safe for future use. Several drugs in each class should be tested (eg. intravenous anaesthetics, neuromuscular blocking agents, opioid analgesics). It is worth including drugs for which skin tests are difficult to interpret.
3. Skin prick tests should be carried out with drugs at the concentration used clinically ('neat') and at 1 in 10 dilution. A positive control (histamine) and a negative control (phenol saline) in duplicate must always be included. A drop of the drug is applied to the skin (usually the volar aspect of the forearm) and a lancet pressed vertically through it, to break the skin surface, but without drawing blood. The technique is similar to skin tests for common allergens. The test sites must be inspected over 15 minutes, looking for wheal and flare. For interpretation, see 5-7 below.
4. Patients should not be taking antihistamines (short acting drugs must be stopped for 72 hours; astemizole for at least 4 weeks) or other drugs (eg. systemic steroids) which may interfere with skin tests.
5. Skin prick tests to drugs used by anaesthetists can be difficult to interpret. Wheals may be small and transient. A wheal 2mm larger than the negative control is regarded as positive. As a general rule, true sensitisation is associated with a positive reaction to the 1 in 10 dilution. Positive reactions to the undiluted agent but not to the 1 in 10 dilution are usually 'false positives', but may be regarded as significant when there is a good clinical history and there are no other positive reactions to relevant drugs, ie. those given at the time of the reaction.
6. Certain drugs (mainly opioids but also some neuromuscular blocking drugs) have intrinsic histamine releasing activity which leads to wheals in a proportion of normal subjects. Usually this is seen only with the undiluted drug, but it can occur at 1 in 10 dilution. For these drugs, a

positive skin reaction may be a false positive or may be clinically relevant, indicating the drug could cause an anaphylactoid or anaphylactic reaction. It is this type of reaction which is most difficult to interpret. Factors which may help in interpretation are the size of the wheal, the drug concentration that gives the positive reaction, the absence of other relevant reactions and the clinical picture. Skin tests should therefore be performed by those experienced in interpretation of responses to anaesthetic drugs.

7. A positive skin prick test can thus indicate (a) an IgE-mediated reaction (true anaphylaxis) or (b) direct histamine releasing effects of the drug (anaphylactoid reaction). Both of these can be important clinically. In IgE-mediated reactions, the skin tests are usually clear cut at 1 in 10 dilution and will often be positive at greater dilution (1 in 100 or 1 in 1,000). In case (b) there are difficulties in making a distinction between significant responses and a false positive reaction.
8. **Summary of interpretation**
 - (i) A positive skin prick test to 1 in 10 dilution should be taken as a true positive.
 - (ii) Positive skin prick tests to the stock concentration ('neat') are usually of doubtful significance - but this will depend on the drug in question and the overall clinical picture. Depending on the circumstance, the anaesthetist should be warned that this drug is a potential risk and should be avoided if possible.

“REPORT ON SUSPECTED ADVERSE DRUG REACTIONS”

- **Recently introduced products**
Please report all suspected reactions, including minor ones, that could conceivably be attributed to the drug. New products are identified by a black triangle in the British National Formulary.
 - Please also report reactions to vaccines
 - Record all other drugs taken in the previous 3 months including self-medication
 - Report suspected drug interactions
- **Established Products**
Please report serious or unusual suspected reactions to all agents, but not minor reactions. Include reactions that are fatal, life-threatening, disabling, incapacitating, or which result in or prolong hospitalisation

Do not be put off reporting because some details are not known.

REPORTING DOCTOR

Name: _____

Professional Address: _____

Telephone: _____ Speciality: _____

Signature: _____ Date: _____

PATIENTS DETAILS

Surname: _____ Other _____

Names: _____

Date of birth or Age: _____ Sex: _____

Hospital (if relevant) _____

Hospital Number _____

Consultant in charge or GP Principal: _____

SUSPECTED DRUG

Brand name of drug and batch number if known	Route	Daily Dose	Date Started	Date Stopped	Therapeutic Indication

Other drugs taken in the last 3 months including self-medication.

Give brand if known. Write none if no other drug has been taken	Route	Daily Dose	Date Started	Date Stopped	Therapeutic Indication

SUSPECTED REACTIONS

Was the patient hospitalised Because of the reaction? Yes <input type="checkbox"/> No <input type="checkbox"/>	Date Reaction Started	Date Reaction Ended	Outcome (eg fatal, recovered, continuing)

RELEVANT ADDITIONAL INFORMATION

Including medical history, investigations, known allergies, suspected drug interactions. For congenital abnormalities state all other drugs taken during pregnancy and the LMP. Please attach additional pages if necessary.

If you would like information about other reports associated with the suspected drug tick here.

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