Owing to the nature of their work, anaesthetists are involved in adverse drug reactions more commonly than most other clinicians. These adverse reactions to drugs can be classified as predictable or unpredictable. Predictable reactions are usually dose dependent, reproducible, and are often accepted as expected side-effects of the drug (e.g. hypotension after injection of thiopental). Unpredictable drug reactions may be classified as anaphylactoid or anaphylactic, and are dose independent.

Anaphylactic and anaphylactoid reactions

Anaphylaxis is a life-threatening syndrome triggered by a wide range of antigens and involves multiple organ systems. The first report of anaphylaxis was described in hieroglyphics in 2640 BC when an Egyptian pharaoh died after a wasp sting.

The term ‘anaphylaxis’ is derived from the Greek ‘ana’ meaning backward and ‘phylaxis’ meaning protection. An anaphylactic reaction is an example of a type I hypersensitivity reaction. It occurs after exposure to a foreign protein (antigen) that stimulates the production of IgE antibodies. After the initial exposure, antibody concentrations decrease, but IgE binds to mast cells and basophils. If there is further exposure, the antigen binds with IgE antibodies and results in the release of mediators, including histamine, slow-reacting substance-A (SRS-A), leukotrienes, tryptase and prostaglandins. These substances increase mucus secretion, bronchial smooth muscle tone and vascular permeability, causing airway oedema, bronchospasm and hypotension.

Anaphylactoid reactions are clinically indistinguishable from anaphylactic reactions, but they are not mediated by sensitizing IgE antibodies nor do they involve previous exposure to the antigen. The underlying mechanisms include the release of vasoactive substances (e.g. histamine), direct histamine release from mast cells or complement activation, by either the classical or alternative pathways. Anaphylactoid reactions are more commonly seen in reactions to contrast media.

Non-immunological histamine release is caused by the direct action of a drug on mast cells. The clinical response depends on both the drug dose and rate of delivery but it is usually benign and confined to the skin. Anaesthetic drugs that release histamine directly include atracurium, mivacurium, morphine and meperidine. Clinical evidence of histamine release, usually cutaneous, occurs in up to 30% of patients during anaesthesia.

Estimation of the frequency of anaphylaxis remains difficult. In Australia, the incidence is between 1 in 10 000 and 1 in 20 000. Extrapolating these figures to the UK predicts between 175 and 1000 reactions per year. This is approximately equivalent to 1 life-threatening reaction per 6000 general anaesthetics. Females are affected more often than males. The estimated mortality, once a reaction has started, is 5%. The first clinical features seen are given in Table 1.

Previous history of drug exposure does not seem necessary, especially with neuromuscular blocking agents. In 80% of reactions to these drugs, there had been no previous history of use. The anaphylactic reaction often begins 30–60 min after the start of the anaesthetic, rather that at induction. Anaphylactic reactions are also more common when drugs are given i.v., so it is essential that every practitioner who gives drugs by this route is able to recognize and treat such reactions.

**Table 1.** Initial presenting feature in anaphylaxis (% of total).


<table>
<thead>
<tr>
<th>Feature</th>
<th>Proportion of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No pulse detected, hypotension</td>
<td>28</td>
</tr>
<tr>
<td>Difficulty inflating lungs</td>
<td>26</td>
</tr>
<tr>
<td>Flushing</td>
<td>21</td>
</tr>
<tr>
<td>Coughing</td>
<td>6</td>
</tr>
<tr>
<td>Rash</td>
<td>4</td>
</tr>
<tr>
<td>Desaturation</td>
<td>3</td>
</tr>
<tr>
<td>Cyanosis</td>
<td>3</td>
</tr>
<tr>
<td>Other—ECG change, wheeze, urticaria</td>
<td>9</td>
</tr>
</tbody>
</table>

**Key points**

Anaphylaxis is a life-threatening syndrome that requires prompt recognition and treatment.

Immediate management includes oxygen administration, epinephrine and i.v. fluids.

Previous exposure to a drug does not seem necessary.

Reactions in anaesthetic practice occur most commonly with neuromuscular blocking agents.

Every anaesthetist should know an anaphylaxis drill.

Appropriate investigation and follow-up is required.

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Causes of life-threatening allergic reactions during anaesthesia

Neuromuscular blocking agents (70%)

Steroid-based compounds (vecuronium and pancuronium) cause anaphylactic reactions, whereas benzylisoquinoliniums (mivacurium and atracurium) tend to cause anaphylactoid reactions. Of drug reactions caused by neuromuscular blocking agents, 43% are caused by succinylcholine, 37% vecuronium and 7% atracurium. More than half of the reactions occur on first exposure. The quaternary ammonium group found in neuromuscular blocking agents is widely present in other drugs, foods, cosmetics and hair care products. This could explain why anaphylaxis to neuromuscular blocking agents is five to ten times more common in females.

Latex (12.6%)

Latex hypersensitivity has been increasingly recognized as a cause, especially in abdominal and gynaecological surgery. There is a recognized cross-reactivity between latex sensitivity and certain foods, especially bananas, chestnuts and avocado.

Colloids (4.7%)

Fluids used for resuscitation after anaphylaxis may themselves cause histamine release and worsen any reaction. The risk is greatest with gelatin solutions. All hyperosmolar solutions can release histamine directly. These solutions, for example mannitol, should be infused slowly.

Induction agents (3.6%)

The incidence of severe reactions to thiopental has been reported as about 1 in 14 000. Reactions to propofol are less common and are least common to etomidate.

Antibiotics (2.6%)

Penicillins are most frequently implicated in hypersensitivity reactions. The incidence of cross-reactivity with cephalosporins is about 8%. Even then, cross-reactivity is often incomplete and cephalosporins can be given to most patients. If, however, there is a history of a severe penicillin reaction, neither cephalosporins nor imipenem should be used. The antigenic stimulus is usually the β-lactam group.

Benzodiazepines (2%)

Benzodiazepines are an occasional cause of allergic reactions.

Opioids (1.7%)

Opioids usually cause anaphylactic reactions; morphine is implicated most commonly. Reactions to synthetic opioids are rare. Morphine, codeine and meperidine can cause a dose-dependent, non-immunological cutaneous histamine release.

Other agents (2.5%)

Radiocontrast media can produce hypersensitivity reactions in up to 3% of patients, although vasomotor symptoms such as flushing, warmth, nausea and cutaneous phenomena are more common. Reactions can be severe and most occur within minutes of administration. The risk of a reaction is markedly increased if the patient has suffered a previous reaction. Newer agents are associated with a lower risk. Other agents that can cause severe reactions during the perioperative period include protamine, aprotinin, atropen and bone cement.

Anaphylaxis drill

The response to treatment may depend on the severity of the reaction. Nonetheless, even severe anaphylaxis can have a prompt and successful response to appropriate treatment.

Every anaesthetist should be familiar with an anaphylaxis drill (Table 2). It should be agreed by departments as the standard procedure and be immediately available in all places where anaesthetics are given. Anaesthetists should rehearse a simulated anaphylaxis drill at regular intervals and should include staff who would normally assist. Treatment of severe cases should normally include epinephrine at an early stage. There should also be a standard procedure about giving advice about further investigations.

All patients who have a serious allergic reaction should be managed or observed in a critical care area so that a biphasic response and potential end organ damage can be recognized and treated.

Investigation

No tests have an immediate benefit on management, so they must not take priority over ensuring an adequate airway, breathing and circulation. Once the patient is stable, they can be performed.

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**Anaphylaxis drill**

**Immediate management**

Stop the administration of all agents likely to have caused the anaphylaxis. Call for help.

Maintain the airway, give oxygen 100% and lie the patient flat with the legs elevated. Give epinephrine. This may be given i.m. in a dose of 0.5–1 mg (0.5–1 ml of 1:1000) and may be repeated every 10 min according to the arterial pressure and pulse until improvement occurs. Alternatively, 50–100 μg i.v. (0.5–1 ml of 1:10 000) over 1 min has been recommended for patients with cardiovascular collapse, with titration of further doses as required. This should be given at a rate of 0.1 mg min⁻¹ stopping when a response has been obtained.

*It is important that undiluted epinephrine 1:1000 is never given i.v.*

Give i.v. fluid with colloid or crystalloid (avoiding colloids that have a higher incidence of allergy). Adult patients may require 2–4 litre.

**Subsequent management**

Give antihistamines (chlorpheniramine 10–20 mg by slow i.v. infusion). The use of H1-receptor antagonists remains unproven, but ranitidine 50 mg is usually administered by slow i.v. infusion. Give corticosteroids (100–500 mg hydrocortisone slowly i.v.).

Bronchodilators may be required for persistent bronchospasm. Catecholamine infusion as CVS instability may last several hours. Epinephrine 0.05–0.1 mg kg⁻¹ min⁻¹ (4 ml h⁻¹ of 1:10 000 for 70 kg adult).

Check ABGs for acidosis and consider bicarbonate 0.5–1.0 mmol kg⁻¹ (8.4% solution = 1 mmol ml⁻¹).
Immediate investigation

Three blood samples need to be taken in order to analyse the mast cell tryptase concentration. Tryptase is a neutral protease released from secretory granules of mast cells during degranulation. Approximately 99% of the body’s total enzyme is located within the mast cell. In vivo half-life is 3 h (compared with 3 min for histamine) and maximum concentrations occur rapidly within 1 h of degranulation. It is stable in isolated plasma or serum. As it is not present in red or white cells, it is not affected by haemolysis. Basal plasma tryptase concentration is 0.8–1.5 ng ml$^{-1}$. It increases after both anaphylactic and anaphylactoid reactions and helps to distinguish these from other causes of an adverse event (i.e. it defines the mechanism, but does not identify the causative agent). Concentrations up to 15 ng ml$^{-1}$ are seen both in pseudoallergy (non-specific or anaphylactoid reactions) and mild anaphylaxis. A higher value (>20 ng ml$^{-1}$) is more likely to indicate an IgE (hence anaphylaxis) response.

Each sample should be 5–10 ml of blood in a clotted tube and taken at the following times, with the appropriate time recorded on the sample: (i) immediately after the reaction has been treated; (ii) about 1 h after the reaction; and (iii) about 6 h or up to 24 h after the reaction.

The samples should be separated and stored at 4°C if they can be analysed within 48 h. Otherwise they should be stored at −20°C until they can be sent for analysis. The rise in tryptase is transient, so timing is important.

Later investigations to identify the causative agent

Any patient who has a suspected anaphylactic reaction associated with anaesthesia should be fully investigated. The standard procedure should include advice about investigation of the reaction and advice to be given to the patient. The anaesthetist who administers the drugs associated with the suspected anaphylactic reaction, in consultation with a consultant if the anaesthetist is a trainee, must be responsible for ensuring that these tests are performed and interpreted adequately.

The patient should be referred to a Regional Allergy Centre for specialist investigation by an allergist. Details which the allergist will require include all drugs given before and during the anaesthetic as well as their timing in relation to the reaction, photocopies of the anaesthetic chart and drug chart, and the timing and results of tests sent. The allergist will perform skin prick tests for general anaesthetic drugs, which show the presence of specific IgE antibodies to these drugs. Intradermal skin tests using more dilute solutions may occasionally be required. In both cases, operator expertise in interpreting the tests is vital. Specific IgE antibodies can be measured in the serum; currently, there is a commercial assay available only for succinylcholine.

Other allergic causes have to be considered as well as the anaesthetic agents. These include antibiotics, analgesics given intraoperatively and latex rubber allergy. This can be specifically assessed by history, supported by skin testing or measuring specific IgE, for example by radio-allergosorbent test (RAST) which is a technique for measurement of antigen-specific IgE antibodies in the serum. Alternatively the CAP test can be performed; it is a fluoro-immunoassay and more sensitive than RAST.

Reporting reactions

All suspected anaphylactic reactions should be reported on a ‘Yellow Card’ even if the reaction is reported elsewhere (e.g. to an allergist). The doctor who administers the drug is responsible for ensuring that the reaction is reported. In addition, the anaesthetist is responsible for the advice given to the patient about future anaesthesia, including a full explanation of what happened. There must also be a full record in the case notes (not just on the anaesthetic chart) 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 Medic-Alert bracelet.

Screening for anaphylaxis

Currently, screening for anaphylaxis has no value. A history of previous exposure is not necessary for an anaphylactic reaction.

Management of a patient with previous anaphylaxis

The causative agent and severity of the previous reaction should be identified, if possible. Regional anaesthesia should be considered, if appropriate. An inhalational technique for induction could also be considered. Patients requiring a general anaesthetic should be premedicated with hydrocortisone, H$_1$- and H$_2$-receptor antagonists and inhaled β-agonists. Full monitoring should be used before the start of anaesthesia and i.v. access obtained with a cannula of at least 18 gauge in an adult.

The patient should be preoxygenated. Vasopressor therapy, in particular, epinephrine, should be immediately available. A safe technique will avoid re-exposure to implicated agents (and related compounds) and the use of drugs with a low potential for hypersensitivity and direct histamine release. These include volatile agents, etomidate, fentanyl and benzodiazepines. All drugs should be given slowly in dilution and full resuscitation facilities must be immediately available.

Key references


See multiple choice questions 95–98.